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Understanding obesity to determine the best therapeutic option: from lifestyle interventions to therapies

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Understanding obesity to determine the best therapeutic option: from lifestyle interventions to therapies

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Editorial: Understanding obesity to determine the best therapeutic option: from lifestyle interventions to therapies

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Editorial on the Research Topic
Understanding obesity to determine the best therapeutic option: from lifestyle interventions to therapies

Obesity is a global health crisis that transcends age, geography, and socioeconomic barriers, significantly increasing the risk of type 2 diabetes, cardiovascular diseases, cancer, and other chronic conditions. The urgency to tackle this multifaceted epidemic requires a multidisciplinary approach that integrates molecular, behavioral, and clinical perspectives. This Research Topic, "*Understanding Obesity to Determine the Best Therapeutic Option*," presents pivotal research aimed at advancing precision medicine and patient-centered approaches for obesity management.

A cornerstone for addressing obesity lies in the promotion of healthy lifestyle habits. Recent findings underscore the importance of discipline-specific interventions to promote health equity across diverse populations (1). Dietary strategies remain central in obesity research. Various types of diets, including low-calorie, low-carbohydrate, and high-protein regimens, are tailored to individual needs. Studies highlight the efficacy of the Mediterranean diet in promoting weight loss and improving metabolic health, due to its rich nutrient profile and anti-inflammatory properties (2). Additionally, ketogenic diets have shown promise by enhancing fat oxidation and reducing appetite, making them viable options for obesity management (3).

Pharmacological therapies are progressively recognized as effective alternatives for obesity treatment, offering promising results for individuals who struggle with lifestyle-based interventions. GLP-1 receptor agonists, such as semaglutide and liraglutide, have demonstrated significant weight loss and metabolic improvements (4) (Tamayo-Trujillo et al.). Moreover, combination therapies targeting appetite regulation and energy expenditure are emerging as innovative approaches in obesity management (Vedrenne-Gutiérrez et al.). Bariatric surgery is another highly effective intervention for managing severe obesity, leading to substantial weight loss and improvements in comorbidities. Studies have shown these procedures are associated with a 59% reduction in all-cause mortality among obese adults with type 2 diabetes and a 30% reduction among those without that condition (5).

Emerging research highlights the roles of genetic and microbial determinants in obesity, providing insights for personalized treatments. Genome-wide association studies (GWAS) have identified genetic variants linked to obesity susceptibility, such as those in the FTO gene, which influence appetite and energy regulation (6). Concurrently, studies reveal that gut microbiota composition significantly affects energy balance and metabolic health, with interventions targeting microbiota showing potential for obesity management (7).

Environmental factors also play a crucial role in obesity risk (8, 9). A 2024 scoping review identified endocrine-disrupting chemicals (EDCs), such as bisphenols, phthalates, parabens, and triclosan, as key contributors, emphasizing the need for preventive strategies (10). These findings stress the importance of considering environmental influences when designing obesity prevention strategies.

Collectively, the 15 manuscripts in this Research Topic offer a comprehensive exploration of the mechanisms and interventions for obesity, spanning lifestyle changes to advanced therapies. These findings highlight the importance of a multidisciplinary and personalized approach to effectively combat this complex public health challenge (Reytor-González et al.).

Lifestyle interventions continue to be indispensable. Studies exploring the Health at Every Size (HAES) paradigm advocate for sustainable and body-positive approaches (Suárez et al.) Meanwhile, innovative dietary strategies, such as intermittent fasting, reveal promising effects on gut microbiota composition and metabolic health, warranting further exploration of their long-term impacts (Cadena-Ullauri et al.). Furthermore, cashew nut and oil interventions demonstrate the potential of dietary bioactives to improve cardiometabolic risk profiles during weight loss (Meneguelli et al.).

Emerging research underscores the critical role of body composition in obesity-related risks. For example, oxidative balance scores provide insights into the interplay between dietary antioxidants, prooxidants, and obesity, offering new avenues for targeted interventions (Zhu et al.). Suárez et al. reported that assessing muscle mass can help detect adult individuals with high risk of developing type 2 diabetes as one of the obesity-related comorbidities. It is essential to promote healthier eating and lifestyle habits among young individuals, as highlighted by Saintila et al., who reported insufficient consumption of whole grains, legumes, vegetables, nuts, and seeds, along with inadequate levels of regular physical activity, hydration, and sunlight exposure among Peruvian university students.

Notably, as reported by Arteaga-Pazmiño et al., understanding dynapenic obesity, the coexistence of excess body weight and low muscle strength, has proven essential for addressing physical performance impairments in aging populations. Additionally, the influence of skeletal muscle weight on anesthesia dosing in obese patients exemplifies the importance of integrating body composition analysis into clinical practice (Hu et al.).

Micronutrient status also plays a vital role in obesity management. Studies in Research Topic highlight the importance of tailored supplementation to address common deficiencies in vitamin D, calcium, and iron (Côté et al.). Interestingly, Zambrano et al. point out that understanding the changes in gut microbiota following bariatric surgery is essential for predicting metabolic outcomes and developing targeted interventions to optimize obesity management. Furthermore, when developing nutrition programs for post-bariatric surgery patients, it is essential to involve a specialist. This approach ensures that frequently reported macro- and micronutrient deficiencies, as highlighted by the study from Afsar and Ozdogan, are effectively addressed before initiating supplementation.

Also, it could be mentioned the broader societal implications of obesity. For instance, Díaz et al. reported the links between obesity and hypovitaminosis D revealing how socio-environmental factors interact with physiological mechanisms.

In conclusion, the multifaceted nature of obesity requires a multidisciplinary and personalized approach to its management. This Research Topic emphasizes the critical role of lifestyle interventions, innovative dietary strategies, and pharmacological advancements in combating obesity. Emerging research on genetic predispositions, gut microbiota, and body composition provides insights into tailored interventions for prevention and treatment. Furthermore, addressing micronutrient deficiencies, particularly post-bariatric surgery, highlights the importance of specialized nutritional strategies. By integrating environmental and socio-cultural factors, these findings pave the way for holistic strategies to effectively tackle this global health crisis.

Author contributions

EF-T: Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FC: Validation, Writing – original draft, Writing – review & editing. JC-M: Validation, Writing – original draft, Writing – review & editing. AR: Validation, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Body mass index and healthy lifestyle practices among Peruvian university students: a comparative study among academic discipline

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Background: Excess body weight and an unhealthy lifestyle are a risk factor for noncommunicable diseases. University students are susceptible to unhealthy habits and obesity. This study compared body mass index (BMI) and healthy lifestyle practices among university students from four academic disciplines: Health Sciences, Business Sciences, Human Sciences and Education, and Engineering/Architecture.

Methods: A cross-sectional study was carried out using a sample of 6,642 university students selected by non-probability convenience sampling. The Diet and Healthy Lifestyle Scale (DEVS), the Peruvian validation of the Vegetarian Lifestyle Index (VLI), was used to assess healthy lifestyle practices.

Results: Students in the areas of Business Sciences and Engineering/Architecture had a higher BMI than their peers in Health Sciences (B = 0.35, 95% CI: 0.15–0.56 and 0.32, 95% CI: 0.13–0.52; $p = 0.001$). Additionally, these students tended to adopt less healthy lifestyle (B = −0.11, 95% CI: −0.20 to −0.01 and −0.09, 95% CI: −0.18 to −0.00; $p < 0.05$) compared to those in Health Sciences.

Conclusion: Although students of Health Sciences and Human Sciences and Education exhibited healthy lifestyle patterns, there is a clear need to improve eating and living habits in general among the university population to mitigate the risk factors associated with non-communicable diseases.

KEYWORDS

body mass index, noncommunicable diseases, obesity, healthy lifestyle, universities

Introduction

Body mass index (BMI) is defined as a measure that compares an individual's weight in relation to height; it is calculated by dividing weight in kilograms by the square of height in meters (kg/m^2) (1). BMI is widely used to classify individuals into different weight categories, which helps identify potential health risks associated with underweight and excess body weight (overweight/obesity) (2). Excess body weight in young people, particularly among university students, represents one of the most important public health problems worldwide.

In Peru, according to actual data from the National Institute of Statistics and Informatics (INEI), 37.5% and 25.6% of individuals aged 15 years and older were overweight and obese, respectively (3); the urban area and women are the most affected by obesity, with a prevalence of 39.0% and 29.8%, respectively (3). These statistics position Peru as one of the countries with the highest prevalence of overweight and obesity in the South American region.

Obesity in the university population is a complex phenomenon influenced by multiple factors (4, 5). The most common causes of obesity include unhealthy eating habits, lack of physical activity, academic stress, irregular schedules, lack of time, consumption of harmful substances (tobacco and alcohol), and genetic factors (6–9). Some studies suggest differences in the prevalence of obesity by field of study. For example, a cross-sectional survey conducted on 584 participants reported that Science and Technology students had the highest proportion of overweight and obese individuals compared to those in Health Sciences (10). It is possible that students in disciplines related to health, such as human nutrition, medicine, and nursing, have better lifestyle habits compared to their peers in other disciplines due to their basic knowledge of healthy lifestyles, which could be attributed to greater health awareness and knowledge (11).

A healthy lifestyle is defined as a set of daily behaviors and choices that contribute to an individual's well-being and optimal health (12). These behaviors include a variety of practices and habits such as healthy eating and nutrition, regular physical activity, adequate water consumption, exposure to sunlight, adequate sleep, among others (13). These habits are related to different aspects of the physical, mental, and social health of university students (14). However, adhering to a healthy lifestyle in a university setting can be difficult for students due to the conditions and characteristics of the environment (15).

The intake of healthy foods, as a component of a healthy lifestyle, is considerably low among young people. In the Peruvian context, according to INEI, only 10.5% of the population over 15 years of age reaches the recommended consumption of at least 5 servings of fruits and vegetables per day (16). In addition, the average daily consumption of fruit in this age group is only 2.0 servings (16), which is below the guidelines established by the World Health Organization (WHO), which recommends consuming 5 or more servings of fruits and vegetables daily to maintain a balanced diet and prevent health conditions such as obesity (17). In addition, it has been observed that no region of the country reaches the ideal average fruit consumption (16). In contrast, both in the general population and in university students, a high consumption of added sugars, processed meats, and saturated fats has been detected, exceeding the daily amounts recommended by the WHO (18). Moreover, the intake of healthy foods has been the subject of studies in several countries (6, 10, 14). In a recent study among university students in Saudi Arabia, only 16.07% and 11.23% of 454 students consumed vegetables and fruits daily, respectively (14). Likewise, another study reported that 47.1% of Science and Technology students consumed meat almost every day (10). This trend in eating habits reflects a significant gap between current dietary practices and national and international nutritional recommendations, underscoring the need to implement strategies to promote healthy eating habits, especially among university students.

Moreover, university students, compared to the general adult population, have reported lower levels of regular physical activity (10, 19–21). The prevalence of physical activity among Peruvian adults is a topic of interest in the field of public health. According to the National Health Survey (ENAHO), 61.9% of this population does not meet international physical activity recommendations (22). Specifically, WHO suggests a minimum of 150 min of moderate physical activity per week for adults (23). Several studies have reported that more than 70% of university students do not reach the recommended goal of 10,000 steps per day (24), This could be due to lack of time, academic factors, among others.

On the other hand, although water is an important chemical element in the body, low water intake is one of the most common health concerns affecting university students (25–27). A study conducted with university students in the United States revealed that only 16.3% of women and 13.3% of men met the recommended daily intake of water (25). Concerns arise when considering these low levels of water intake among university students, especially given the critical relevance of water to various physiological functions of the body. Water is essential for the regulation of body temperature, the effective transport of nutrients through the body, and the proper elimination of waste and toxins, all of which are essential for maintaining good general health (28). Furthermore, adequate sunlight exposure as a healthy lifestyle factor is essential for an individual's health and well-being (29). University students, particularly those in the field of Health Sciences field, have reported lower levels of sunlight exposure (30). Study in Sri Lanka revealed limited sunlight exposure among university health care students (30). In addition, the influence of modern urban lifestyles, prevalent in this population, has been identified as one of the causes of reduced sunlight exposure (31). Factors such as poor knowledge about the importance of vitamin D, spending long hours in academic facilities such as laboratories, and predominantly sedentary study habits contribute to this low sunlight exposure in students (30, 32). However, it is important to maintain a balance between the benefits of sunlight exposure and the risk of skin damage, including skin cancer (33). This highlights the importance of implementing public health strategies focused on promoting an appropriate balance, optimizing the benefits of sunlight while minimizing the risks associated with excessive exposure.

Despite the growing evidence on the importance of a healthy lifestyle and its impact on student well-being, there is a notable lack of research comparing these variables between different academic disciplines. Several studies have examined the BMI and lifestyles of university students (4, 11, 34, 35), however, most focus on the difference in gender and years of study and do not make clear distinctions between academic disciplines. This lack of specificity prevents a complete understanding of how different fields of study can influence students' health and behavior. Understanding these specific disparities is important, as it provides a unique perspective on health determinants in university settings and offers the opportunity to develop more effective targeted interventions and public health policies. The identification of specific healthy lifestyle patterns and associated health risks in different academic areas not only underscores the need for personalized health promotion strategies but could also contribute to the prevention of noncommunicable diseases among the university population, a key demographic group in the formation of future generations and in the promotion of healthy lifestyles in society. Therefore, this study aims to investigate the differences in BMI and healthy lifestyle practices among students from different disciplines at a private university in Peru.

Materials and methods

Design and participants of the study

This cross-sectional comparative study was carried out at a private Peruvian university with campuses in the three main geographical regions of the country: coast, highlands, and jungle. This purposeful selection allows for a broad cultural and socioeconomic diversity inherent to these regions, reflecting a wider spectrum of the Peruvian student population. The inclusion of campuses in these geographically and culturally distinct areas offers a unique opportunity to examine BMI and healthy lifestyle practices among university students in different environmental and cultural contexts. Data collection was carried out during the enrollment period for the first academic cycle of the year, in the months of February and March 2021. A non-probability convenience sampling method was used to recruit participants. The invitation to students to participate in the study was made through the university's academic portal, where detailed information on the objectives of the study was provided. This information was available on the survey's homepage. Subsequently, electronic informed consent was obtained from the students who chose to participate. In total, 6,642 students completed the survey. Adult students between 18 and 29 years of age were considered eligible for the study. We excluded those who did not meet the age criteria, graduate students, those who provided inadequate responses to specific survey questions, and those who did not give their consent. The project was reviewed and approved by the Research Ethics Committee of the Universidad Peruana Unión (approval number: 2021-CEUPeU-0009), and the corresponding permission was obtained from the academic area of the university. The study was carried out according to the ethical standards established in the Declaration of Helsinki and its amendments.

Variables of study

Body mass index

As part of the study, data on the weight and height of the students were collected, which were self-reported by the participants. Using this information, the BMI of each student was calculated. The classification of body mass index (BMI) was performed according to WHO criteria, which define the following categories: (a) underweight, with a BMI of less than 18.5; (b) normal weight, with a BMI between 18.5 and 24.9 kg/m^2; (c) overweight, with a BMI between 25.0 and 29.9 kg/m^2; and (d) obese, with a BMI of 30 or more (36).

Healthy lifestyle practices

To assess healthy lifestyle practices, we used the Diet and Healthy Lifestyle Scale (DEVS) (37). This instrument represents the validated Peruvian version of the Vegetarian Lifestyle Index (VLI) (38), which consists of 14 items, 11 of which include topics related to whole foods of plant origin, such as fruits, vegetables, legumes, nuts, seeds, and whole grains. Similarly, foods of animal origin, such as milk and dairy products, eggs, and foods that are reliable sources of vitamin B-12, were considered. Sweets were also considered. Additionally, the last 3 items represent lifestyle characteristics and include regular physical activity, adequate water intake, and moderate sunlight exposure. For each question, the response options were limited to 3. The 14 items are summed to obtain a total score ranging from 0 to 14 points, considering the following scoring system: 0, 0.5, or 1 point. Participants were assigned a score based on how well they followed the recommendations: They were awarded 1 point for full compliance, 0.5 points for partial compliance, and 0 points if there was no compliance. For example, participants who consumed ≥6 servings/day of whole grains received a score of 1, those who consumed ≥3 and < 6 servings/day received a score of 0.5; and if they consumed less than 3 servings/day of whole grains they received a score of 0. In addition, inverse scoring was applied for the following components: vegetable oils, dairy products, eggs, sweets, and consumption of foods of animal origin, whose recommendations were to consume in moderation or in moderate amounts, so that higher intakes of these foods received lower scores. For example, participants who consumed >5 servings/week of sweets received 0 points. Those who consumed >2 and ≤ 5 servings/week received 0.5 points. While those who consumed 0 to 2 servings per week received 1 point. On the other hand, in terms of lifestyle variables, we considered the following: For sunlight exposure: <5 min/day = 0 point (low), ≥5 and <10 min/day = 0.5 points (medium), and ≥10 min/day = 1 point (high). Water intake: <4 glasses of water/day = 0 point (low), ≥4 and <8 glasses of water/day = 0.5 points (medium), and ≥8 glasses of water/day = 1 point (high). Daily exercise: 0 min/day of any moderate or vigorous exercise = 0 point (low), >0 and <30 min/day of moderate exercise or >0 and <15 min/day of vigorous exercise, and ≥30 min/day of moderate exercise or ≥15 min/day of vigorous exercise = 1 point (high). Higher total scores indicate a healthy lifestyle (Appendix A) (38, 39).

Sociodemographic information

Information was collected based on 8 questions considering the following categories: sociodemographic data, including information on age (years), sex, region of origin, place of residence, marital status, and religion. In addition, academic discipline and the level of parental education were considered.

Statistical analysis

The descriptive analysis consisted of the description of the variables with absolute and relative frequencies for the categorical variables and mean with standard deviation for the numerical variables. Subsequently, we compare the general characteristics, BMI, and healthy lifestyle according to academic disciplines. We used the Kruskal-Wallis test and the independence chi-square test of to assess whether there are statistically significant differences in the independent numerical and categorical variables, respectively. Finally, we created simple and multiple robust variance linear regression models to evaluate the association between lifestyle and anthropometric parameters with academic disciplines. We considered a value of p of less than 0.05 and the analysis was performed with the R program version 4.3.2.

Results

Table 1 presents the sociodemographic data of university students divided by academic discipline. The total sample is 6,642 students. The average age is 21.4 years. There is a slight majority of females (54.4%)

TABLE 1 General characteristics of Peruvian university students according to academic disciplines.

Characteristics	All	Academic disciplines				
	$N = 6,642$[a]	Health Sciences	Business Sciences	Human Sciences and Education	Engineering/ Architecture	p[b]
		$N = 2,135$[a] (32.1%)	$N = 1,748$[a] (26.3%)	$N = 715$[a] (10.8%)	$N = 2,044$[a] (30.8%)	
Age	21.4 (3.4)	21.2 (3.3)	21.5 (3.7)	22.5 (4.1)	21.1 (2.9)	<0.001
Age group (years)						<0.001
≥18	1,075 (16.2%)	376 (17.6%)	274 (15.7%)	89 (12.4%)	336 (16.4%)	
19–24	4,580 (69.0%)	1,479 (69.3%)	1,197 (68.5%)	444 (62.1%)	1,460 (71.4%)	
>24	987 (14.9%)	280 (13.1%)	277 (15.8%)	182 (25.5%)	248 (12.1%)	
Sex						<0.001
Female	3,613 (54.4%)	1,594 (74.7%)	1,003 (57.4%)	369 (51.6%)	647 (31.7%)	
Male	3,029 (45.6%)	541 (25.3%)	745 (42.6%)	346 (48.4%)	1,397 (68.3%)	
Region of origin						<0.001
Coast	1,455 (21.9%)	502 (23.5%)	280 (16.0%)	256 (35.8%)	417 (20.4%)	
Jungle	1,404 (21.1%)	359 (16.8%)	478 (27.3%)	95 (13.3%)	472 (23.1%)	
Highlands	3,627 (54.6%)	1,205 (56.4%)	978 (55.9%)	333 (46.6%)	1,111 (54.4%)	
Foreign	156 (2.3%)	69 (3.2%)	12 (0.7%)	31 (4.3%)	44 (2.2%)	
Lugar de residencia						0.166
Rural	1,886 (28.4%)	589 (27.6%)	518 (29.6%)	220 (30.8%)	559 (27.3%)	
Urbano	4,756 (71.6%)	1,546 (72.4%)	1,230 (70.4%)	495 (69.2%)	1,485 (72.7%)	
Religion						<0.001
Seventh-day Adventist	3,643 (54.8%)	1,254 (58.7%)	786 (45.0%)	522 (73.0%)	1,081 (52.9%)	
Baptist	370 (5.6%)	107 (5.0%)	117 (6.7%)	29 (4.1%)	117 (5.7%)	
Catholic	2,220 (33.4%)	670 (31.4%)	718 (41.1%)	126 (17.6%)	706 (34.5%)	
Others	779 (11.7%)	104 (4.9%)	127 (7.3%)	38 (5.3%)	140 (6.8%)	
Marital status						<0.001
Married	375 (5.6%)	105 (4.9%)	131 (7.5%)	66 (9.2%)	73 (3.6%)	
Single	6,267 (94.4%)	2,030 (95.1%)	1,617 (92.5%)	649 (90.8%)	1,971 (96.4%)	
Parental education						<0.001
Basic	3,801 (57.2%)	1,173 (54.9%)	1,094 (62.6%)	402 (56.2%)	1,132 (55.4%)	
Technical	1,182 (17.8%)	366 (17.1%)	302 (17.3%)	126 (17.6%)	388 (19.0%)	
Undergraduate	1,023 (15.4%)	371 (17.4%)	218 (12.5%)	131 (18.3%)	303 (14.8%)	
Postgraduate	636 (9.6%)	225 (10.5%)	134 (7.7%)	56 (7.8%)	221 (10.8%)	

[a]Mean (SD); *n* (%), [b]Kruskal-Wallis test; chi-square test of independence.

in the total student population. The students come mainly from the highlands (54.6%). The Faculty of Human Sciences and Education has the highest proportion of students from the Coast (35.8%). Most of the students live in urban areas (71.5%), with a similar proportion in all academic disciplines. Most are Adventists (54.8%), followed by Catholics (33.4%). Most of the students are single (94.4%). Most of the students' parents have basic education (57.2%).

The lowest BMI was observed in students of Health Sciences students (23.5, $p = 0.004$; Figure 1). Engineering/Architecture discipline was associated with excess body weight (overweight/obesity; $p = 0.040$). The Healthy lifestyle scale score was significantly lower in Business Science students (6.44, $p < 0.001$; Figure 2; Table 2).

In relation to the dietary component of healthy lifestyle practices, in general, the highest proportion of students had low consumption of whole grains, vegetables, fruits, nuts, and seeds. Furthermore, low levels of physical activity, water consumption, and adequate sunlight exposure were observed. Specifically, considering the recommended intake of different food groups, Business Studies and Engineering/Architecture were significantly associated with a low consumption of legumes (<1 serving/day; $p < 0.001$). Low intake of nuts and seeds (<4 servings/week; $p < 0.001$) was associated with Entrepreneurial Sciences. High dairy intake (>2 servings/day; $p = 0.029$) is associated with Business Science and Engineering/Architecture. Human Sciences and Education students reported

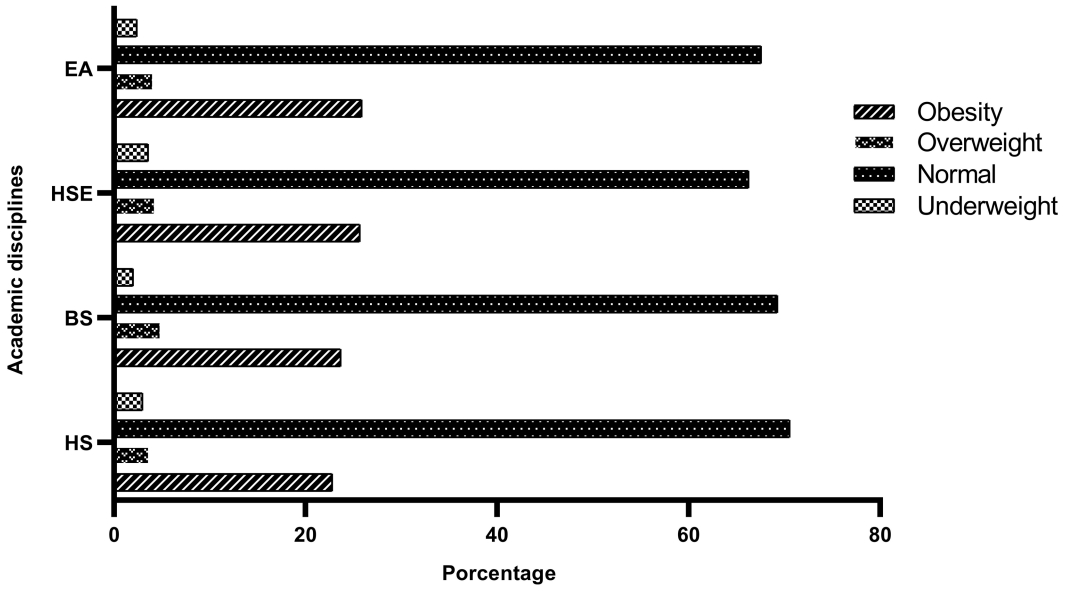

FIGURE 1
Percentage of BMI categories according to academic discipline. HS, Health Sciences; BS, Business Sciences; HSE, Human Sciences and Education; EA, Engineering/Architecture.

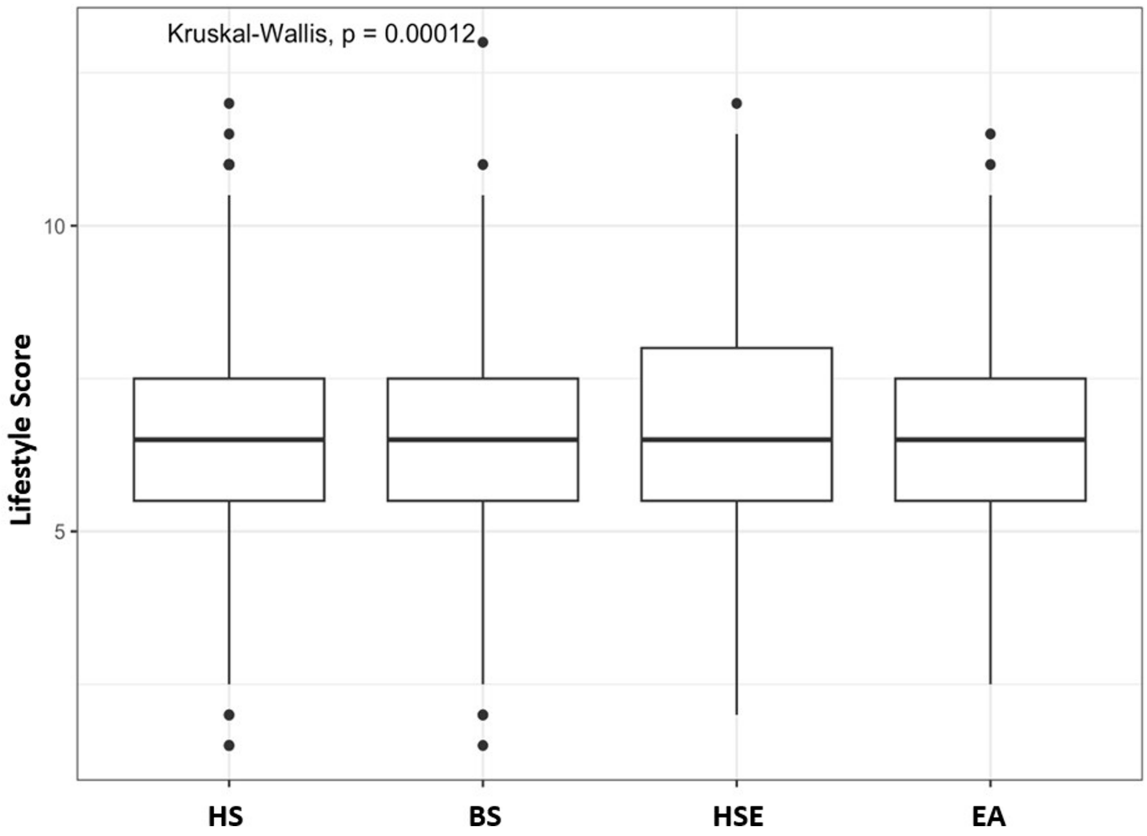

FIGURE 2
Low and whisker plot of lifestyle scores according to study disciplines. HS, Health Sciences; BS, Business Sciences; HSE, Human Sciences and Education; EA, Engineering/Architecture; Kruskal-Wallis, $p = 0.00012$.

higher consumption of sweets (>5 servings/week; $p < 0.001$) and lower intake of foods sources of vitamin B-12 (<1.0 mcg serving equivalent/day; $p = 0.010$). Business Science students consumed meat more frequently (>1 time/week; $p < 0.001$) and reported low water intake (<4 glasses of water/day, $p < 0.001$). There was no significant association with the consumption of whole grains,

TABLE 2 Anthropometric parameters and healthy lifestyle according to academic discipline in Peruvian university students.

Characteristics	All	Academic disciplines				
	$N = 6,642$[a]	Health Sciences	Business Sciences	Human Sciences and Education	Engineering/ Architecture	p[b]
		$N = 2,135$[a] (32.1%)	$N = 1,748$[a] (26.3%)	$N = 715$[a] (10.8%)	$N = 2,044$ [a] (30.8%)	
Weight	63 (11)	60 (10)	63 (11)	63 (11)	65 (11)	<0.001
Height	1.62 (0.08)	1.60 (0.08)	1.62 (0.08)	1.62 (0.09)	1.65 (0.08)	<0.001
BMI	23.8 (3.2)	23.5 (3.1)	23.9 (3.2)	23.7 (3.2)	23.9 (3.3)	0.004
BMI categorized						0.040
Underweight	173 (2.6%)	63 (3.0%)	35 (2.0%)	26 (3.6%)	49 (2.4%)	
Normal	4,574 (68.9%)	1,507 (70.6%)	1,212 (69.3%)	474 (66.3%)	1,381 (67.6%)	
Obesity	279 (4.2%)	78 (3.7%)	86 (4.9%)	31 (4.3%)	84 (4.1%)	
Overweight	1,616 (24.3%)	487 (22.8%)	415 (23.7%)	184 (25.7%)	530 (25.9%)	
Healthy lifestyle	6.51 (1.50)	6.55 (1.51)	6.44 (1.50)	6.73 (1.57)	6.46 (1.47)	<0.001

[a]Mean (SD); *n* (%); % according to faculty add up to 100% per column, [b]Kruskal-Wallis test; Chi-square test of independence, BMI, Body mass index.

vegetables, fruits, eggs, regular physical activity, and adequate sunlight exposure ($p > 0.05$; Table 3).

In Table 4, students in Business Sciences (B = −0.11, 95% CI: −0.20 to −0.01; $p = 0.024$) and Engineering/Architecture (B = −0.09, 95% CI: −0.18 to −0.00; $p = 0.047$) had a lower mean score on the measure of healthy lifestyle compared to those in Health Sciences; in contrast, students in Human Sciences and Education had the highest average score. Similarly, students enrolled in Business Sciences (B = 0.35, 95% CI: 0.15–0.56; $p = 0.001$) and Engineering/Architecture (B = 0.32, 95% CI: 0.13–0.52; $p = 0.001$) had a significantly higher average BMI than those in Health Sciences. The coefficients remained in the same direction after adjusting for age, sex, and parental education.

Discussion

The transition to university life represents a critical period in the development of habits and behaviors that can have a lasting impact on students' health status. In this context, lifestyle plays an important role, especially regarding the consumption of plant-based foods, regular physical activity, among others. Eating behaviors, along with other aspects of lifestyle, are influenced by a variety of factors, including the student's field of study. The present study compared BMI and healthy lifestyle practices, considering specific dietary behaviors, such as the intake of whole grains, legumes, vegetables, fruits, nuts, and seeds among university students from different academic areas including Health Sciences, Business Sciences, Human Sciences and Education, and Engineering/Architecture. This research seeks to understand how academic disciplines, with their specific demands, can influence the life habits of students.

BMI

Although obesity commonly manifests itself in the early stages, university students also go through a worrisome phase in which their lifestyle can be subjected to unhealthy changes, often resulting in weight gain (14). The probability of being overweight or obese is approximately the same among young men and women (40). However, research on university students shows an increasing trend of obesity among men (4, 5).

In the current study, regression analysis found that Business and Engineering/Architecture students were more likely to report excess body weight than Health Sciences students, who had the lowest mean BMI score. Similarly, a comparable study conducted with 584 participants during the COVID-19 pandemic reported that students in Science and Technology disciplines had a higher proportion of individuals with overweight and obesity compared to those in Health Sciences (10). Furthermore, in our study, a higher prevalence of individuals with excess body weight (28.5%) and a lower prevalence of underweight individuals (2.6%) were found. These findings are consistent with studies conducted in the university population (34). Differences in the prevalence of excess weight among students from different disciplines can be attributed to factors such as academic stress, irregular schedules, academic workload, sedentary lifestyle, and health and nutrition education (6). In fact, academic stressors can cause systemic imbalance, affecting both the physical and psychological well-being of students, and leading to behaviors that can increase the risk of obesity (41). Therefore, the current study highlights the need to address the lifestyles and eating habits of university students, considering the particularities of each discipline of study. Promoting strategies to manage BMI-related issues could be a key approach to prevent the development of obesity-related chronic diseases in the long term.

Healthy lifestyle practices

Adequate food intake

Consuming of whole grains, legumes, vegetables, fruits, nuts, and seeds offers multiple health benefits. For example, whole grains improve digestion and reduce the risk of chronic diseases (42). In the case of legumes, they provide protein and fiber and are beneficial for weight control and cardiovascular health (43). Vegetables and fruits,

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TABLE 3 Healthy lifestyle practices according to academic discipline in Peruvian university students.

Items of healthy lifestyle practices	All	Academic disciplines				
	N = 6,6,421	Health Sciences	Business Sciences	Human Sciences and Education	Engineering/ Architecture	*p*[b]
		N = 2,135[a] (32.1%)	*N* = 1,748[a] (26.3%)	*N* = 715[a] (10.8%)	*N* = 2,044 [a] (30.8%)	
Whole grains						0.470
<3 servings/day	3,840 (57.8%)	1,264 (59.2%)	1,022 (58.5%)	405 (56.6%)	1,149 (56.2%)	
≥3 and <6 servings/day	2,409 (36.3%)	755 (35.4%)	621 (35.5%)	262 (36.6%)	771 (37.7%)	
≥6 servings/day	393 (5.9%)	116 (5.4%)	105 (6.0%)	48 (6.7%)	124 (6.1%)	
Legumes, soy, and meat substitutes						<0.001
<1 serving/day	2,550 (38.4%)	757 (35.5%)	746 (42.7%)	247 (34.5%)	800 (39.1%)	
≥1 and <3 servings/day	3,388 (51.0%)	1,149 (53.8%)	824 (47.1%)	366 (51.2%)	1,049 (51.3%)	
≥3 servings/day	704 (10.6%)	229 (10.7%)	178 (10.2%)	102 (14.3%)	195 (9.5%)	
Vegetables						0.120
<4 servings/day	3,077 (46.3%)	985 (46.1%)	851 (48.7%)	332 (46.4%)	909 (44.5%)	
≥4 and <8 servings/day	2,955 (44.5%)	948 (44.4%)	730 (41.8%)	320 (44.8%)	957 (46.8%)	
≥8 servings/day	610 (9.2%)	202 (9.5%)	167 (9.6%)	63 (8.8%)	178 (8.7%)	
Fruits						0.642
<2 servings/day	2,398 (36.1%)	763 (35.7%)	639 (36.6%)	261 (36.5%)	735 (36.0%)	
≥2 and <4 servings/day	3,134 (47.2%)	989 (46.3%)	821 (47.0%)	337 (47.1%)	987 (48.3%)	
≥4 servings/day	1,110 (16.7%)	383 (17.9%)	288 (16.5%)	117 (16.4%)	322 (15.8%)	
Nuts and seeds						<0.001
<4 servings/week	3,933 (59.2%)	1,285 (60.2%)	1,069 (61.2%)	407 (56.9%)	1,172 (57.3%)	
≥4 servings/week and <1.5 servings/day	1,917 (28.9%)	600 (28.1%)	482 (27.6%)	193 (27.0%)	642 (31.4%)	
≥1.5 servings/day	792 (11.9%)	250 (11.7%)	197 (11.3%)	115 (16.1%)	230 (11.3%)	
Vegetable oils						0.002
>4 servings/day	357 (5.4%)	88 (4.1%)	100 (5.7%)	48 (6.7%)	121 (5.9%)	
>2 and ≤4 servings/day	1,823 (27.4%)	574 (26.9%)	466 (26.7%)	175 (24.5%)	608 (29.7%)	
≤2 servings/day	4,462 (67.2%)	1,473 (69.0%)	1,182 (67.6%)	492 (68.8%)	1,315 (64.3%)	
Dairy products						0.029
>2 servings/day	745 (11.2%)	208 (9.7%)	209 (12.0%)	81 (11.3%)	247 (12.1%)	
>0 and ≤2 servings/day	4,189 (63.1%)	1,372 (64.3%)	1,098 (62.8%)	423 (59.2%)	1,296 (63.4%)	
0 ration/day	1,708 (25.7%)	555 (26.0%)	441 (25.2%)	211 (29.5%)	501 (24.5%)	
Eggs						0.059
>1 serving/day	1,157 (17.4%)	371 (17.4%)	331 (18.9%)	124 (17.3%)	331 (16.2%)	
>0 and ≤1 serving/day	4,389 (66.1%)	1,445 (67.7%)	1,133 (64.8%)	460 (64.3%)	1,351 (66.1%)	
0 serving/day	1,096 (16.5%)	319 (14.9%)	284 (16.2%)	131 (18.3%)	362 (17.7%)	

(Continued)

TABLE 3 (Continued)

Items of healthy lifestyle practices	All	Academic disciplines				
	N = 6,6,421	Health Sciences	Business Sciences	Human Sciences and Education	Engineering/ Architecture	*p*[b]
		N = 2,135[a] (32.1%)	*N* = 1,748[a] (26.3%)	*N* = 715[a] (10.8%)	*N* = 2,044 [a] (30.8%)	
Sweets						<0.001
>5 servings/week	461 (6.9%)	137 (6.4%)	116 (6.6%)	57 (8.0%)	151 (7.4%)	
>2 and ≤5 servings/week	2,339 (35.2%)	669 (31.3%)	634 (36.3%)	213 (29.8%)	823 (40.3%)	
0–2 servings/week	3,842 (57.8%)	1,329 (62.3%)	998 (57.1%)	445 (62.2%)	1,070 (52.3%)	
Reliable sources of vitamin B-12						0.010
<1.0 mcg serving equivalent/day	2,152 (32.4%)	686 (32.1%)	546 (31.2%)	264 (36.9%)	656 (32.1%)	
≥1.0 and <2.0 mcg serving equivalent/day	1,268 (19.1%)	448 (21.0%)	329 (18.8%)	111 (15.5%)	380 (18.6%)	
≥2.0 mcg serving equivalent/day	3,222 (48.5%)	1,001 (46.9%)	873 (49.9%)	340 (47.6%)	1,008 (49.3%)	
Flesh-food intake						<0.001
>1 time/week	2,696 (40.6%)	896 (42.0%)	742 (42.4%)	244 (34.1%)	814 (39.8%)	
>1 time/month and ≤1 time/week	2,942 (44.3%)	903 (42.3%)	779 (44.6%)	325 (45.5%)	935 (45.7%)	
≤1 time/month	1,004 (15.1%)	336 (15.7%)	227 (13.0%)	146 (20.4%)	295 (14.4%)	
Daily exercise						0.632
0 min/day of any moderate or vigorous exercise	1,641 (24.7%)	522 (24.4%)	445 (25.5%)	159 (22.2%)	515 (25.2%)	
>0 and <30 min/day of moderate exercise or >0 and <15 min/day of vigorous exercise	3,588 (54.0%)	1,162 (54.4%)	924 (52.9%)	394 (55.1%)	1,108 (54.2%)	
≥30 min/day of moderate exercise or ≥15 min/day of vigorous exercise	1,413 (21.3%)	451 (21.1%)	379 (21.7%)	162 (22.7%)	421 (20.6%)	
Water intake						<0.001
<4 glasses of water/day	2,104 (31.7%)	682 (31.9%)	563 (32.2%)	203 (28.4%)	656 (32.1%)	
≥4 and <8 glasses of water/day	3,292 (49.6%)	1,007 (47.2%)	891 (51.0%)	336 (47.0%)	1,058 (51.8%)	
≥8 glasses of water/day	1,246 (18.8%)	446 (20.9%)	294 (16.8%)	176 (24.6%)	330 (16.1%)	
Sunlight exposure						0.235
<5 min/day	2,274 (34.2%)	764 (35.8%)	563 (32.2%)	243 (34.0%)	704 (34.4%)	
≥5 and <10 min/day	3,038 (45.7%)	967 (45.3%)	805 (46.1%)	325 (45.5%)	941 (46.0%)	
≥10 min/day	1,330 (20.0%)	404 (18.9%)	380 (21.7%)	147 (20.6%)	399 (19.5%)	

[a]*n* (%), [b]chi-square test of independence.

TABLE 4 Simple and multiple regression models between academic discipline and lifestyle and anthropometric parameters.

	Simple regression			Multiple regression[a]		
Academic disciplines	B	95% CI	*p*	B	95% CI	*p*
	Healthy lifestyle practices					
Health sciences	Ref.			Ref.		
Business Sciences	−0.11	−0.20 – −0.01	0.024	−0.15	−0.24 – −0.05	0.003
Human Sciences and Education	0.18	0.06–0.31	0.005	0.14	0.01–0.27	0.037
Engineering/Architecture	−0.09	−0.18 – −0.00	0.047	−0.22	−0.31 – −0.12	<0.001
	BMI					
Health sciences	Ref.			Ref.		
Business Sciences	0.35	0.15–0.56	0.001	0.33	0.12–0.53	0.002
Human Sciences and Education	0.19	−0.08 – 0.46	0.161	0.02	−0.25 – 0.29	0.874
Engineering/Architecture	0.32	0.13–0.52	0.001	0.36	0.15–0.56	0.001

[a]Adjusted for age group, sex, and parental education. BMI, Body mass index.

rich in vitamins, minerals, and antioxidants, reduce the risk of heart disease and cancer (44). Nuts and seeds, sources of healthy fats and proteins, contribute to cardiovascular health and cholesterol control (45). Although these foods are essential for a balanced diet, positively impacting health and prevention of noncommunicable diseases, in the current study, in general, the highest proportion of students had a low consumption of whole grains, vegetables, fruits, nuts, and seeds. Specifically, according to the results of the regression analysis, students in Business and Engineering/Architecture had a lower average lifestyle score compared to those in the Health Sciences faculty. In addition, the students in Human Sciences and Education had the highest healthy lifestyle score.

These findings are similar to those found in previous studies conducted in university students in several countries. In a recent study of Saudi Arabian university students, only 16.07% and 11.23% of 454 students consumed vegetables and fruits daily, respectively (14). Furthermore, it was found that only a small proportion of Thai university students consumed vegetables and fruits at the recommended levels (10). Similarly, among Turkish university students, it was found that 66.1% of men and 63.1% of women had insufficient consumption of fruits and vegetables (46). Additionally, it was found that the dietary habits of Spanish students were poor in terms of legume intake, showing that 75.8% had inadequate consumption (≤2 times/week) of legumes (47). Regarding the consumption of nuts and seeds, our study is consistent with the findings of research that demonstrated legumes, nuts, and seeds were the least consumed food groups among students (48). Given the importance of consuming these foods for health, it is suggested that strategies be implemented to increase their intake among university students.

Likewise, the current study revealed significant differences in consumption patterns among students in various academic disciplines. Compared to Health Sciences students, it was found that students from Business Sciences, Engineering/Architecture, and Humanities and Education faculties are associated with a higher consumption of dairy products, exceedingly more than 2 portions per day. Moreover, egg consumption exceeded 1 portion daily, while the intake of sweets was greater than 5 portions per week. Students may be unaware of the health impacts associated with excessive consumption of added sugar (49). Likewise, other studies carried out in university students have reported similar findings. For example, the results of a cross-sectional study in university students indicated that 45.8% consumed sweets daily (50). Also, the prevalence of daily consumption of sugar-sweetened beverages and sugar-sweetened fruit in the last month and daily was 91 and 50%, respectively (51). Likewise, in the current study, meat consumption was frequent, exceeding 1 time per week. These findings are similar to a study that reported that 47.1% of Science and Technology students consumed meats almost every day (10). These consumption patterns contrast with the general recommendations for a balanced and healthy diet, which suggest a moderate intake of dairy products and eggs, limiting the consumption of sweets and meat, especially processed meats (52). These findings highlight the need to promote nutritional education among university students, regardless of their field of study, to encourage healthy eating habits.

Adequate water intake

Water is the main chemical component of the body, accounting for approximately 50 to 70% of body weight (53). Scientific evidence and current daily water intake recommendations from national organizations, such as the Ministry of Health of Peru, Institutes of Medicine, and the European Food Safety Authority, agree that for optimal health, it is important to consume between 8 to 12 glasses of water a day (53–55). However, low water intake is one of the most common health concerns affecting both the general population and university students, with the latter being especially more susceptible (25–27). In the current study, only 18.58% of students reported meeting these water intake recommendations. Specifically, Engineering/Architecture and Business Sciences students reported the lowest proportions of adequate water intake, at 16.1% and 16.8%, respectively.

Previous studies have shown similar trends in low water intake among university students (25–27, 56). For example, a study of U.S. university students during the COVID-19 pandemic found that only 16.3% of women and 13.3% of men consumed the recommended amount of water daily (25). Another study conducted in Iranian university students reported that the average daily fluid intake of individuals, especially water, was below the recommended

values (27). Similarly, the results of the current study are consistent with the findings of a previous study in Turkish university students, where it was reported that only 19% met their water needs with drinking water recommended for adults (26). These findings are concerning, considering the importance of water for numerous physiological functions in the body, including regulating body temperature, transporting nutrients, and eliminating waste (28). Insufficient water intake can lead to dehydration, affecting cognition, physical performance, and general well-being of university students (56). While the exact reasons for these findings cannot be determined with complete accuracy, they could be attributed to a lack of awareness about hydration needs, a preference for other beverages, busy lifestyles, and limited access to drinking water throughout the day. All these factors could contribute to insufficient water intake in this population. However, we cannot provide a comprehensive explanation for the reduction in water intake previously discussed. Nonetheless, the current results are in line with several previous studies, underscoring the need to promote greater awareness about the importance of adequate hydration among university students. Universities could play an important role in this regard by implementing hydration education programs and ensuring easy access to drinking water sources on campuses. Additionally, it would be beneficial to integrate public health messages on hydration into student wellness campaigns, given the clear need to improve water intake habits among students, especially in fields like Engineering/Architecture and Business Sciences.

Regular physical activity

Sedentary lifestyles can negatively impact students' health, increasing the risk of non-communicable diseases, such as obesity, heart disease and diabetes, and poor academic performance (10, 23). Numerous studies have confirmed the importance of physical exercise in promoting health, constituting an essential component in global intervention strategies, integrating health policies in developed and developing countries (10, 21, 57, 58). In the current study, the results indicate less physical activity and align with trends observed in previous studies (10, 19–21). For example, Arias-Palencia et al. (21) demonstrated that most Spanish university students engaged in less physical exercise than recommended. Additionally, several studies conducted during COVID-19 confinement revealed a reduction in physical exercise among young people, especially among university students (10, 19, 20). It is important to note that the WHO recommend a minimum of 150 min of moderate physical activity per week for individuals between 18 and 67 years of age (23). Furthermore, in our study, although there were no significant differences, students from Human Sciences and Education and Health Sciences, reported slightly higher levels of moderate and vigorous physical exercise, compared to Business Sciences and Engineering/Architecture. This aligns with a study conducted with German university students that measured physical activity in terms of metabolic equivalent of task (MET) minutes per week. It showed that students in Natural Sciences, Mathematics, and Computer Science, with 3,427 MET-minutes per week, and those in Language, Humanities, and Cultural Studies, with 3,553 MET-minutes per week, reported the lowest levels of physical activity. On the other hand, students in Education (4,312 MET-minutes per week), Medicine (3,981 MET-minutes per week), and Social Sciences, Communication, and Sports (3,844 MET-minutes per week) recorded the highest levels of physical activity (58). Contrary findings were observed in a study that demonstrated that, although Health Sciences students possessed medical knowledge, their adherence to physical exercise recommendations turned out to be like students from other disciplines (10). This indicates that health knowledge does not necessarily translate into increased physical exercise among these students. The reduction and differences in physical activity among students from different disciplines may be due to multiple causes, including an increase in academic and social obligations, changes in their environment and lifestyle, as well as limited time or resources. This understanding is important for developing personalized strategies to promote physical exercise among the general student population, regardless of their field of study.

Adequate sunlight exposure

Sunlight is essential for the physical health and mental well-being of individuals (29). Both observational and experimental evidence has consistently reaffirmed the positive effects of sunlight exposure (59); these include the prevention and treatment of various dermatological conditions, such as psoriasis and eczema (29). Sunlight acts therapeutically on these skin disorders, improving symptoms and the quality of life of those affected (60). In addition, sunlight exposure is essential for the photosynthesis of vitamin D in the skin, a process essential for the maintenance of bone and muscle health (61). Vitamin D, synthesized through sun exposure, plays a significant role in regulating calcium and phosphorus, key elements for bone strength and development (60). In our study, we found that only 20.0% of students reported compliance with sunlight exposure recommendations. Specifically, students from Health Sciences and Engineering/Architecture reported the lowest proportions of sunlight exposure, with 18.9 and 19.5%, respectively. This finding is consistent with previous studies that have also reported low sunlight exposure in university populations. For example, a study found that many university students in the United Arab Emirates did not receive sufficient sunlight, which could pose a public health problem due to a potential vitamin D deficiency (32). Additionally, a similar study found low sun exposure practices among Sri Lankan university students in healthcare studies (30), aligning with our findings. Moreover, other studies have highlighted how modern urban lifestyles, common among university students, limit sunlight exposure (31). This is exacerbated by technology and preference for indoor activities, which further reduces opportunities for exposure to natural sunlight (62, 63). On the other hand, a lack of knowledge about vitamin D, long hours spent in academic facilities, and sedentary study habits are some of the reasons for low sunlight exposure (30, 32); this is particularly relevant for Health Sciences and Engineering/Architecture students, whose rigorous academic programs often involve a greater amount of time spent indoors. The low sunlight exposure in these groups of university students suggests the need to encourage outdoor activities. Universities could design academic schedules that allow for outdoor breaks or promote extracurricular activities that occur in outdoor environments. However, it is important to balance sun exposure with the risk of skin damage, including skin cancer (33), which

implies the need for public health strategies that promote a balance between obtaining benefits and minimizing the risks associated with sun exposure.

Limitations and future research

One of the key limitations of this study lies in its conduct at a university affiliated with the Seventh-day Adventist Church, a denomination known for promoting healthy lifestyle practices among its members, including specific diets and eating patterns. This orientation toward healthy lifestyle habits could influence student behavior patterns, regardless of their personal religious belief as the institution philosophy can indirectly promote certain dietary and health practices among the entire student community. Although there is a diverse representation of religious beliefs at the university, the influence of Adventist philosophy in the university environment may have contributed to some homogenization of students' lifestyle practices, thus limiting the generalizability of our findings to populations with different religious and cultural backgrounds. Future studies could include a more diverse sample of adults and children from other geographic areas to examine BMI and lifestyle practices. On the other hand, it is important to note that the study did not consider other relevant aspects of lifestyle, such as alcohol and tobacco consumption and adequate rest; the omission of these factors widely recognized for their impact on health can limit understanding of how various lifestyle elements interact with study disciplines in university students. Therefore, future research should include these factors to provide a more complete and nuanced analysis of the lifestyle and field of study. Another significant limitation of this study is its cross-sectional nature, which implies that it cannot provide information on how the phenomena studied develop over time or establish causal relationships between variables, which may also limit the generalizability of the findings, as it only provides a snapshot relationship at a specific point in time without considering the evolution or change of behaviors and attitudes over time. Longitudinal studies are suggested to better understand how BMI and lifestyle of students evolve over time. Moreover, it is important to mention that the weight and height of the participants were self-reported. People tend to underestimate their weight and overestimate their height, which could introduce significant errors and biases in the data collected. Anthropometric data were collected in this manner due to restrictions imposed in the context of the COVID-19 pandemic. Additionally, lifestyle practices were based on self-reported reports, which could cause response biases, as participants may have difficulty accurately recalling their lifestyle habits or may tend to present a more favorable image of their behavior. Consequently, it is important that future research employ more objective and accurate methods to collect data on lifestyle patterns. Finally, we acknowledge participant self-selection as an inherent limitation of our study. It is possible that those individuals who chose to respond to our survey were motivated, in part, by their healthy lifestyle. This may introduce a bias in our sample, as students with more health-conscious practices may be overrepresented compared to those whose lifestyle habits are less healthy. Such a self-selection bias limits the ability to generalize our findings to the entire university student population. In future research, it would be beneficial to implement strategies that encourage the participation of a more representative sample of the diversity of lifestyles present in the university community.

Public health implications

Despite the limitations of the current study, we believe that the results obtained are of significant relevance, especially in the context of the formulation of public health and educational policy. These findings provide comprehensive formulation on the lifestyles of a young, academically educated population, which is important, as it often sets guidelines for behaviors and habits that last throughout life. This detailed understanding can be invaluable in developing targeted strategies to promote healthy habits in the early stages, which have the potential to positively influence long-term health and well-being. These strategies could include the promotion of nutrition education, regardless of their field of study, to encourage healthy eating habits; integration of public health messages on hydration in student wellness campaigns, due to the need to improve water intake habits among students; development of individualized interventions to promote physical activity among the student population; and the design of academic schedules that favor active outdoor breaks and the promotion of extracurricular activities that occur in outdoor environments.

Conclusion

In summary, this study reveals that students belonging to areas such as Business Sciences and Engineering/Architecture have a higher BMI compared to those in the Health Sciences field. In addition, these groups tend to lean toward less healthy lifestyles. In general, it was observed that the students reported insufficient consumption of foods such as whole grains, legumes, vegetables, nuts, and seeds. Likewise, the levels of regular physical activity, adequate hydration, and adequate sunlight exposure were low. Although the students of Human Sciences and Education and Health Sciences exhibited healthier eating patterns and lifestyles, there is a clear need to improve eating and living habits in general among the university student population to mitigate the risk factors associated with non-communicable diseases.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Research Ethics Committee of the Universidad Peruana Unión (approval number: 2021-CEUPeU-0009). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JS: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review & editing. YC-M: Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. SC-C: Investigation, Project administration, Writing – review & editing. AS-B: Data curation, Investigation, Writing – review & editing. CR-V: Data curation, Investigation, Resources, Writing – review & editing. SO-G: Data curation, Investigation, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1361394/full#supplementary-material

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Microbiota dynamics preceding bariatric surgery as obesity treatment: a comprehensive review

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The review present data on the intricate relationship between bariatric surgery, gut microbiota, and metabolic health in obesity treatment. Bariatric surgery, is recognized as an effective intervention for managing morbid obesity, including various techniques with distinct mechanisms of action, efficacy, and safety profiles including Roux-en-Y Gastric Bypass (RYGB), Sleeve Gastrectomy (SG), Laparoscopic Adjustable Gastric Banding (LAGB), and Biliopancreatic Diversion (BPD). RYGB and SG are the most prevalent procedures globally, inducing gut microbiota changes that influence microbial diversity and abundance. Post-surgery, alterations in bacterial communities occur, such as the increased of *Escherichia coli* inversely correlated with fat mass and leptin levels. During digestion, microbiota produce physiologically active compounds like bile acids (Bas) and short-chain fatty acids (SCFAs). SCFAs, derived by microbial fermentation, influence appetite, energy metabolism, and obesity-related pathways. Bas, altered by surgery, modulate glucose metabolism and insulin sensitivity. Furthermore, SG and RYGB enhance incretin secretion, particularly glucagon-like peptide 1 (GLP-1). Therefore, understanding microbiota changes after bariatric surgery could be crucial for predicting metabolic outcomes and developing targeted interventions for obesity management.

KEYWORDS

bariatric surgery, gut microbiota, obesity, microbiota dynamics, obesity treatment

Introduction

The treatment of obesity presents numerous challenges due to its complex and multifactorial nature. In recent years, this condition has emerged as a global epidemic. In response to this growing health crisis, bariatric surgery has emerged as an effective intervention for managing morbid obesity and its associated comorbidities (1–3). Bariatric surgery modifies the gastrointestinal system to alter nutrient absorption (malabsorptive mechanisms) and/or restrict food intake (restrictive mechanisms) as an approach for weight management. Candidates for this surgical intervention typically have a body mass index (BMI) of 40 kg/m² or higher, or a BMI of 35 kg/m² or higher with significant comorbidities (3).

Various techniques are employed in bariatric surgery, each with its unique mechanism of action and associated considerations. Among the most commonly utilized techniques are biliopancreatic diversion (BPD), adjustable gastric banding (LAGB), sleeve gastrectomy (SG), and Roux-en-Y gastric bypass (RYGB). The selection of the appropriate bariatric procedure depends on several factors including the severity of obesity, presence of comorbidities, and patient preferences (4).

Roux-en-Y gastric bypass (RYGB)

RYGB stands as one of the oldest and most popular bariatric procedures, ranking as the second most common worldwide (5). During this procedure, significant portions of the stomach and proximal small intestine are bypassed, resulting in the creation of a small gastric pouch directly connected to the small intestine. RYGB achieves weight loss by combining malabsorptive and restrictive mechanisms (6).

Studies consistently demonstrate that RYGB leads to substantial weight loss and improvement in associated comorbidities such as type 2 diabetes and hypertension (7, 8). However, RYGB poses inherent risks including intestinal blockage, internal hernia, and long-term metabolic issues stemming from nutrient malabsorption. Despite these risks, RYGB remains popular due to its proven effectiveness in promoting weight loss and metabolic health (5, 8, 9).

Sleeve gastrectomy (SG)

SG has gained prominence in recent years due to its less invasive nature compared to RYGB, while also preserving normal stomach function. Currently, it stands as the most common bariatric surgery (10, 11). This procedure involves the removal of a large portion of the stomach, leaving behind a narrow gastric tube that restricts food intake (10).

Both SG and RYGB yield similar outcomes in terms of weight loss and improvement in metabolic comorbidities. Additionally, SG, not requiring intestinal anastomosis, may be associated with a lower incidence of long-term complications such as intestinal blockage and internal hernia. Nevertheless, SG is not without risks, with potential postoperative issues including staple line leaking and stomach stricture (12).

Laparoscopic adjustable gastric banding (LAGB)

LAGB is a restrictive procedure wherein a silicone band is placed around the stomach to create a small upper gastric pouch. Unlike RYGB and SG, LAGB offers reversibility and adjustability, making it an attractive option for certain patients (13).

Although LAGB was previously popular due to its reversible and minimally invasive nature, its utilization has declined in recent years due to lower rates of sustained weight reduction and increased risk of long-term complications such as band slippage and stomach erosion (14, 15).

Biliopancreatic diversion (BPD)

BPD combines gastric bypass with distal gastrectomy, resulting in a reduced intestinal absorption area and nutritional malabsorption (16). While BPD is highly effective for weight loss and improving metabolic comorbidities, it also raises the risk of long-term complications such as protein and vitamin deficiencies (17, 18).

The primary objective of the present mini review is to describe the most prevalent bariatric surgery techniques used in the treatment of obesity, including RYGB, SG, LAGB, and BPD. The manuscript explores how these surgical procedures alter the complex environmental community of microorganisms, part of our microbiota, and the effect that these changes have on human health and obesity. Furthermore, the article discusses the clinical aspects of bariatric surgery, including weight loss outcomes, post-operative complications, and contributions to metabolic health enhancement. It emphasizes the importance of the gut microbiota composition in weight management, influencing lipid metabolism, hormone signaling, and glucose homeostasis.

Bariatric surgery as treatment for obesity

According to the World Health Organization, more than 650 million adults were obese in 2016, with a perspective of an increment (19). Besides, obesity is associated with elevated risk of various comorbidities, including type 2 diabetes, heart conditions, hypertension, among others (20). Consequently, bariatric surgery has emerged as an effective and long-lasting option for achieving significant health improvements.

Bariatric surgery is considered a potential treatment intervention for obesity, commonly for subjects with a BMI of 40 kg/m^2 or higher, or a BMI of 35 kg/m^2 or higher with significant comorbidities. The primary goal of bariatric surgery is to reduce the size of the stomach or alter the digestive tract to induce the decrease the volume of food taken and its absorption, with an impact from hormonal to molecular changes (21, 22). Consequently, bariatric surgery can result in a 50–70% in short term weight loss or 20–30% loss of the patient's initial weight (23).

The mechanisms of action, effectiveness, and safety profiles vary among the different types of bariatric surgery. The RYGB and SG are the most common procedures worldwide, accounting for 72,645 individuals (38.2%) and 87,467 individuals (46%) of all primary operations since 2014, respectively. On the other hand, One-anastomosis gastric bypass (OAGB) and gastric bypass (GB) surgeries are less frequently performed, representing 14,516 individuals (7.6%) and 9,534 individuals (5%) of all primary operations since 2014, respectively (24, 25). After one-year post-surgery, the mean weight loss was 28.9% with an improving in metabolic health. Remarkably, 66.1% of patients with type 2 diabetes did not need more medication. Consequently, the

degree of diabetes remission correlated closely with weight loss achieved (25).

Despite the significant benefits of bariatric surgery, it is crucial to acknowledge potential complications associated with these procedures. Data from clinical studies and registry analyses into the rates of postoperative complications are limited. However, a systematic review reported that the most common complications within 30 days after bariatric procedures, includes anastomotic leak, myocardial infarction, pulmonary embolism (26). Another study reported that the most common complication after surgery is peritonitis with an incidence of 1–6% after GB and 3–7% after SG (27). The most frequent late postoperative complications are dumping syndrome and cholecystitis, each occurring in up to 30% of cases (27). Additionally, the perioperative mortality rate is <1% (27). Despite advancements in surgical techniques and perioperative care leading to improvements in safety outcomes, it is essential for healthcare providers and patients to be aware of the potential risks associated with bariatric surgery.

Minimally invasive approaches, such as laparoscopic and robotic-assisted procedures, have become increasingly common in bariatric surgery. These techniques result in shorter hospital stays, faster recovery times, and improved patient outcomes. Additionally, multidisciplinary care involving nutritionists, psychologists, and other healthcare professionals plays a crucial role in mitigating complications and supporting patients throughout their bariatric surgery (28). Furthermore, studies suggest that individuals with obesity who undergo bariatric surgery should engage in moderate physical activity and make dietary changes to sustain their weight loss (29, 30).

Consequently, bariatric surgery is a noteworthy treatment for obesity, offering significant weight loss outcomes and improvements in metabolic health. While RYGB and SG continue to be the predominant surgical modalities, ongoing research and advancements in surgical techniques aim to further enhance the safety and efficacy of these procedures.

The relationship between obesity and microbiota

Recent research has elucidated the intricate relationship between obesity and the gut microbiota, particularly focusing on the modulation of host metabolism by microbiota-derived metabolites. Short-chain fatty acids (SCFAs), such as acetate, propionate and butyrate, are produced through the fermentation of dietary fiber by gut bacteria. SCFAs act as a signaling molecules influencing metabolic processes crucial for energy homeostasis and lipid metabolism (31, 32). Furthermore, the gut microbiota impacts host metabolism by regulating the expression of genes involved in adipogenesis, lipid metabolism, and insulin sensitivity. Dysbiosis, observed in obese individual, contributes in disturbances involving host-microbiota interactions.

Obesity is associated with chronic low-level inflammation in several tissues, which has been correlated with metabolic diseases like type 2 diabetes, insulin resistance, and cardiovascular diseases. One of the effects of this chronic inflammation is gut barrier impairment. It has been proposed that hyperglycemia and a low gut bacteria diversity could lead to gut barrier permeabilization, allowing the entry of antigenic compounds like lipopolysaccharides to blood circulation. These antigenic compounds can induce endotoxemia, insulin resistance and chronic immune system activation (33). Therefore, modulating gut microbiota after bariatric surgery could potentially improve the intestinal barrier and restore metabolic homeostasis (33).

Emerging evidence suggests the role of gut microbiota in obesity. Studies comparing the microbial communities in obese individuals with non-obese, have consistently revealed differences in the abundance Firmicutes and Bacteroidetes (34–36). Another study demonstrated an increase in *Bacteroidetes thetaiotaomicron*, a glutamate fermenting commensal, in obese individuals who follows a weight-loss intervention (like sleeve gastrectomy) (37). Consequently, *B. thetaiotaomicron* reduces plasma glutamate concentration and may protect against body weight gain induced by diet and adiposity (37). Moreover, research has shown that *Bacteroidetes uniformis* relieves high-fat-diet induced obesity, complementing the effect of *B. thetaiotaomicron* (38). Specifically, *B. uniformis* increases TNF-α production by dendritic cells (DCs) in response to purified lipopolysaccharide stimulation (reduced by high-fat-diet) (38).

Consequently, the increased abundance and diversity of SCFA-producing bacteria, lead to heightened production of host glucagon-like peptide 1 (GLP-1), which contributes to glucose-dependent stimulation of insulin secretion, inhibition of food intake, increase of natriuresis and diuresis, among other metabolic effects (39). Dysregulation of these pathways may contribute to overeating and weight gain, highlighting the molecular basis of the gut-brain axis in obesity (40). Furthermore, the gut microbiota produces metabolites that play critical roles in lipid metabolism, energy expenditure, and inflammation, thus shaping the metabolic phenotype of the host (31, 41, 42). Strategies aimed at modulating gut microbiota composition and activity, such as probiotics, prebiotics, and fecal microbiota transplantation, have shown potential in improving metabolic dysfunction associated with obesity.

Furthermore, the consumption of the probiotic *Lactobacillus gasseri BNR17* has been approved by the Korean FDA as an ingredient to reduce visceral adipose tissue in adults with obesity (43). Moreover, some studies are based on *Akkermansia muciniphila, Faecalibacterium prausnitzii* and *Clostridia strains* considered as possible probiotics, most of them present in the human intestinal microbiota. These strains produce butyrate and other short-chain fatty acids (SCFAs), compounds that are decreased in people with obesity (44).

Microbiota changes preceding bariatric surgery

Recent studies have highlighted the significant role of the gut microbiota before and after bariatric surgery, associating the complex interplay between gut microbiota, surgical interventions, and metabolic health outcomes (Table 1). A ten-year review study described the alterations in gut microbiota composition in obese individuals before and after bariatric surgery, showing that changes in the composition and function of gut microbiota affect metabolic

TABLE 1 Differential changes in gut microbial composition post-bariatric surgery.

Types of bariatric surgery	Bacteria	Abundance	Outcome	References
RYGB	*Bacteroides*	Increase	These changes occurred after surgery and were inversely correlated with fat mass and leptin levels.	(45)
	Prevotella	Increase		
	Escherichia coli	Increase		
	Lactobacillus	Decrease		
	Leuconostoc	Decrease		
	Pediococcus	Decrease		
	Enterobacter cancerogenus	Increase	These changes improved host lipids and glucose levels.	(46)
	Firmicutes	Decrease		
	Bacteroidetes	Decrease		
	Proteobacteria	Increase	The fecal profiles reflected an increased activity of oligosaccharide fermentation in the gut and the generation of amines, which may contribute to body weight loss.	(47, 48)
	Bacteroides thetaiotaomicron	Decrease		
SG	Bacteroidetes/ Firmicutes ratio	Decrease	The capacity for butyrate fermentation decreased. This could be attributed to changes in the abundance of Firmicutes	(45)
	Akkermansia muciniphila	Increase	The increase in this species after surgery is related to better glucose homeostasis and lipid metabolism.	(49)
	Bacteroidetes	Increase	These changes in microbial abundance after surgery play a role in reducing low-grade inflammation.	(49)
	Firmicutes	Decrease		

RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

functions in obese patients, leading to significant physiological regulation (50).

The type of bariatric surgery performed influences the changes in gut microbiota. Several studies have investigated changes following RYGB, noting variation in microbial diversity across intestinal segments after surgery (51). Furthermore, other studies have reported the changes in the microbial communities. For example, one study found that the *Bacteroides/Prevotella* was lower in obese subjects and increased post-surgery. Additionally, lactic and acid bacteria (*Lactobacillus, Leuconostoc, Bifidobacterium, and Pediococcus group*) were reduced, while *Escherichia coli* increased after surgery and inversely correlated with fat mass and leptin levels independent of dietary changes (45). Another study reported that after RYGB, *Enterobacter cancerogenus* (*Proteobacterium*) increased, while Firmicutes and Bacteroidetes decreased, improving in host lipids and glucose levels (46). Similarly, other studies also reported a decrease in Firmicutes and Bacteroidetes (specifically *Bacteroides thetaiotaomicron)* after surgery while Proteobacteria species increased (47, 48).

Studies on SG, also found significant shifts in the gut microbiota. A next -generation sequencing analyses revealed a decrease in energy-reabsorbing potential after SG, indicated by the Bacteroidetes/Firmicutes ratio. Additionally, the capacity for butyrate fermentation decreased, attributed to Firmicutes changes (52).

The impact of microbial shifts extends beyond weight loss. For instance, the increase of *Akkermansia muciniphila* post-surgery is linked to improved glucose homeostasis and lipid metabolism critical in the remission of type 2 diabetes. Besides, the decrease in Firmicutes and increase in Bacteroidetes after surgery play a role in reducing low-grade inflammation associated with obesity and metabolic syndrome (49).

Understanding these bacterial changes (Figure 1) is essential for predicting the bariatric surgery outcomes. However, future research may focus on preoperative and postoperative modulation of the gut microbiota to enhance bariatric procedures.

Discussion

The human intestine harbors over 100 trillion microbial cells, which significantly influences metabolic regulation through symbiotic interactions with the host (53). During digestion, the gut microbiota generates various physiologically active compounds, including BAs, SCFAs, and long-chain fatty acids (LCFAs) (31). The activity and composition of the gut microbiota can be altered by various factors such as nutritional intake, gastric emptying, and gastric acid production, thereby being influenced by different bariatric surgical methods (54, 55).

The chronic inflammatory process observed in various tissues of individuals with obesity has been linked to gut mucosa

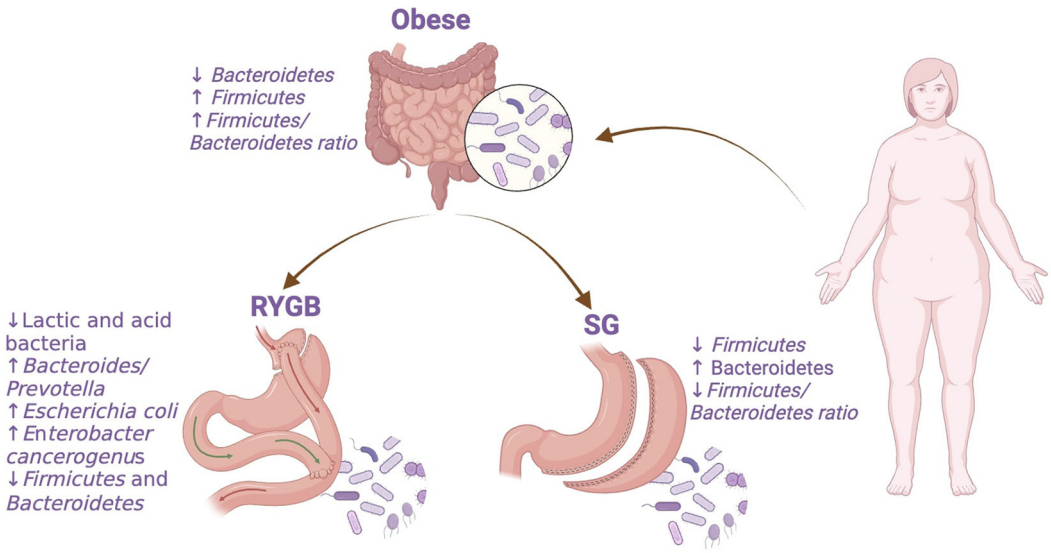

FIGURE 1
Bacterial abundance changes in obese individuals before and after bariatric surgery. RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy. The figure was created with BioRender.com.

impairment. This impairment is associated with reduced synthesis of the mucus protein layer, allowing the release of pro-inflammatory cytokines (IL-1b, IL-6, IL-12, IL-18). Bariatric surgery has been related to an improved intestinal barrier synthesis due to the expression of ZO-1, occludin, and claudin-1 tight junction proteins. Moreover, the restoration of bacteria involved in SCFA synthesis, which has been observed after bariatric surgery (33), has also been linked to intestinal barrier restoration (56). Therefore, the restoration of intestinal mucosa layer could potentially improve the inflammatory process and restore the metabolic homeostasis.

Among the bariatric procedures, SG and RYGB stand out as the most widely practiced, both contributing to an increase in the secretion of incretins by augmenting the number of secreting cells, particularly GLP-1 (57).

Short-chain fatty acids, including butyrate, propionate, and acetate, are key metabolites derived from the metabolism of complex carbohydrates by gut microbiota (58). While studies indicate higher fecal concentrations of SCFAs in obese individuals, their role in energy metabolism and obesity remains controversial due to their dual effects on hunger reduction, lipogenesis inhibition, and induction of browning in white adipose cells (40, 59, 60). SCFAs exert their appetite-suppressing effects by interacting with isolated neurons in the nodal ganglia, triggering intracellular Ca^{2+} signaling, and elevating serum levels of leptin, GLP-1, and peptide YY (PYY) (61, 62).

Following bariatric surgery, fecal SCFA levels decrease, primarily attributed to low-carbohydrate diets, possibly indicating inefficient utilization of dietary SCFAs for energy during weight loss (63). RYGB surgery reduces stomach acid secretion, leading to higher levels of partially digested proteins in the intestine and resulting in putrescine generation. Additionally, an increase in *Klebsiella* bacteria post-RYGB further contributes to putrescine production. The metabolism of putrescine yields gamma-aminobutyric acid (GABA), exacerbating insulin resistance and elevating GLP-1 levels (64).

After RYGB, there is an increase in the abundance of *Streptococcus, Veillonella,* and *Akkermansia* species. *Streptococcus* and *Veillonella* metabolize lactate, impacting butyrate metabolism and epithelial barrier integrity, which may potentially ameliorate metabolic disorders, and reduce systemic inflammation. *Akkermansia muciniphila*, has been associated with protection against diabetes and obesity in animal studies, may improve insulin sensitivity and reduce inflammation, further enhancing intestinal epithelial integrity in humans (65, 66).

Bariatric surgery induces alterations in BA metabolism, enhancing energy homeostasis. BAs play an important role in gut microbiota composition and post-surgery weight loss by modulating glucose metabolism, increasing insulin sensitivity, and reducing gluconeogenesis through elevated GLP-1 secretion and activation of G protein-coupled receptor (TGR5) and nuclear receptor (FXRα) pathways (67–70).

Ilhan et al. (71) reported decreased fecal BA concentration in obese patients post-RYGB. This decrease was associated with microbiota composition changes (71). RYGB-induced architectural modifications enhance the BA influx into the lower intestine. This facilitates reabsorption of conjugated BAs in the terminal ileum and conversion of primary to secondary BAs by gut microbes in the colon. These metabolic improvements, including gut microbiota repopulation and altered primary/secondary BAs ratio, had a positive impact on metabolic syndrome (45, 72).

In contrast, Evers et al. (73) observed decreased levels of lithocholic acid (LCA) in the colon and increased levels in the portal vein post-SG. LCA promotes CA7S production in the livers of mice and humans, impacting host metabolism. The researchers also determined that LCA activates the vitamin D receptor and induces

cholic acid sulfonation both *in vitro* in human hepatocytes and *in vivo* in mice. The CA7S synthesized by LCA in human hepatocytes can trigger GLP-1 secretion in enteroendocrine cells, establishing a link between BA level alterations post-SG and the favorable effects on energy and glucose homeostasis (73).

Conclusion

In conclusion, the comprehensive review of microbiota dynamics preceding bariatric surgery emphasizes the role of gut microbiota in the management of obesity and associated metabolic disorders. The observed alterations in gut microbial composition following bariatric procedures, such as Roux-en-Y gastric bypass and sleeve gastrectomy, highlight the potential for microbiota modulation as a therapeutic strategy to enhance surgical outcomes. These alterations, including changes in microbial diversity and abundance, have been linked to improvements in glucose homeostasis, lipid metabolism, and inflammation, crucial factors in achieving remission of type 2 diabetes and metabolic syndrome. Understanding the complex interplay between gut microbiota, surgical interventions, and metabolic health outcomes is essential for optimizing patient care and developing targeted interventions to enhance the efficacy of bariatric surgery. Further research into preoperative and postoperative microbiota modulation holds promise for improving the safety and long-term success of bariatric procedures, ultimately offering hope for individuals grappling with obesity and its related complications.

Author contributions

AZ: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. EP-C: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. VR-P: Investigation, Writing – review & editing. SC-U: Investigation, Writing – review & editing. RT-T: Investigation, Writing – review & editing. PG-R: Investigation, Writing – review & editing. RZ-V: Investigation, Writing – review & editing. DS-R: Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The effect of intermittent fasting on microbiota as a therapeutic approach in obesity

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Obesity, a public health challenge, arises from a complex interplay of factors such as dietary habits and genetic predisposition. Alterations in gut microbiota, characterized by an imbalance between Firmicutes and Bacteroidetes, further exacerbate metabolic dysregulation, promoting inflammation and metabolic disturbances. Intermittent fasting (IF) emerges as a promising dietary strategy showing efficacy in weight management and favoring fat utilization. Studies have used mice as animal models to demonstrate the impact of IF on gut microbiota composition, highlighting enhanced metabolism and reduced inflammation. In humans, preliminary evidence suggests that IF promotes a healthy microbiota profile, with increased richness and abundance of beneficial bacterial strains like *Lactobacillus* and *Akkermansia*. However, further clinical trials are necessary to validate these findings and elucidate the long-term effects of IF on microbiota and obesity. Future research should focus on specific tissues and cells, the use of advanced -omics techniques, and exploring the interaction of IF with other dietary patterns, to analyze microbiota composition, gene expression, and potential synergistic effects for enhanced metabolic health. While preliminary evidence supports the potential benefits of IF in obesity management and microbiota regulation, further research with diverse populations and robust methodologies is necessary to understand its implications and optimize personalized dietary interventions. This review explores the potential impact of IF on gut microbiota and its intricate relationship with obesity. Specifically, we will focus on elucidating the underlying mechanisms through which IF affects microbiota composition, as well as its subsequent effects on obesity.

KEYWORDS

obesity, microbiota, intermittent fasting, diet, dietary habits

Introduction

Obesity is a chronic disease that arises from an imbalance in energy between energy intake and expenditure, influenced by behaviors such as eating patterns and physical activity, along with physiological factors like resting metabolic rates and energy expenditure during activity (1, 2). The World Health Organization (WHO) utilizes body mass index (BMI) to classify obesity in adults. For instance, individuals with a BMI >30 kg/m^2 are considered obese.

The classification is further subdivided into three classes. Class I individuals have a BMI between 30.0–34.9 kg/m2; Class II, between 35.0–39.9 kg/m^2; and Class III, a BMI of more than or equal to 40 kg/m^2 (3, 4). Class II/III obesity presents higher risks of all-cause mortality, severe health effects, and limits in daily living activities when compared to class I obesity. People with class I obesity are more likely to experience conditions such as hypertension and diabetes mellitus type 2 (5). Class II obesity further increases the risk of secondary diseases such as heart attacks and strokes, aggravating difficulties in performing some actions. Meanwhile, the likelihood of developing secondary conditions is at high risk in type III obesity, often accompanied by symptoms such as severe joint pain, excessive sweating, and breathing difficulties (5, 6).

Furthermore, obesity is a public health challenge for societies and healthcare systems across the world (7). It is one of the main risk factors for several chronic diseases, including gout, osteoarthritis, hypertension, coronary heart disease, stroke, certain cancers, type 2 diabetes, gallbladder disease, and pulmonary diseases (3, 8). In 2016, the estimated prevalence of obesity was 13% (11% of men and 15% of women) (9). WHO estimates that approximately 167 million people will be overweight or obese by 2025 (10). The rising rates and global prevalence of obesity are primarily due to sedentary lifestyles, excessive nutrition, and physical inactivity.

Nutrition and physical exercise are the primary strategies for preventing and managing obesity and its associated metabolic consequences (11). For instance, intermittent energy restriction combined with a Mediterranean diet has emerged as a promising approach to reducing body fat and improving insulin resistance. A recent pilot study conducted among East Asians in Hawaii demonstrated the feasibility and potential efficacy of this combination in reducing visceral adipose tissue (VAT). In this study, participants who followed a Mediterranean diet combined with intermittent fasting (IF) experienced significantly greater reductions in VAT and total fat mass (12).

Understanding the mechanisms behind obesity and the potential impact of interventions like IF is crucial for addressing this global health challenge. This comprehension allows for the development of targeted and effective strategies to prevent and manage obesity-related complications. It also provides insights into how lifestyle modifications, such as dietary interventions, can positively influence insulin sensitivity, fat and glucose metabolic health and overall well-being (13).

Intermittent fasting has attracted substantial scientific and public interest as a dietary strategy for combating obesity (14). IF includes periods of regular caloric intake alternated with complete or partial voluntary abstinence from food and liquid intake (14, 15). There are various IF patterns; the most common are the daily time-restricted fasting (16-h fasting and 8-h eating windows) or the 5:2 diet 2 days of fasting per week and unrestricted eating for the remaining 5 days (15, 16).

The gut microbiota, comprising trillions of microorganisms, produces different physiologically active substances, including short-chain fatty acids and vitamins, as well as potentially harmful products such as neurotoxins and carcinogens (17). A healthy gut microbiota is vital for maintaining metabolic balance and immune function, but dysbiosis can contribute to metabolic disorders and obesity (18). In obesity, alterations in gut microbiota composition can lead to reduced diversity, impacting metabolic energy utilization. For instance, dysbiosis can alter commensal bacteria and their metabolites within the intestinal environment, affecting T cell development and immune responses and causing pro- and anti-inflammatory reactions (19, 20).

Therefore, this review aims to provide an overview of research investigating the influence of intermittent fasting on the gut microbiota and its association with obesity. Our focus will be on elucidating the underlying mechanisms through which IF affects microbiota composition, as well as its subsequent effects on obesity.

Intermittent fasting

Intermittent fasting (IF) is a dietary strategy defined as intermittent periods of fasting and feeding (21). Time-restricted feeding (TRF), alternate-day fasting (ADF), and the 5:2 diet are the most popular types of IF. TRF is a dietary regimen that limits the feeding time window within a 24-h period. The eating window in TRF ranges from 4 to 12 h, providing flexibility in individual eating patterns (22).

ADF involves alternating between "fast days," where individuals consume only 25% of their energy needs, and "feed days," where they eat freely and to appetite. This approach, known for its flexibility, offers an effective weight loss alternative (23, 24). These approaches result in a 1–12% weight reduction over 2–12 months. Moreover, the 5:2 diet involves restricting calorie consumption on two non-consecutive days per week, while on the remaining 5 days, a usual diet is consumed (25).

Furthermore, following alternate feeding and fasting cycles in line with the circadian rhythm, such as eating during the day and prolonging the fasting period overnight, might improve nutrient metabolism. This method allows people to eat freely (with no limitations) during the feeding window, reducing the need to rigorously watch calorie intake outside of the fasting phase (26, 27).

IF triggers several physiological changes within the body, altering metabolism through enzymatic processes in the liver, which causes a drop in insulin levels, increasing glucagon release. These processes cause a shift from glucose to stored fats as energy sources (28, 29). Furthermore, fasting lowers circulating glucose levels by depleting glycogen reserves, resulting in the production of ketone bodies from fatty acids in the liver, which provides an alternate fuel source for many organs, including the brain. Fasting also stimulates autophagy, a cellular recycling mechanism that helps eliminate damaged organelles and proteins, boosting cellular health and lifespan. These physiological modifications help to increase metabolic flexibility and energy consumption during fasting (30, 31).

In obesity, various cellular and molecular processes induce inflammation, especially in adipose tissues, which leads to the release of inflammatory mediators like tumor necrosis factor α (TNF-α), C-reactive protein (CRP), and interleukin 6 (IL-6). Obesity also reduces adiponectin production, leading to a pro-inflammatory state and oxidative stress (32). The activation of NF-κB pathways induces the production of several pro-inflammatory cytokines in adipocytes, which contribute to insulin resistance and pro-inflammatory macrophages. Visceral adipose tissue growth further promotes macrophage recruitment and secretion of inflammatory markers such as CRP, TNF-alpha, and IL-6. Thus, reducing visceral fat through weight reduction may aid in lowering systemic inflammation (33–35).

IF has received attention for its potential benefits in weight control and metabolic health. This dietary approach triggers changes in

hormone levels and initiates a metabolic switch, transitioning the body from utilizing glucose as a fuel source to fatty acid-derived ketones. The metabolic switch occurs once liver glycogen stores are depleted, typically beyond 12 h after food intake cessation. This evolutionary trigger shifts metabolism from lipid/cholesterol synthesis and fat storage to fat mobilization through fatty acid oxidation and the production of fatty acid-derived ketones, preserving muscle mass and function (21, 28).

IF also increases the synthesis of adiponectin, a hormone that regulates glucose and breaks down fatty acids (36). Furthermore, IF induces cellular and mitochondrial changes, increasing mitochondrial performance and efficiency. Moreover, IF can potentially influence gene expression and signaling pathways associated with metabolism, inflammation, and oxidative stress, impacting metabolic health and disease risk (28, 31). These processes demonstrate intermittent fasting's diverse influence on weight control and metabolic balance, indicating its potential as a therapeutic tool for improving health outcomes.

Intermittent fasting, while potentially beneficial, has certain risks and contraindications. For example, IF is not recommended for pregnant or breastfeeding women, frail older adults, individuals with compromised immunity, or people with or at risk for eating disorders due to potential negative health consequences. Moreover, people with diabetes may be more likely to experience hypoglycemia (low blood sugar) during fasting. Additionally, several medications can interact negatively with fasting, posing a risk to individuals with specific medical conditions who require regular medication intake (28).

A study examining 147 individuals with a high BMI following an intermittent fasting regimen revealed common adverse effects, including headache (61.3%), lethargy (68%), mood changes (57.8%), and dizziness and polyuria (55.8 and 46.2%, respectively) (37). Headache, a prevalent side effect during fasting, is often attributed to hypoglycemia and manifests as a diffuse, non-pulsating headache. It is crucial to acknowledge these potential risks and side effects associated with intermittent fasting to ensure safe and informed implementation of this dietary approach (37, 38). On the other hand, various studies have evaluated the benefits of intermittent fasting and have found significant results, including reductions in glucose and insulin levels, as well as notable weight loss and decreased BMI (39–41).

Microbiota and obesity

Gut bacteria have an important role in the development and progression of obesity. The human gut microbiota is a complex ecosystem that contains around 10^{14} bacterial cells. The diversity of the gut microbiota can influence the human body's capacity to obtain nutrients and control energy consumption. Humanized mouse models have been useful in understanding the role of the microbiota in obesity, given that they provide a controlled environment to study the interactions between the human intestinal microbiota and host physiology. These models allow researchers to introduce human microbiota into mice, allowing us to observe how specific microbial compositions influence various metabolic processes and contribute to the development of obesity (42). Studies have consistently shown alterations in the composition of gut bacteria in obese individuals, with an increased abundance of Firmicutes and a decreased abundance of Bacteroidetes at the phylum level. Although findings regarding this imbalance may vary across studies, a pattern emerges regarding the diversity of Firmicutes and Bacteroidetes (43, 44). Specifically, the reduction of Bacteroidetes has been linked to fat loss, while the increase in Firmicutes is associated with higher digestible energy intake and fat storage (42, 45).

The gut microbiota profoundly influences energy homeostasis, inflammation, and insulin sensitivity through intricate mechanisms (46). Dysbiosis changes in the gastrointestinal tract, leading to increased gut permeability, result in elevated translocation of bacterial endotoxins, primarily lipopolysaccharide (LPS), into the bloodstream. Activation of the innate immune system via Toll-like receptor 4 (TLR4) by LPS triggers the expression of proinflammatory cytokines, fostering low-grade systemic inflammation associated with insulin resistance, hyperglycemia, and hyperinsulinemia, especially observed in individuals with obesity and type 2 diabetes (47, 48).

Furthermore, the gut microbiota actively participates in carbohydrate metabolism by fermenting polysaccharides from food, generating monosaccharides and short-chain fatty acids (SCFAs) (49). The gut microbiota influences energy metabolism by modulating the production of SCFAs, which act through various receptors in different tissues, including adipose tissue and the colon. SCFAs improve glucose homeostasis, insulin sensitivity, and gut barrier integrity, attenuating inflammation and promoting metabolic health. Additionally, the gut microbiota synthesizes branched-chain amino acids (BCAAs) and regulates bile acid metabolism, both of which impact insulin resistance and lipid metabolism (47, 50). Overall, the gut microbiota is a dynamic ecosystem with profound implications for host physiology and metabolic health (Figure 1).

Interplay between intermittent fasting, microbiota, and obesity

A balanced and healthy microbiota maintains a stable ratio of Bacteroidetes to Firmicutes, promoting the production of beneficial metabolites (51). Conversely, individuals with obesity often show imbalances characterized by an increased abundance of Firmicutes and a reduction in Bacteroidetes (51). Moreover, research has found a correlation between the presence of LPS and LPS-producing bacteria with obesity (52). The functionality of the gut microbiota depends on various aspects, including the mode of delivery at birth, medication use, genetics, ethnicity, and dietary habits (53).

Different dietary patterns may favor or affect microbiota homeostasis, influencing the production of metabolites, especially SCFAs, which can participate in various metabolic processes by interacting with endocrine hormones and cell receptors (51). For instance, studies have shown that propionate, a SCFA produced by gut microbiota, can stimulate the release of glucagon-like peptide 1 (GLP-1), thereby promoting weight reduction in overweight adults (54).

Using mice as a model organism

Intermittent fasting has been proposed as a potential dietary strategy for weight management; however, the effect on microbiota and how it is associated with obesity needs to be further elucidated.

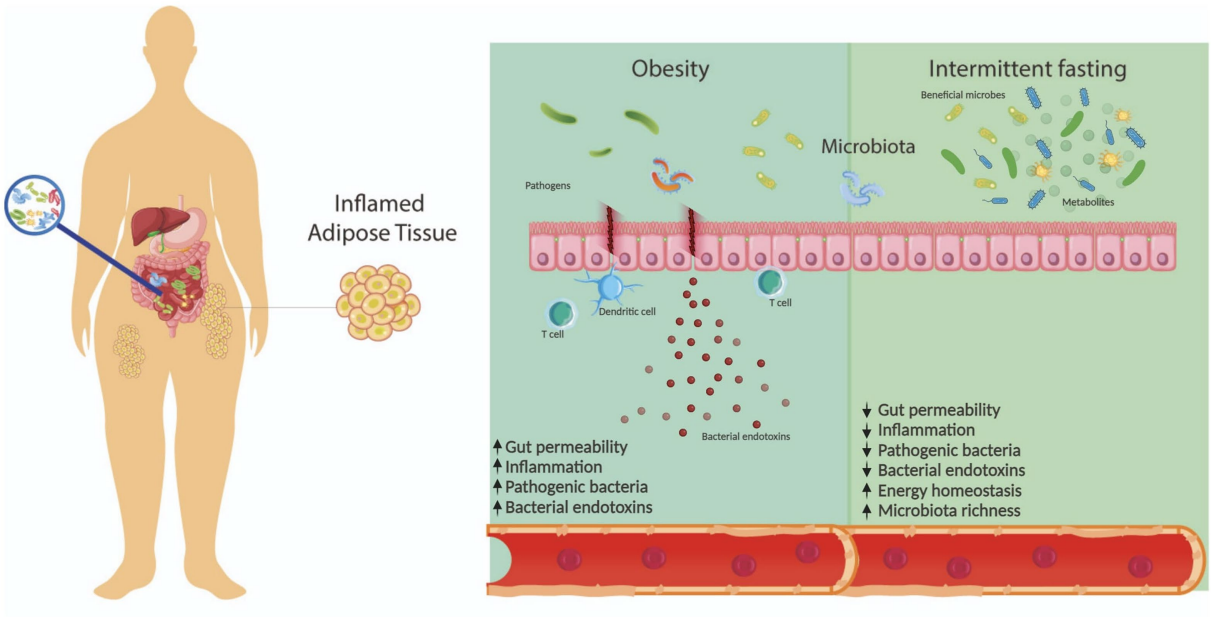

FIGURE 1
Gut microbiota is influenced by various factors, including diet. In this context, gut microbiota composition is dysregulated in patients with obesity, affecting other processes such as inflammation and gut permeability. Intermittent fasting is a promising approach for weight management and has shown potential benefits to the gut microbiota, including increased microbiota richness and energy homeostasis.

Several studies have used mice as model organisms to study this correlation. For example, Beli et al. (55) analyzed the effects of IF on *db/db* mice, commonly used as model organisms for diabetes type II and obesity (56). The research team determined that the gut microbiota of the *db/db* mice was modified by following an IF dietary pattern for 7 months. Specifically, there was an increase in the abundance of Firmicutes, alongside a decrease in the proportion of Bacteroidetes and Verrucomicrobia. Furthermore, *Lactobacillus,* a health-associated genus, was enriched in the IF *db/db* mice (55). These findings have been associated with the concept of 'healthy obesity', which is correlated with metabolic health, and an enhanced capacity for energy harvest (57). It is noteworthy that the body weight of the mice did not increase during the study (55).

Furthermore, Li et al. (58) investigated the effects of IF on mice gut microbiota and its association with obesity. The authors found that an IF regimen activated white adipose tissue browning, which mitigated the effects of obesity. The gut microbiota of these IF mice showed an increased abundance of Firmicutes, particularly *Lactobacillus*; while exhibiting a decrease in the proportion of Tenericutes, Actinobacteria, and Bacteroidetes. Moreover, the IF treatment also led to higher levels of acetate and lactate. Interestingly, transplanting the microbiota of IF mice into microbiota-depleted mice also activated white adipose tissue browning (58).

Additionally, Li et al. (59) explored the effects of IF on mice gut microbiota. In this study, the authors found that IF altered the gut microbiota, even in different fasting periods. The results showed decreased levels of *Alistipes* and increased levels of *Akkermansia* (59). *Akkermansia* has been associated with reduced triglyceride accumulation and inflammation (60), whereas *Alistipes* has been correlated with increased inflammation (61). Remarkably, all mice involved in the study experienced reductions in body weight (59).

Clinical research

Intermittent fasting is a dietary pattern that has been associated with a reduction in obesity in humans. Furthermore, IF has been correlated with a healthy microbiota profile and the production of beneficial metabolites, including lactate and acetate (51). For instance, Cignarella et al. (62) found that IF promoted gut microbiota richness, particularly favoring the presence of *Lactobacillus* and *Akkermansia muciniphila*, which have been linked to positive effects on metabolic disorders, including obesity. Interestingly, the authors concluded that IF may modulate immune response by interacting with the microbiota, especially given the increased abundance of *Lactobacilli*, which has been described as having immunomodulatory properties (62).

Similarly, Guo et al. (63) investigated the impact of IF on the microbiota of patients with metabolic syndrome and central obesity. The research team observed an increase in the abundance of the *Rumonococcaceae* family, as well as the genera *Clostridium* and *Roseburia*, further augmenting the proportion of Firmicutes. The *Roseburia* genus has been associated with positive effects on health, such as intestinal inflammation reduction, energy homeostasis maintenance, and immune system maturation (63, 64). Furthermore, Spearman correlation analyses revealed an association between IF gut microbiota and lipid profiles (63). Notably, the authors concluded that IF had a positive impact on gut microbiota and microbial-derived metabolites, ultimately leading to improvements in some aspects of cardiometabolic health (63).

Conversely, Gabel et al. (65) studied the effects of IF on the gut microbiota of adults with obesity. The participants underwent a daily 8-h time-restricted feeding intervention for 12 weeks. Although no significant changes were observed in the microbiota compared to baseline analyses, the participants experienced reductions in body

weight (65). Interestingly, the authors suggested that the lack of microbiota changes might be attributed to the specific type of IF diet or to the relative smaller weight reduction compared with previous studies. Table 1 describes the studies mentioned in the present mini-review.

The molecular mechanisms underlying the beneficial effects of IF on gut microbiota and obesity need to be further elucidated. It has been described that IF induces a metabolic shift from glucose to ketones, thereby promoting ketogenesis. Notably, ketones are synthesized in the liver from fatty acids, further stimulating fat breakdown (66, 67). Furthermore, research has found that bacteria from the *Lactobacillaceae* family can enhance the expression of the fasting-induced adipocyte factor (FIAF), which inhibits lipoprotein lipase (LPL). This inhibition prevents the conversion from triglycerides to fat, regulating lipid metabolism and having a protective effect against obesity (68).

Clinical implications

Obesity, gut microbiota, and IF constitute a complex network of interactions with significant clinical implications. In this context, obesity can alter gut microbiota, which in turn, may trigger inflammatory cascades and release metabolites that exacerbate obesity-related complications. However, IF emerges as a potential alternative capable of addressing both obesity and gut microbiota dysbiosis (69, 70). Research the potential benefits of IF, including enhanced gut microbial richness and increased abundance of beneficial bacteria such as *Lactobacilli*. Moreover, IF has also been associated with weight loss and improvements in various obesity-related markers (58, 62, 63). Thus, IF represents a valuable tool for promoting metabolic health and fostering a balanced microbiota.

Limitations

One of the primary limitations in understanding the effects of IF on obesity and microbiota is that most studies have been performed on Western populations (71, 72). Research has suggested that ethnicity notably influences gut microbiota, with studies showing significant variations in gut microbiota as early as 3 months of age (73). Additional limitations include that many studies have been performed with relatively small sample sizes. Research involving larger and more diverse groups of participants is fundamental to comprehensively understanding the impact of IF on microbiota and obesity. Moreover, individual differences between participants in terms of metabolic rate, sex, food preferences, BMI,

TABLE 1 Gut microbiota differential changes depending on condition.

Condition	Organism	Bacteria	Abundance	Outcome	Reference
IF	*db/db* mice	Firmicutes Bacteroidetes Verrucomicrobia	Increased Decreased Decreased	These results have been associated with the concept of healthy obesity and an enhanced capacity for energy harvest	Xiao et al. (57)
IF	Mice	Firmicutes *Lactobacillus* Tenericutes Actinobacteria Bacteroidetes	Increased Increased Decreased Decreased Decreased	Activation of white adipose tissue browning	Li et al. (58).
IF	Mice	*Alistipes Akkermansia*	Decreased Increased	*Akkermansia* has been associated with reduced triglyceride accumulation and inflammation, whereas *Alistipes* has been correlated with increased inflammation	Li et al. (59)
IF	Human	*Lactobacillus Akkermansia municiphila*	Increased Increased	Positive effects on metabolic disorders, including obesity	Cignarella et al. (62)
IF	Human	*Rumonococcaceae* *Clostridium Roseburia*	Increased Increased Increased	Positive effects on health, such as intestinal inflammation reduction, energy homeostasis maintenance, and immune system maturation	Guo et al. (63)
IF	Human	No changes	No changes	Weight reduction	Gabel et al. (65).

socioeconomic status, and fitness levels could influence the studies' results, further complicating analyzing the data. Nutritional interventions present further challenges, as they require modifying the participants' lifestyle and control over various variables such as food choices and cooking methods. These factors can significantly impact study results. Additionally, this type of research generally includes the use of food records, which may be burdensome for participants (74).

Future directions

The potential of IF to modulate gut microbiota has shown promise as a way to manage weight and regulate gut microbiota. A bibliographic search conducted on the database ClinicalTrials.gov, an official website of the U.S. Department of Health and Human Services, National Institutes of Health, National Library of Medicine, and National Center for Biotechnology Information, using keywords such as "Obesity" for Condition/disease, "Microbiota" for Other terms, and "Intermittent fasting" for Intervention/treatment, revealed that there are currently seven studies involving these search terms. However, no results have been posted for any of these studies to date. Therefore, further research is crucial to fully understand the impact of IF on gut microbiota and obesity (75).

Future research on IF could explore the diverse variations of the IF diet. For instance, studies should investigate different fasting schedules, such as Time-Restricted Feeding and Alternate-Day Fasting, to determine the effects of each regimen on obesity and gut microbiota composition.

Moreover, determining the impact of IF on specific tissues and types of cells is crucial to comprehend its molecular mechanisms. For example, liver cells regulate metabolic processes, whereas adipose tissue cells have a key role in energy homeostasis; therefore, the effects that IF will have on overall health will depend on how IF interacts with each particular tissue and type of cell.

Furthermore, incorporating the use of innovative -omics techniques that provide a comprehensive analysis of biological systems at various molecular levels, such as genomics, transcriptomics, proteomics, and metabolomics, and can offer a comprehensive perspective on microbiota composition, metabolites, and gene expression patterns in response to IF. These technologies enable the identification of novel biomarkers, pathways, and therapeutic targets against obesity. Additionally, they could pave the way for targeted interventions and personalized approaches to weight management.

Lastly, analyzing the interplay of IF with other diets could yield valuable information, which can lead to the development of customized dietary patterns tailored to specific health goals. For instance, understanding how IF interacts with diets, such as the Mediterranean, could reveal synergistic effects that improve gut microbiota composition, metabolic health, and weight management.

In conclusion, research has shown that IF is a dietary pattern with the potential to positively influence human health by interacting with gut microbiota and ameliorating the effects of obesity. While existing research suggests a beneficial impact of IF on human health, including improved metabolic health and weight management, further studies are required to improve our understanding of this interaction. It is important to highlight that these studies should improve data analysis and collection, include diverse populations, and determine the molecular mechanisms involved.

Author contributions

SC-U: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. PG-R: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. VR-P: Investigation, Writing – review & editing. RT-T: Investigation, Writing – review & editing. EP-C: Investigation, Writing – review & editing. RZ-V: Investigation, Writing – review & editing. DS-R: Investigation, Writing – review & editing. AZ: Conceptualization, Investigation, Supervision, Writing – review & editing.

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Molecular mechanisms of semaglutide and liraglutide as a therapeutic option for obesity

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Obesity, a chronic global health problem, is associated with an increase in various comorbidities, such as cardiovascular disease, type 2 diabetes mellitus, hypertension, and certain types of cancer. The increasing global prevalence of obesity requires research into new therapeutic strategies. Glucagon-like peptide-1 receptor agonists, specifically semaglutide and liraglutide, designed for type 2 diabetes mellitus treatment, have been explored as drugs for the treatment of obesity. This minireview describes the molecular mechanisms of semaglutide and liraglutide in different metabolic pathways, and its mechanism of action in processes such as appetite regulation, insulin secretion, glucose homeostasis, energy expenditure, and lipid metabolism. Finally, several clinical trial outcomes are described to show the safety and efficacy of these drugs in obesity management.

KEYWORDS

obesity, molecular mechanism, semaglutide, liraglutide, weight loss

Introduction

Obesity is a chronic disease, and its prevalence has increased worldwide (1). According to the World Health Organization (WHO), there were approximately 1.9 billion overweight adults in 2016, of which 650 million were obese (2, 3). Genetic, environmental, and behavioral interactions have been linked to obesity; thus, the consumption of high-calorie foods associated with sedentary lifestyles increases the number of obese people in the world (4). Therefore, obesity can lead to a high risk of cardiovascular diseases, type 2 diabetes mellitus (DM2), hypertension, and some types of cancer. In addition, other diseases, such as dyslipidemia and even depression, are associated with obesity (5, 6).

Despite the increase in weight management approaches, the pandemic of obesity is still rising. However, strategies to control this phenomenon have primarily focused on physical exercise, behavioral factors, surgery (including bariatric surgery), and pharmaceutical interventions (7).

Pharmacological strategies have been fundamental for reducing the obesity pandemic (8). In this context, the group of glucagon-like peptide 1 receptor agonists (GLP-1RA), which mimic the natural hormone glucagon-like peptide 1 (GLP-1), has been mainly used for the treatment of DM2 (9). In addition, studies have shown that these drugs can have pleiotropic

effects such as blood pressure lowering, weight reduction, endothelial protection, and insulin sensitivity (Figure 1). For instance, semaglutide and liraglutide, two GLP-1RA agonist drugs, have been associated with weight loss and body weight maintenance (10–12).

The present review aims to elucidate and describe the molecular mechanisms of the GLP-1RA drugs, semaglutide and liraglutide, and their effectiveness and potential as a therapeutic option against obesity.

Methodology

The scientific papers search was performed in Google Scholar and PubMed databases. The following individual and combined search terms were used: "GLP-1," "Semaglutide and Liraglutide," "molecular mechanism," "lipid metabolism," "insulin metabolism," "glucose homeostasis," "energy expenditure" "obesity treatment," "type 2 diabetes mellitus," "side effects," "clinical trials," "treatment option," "fatty liver disease," "hypertension," "neurodegenerative diseases," "cardiovascular diseases," "therapeutic options." Only articles published in the last 10 years are included, although older pivotal studies were added.

Molecular mechanisms of semaglutide and liraglutide

GLP-1 receptor activation

GLP-1 is an incretin hormone secreted by enteroendocrine L-cells and α-cells in the pancreas and central nervous system. GLP-1 activates insulin secretion in response to elevated plasma glucose levels (13). In addition, GLP-1 activation increases neogenesis and proliferation while decreasing apoptosis of pancreatic β-cells (14). This GLP-1 hormone binds to the G protein-coupled GLP-1 receptor (GLP-1R) and activates key intracellular metabolic pathways. For instance, the GLP-1 hormone can trigger the adenylate cyclase (AC) metabolic pathway, leading to elevated levels of intracellular cyclic AMP (cAMP), subsequently activating the protein kinase A (PKA). PKA promotes exocytosis of insulin-containing vesicles from pancreatic β-cells and increases glucose-dependent insulin secretion (15). Conversely, GLP-1 can inhibit glucagon release from pancreatic α-cells, decreasing liver production of glucose (16).

Furthermore, cAMP-dependent mechanisms acting through PKA, and the exchange protein directly activated by cAMP (EPAC) inhibit ATP-dependent potassium channels and increase the activity of calcium channels. The influx of more calcium ions into the cell activates glucose-induced membrane depolarization and elevated cell sensitivity to glucose (17).

In addition, GLP-1 can stimulate the epidermal growth factor (EGF), triggering the phosphatidylinositol-3 kinase (PI3K), which activates transcription factors associated with β-cell growth while inhibiting those linked to β-cell apoptosis (18).

Moreover, these mechanisms are a consequence of Gβγ signaling, facilitated by the interaction of GLP-1R with distinct G proteins, which can activate various metabolic pathways using the identical ligand. Consequently, the metabolic pathways initiated by Gα proteins within GLP-1R involve cAMP activation, extracellular signal-regulated kinases 1 and 2 (ERK 1/2) and increased intracellular calcium levels (17, 19).

Chemical structure of semaglutide and liraglutide and its interaction with GLP-1 receptor

One of the pharmacological approaches against diseases like diabetes and obesity involves prolonging the time of action of GLP-1. For example, some GLP-1RA drugs, such as semaglutide and liraglutide, have already been approved by the United States Food and Drug Administration (FDA) for DM2 and chronic weight control (20).

Semaglutide and liraglutide were derived from the native structure of GLP-1. Semaglutide is a drug with 94% homology with human GLP-1. Its chemical structure consists of 31 amino acids with two amino acid substitutions (Aib8 and Arg34). Notably, the substitution

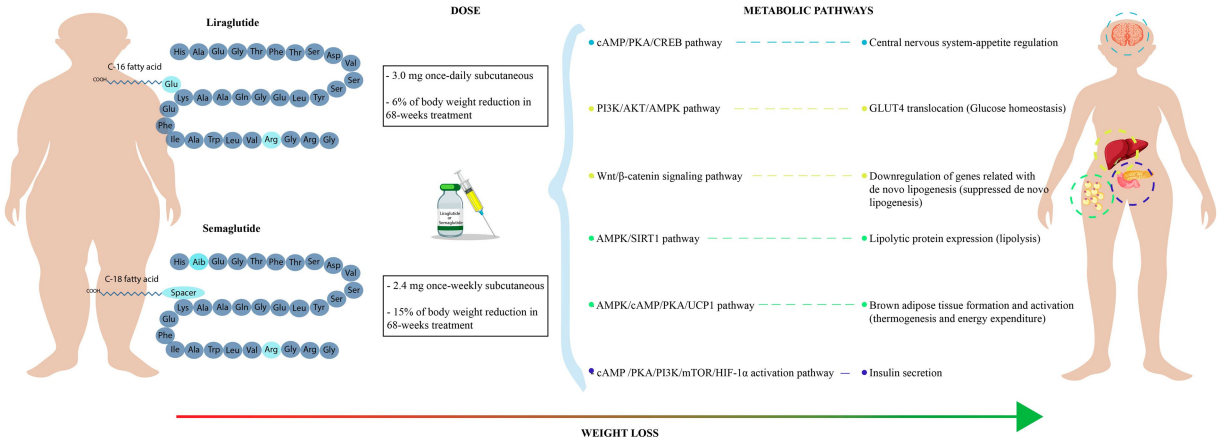

FIGURE 1
Metabolic outcomes of semaglutide and liraglutide treatment. It shows the molecular structure and recommended dose of GLP-1RA (semaglutide and liraglutide). Mechanisms of action of semaglutide and liraglutide in several metabolic pathways related with body weight loss.

at position 8 reduces susceptibility to degradation by dipeptidyl peptidase-4 (DPP-4) (21, 22). Conversely, liraglutide, another GLP-1RA, has 97% homology with human GLP-1. Its chemical structure, unlike semaglutide, has an Arginine-Lysine substitution at position 34 and a fatty acid residue is attached to Lysine 26. This modification enhances albumin binding, contributing to an increase in the half-life of the drug to 11 to 13 h (14).

Both, semaglutide and liraglutide, by binding to GLP-1R, can activate cAMP and PKA signaling cascades. As a result, there is an increased insulin secretion in the pancreatic β-cells and suppression of glucagon release. Furthermore, these pathways have also been linked to appetite regulation, modulation of gastric emptying, and cardiovascular effects (23, 24).

Semaglutide and liraglutide effects on central nervous system regulation

GLP-1 and GLP-1RA are involved in the activation of various central nervous system (CNS) processes, including satiety, thermogenesis, blood pressure, neurogenesis, and inflammation reduction (15). GLP-1 increases the expression of the cAMP, PKA, and CREB metabolic pathways. Additionally, GLP-1 modulates the phosphorylation of AKT, ERK, GSK-3B, and mTOR to increase cell viability and growth (25, 26).

Obesity has been associated with chronic inflammation, and GLP-1RA can modulate these inflammatory processes (27). GLP-1R is present in macrophages, lymphocytes, and monocytes which regulate immune cell signaling by suppressing proinflammatory cytokines such as TNF-α, IL-6, and IL-1β (28). In addition, studies have shown that GLP-1RAs decrease oxidative stress and improve endothelial function contributing to a reduction of inflammation in obesity (29).

Moreover, GLP-1 promotes neurogenesis by reducing inflammation and decreasing the expression of proinflammatory cytokines IL-6, IL-10, and microglial activation (25). GLP-1R is present in different brain regions, such as the cerebral cortex, thalamus, hypothalamus, substantia nigra, and cerebellum, having crossed the blood–brain barrier, influencing processes like appetite control and satiety (15). The GLP-1RA drugs semaglutide and liraglutide, due to their longer half-lives, may have more prolonged effects in the CNS and regulate appetite metabolic processes (30).

Studies have observed that GLP-1RA decreases food intake, slows gastric emptying, and promotes the release of hormones such as leptin and peptide YY, involved in satiety (7). The hormone leptin is fundamental in the regulation of body weight since it suppresses the orexigenic (appetite-inducing) pathway and activates the anorexigenic (satiety-inducing) pathway (8). Therefore, GLP-1RA may target different pathways to control appetite and inflammatory processes which would contribute to the treatment of obesity.

Metabolic effects

Semaglutide and liraglutide on insulin secretion

The effect of GLP-1 and GLP-1RA in pancreatic β-cells promotes glucose catabolism and insulin secretion (15, 31). This process relies on the mTOR-dependent HIF-1α activation pathway, which starts with the binding of the GLP-1 to the GLP-1R, activating the AC. Subsequently, AC increases the cAMP expression, which promotes the activation of both, PKA and EPAC. Activated PKA promotes the PI3K/mTOR pathway in β-cells, leading to the activation of the Hypoxia-Inducible Factor 1 (HIF-1). The transcriptional factor HIF-1 induces glycolytic genes activation in response to hypoxia and growth factors. Enhanced glycolysis facilitates citric acid cycle activation, elevating intracellular ATP concentration. High ATP amounts induce the closure of potassium channels, depolarizing the cell membrane, leading to calcium influx and insulin vesicle release. This release can be rapid, with a peak at 10 min post-initial glucose stimulus, followed by a sustained release from major insulin granules (approximately 90–95%) lasting up to 60 min under normal conditions (15, 31). However, the low half-life of GLP-1 incretin could affect this process in individuals with DM2 or obesity (32, 33). Therefore, GLP-1RA drugs like liraglutide or semaglutide can counteract DPP-4 degradation, prolonging the GLP-1R signal and maintaining insulin secretion via the mTOR-dependent HIF-1α pathway (34).

Semaglutide, liraglutide and glucose homeostasis

Liraglutide and semaglutide are mainly prescribed for the treatment of DM2 (34). These GLP-1RA drugs can improve blood glucose levels and reduce body weight (14, 35). There are various mechanisms involved in glucose homeostasis, like glucose-dependent insulin secretion, insulin biosynthesis, and glucagon regulation (34). Moreover, studies have shown that GLP-1RA could regulate glucose homeostasis in an insulin-independent mechanism via the 5′-AMP-activated protein kinase (AMPK) pathway (36, 37). The AMPK pathway is activated by the PI3K/AKT pathway, which promotes the translocation of the glucose transporter 4 (GLUT4) from intracellular vesicles to the plasma membrane. The increased levels of GLUT4 in the plasma membrane stimulate glucose uptake, promoting glucose homeostasis (36–38).

Lipid metabolism

Semaglutide and Liraglutide effects on lipid metabolism

GLP-1RA drugs have been associated with reduced food intake and body weight loss (39). The molecular mechanisms involve the stimulation of the Wnt/β-catenin signaling pathway by GLP-1R. Activation of the Wnt/β-catenin pathway has negative effects on adipogenesis by downregulating the expression of genes related to *de novo* lipogenesis. These downregulated genes include *DGAT1, SCD1, ApoB, FABP1,* and *FOXA1*, which are involved in fatty acid and triglycerides synthesis. Moreover, a decreased expression of the *FABP1* and *FOXA1* genes leads to decreased uptake of free fatty acids. The AMPK pathway also plays a role in inhibiting lipogenesis by regulating lipogenic genes like acetyl-CoA carboxylase. Inhibition of the acetyl-CoA carboxylase suppresses the *de novo* lipogenesis and improves fatty acids oxidation (37, 40).

The effect of GLP-1RA drugs in adipose tissue involves the lipolytic process. These agonists stimulate the AMPK pathway, leading to the activation of Sirtuin 1 (SIRT1), a NAD^+-dependent deacetylase that upregulates the expression of lipolytic proteins like triacylglycerol lipase. Consequently, triglyceride depletion occurs in white adipose tissue, resulting in reduced fat accumulation and improved energy

expenditure. Moreover, GLP-1RA negatively influences the expression of peroxisome proliferator-activated receptors (PPARs), leading to a downregulation of proteins associated with lipid metabolism (37, 41, 42).

Semaglutide and liraglutide in thermogenesis and energy expenditure

GLP-1 and GLP-1RA stimulate the GLP-1R in the central nervous system to modulate lipid metabolism in white and brown adipose tissues leading to a reduction in body weight. This process involves AMPK activation in the hypothalamic ventromedial nucleus by GLP-1 or GLP-1RA, promoting brown adipose tissue thermogenesis and white adipose tissue browning. The activated AMPK pathway enhances brown tissue activation via transcriptional regulators of genes involved in brown tissue development (PR domain containing 16, peroxisome proliferator-activated receptor γ, peroxisome proliferator-activated receptor γ coactivator 1α). Moreover, AMPK stimulates the activation of the cAMP/PKA pathway in brown adipocytes, triggering lipolysis through the release of free fatty acids and upregulation of uncoupling protein 1 (UCP1). Additionally, the cGMP second messenger is involved in mitochondrial biogenesis and UCP1 activation in brown adipose via the nitric oxide-sensitive soluble guanylyl cyclase pathway. UCP1 is essential for releasing electrons during oxidative phosphorylation in the inner mitochondrial membrane, generating heat (thermogenesis). Increased expression of UPC1 and a higher number of mitochondria are characteristics of activated brown adipose tissue, facilitating the lipolytic cycle (43–45).

Another effect of GLP-1RA is the increase of sympathetic nervous system (SNS) activity. Activated SNS promotes brown adipose tissue thermogenesis and white adipose tissue browning via hypothalamic AMPK activity. Furthermore, the thyroid hormone (TH) is an essential regulator of brown adipose tissue activity. In this context, GLP-1RA drugs could activate the thermogenic proteins in brown adipocytes, increasing intracellular type 2 deiodinase (D2) expression and subsequent TH activation. Therefore, TH activates brown adipocytes and promotes oxygen consumption and thermogenesis (43, 46, 47).

Discussion

The metabolic effect of semaglutide and liraglutide in obese people is remarkable. The main mechanism of action of these GLP-1RA is the stimulation of the GLP-1R that triggers the activation of several metabolic pathways involved in insulin secretion, lipid metabolism, energy expenditure, pro-survival and anti-apoptotic cellular signaling, and oxidative stress prevention, in several tissues like the pancreas, central nervous system, heart, muscle, kidneys, gut, among others (15). The wide distribution of the GLP-1R has allowed the study of semaglutide and liraglutide pharmacological protocols to improve metabolic diseases in several experimental models (26, 40, 48–50). The assessment of these GLP-1RA could elucidate the role of these drugs in the cellular signaling process of obese-related diseases, which could support the development of new pharmacological approaches. For instance, the combination of GLP-1RA and enzyme inhibitors of proinflammatory, lipogenesis, pro-apoptotic, and pro-oxidative stress processes could be evaluated in metabolic diseases. Although, rigorous safety and efficacy-controlled trials must be carried out, like those performed to assess the effect of semaglutide and liraglutide in obese or DM2 individuals.

Clinical trials have evaluated the effectiveness of GLP-1RA drugs, semaglutide, and liraglutide, in treating obesity. The Semaglutide Treatment Effect in People with Obesity (STEP) program evaluated the once-weekly administration of 2.4 mg subcutaneous semaglutide in people with obesity or overweight. In the STEP 1 trial, 1961 participants underwent dietary and exercise interventions. In this trial, 69 to 79% of the participants lost weight with an average weight reduction of ≥10% after 68 weeks of treatment compared with placebo group (12–17%) (51). Additionally, the STEP trials evaluated patients with obesity and DM2; the results supported the recommended dose of 2.4 mg of semaglutide per week for weight loss in individuals with obesity, with or without DM2 (52).

Similarly, in the Peptide Innovation for Early Diabetes Treatment (PIONEER) clinical trial, oral semaglutide was tested in patients with DM2. Results showed that oral semaglutide has a significantly higher efficacy compared to placebo and other DPP4 inhibitor drugs (53). Moreover, the results from the PIONEER clinical trials suggested that oral semaglutide effectively reduced HbA1c and body weight, showing responsiveness in diverse age groups with a diagnosis of DM2 (54).

The efficiency of liraglutide was evaluated in the clinical trial called SCALE (Satiety and Clinical Adiposity: Evidence for liraglutide), where it was determined that a dosage of 3.0 mg induced an 8% weight loss equivalent to 8.4 kg of the initial weight in over 56 weeks. In comparison, the placebo group experienced a decrease of 2.6% equivalent to 2.8 kg. Participants also improved weight-related comorbidities through lifestyle and diet adjustments (55).

Azuri et al. showed that semaglutide had a better performance than liraglutide in terms of weight loss (12.4% [95% CI: 11.5–13.4%] vs. 5.4% [95% CI: 5–5.8%]). Moreover, this study reported that semaglutide had a lower economic spend than liraglutide for obesity management (56). This highlights the potential use of semaglutide due to its low cost and superior performance.

The posology of semaglutide and liraglutide also showed differences in body weight reduction. In obese individuals without diabetes mellitus, a once-weekly subcutaneous semaglutide (2.4 mg) dose had a significant body weight change compared with a once-daily subcutaneous liraglutide (3.0 mg) dose after 68 weeks. Participants under the semaglutide treatment showed a 15% weight loss than baseline, while liraglutide recipients experienced a 6% weight loss (57). Therefore, semaglutide also has an advantage due to the smaller number of doses and greater weight loss.

A meta-analysis revealed that a 2.4 mg dose of semaglutide led to a reduction of 12.4 kg of body weight, while doses of 3.0 mg of liraglutide, 1.0 mg of semaglutide, and 1.8 mg of liraglutide led to reductions in body weight of 5.2 kg, 3.7 kg, and 1.8 kg, respectively. The evaluation of these doses was performed in various periods, ranging from 20 weeks to 68 weeks. The most effective treatment involved a weekly dose of 2.4 mg semaglutide for 68 weeks. Moreover, for the dose of 2.4 mg semaglutide, the decrease in glycated hemoglobin was the highest (1.48% reduction with 2.4 mg semaglutide dose) compared with the other doses (58). Once again, semaglutide demonstrates a higher performance compared with liraglutide, although individual medical status must be assessed before the prescription of this treatment to prevent side effects.

Another important component of the treatment with GLP-1RA is the inclusion of lifestyle interventions, including exercise and a

low-calorie diet (1, 59). This factor is significant for weight loss sustaining, given that after subcutaneous semaglutide (2.4 mg) treatment suspension, studies have shown that there may be a weight regain worsening cardiometabolic parameters (60). This highlights that GLP-1RA treatment must be continuous, along with a healthy lifestyle. Therefore, monitoring after several years of semaglutide or liraglutide withdrawal should be performed to verify metabolic status and weight. For instance, the outcomes of semaglutide and liraglutide in patients with DM2 have shown a cardiovascular risk factors reduction and an improvement in glucose levels and nutritional status (22, 58, 61–63).

The safety profile of GLP-1RA drugs generally indicates a low incidence of side effects, although it depends on the dose and the administration mode. For instance, oral semaglutide (14 mg) exhibited more side effects (such as vomiting or gastrointestinal issues) than subcutaneous liraglutide (1.2 mg); however, these side effects were no different from those observed with subcutaneous semaglutide treatment (64). Moreover, the use of semaglutide has been related to the increased risk of cholelithiasis (65).

The effectiveness of these GLP-1RA drugs, especially semaglutide, is associated with an improvement in other diseases like cardiovascular diseases (22, 50). Studies suggest that DM2 accompanied by insulin resistance may contribute to memory impairment and the development of neurodegenerative diseases such as Alzheimer's and Parkinson's disease (66). Furthermore, these GLP-1RA medications have also been related to a reduction of neuroinflammation, probably due to its possible role in neuronal insulin signaling pathway restoration (49, 67, 68). Hence, semaglutide and liraglutide could also have the potential to ameliorate neurodegeneration processes observed in pathologies like Alzheimer's and Parkinson's diseases, although further research is needed (48, 69). Moreover, clinical trials have reported a reduction of the inflammatory C-reactive protein (70), which could indicate that this drug may also regulate the immune system, although this approach requires further assessment. Therefore, given the association with improved nutritional status under semaglutide treatment, this GLP-1RA could be explored in other obesity-related conditions, including fatty liver disease, dyslipidemia, hypertension, and potentially even cancer.

Conclusion

Obesity is a current public health issue that must be addressed to avoid and prevent several underlying pathologies like cardiovascular diseases, fatty liver disease, DM2, hypertension, and cancer. Therefore, lifestyle and pharmacological options must be evaluated to improve or prevent those obesity underlying pathologies. Between the pharmacological options, the GLP-1RA, originally approved for the treatment of DM2, have been demonstrated to be useful for body weight reduction in obese individuals. The main molecular mechanisms of GLP-1RA in obesity reduction include the increased production of insulin by the cAMP/PKA pathway in pancreatic β-cells, along with an augmented translocation of GLUT-4 in the cellular membrane for improved glucose homeostasis, and energy expenditure by lipolytic cycle stimulation. The GLP-1RA with better outcomes in clinical trials is semaglutide since this drug can reduce up to 15% of the baseline weight after a 2.4 mg subcutaneous weekly dose. Moreover, semaglutide has shown a reduction of cardiovascular risk factors and inflammatory proteins observed in obese individuals. Therefore, semaglutide could improve other obesity-related pathologies like cardiovascular, hypertension, or fatty liver diseases.

Author contributions

RT-T: Conceptualization, Writing – original draft, Writing – review & editing. VR-P: Conceptualization, Writing – original draft, Writing – review & editing. SC-U: Writing – original draft, Writing – review & editing. PG-R: Writing – original draft, Writing – review & editing, Writing – original draft. EP-C: Writing – original draft, Writing – review & editing. RZ-V: Writing – original draft, Writing – review & editing. DS-R: Conceptualization, Resources, Writing – original draft, Writing – review & editing. AZ: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association of the oxidative balance score with obesity and body composition among young and middle-aged adults

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Objective: The oxidative balance score (OBS) is important for determining the cause of obesity and its complications. We aimed to evaluate the association between OBS and obesity and other segmental body composition parameters among young and middle-aged U.S. adults.

Methods: 9,998 participants from the National Health and Nutrition Examination Survey 2011–2018 were included. Lean mass percentage (LM%) and FM% were evaluated by dual-energy x-ray absorptiometry. Obesity was defined as body FM% ≥25% in men and ≥ 35% in women. The OBS was scored by 5 pro-oxidant and 21 antioxidant factors. Associations of quartiles of OBS with obesity risk were estimated using multivariable logistic regression models. Multivariable linear regression was conducted to estimate the association between OBS and segmental body composition measures including the arm LM%, leg LM%, torso LM%, whole LM%, arm FM%, leg FM%, torso FM% and total FM%.

Results: Compared to participants in the lowest quartile of OBS, those in the highest quartile of OBS were associated with a lower risk of BMI-defined obesity BMI-defined obesity [0.43 (0.36, 0.50)] and FM%-related obesity [0.43 (0.35, 0.52)]. Additionally, OBS was negatively associated with FM% of the limb and torso but positively associated with the percentage of lean mass (LM%) of the limb and trunk.

Conclusion: OBS was negatively associated with the risk of obesity and segmental FM%, but was positively associated with segmental LM% among US adults, indicating that adhering to an anti-oxidative diet and lifestyle management may be beneficial for preventing segmental obesity.

KEYWORDS

oxidative balance, obesity, body composition, fat mass, lean mass

1 Introduction

Obesity, defined as the physically excessive accumulation of body fat (1), has become a major health problem worldwide. The World Health Organization (WHO) standardized body mass index (BMI) over 30 kg/m^2 in Caucasians as an index of obesity irrespective of age and sex (2). In adult life, however, body composition slowly changes with age, including the

degeneration of lean mass and the accumulation of fat tissue (3, 4). Notably, alterations in body composition sometimes may not be accompanied by significant changes in BMI (5). In this context, using BMI alone cannot discriminate individuals with normal weight obesity (NWO), also called occult obesity, from individuals without obesity. A growing number of studies have linked NWO with increased risk of metabolic syndrome (MetS), cardiac morbidity and mortality (6, 7). Therefore, accurate determination of real obesity is vital.

Segmental body composition may help clinicians better distinguishing lean mass from adipose tissue in individual regions (8) and help to define the clinical status of individuals with obesity rather than BMI (9), which has been of interest to clinicians in recent years. Empirical data suggest that lean mass percentage (LM%) is negatively associated with the risk of hypertension (10), diabetes (11), and hypercholesterolemia (12). Given this, when managing our figure, not only should we focus on body weight and BMI but also body composition in different segments.

In addition to a state of positive energy balance, oxidative stress is another vital factor contributing to adipogenesis and lipogenesis in the development of obesity (13, 14). Oxidative stress is a complex process results from the imbalance between protective substances produced by antioxidants and reactive oxygen species produced by pro-oxidants (15), and it is closely related to human diseases, including cardiovascular disease, cancer, and aging (16–18). Due to its significant impact on overall health, evaluating the oxidative balance in individuals is crucial now and in the future. By monitoring oxidative stress status, healthcare professionals can take proactive steps, through a combination of healthy lifestyle and dietary choices, to maintain individuals' health and well-being, ultimately promoting longevity, improving quality of life.

Lifestyle and dietary intervention exert important effects on the cellular redox status. Mounting evidence has shown that drinking (19), smoking (20) and excessive iron (21) accelerate oxidative stress, while higher consumption of certain nutrients, such as vitamin C (22), vitamin D (23), vitamin E (24), selenium (25), zinc (26), calcium (27) and magnesium (28) protects against oxidative stress related cellular damage. Nevertheless, it is hard to truly reflect the body's oxidative levels. The oxidative balance score (OBS) was developed for quantifying the physical oxidative stress burden of dietary and lifestyle pro-oxidants and antioxidant factors (16). In general, a higher OBS indicates that antioxidant factors are more dominant than pro-oxidants (29), and OBS was shown to be associated with oxidative stress (30, 31) in previous National Health and Nutrition Examination Survey (NHANES) studies.

However, based on prior studies, there is still on consistent conclusions on the association between OBS and the risk obesity (32, 33). Zahra Noruzi et al's study showed no significant relationship between OBS and MetS in Iranian (32), while another study revealed that participants in the highest quartile of OBS were less likely to be at risk for MetS than those in the lowest quartile (33). In addition, Yeo et al. (34) reported that Korean individuals with higher OBS had a significantly smaller neck circumference (NC), which was associated with central obesity in the general population (35). Wang et al. (36) reported that higher OBS was significantly correlated with lower risks of abdominal obesity and visceral fat accumulation. Nevertheless, studies about segmental fat mass and lean mass percentage were relatively rare. Notably, single parameters such as waist circumference (WC) and NC cannot reflect specific segmental or local obesity statuses. To further clarify the association between OBS and segmental obesity, we further evaluated fat mass and lean mass percentage in individual regions.

The aim of the present study was to evaluate the relationship between OBS and obesity as well as other segmental body composition parameters using data from the NHANES. We hypothesize that there may be a potential negative relationship between OBS and the risk of obesity and FM%, while positive with LM%.

2 Materials and methods

2.1 Study population

The subjects of this cross-sectional study were from the NHANES 2011–2018 database. The NHANES is designed to assess the nutritional and health status of the noninstitutionalized population in U.S., and is conducted every 2 years. In every cycle, approximately 5,000 people were selected by a complex multistage sampling strategy, and all participants completed structured questionnaires at home and underwent physical examination at a mobile examination center (MEC). All procedures were approved by the National Center for Health Statistics, and an informed consent form was signed by each subject. All participants signed a written informed consent form.

2.2 Oxidative balance score calculation

Both dietary and lifestyle antioxidant/prooxidant factors contributed to OBS (37). The dietary intake information was obtained via 24-h dietary recall interviews at the mobile examination center (MEC). The dietary intake data are used to estimate the types and amounts of foods and beverages consumed during the 24-h period prior to the interview, and to estimate intakes of energy, nutrients, and other food components. In this study, the lifestyle factors associated with OBS included alcohol intake, smoking status, BMI, and physical activity. Participants were categorized according to sex-specific tertiles of energy-adjusted dietary nutrients. Alcohol intake was obtained from the 24-h dietary recall interviews. Nondrinkers, nonheavy drinkers (0 to 30 g/d for males and 0 to 15 g/d for females), and heavy drinkers ($\geq$30 g/d for males and $\geq$ 15 g/d for females) received 2, 1, or 0 points, respectively. To simultaneously assess passive smoking, the serum concentration of cotinine was used to assess smoking status. BMI was calculated as weight (kg)/height squared (m^2). Participants were categorized into inactive group (no leisure-time physical activity), insufficiently active group (leisure-time moderate activity 1–5 times per week or leisure-time vigorous activity 1–3 times per week) and active group (those who had more leisure-time moderate or vigorous activity than above) as previously reported (38) and these three groups received 0, 1, and 2 points, respectively.

The pro-oxidants consisted of total fat and iron intake, alcohol consumption, and BMI. The antioxidants included dietary fiber, α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein+zeaxanthin, riboflavin, niacin, vitamin B6, total folate, vitamin B12, vitamin C, vitamin E, calcium, magnesium, zinc, copper, selenium, vitamin D and physical activity. Finally, the 5 priori defined pro-oxidant and 20 antioxidant factors were equally weighted to construct the OBS. Except

for physical activity and alcohol intake, other antioxidants were assigned 0, 1 or 2 points for tertile 1, tertile 2 or tertile 3, respectively, whereas pro-oxidants were reverse scored (Supplementary Table S1).

2.3 Outcome

DXA scans were performed on a Hologic QDR 4500 fan beam densitometer (Hologic, Inc., Bedford, MA) according to the manufacture's guidelines. DXA was administered by trained and certified radiology technologists, and an expert review was conducted. Available data were used to calculate the percentage of total and regional fat mass and lean mass. The LM% was equal to the lean mass (the sum of nonbone and nonfat mass) of the left arm divided by the total weight of the left arm. The FM% was calculated as the fat mass of the left arm divided by the total weight of the left arm. The LM% and FM% of the other segments were calculated with reference to the left arm. According to our preliminary analysis, the limb LM% and FM% on the left and right went hand in hand (Supplementary Figure S1), so the average of LM% and FM% of the limbs were calculated. We focused on the arm LM%, arm FM%, leg LM%, leg FM%, trunk LM%, trunk FM%, total LM% and total FM%. Based on the guideline of the American Association of Clinical Endocrinologists and the American College of Endocrinology, an FM% ≥ 25% for men or an FM% ≥ 35% for women was defined as obesity (39–42). BMI (in kg/m^2) ≥30 was defined as obesity, calculated as weight (kg) divided by height (m)^2 (43).

2.4 Covariates

Demographics information, including age, sex, race, education, and the ratio of family income to poverty (PIR) was collected. The race was classified as non-Hispanic White, non-Hispanic Black, Mexican American and other. Education level was classified as less than high school, high school or equivalent and college or above. PIR was calculated by dividing family (or individual) income by the poverty guidelines specific to the survey year, and was classified into three categories: <1.3, 1.3–3.5, and > 3.5 based on previous guidelines (44). Self-reported diseases, including hypertension and diabetes, were also included as covariates. The missing data for PIR, hypertension, and diabetes were coded as "unknown".

2.5 Statistical analysis

Continuous variables are presented as the mean with standard error, and categorical variables are presented as weighted percentages. Differences in OBS quartiles were compared by using the weighted chi-square test. Weighted variance analysis was used for continuous variables. Weighted multivariate logistic regression was performed to estimate the independent relationship between OBS and the risk of FM%-defined obesity. Weighted multivariable linear regression analysis was conducted to investigate the associations between OBS and segmental LM% and FM%. Odds ratios (ORs) or β estimates with 95% confidence intervals (95% CIs) were calculated. In Model 1, no covariates were adjusted. Model 2 was adjusted for age (continuous), sex (male, female), race (non-Hispanic White, Black, Mexican American, Hispanic, and other ethnicity), education level (less than high school, high school, more than high school, or missing) and PIR (<1.3, 1.3–3.5, >3.5 or missing). Model 3 was adjusted for Model 2 plus hypertension (yes, no, or missing), diabetes (yes, no, or missing) and energy intake (continuous).

In addition, weighted restricted cubic spline analyses (RCS) with four knots were conducted to explore the dose–response relationship between OBS and the risk of FM% defined obesity as well as segmental body composition parameters. Age, gender, race, education level, family poverty income ratio, diabetes, hypertension and energy intake were adjusted as covariates. In the exploratory analyses, subgroup analyses by age, sex, race, PIR, education level and energy intake were performed. Sensitivity analyses by restricted the analysis to participants with the data of C-reactive protein (CRP) data were conducted. All analyses were performed using EmpowerStats 2.0 and R version 3.6.2; a p-value <0.05 with a two-sided test was considered to indicate statistical significance.

3 Results

3.1 Baseline characteristics

Participants aged 18 to 59 years who completed the DXA examinations between 2011 and 2018 were included. We excluded pregnancy, individuals who weighed more than 450 pounds or taller than 6′5″ and other cases whose DXA examination were invalid. Individuals were also excluded for missing any data on the OBS components (Supplementary Table S1). Finally, 9,998 participants were enrolled. The flowchart is shown in Figure 1.

The baseline characteristics of the individuals based on quartiles of the OBS are shown in Table 1. Age, sex, race/ethnicity, family PIR, education level, hypertension status, energy intake, as well as segmental FM% and LM% were significantly different between the OBS quartiles (all $p < 0.001$). Participants in higher OBS quartiles were older and had a higher education level and incomes, but a lower energy intake. In addition, participants in higher OBS quartiles tended to have a lower incidence of FM%-defined obesity (Q1:74.20%, Q2: 69.78%, Q3: 66.60%, Q4: 62.20%, p trend <0.001) and BMI-defined obesity (Q1:43.47%, Q2: 36.72%, Q3: 34.50%, Q4: 25.39%, p trend <0.001) than those in the lowest quartile. Compared with those in Q1, participants in higher quartiles had higher segmental LM% while a lower FM% (all $p < 0.001$).

3.2 Associations between OBS and the risk of obesity

The associations between OBS and the risk of obesity are shown in Table 2. Each 1-SD increase in the OBS was associated with a 29% lower OR of BMI-defined obesity (OR = 0.71, 95% CI = 0.66, 0.76; $p < 0.001$) in the fully adjusted model. Compared to those in the lowest quartile of OBS (Q1), participants in the highest quartile of OBS (Q4) had a 57% lower risk of BMI-defined obesity (OR = 0.43, 95% CI = 0.36, 0.50; p trend <0.001).

According to the multivariate model, per 1-SD increase in the OBS was associated with a 29% lower OR of FM%-defined obesity (OR = 0.71, 95% CI = 0.66, 0.76; $p < 0.001$). Compared to those in the

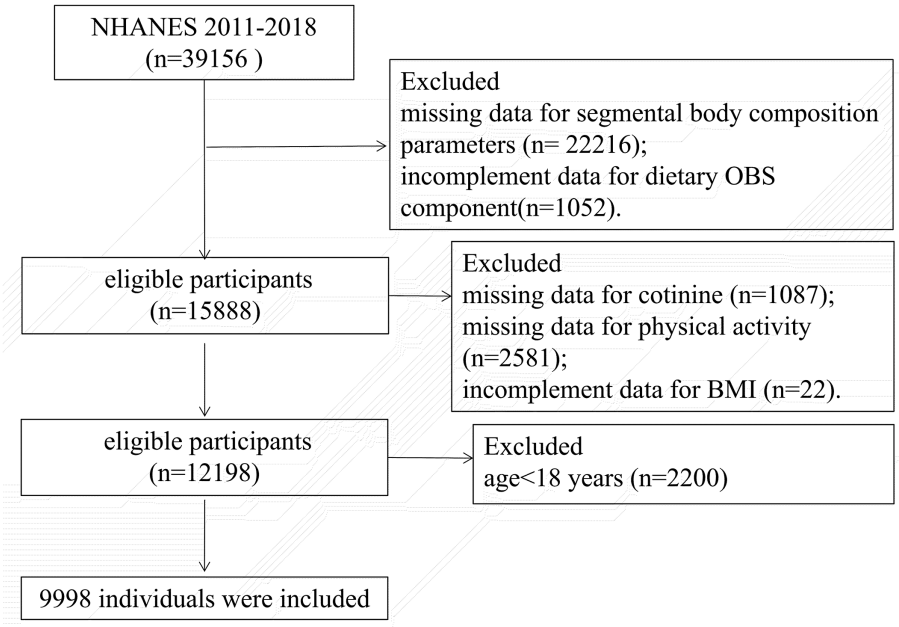

FIGURE 1
The flowchart of the sample selection.

lowest quartile of OBS (Q1), participants in the highest quartile of OBS (Q4) had a 57% lower risk of FM%-defined obesity (OR = 0.43, 95% CI = 0.35, 0.52; *p* trend <0.001).

Additionally, as shown in Figure 2, RCS analysis revealed a significant negative relationship between OBS and the risk of BMI-defined obesity and FM% defined obesity (*p* overall <0.001).

3.3 Associations between OBS and segmental body composition parameters

Overall, we observed a significant negative association between OBS and segmental FM% and a positive between OBS and LM% (Figure 3). As shown in Table 3, the multivariable linear regression model showed that each 1-SD increase in OBS was negatively associated with segmental FM%, with β estimates (95% CIs) of −1.07 (−1.27, −0.86), −0.86 (1.04, −0.68), −1.32 (−1.52, −1.12), and −1.06 (−1.23, −0.89) for arm FM%, leg FM%, torso FM% and total FM%, respectively. Similarly, a 1-SD increase in the OBS was positively associated with segmental LM%, with β estimates (95% CIs) of 0.99 (0.80, 1.18), 0.79 (0.62, 0.96), 1.26 (1.07, 1.45), and 0.98 (0.83, 1.14) for the arm LM%, leg LM%, torso LM% and total LM%, respectively. RCS analyses further revealed a negative association between OBS and segmental FM%, but a positive association between OBS and LM% (all *p* overall <0.001).

When OBS was treated as a categorical variable, higher OBS quartiles were associated with decreased segmental FM%; the β estimates (95% CIs) for the highest quartile (Q4) were −2.76 (−3.35, −2.17), −2.19 (−2.72, −1.65), −3.37 (−3.94, −2.80), and −2.72 (−3.22, −2.23) for the arm FM%, leg FM%, torso FM% and total FM%, respectively (all *p* trend <0.001), when compared with the lowest OBS quartile (Q1), suggesting a stable negative relationship between OBS and FM%. Accordingly, a higher OBS was associated with increased segmental LM%; the β estimates (95% CIs) for Q4 were 2.56 (2.01, 3.11), 2.01 (1.51, 2.51), 3.23 (2.68, 3.78) and 2.52 (2.06, 2.98) for the arm LM%, leg LM%, torso LM% and total LM%, respectively (reference to Q1) (all *p* trend <0.001).

3.4 Subgroup and sensitivity analyses

Subgroup analyses were also conducted to evaluate the possible effect modifications of the association between OBS and obesity as well as segmental FM% and LM%. After stratification by sex, age, race, Family PIR, education level and energy intake, the associations of OBS with obesity were inconsistent in different gender (both *p* interaction <0.01), race/ethnicity (both *p* interaction <0.05) and those with different education level (both *p* interaction <0.001), but remained consistent across categories of age, family PIR and energy intake (all *p* interaction >0.05) (Supplementary Tables S2, S3). Similar results were also observed for the associations between OBS and segmental FM% and LM%. Notably, the associations of OBS with Torso FM% and LM% remained consistent across the different age subgroups (*p* interaction >0.05), while the associations of OBS with limb FM% and LM% were stronger in those aged <40 years (*p* interaction <0.05) (Supplementary Tables S4–S9).

CRP is a reliable biomarker of inflammation (45). To adjust for possible confounding by CRP levels, we restricted the analysis to participants with the data of CRP data. Subjects with CRP levels had a similar OBS (25.62 ± 0.25) to those of people without CRP levels (25.42 ± 0.25, *p* = 0.576). Subjects with a higher OBS had a significantly lower CRP level (Supplementary Figure S2). After adjusting for age, sex, race, education level, family PIR, hypertension status, diabetes, energy intake and CRP level, the negative associations between OBS and obesity, as well as other segmental body composition parameters, were also stable (Supplementary Tables S10, S11).

TABLE 1 The baseline characteristics of participants from National Health and Nutrition Examination Survey, United States, by quartiles of the OBS.

	Overall (2–47)	Q1 (2–18)	Q2 (19–24)	Q3 (25–30)	Q4 (31–47)	*p*-value
Age, year	38.13 ± 0.28	36.66 ± 0.44	38.01 ± 0.33	38.00 ± 0.35	39.45 ± 0.46	<0.001
Male, *n* (%)	5,068 (51.63)	1,092 (49.40)	1,301 (55.00)	1,299 (54.08)	1,376 (48.40)	<0.001
Race, *n* (%)						<0.001
Non-Hispanic White	3,466 (61.54)	879 (62.18)	869 (61.43)	812 (60.01)	906 (62.45)	
Non-Hispanic Black	2023 (10.67)	660 (16.13)	601 (12.79)	445 (9.53)	317 (5.81)	
Mexican American	1,585 (10.91)	279 (9.10)	390 (10.90)	447 (12.70)	469 (10.76)	
Other Hispanic	1,056 (7.44)	184 (5.68)	271 (8.20)	269 (7.48)	332 (8.08)	
Other race	1868 (9.44)	234 (6.91)	328 (6.68)	509 (10.28)	797 (12.90)	
Family PIR, *n* (%)						<0.001
<1.3	3,119 (23.99)	890 (31.15)	840 (26.57)	743 (23.33)	646 (17.10)	
1.3–3.5	3,277 (34.53)	749 (37.33)	855 (38.34)	815 (34.80)	858 (29.06)	
>3.5	2,827 (41.48)	443 (31.51)	573 (35.09)	724 (41.87)	1,087 (53.84)	
Education level, *n* (%)						<0.001
Less than high school	563 (3.68)	88 (2.87)	139 (3.91)	149 (3.70)	187 (4.07)	
High school	3,679 (32.52)	1,065 (45.54)	1,005 (36.30)	887 (31.09)	722 (20.94)	
More than high school	5,754 (63.80)	1,083 (51.59)	1,315 (59.80)	1,445 (65.21)	1911 (74.99)	
Diabetes, *n* (%)	667 (5.25)	136 (5.32)	155 (4.88)	188 (5.60)	188 (5.21)	0.835
Hypertension, *n* (%)	2,121 (20.70)	512 (21.32)	574 (23.42)	514 (20.87)	521 (17.83)	0.005
Energy intake, kcal/day	2,271.53 ± 13.14	2,459.73 ± 36.88	2,423.61 ± 26.59	2,288.93 ± 25.22	1,990.72 ± 18.91	<0.001
Arm FM%	33.24 ± 0.16	34.71 ± 0.35	32.88 ± 0.34	32.65 ± 0.29	32.96 ± 0.29	<0.001
Leg FM%	34.87 ± 0.16	36.17 ± 0.31	34.72 ± 0.29	34.23 ± 0.27	34.57 ± 0.26	<0.001
Torso FM%	31.48 ± 0.17	32.88 ± 0.31	31.50 ± 0.28	31.22 ± 0.27	30.63 ± 0.25	<0.001
Total FM%	32.51 ± 0.14	33.82 ± 0.28	32.44 ± 0.27	32.09 ± 0.24	31.95 ± 0.23	<0.001
Arm LM%	62.91 ± 0.15	61.55 ± 0.33	63.29 ± 0.32	63.52 ± 0.29	63.14 ± 0.28	<0.001
Leg LM%	61.80 ± 0.15	60.60 ± 0.30	61.95 ± 0.28	62.43 ± 0.26	62.04 ± 0.24	<0.001
Torso LM%	66.94 ± 0.16	65.59 ± 0.29	66.93 ± 0.27	67.20 ± 0.26	67.74 ± 0.24	<0.001
Total LM%	64.52 ± 0.14	63.29 ± 0.27	64.60 ± 0.25	64.93 ± 0.23	65.00 ± 0.22	<0.001
FM% defined obesity, *n* (%)	6,748 (67.74)	1,620 (74.20)	1,684 (69.78)	1,663 (66.60)	1781 (62.20)	<0.001
BMI defined obesity, *n* (%)	3,469 (34.32)	991 (43.47)	929 (36.72)	840 (34.50)	709 (25.39)	<0.001

Continuous variables are presented as means ± SE or numbers (percentages) for categorical variables unless otherwise indicated. *p* value was estimated using chi-square for proportions, variance analysis for means. All estimates accounted for complex survey designs, and all percentages were weighted. Family PIR, ratio of family income to poverty; FM%, fat mass percentage; LM%, lean mass percentage; OBS, oxidative balance scores.

4 Discussion

In the present nationwide cross-sectional study, we found that OBS was negatively associated with the risk of obesity and segmental FM% but positively associated with segmental LM%. These associations were independent of confounding factors and remained consistent in all the subgroup and sensitivity analyses. Accordingly, our results provide evidence for the importance of optimizing diet and lifestyle as crucial strategies in the prevention of segmental obesity in U.S. adults.

To our knowledge, this is the first study evaluating the association between OBS and FM% defined obesity as well as the percentage of segmental fat and lean mass. So far, previous epidemiological studies have explored OBS and the risk of central obesity. Noruzi et al. (32) reported that higher OBS was associated with a lower risk of abdominal obesity defined by high circumference, while another study suggested that there was no association between them in Tehranian adults (33). In addition, Yeo et al. (34) explored the association between OBS and central obesity and showed that Korean adults with a higher OBS had a smaller NC. Similar to our study, Wang et al. (36) reported that higher OBS was significantly correlated with lower risks of abdominal obesity and visceral fat accumulation. However, in Wang's (36) study, they did not use segmental fat mass and lean mass, but focused on the association of OBS with total abdominal fat mass and visceral adipose tissue mass percentages. Our study reaffirms previous observations suggesting a dysregulated oxidative balance in individuals with obesity or unfavorable body composition. As for segmental body fat percentage, especially in the upper limbs and torso, may be more essential than overall when evaluating metabolic risk (12). Our results imply the significance of an anti-oxidative diet and lifestyle may be beneficial for metabolic disease. In addition, the identification of oxidative stress as a potential contributor to obesity underscores the

TABLE 2 Association between OBS and the risk of obesity.

Variable	OR (95% CI)		
BMI defined obesity[a]	Model 1	Model 2	Model 3
OBS, Per 1-SD increase	0.72 (0.68, 0.77)*	0.72 (0.67, 0.77)*	0.71 (0.66, 0.76)*
OBS categories			
Quartile 1	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Quartile 2	0.75 (0.65, 0.87)*	0.73 (0.63, 0.84)*	0.72 (0.62, 0.82)*
Quartile 3	0.69 (0.58, 0.81)*	0.67 (0.56, 0.81)*	0.66 (0.55, 0.80)*
Quartile 4	0.44 (0.38, 0.51)*	0.44 (0.37, 0.51)*	0.43 (0.36, 0.50)*
P for trend	<0.001	<0.001	<0.001
FM% defined obesity[b]	Model 1	Model 2	Model 3
OBS, Per 1-SD increase	0.80 (0.75, 0.85)*	0.75 (0.70, 0.80)*	0.71 (0.66, 0.76)*
OBS categories			
Quartile 1	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Quartile 2	0.80 (0.65, 1.00)	0.74 (0.60, 0.92)*	0.72 (0.58, 0.89)*
Quartile3	0.69 (0.57, 0.84)*	0.63 (0.51, 0.76)*	0.59 (0.48, 0.73)*
Quartile 4	0.57 (0.48, 0.68)*	0.48 (0.40, 0.58)*	0.43 (0.35, 0.52)*
P for trend	<0.001	<0.001	<0.001

Model 1: Without adjustment.
Model 2: Adjusted for age, gender, race, education level and family poverty income ratio.
Model 3: Further adjusted for diabetes, hypertension and energy intake.
Data are expressed as OR (95% CI). OBS, oxidative balance scores.
*$p < 0.01$.[a]BMI (in kg/m^2) ≥ 30 was defined as obesity according to clinical guidelines.
[b]An FM% ≥ 25% for men or an FM% ≥ 35% for women was defined as obesity.

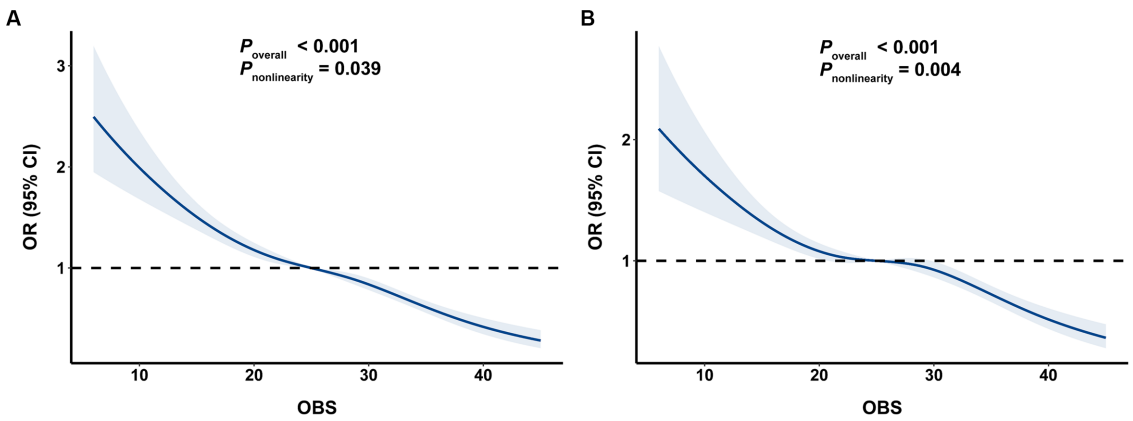

FIGURE 2
The associations of OBS with risk obesity. **(A)** OBS and BMI-defined obesity, **(B)** OBS and FM%-defined obesity. OBS, oxidative balance score; BMI, body mass index; FM%, fat mass percentage.

importance of targeting oxidative balance in therapeutic interventions. Appropriate dietary and lifestyle modifications may hold promise in mitigating obesity-associated health risks and improving metabolic health outcomes in young and middle-aged adults.

Dietary status may directly impact our immune system and play a part in systemic chronic inflammation (46). Western diet, characterized by high consumption of red meat, refined grains and sugar-sweetened beverages can increase oxidative stress biomarkers (47). Within the health dietary models, the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet stand out. The Mediterranean diet (48), which emphasizes the intake of fruit and dairy, fish, poultry and wine, contributes to decrease in circulating oxidative stress biomarkers (49). The DASH diet, characterized by high consumption of fruits and vegetables, has the potential to reduce oxidative stress and inflammation levels (50). To some extent, combining various dietary and lifestyle factors to compose a comprehensive indicator could accurately indicate the physical oxidative stress level. OBS, in recent years, has attracted much attention due to its impact on health outcomes. OBS was found to be closely related to obesity (32), hypertension (51), chronic cardiovascular disease (45) and cancer (16). According to our results, OBS was negatively associated with the risk of obesity and segmental

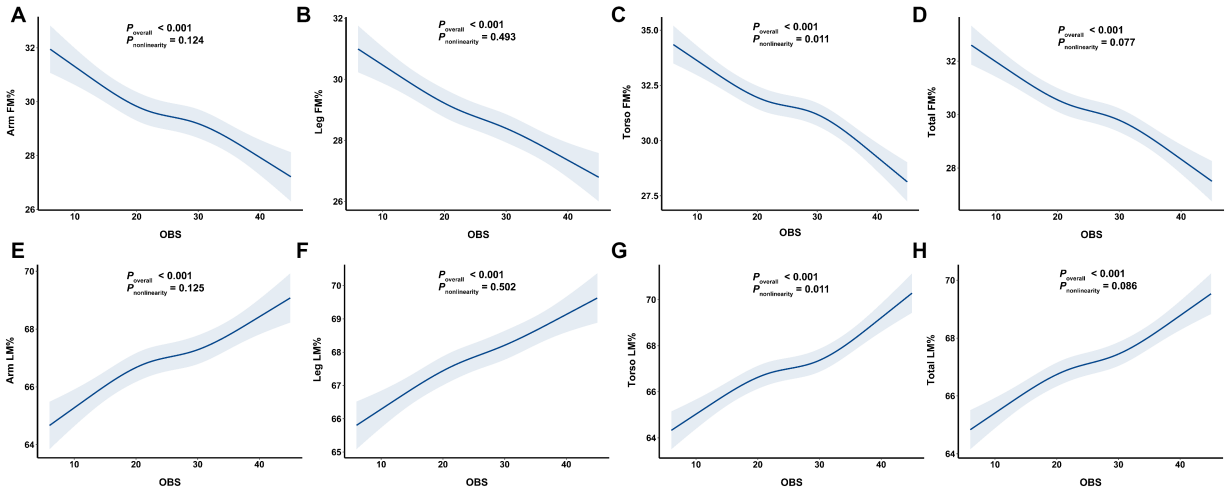

FIGURE 3
The associations of OBS with segmental body composition parameters. **(A)** OBS and arm FM%, **(B)** OBS and leg FM%, **(C)** OBS and torso FM%, **(D)** OBS and total FM%, **(E)** OBS and arm LM%, **(F)** OBS and leg LM%, **(G)** OBS and torso LM%, **(H)** OBS and total LM%. OBS, oxidative balance score; FM%, fat mass percentage; LM%, lean mass percentage.

TABLE 3 The association between the OBS with segmental body composition parameters.

	OBS	Per 1-SD increase	Q1 (2–18)	Q2 (19–24)	Q3 (25–30)	Q4 (31–47)	*p* for trend
		β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	
Arm FM%	Model 1	−0.60 (−0.88, −0.32)*	Ref	−1.81 (−2.75, −0.88)*	−2.05 (−3.03, −1.07)*	−1.74 (−2.56, −0.92)*	<0.001
	Model 2	−0.91 (−1.10, −0.72)*	Ref	−1.11 (−1.69, −0.53)*	−1.56 (−2.15, −0.97)*	−2.38 (−2.94, −1.81)*	<0.001
	Model 3	−1.07 (−1.27, −0.86)*	Ref	−1.18 (−1.74, −0.61)*	−1.75 (−2.35, −1.16)*	−2.76 (−3.35, −2.17)*	<0.001
Leg FM%	Model 1	−0.56 (−0.82, −0.31)*	Ref	−1.45 (−2.25, −0.65)*	−1.94 (−2.78, −1.10)*	−1.60 (−2.32, −0.88)*	<0.001
	Model 2	−0.72 (−0.90, −0.54)*	Ref	−0.69 (−1.22, −0.17)*	−1.32 (−1.85, −0.78)*	−1.85 (−2.37, −1.33)*	<0.001
	Model 3	−0.86 (−1.04, −0.68)*	Ref	−0.77 (−1.29, −0.24)*	−1.47 (−2.01, −0.94)*	−2.19 (−2.72, −1.65)*	<0.001
Torso FM%	Model 1	−0.85 (−1.07, −0.64)*	Ref	−1.38 (−2.19, −0.57)*	−1.67 (−2.49, −0.84)*	−2.25 (−2.91, −1.59)*	<0.001
	Model 2	−1.17 (−1.36, −0.97)*	Ref	−1.27 (−1.87, −0.66)*	−1.71 (−2.35, −1.06)*	−3.01 (−3.57, −2.45)*	<0.001
	Model 3	−1.32 (−1.52, −1.12)*	Ref	−1.34 (−1.94, −0.74)*	−1.89 (−2.53, −1.26)*	−3.37 (−3.94, −2.80)*	<0.001
Total FM%	Model 1	−0.69 (−0.90, −0.48)*	Ref	−1.39 (−2.13, −0.65)*	−1.73 (−2.51, −0.96)*	−1.88 (−2.50, −1.25)*	<0.001
	Model 2	−0.92 (−1.09, −0.76)*	Ref	−0.99 (−1.49, −0.48)*	−1.47 (−2.01, −0.93)*	−2.39 (−2.87, −1.91)*	<0.001
	Model 3	−1.06 (−1.23, −0.89)*	Ref	−1.06 (−1.56, −0.56)*	−1.64 (−2.17, −1.10)*	−2.72 (−3.22, −2.23)*	<0.001
Arm LM%	Model 1	0.54 (0.28, 0.81)*	Ref	1.73 (0.84, 2.62)*	1.96 (1.03, 2.90)*	1.58 (0.80, 2.36)*	<0.001
	Model 2	0.84 (0.66, 1.01)*	Ref	1.02 (0.48, 1.56)*	1.46 (0.91, 2.01)*	2.19 (1.66, 2.71)*	<0.001
	Model 3	0.99 (0.80, 1.18)*	Ref	1.09 (0.56, 1.62)*	1.65 (1.09, 2.20)*	2.56 (2.01, 3.11)*	<0.001
Leg LM%	Model 1	0.51 (0.26, 0.75)*	Ref	1.35 (0.60, 2.10)*	1.83 (1.03, 2.63)*	1.44 (0.76, 2.12)*	<0.001
	Model 2	0.66 (0.49, 0.82)*	Ref	0.62 (0.13, 1.11)*	1.23 (0.73, 1.73)*	1.68 (1.19, 2.17)*	<0.001
	Model 3	0.79 (0.62, 0.96)*	Ref	0.69 (0.20, 1.18)*	1.38 (0.88, 1.88)*	2.01 (1.51, 2.51)*	<0.001
Torso LM%	Model 1	0.81 (0.60, 1.02)*	Ref	1.34 (0.56, 2.12)*	1.62 (0.81, 2.42)*	2.15 (1.52, 2.79)*	<0.001
	Model 2	1.11 (0.93, 1.30)*	Ref	1.21 (0.62, 1.80)*	1.64 (1.01, 2.26)*	2.88 (2.34, 3.42)*	<0.001
	Model 3	1.26 (1.07, 1.45)*	Ref	1.28 (0.70, 1.87)*	1.82 (1.20, 2.43)*	3.23 (2.68, 3.78)*	<0.001
Total LM%	Model 1	0.62 (0.43, 0.82)*	Ref	1.31 (0.62, 2.01)*	1.64 (0.91, 2.38)*	1.71 (1.13, 2.30)*	<0.001
	Model 2	0.85 (0.70, 1.00)*	Ref	0.90 (0.43, 1.37)*	1.37 (0.87, 1.87)*	2.20 (1.75, 2.64)*	<0.001
	Model 3	0.98 (0.83, 1.14)*	Ref	0.97 (0.50, 1.43)*	1.53 (1.03, 2.03)*	2.52 (2.06, 2.98)*	<0.001

Model 1: Without adjustment.
Model 2: Adjusted for age, gender, race, education level and family income.
Model 3: Further adjusted for diabetes, hypertension and energy intake.
FM%, fat mass percentage; LM%, lean mass percentage; OBS, oxidative balance scores.
Data were expressed as β (95%CI).
*$p < 0.05$.

FM%. By elucidating the association between OBS and specific parameters of body composition, such as FM% and LM%, our findings offer mechanistic insights into the pathophysiology of obesity.

Although the association between OBS and obesity was not modified by age, PIR or energy intake (all p interaction >0.05). We observed significant sex, race and education level interactions, whereby the association of OBS with obesity were stronger in females, non-Hispanic White and Black individuals and people with more than high school education level. One reason for this gender discrepancy was that women have a greater antioxidant capacity than men, possibly owing to higher antioxidant enzyme activity (52) and higher free radicals scavenging ability in the presence of estrogen (53). Although the mechanism of this interaction remains to be elucidated, these findings may suggest that a predominance of antioxidant diet and lifestyle factors may be more protective against the gradual degeneration of lean mass in women, non-Hispanic White and Black and people with higher education levels.

Additionally, this study revealed that the associations of OBS with FM% and LM% of the trunk remained consistent in different age subgroups, while the associations of OBS with limb FM% and LM% were stronger in the younger group aged <40 years. Although the elderly individuals were prone to having an antioxidant dietary and life style, which had a higher OBS level (26.01 ± 0.24) than the middle-aged group (25.07 ± 0.18, $p < 0.001$), they still had a greater rate of obesity than did the younger individuals (76.44% vs. 60.09%, $p < 0.001$). One plausible mechanism explaining this disparity was that a higher OBS could not prevent the gradual degeneration of lean mass and the accumulation of fat mass with aging in elderly individuals (3, 4).

There are several strengths of this study. First, the present study with a large sample-size is based on data from the nationwide. Second, NHANES used a complex and multistage probability sampling design, and the present study adopted appropriate weighted analyses, so the findings is widely usable in the US population. Third, confounding factors, including sociodemographic characteristics and dietary intake are considered in weighted multiple regression analysis. Moreover, subgroup analyses confirm the results are basically robust. However, the limitations of this study cannot be neglected. First, because of the cross-sectional design and simultaneous measurement of exposure and results, it may be difficult to infer causality between OBS and segmental body composition. Therefore, prospective studies are required to further clarify the relationship. Second, the DXA data for participants aged ≥60 years old are not available, which limits the generalization to a wider age group (aged ≥60). Third, to date, no OBS biomarker is found to verify the effectiveness of OBS for assessing oxidative balance. Finally, although multiple potential confounding variables are adjusted in our analyses, residual confounding, such as medication use cannot be eliminated.

5 Conclusion

In conclusion, a higher OBS was negatively associated with the risk of FM%-defined obesity and positively associated with segmental lean mass. Our results underscore the significance of adhering to an anti-oxidative diet and lifestyle interventions for lowering segmental obesity in U.S. adults. However, further prospective studies are needed to verify our findings.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZZ: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. HB: Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. ZL: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. MF: Writing – original draft. GL: Validation, Writing – review & editing. LC: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1373709/full#supplementary-material

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Micronutrient status 2 years after bariatric surgery: a prospective nutritional assessment

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Background: Among commonly performed bariatric surgeries, biliopancreatic diversion with duodenal switch (BPD-DS) provides greater weight loss than Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG), with sustained metabolic improvements. However, the risk of long-term nutritional deficiencies due to the hypoabsorptive component of BPD-DS hinders its widespread use.

Objective: The aim of the study was to examine nutritional status over 2 years after BPD-DS, RYGB or SG.

Methods: Patients were recruited in the REMISSION trial (NCT02390973), a single-center, prospective study. Out of 215 patients, 73, 48 and 94, respectively, underwent BPD-DS, RYGB or SG. Weight loss, micronutrient serum levels (including iron, calcium, parathormone, vitamins A, B12 and D), and nutritional supplementation were assessed over 2 years. Patients were supplemented according to the type of surgery and individual micronutrient level evolution.

Results: At baseline, BPD-DS patients were younger than SG patients ($p = 0.0051$) and RYGB patients had lower body mass index ($p < 0.001$). Groups had similar micronutrient levels before surgery, with vitamin D insufficiency as the most prevalent nutritional problem (SG: 38.3%, RYGB: 39.9%, BPD-DS: 54.8%, $p = 0.08$). BPD-DS patients showed lower levels of iron, calcium and vitamin A than SG patients at 24 months. Groups had similar levels of vitamin D at 24 months. Prevalence of vitamin D, calcium, iron, vitamin A and vitamin B12 deficiency was similar among groups at 24 months. Rates of vitamin D insufficiency and iron deficiency were lower at 24 months than at baseline. Micronutrient intake was consistent with recommendations in groups post-surgery, but most BPD-DS patients took vitamin A and vitamin D supplement doses above initial recommendations.

Conclusion: With appropriate medical and nutritional management, all surgeries led to similar rates of vitamin D, calcium, iron, vitamin A and vitamin B12 deficiencies at 24 months. However, initial vitamin A and vitamin D supplementation recommendations for BPD-DS patients should be revised upwards.

KEYWORDS

sleeve gastrectomy, roux-en-Y gastric bypass, biliopancreatic diversion with duodenal switch, micronutrient deficiency, vitamin and mineral supplementation, severe obesity, bariatric surgery

1 Introduction

Obesity is now recognized as a complex chronic disease characterized by an abnormal or excessive adiposity that impairs health (1). In severe obesity, lifestyle interventions are often ineffective to achieve sustainable weight loss and metabolic improvements that persist in the long term (2). Bariatric surgery is now recognized as one of the main pillars of obesity treatment (1). Indeed, it has been shown to be more effective than medication or nutritional counseling for glycemic control improvement of people living with severe obesity and type 2 diabetes (T2D) (3).

Among commonly performed surgical procedures to induce weight loss, sleeve gastrectomy (SG) is currently the most popular approach worldwide (4). It is a restrictive bariatric operation consisting of the resection of two-thirds of the greater curvature of the stomach while preserving the pylorus (5). SG leads to weight loss and comorbidities remission, but weight regain and T2D relapse is observed in some patients (6). Roux-en-Y gastric bypass (RYGB) is the second most frequently performed bariatric surgery worldwide (4). It is a mixed procedure, combining an important restrictive component and a small hypoabsorptive component with a 300 cm common limb (7). RYGB has been reported to have rates of T2D remission and complication similar to SG (8). Another type of mixed surgical approach offered to patients is the biliopancreatic diversion with duodenal switch (BPD-DS). This surgery includes a SG and a significant hypoabsorptive component, with a common limb of only 100 cm (5). BPD-DS leads to important and sustained weight loss with 80–90% T2D remission in the long term (6, 9). However, BPD-DS represented only 1.3% of the weight loss surgeries performed in 2021, mostly due to the perceived risk of long-term complications and technical complexity associated with the procedure (4, 10).

Many types of complications can occur after bariatric surgery, nutritional deficiency being one of them (11, 12). The nutritional risk associated with bariatric surgery differs according to the type of procedure and may influence the selection of a specific surgery for a given patient (10, 12). Restrictive procedures like SG reduce food intake and have a small impact on nutrient absorption resulting from gastric fundus resection. SG is associated with iron, folate, vitamin B12, vitamin D and calcium deficiency (12–15). Mixed procedures like RYGB and BPD-DS, in addition to reducing food intake, decrease the absorption of nutrients by bypassing their main absorption sites in the intestine. Therefore, high rates of liposoluble vitamins, minerals and trace element deficiencies have been observed after RYGB and BPD-DS (12–15). Because of its short common limb, BPD-DS is reported in the literature with the highest rates of micronutrient deficiencies when compared to SG or RYGB (14). Considering the nutritional risk associated with bariatric surgery, lifelong nutritional monitoring and supplementation is recommended (12, 14, 15), and low adherence to supplementation recommendations represents an additional risk component after surgery (12).

Abbreviations: ASPEN, The American Society for Parenteral and Enteral Nutrition; BPD-DS, biliopancreatic diversion with duodenal switch; IUCPQ-ULaval, *Institut universitaire de cardiologie et de pneumologie de Québec – Univserité Laval*; PTH, parathormone; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; T2D, type 2 diabetes.

Nutritional management of bariatric patients is complex because nutritional deficiencies have been reported even before surgery (13). The presence of nutritional problems in obesity seems paradoxical in a context of high caloric intake but can be explained by multifactorial causes. Consumption of energy-dense food with a low-nutrient density may contribute to micronutrient deficiencies (13, 16). Also, low-grade chronic inflammation, present in the obesity state, may affect micronutrient absorption such as iron (13, 16). Furthermore, increased adiposity may impact micronutrient status, especially for nutrients that are soluble in adipose tissue like vitamin D (17). Vitamin D appears to be the most frequent micronutrient deficiency observed in patients prior to bariatric surgery, but iron and vitamin A deficiencies are also frequent in that population (16, 18, 19). Addressing these deficiencies before weight loss surgery is essential to avoid adverse nutritional outcomes during follow-up (18, 19).

Although the nutritional risk of SG and RYGB is well described in the literature, most of the available data are from retrospective studies. Only a few studies have examined the risk associated with BPD-DS on micronutrient status. Furthermore, the literature on micronutrient status after bariatric surgery is difficult to assess because reference values used to determine deficiency differ considerably among studies and information on vitamin and mineral intake is often variable or unreported. Finally, prospective studies comparing micronutrient status and deficiencies following SG, RYGB and BPD-DS are scarce. To gain a better understanding of the nutritional risk associated with commonly performed surgeries, the objective of the study was to examine micronutrient levels, micronutrient deficiencies and adherence to initial vitamin and mineral supplementation recommendations in a prospective design over 2 years after SG, RYGB or BPD-DS.

2 Methods

2.1 Study participants

To compare the effect of SG, RYGB and BPD-DS on nutritional status, 215 participants were examined in a 5-year, single-center, prospective design. This study is part of the REMISSION trial (NCT02390973) evaluating T2D remission and metabolic recovery following SG, RYGB or BPD-DS. Although BPD-DS is less frequently performed compared to RYGB or SG, it was included because it has been shown as the most effective procedure for weight loss and T2D resolution. Of the 215 participants, 193 have completed the 2-year follow-up while 7 participants dropped out and 15 had not yet completed their 24 months follow-up at the time this study was conducted. The follow-up of the cohort is still ongoing and continues up to 5 years. Inclusion criteria were the following: patients with a body mass index (BMI) $\geq$35 kg/m^2 living with T2D who required surgery and met the NIH Guidelines for bariatric surgery (20); patients who had 1 year of follow-up completed in January 2022. Exclusion criteria were general contra-indications for bariatric surgery, a BMI <35 kg/m^2, age under 18 or over 60 years, abnormal bowel habits including irritable bowel syndrome, pregnancy, cirrhosis or albumin deficiency and previous bariatric surgery. The Research Ethics Committee of the *Institut universitaire de cardiologie et de pneumologie de Québec – Université Laval* (IUCPQ-ULaval) approved

this study (#2015–2,466, 21,160). All participants provided informed consent to participate in the study.

2.2 Surgical procedures

All surgeries were performed laparoscopically. A 250 cm^3 vertical SG was created with a 34–44 French Bougie starting 7–8 cm from the pylorus (21). The RYGB was performed by creating a 30–50 cm^3 proximal gastric pouch connected to the proximal small intestine by bypassing the first 100 cm. A 100-cm alimentary limb was then anastomosed to the gastric pouch, with a 300-cm common channel (22). For the BPD-DS, a 250 cm^3 SG was created and the duodenum was transected about 4 cm distal from the pylorus and anastomosed to a 250-cm alimentary limb, with a 100-cm common channel (23).

2.3 Study design

Participants received preoperative and postoperative care by a multidisciplinary team composed of bariatric surgeons, bariatric nurses, dieticians, social workers and other health professionals if needed. They were followed longitudinally at 4, 8, 12 and 24 months after surgery to assess anthropometric measurements, medical evaluation and evolution of comorbidities. Nutritional status was evaluated according to micronutrient serum levels including vitamin A, vitamin B12 and vitamin D (25-OH-D), folate, calcium, parathormone (PTH), sodium, potassium, chloride, magnesium, phosphorus, iron, ferritin, transferrin and hemoglobin. Albumin and prealbumin serum levels were also assessed. Assays were performed at the laboratory of the IUCPQ-ULaval. Nutritional deficiencies were determined according to blood level reference values used for clinical practice at the IUCPQ-ULaval (Supplementary Table S1). Suboptimal vitamin D status was separated in two categories: insufficiency (levels of 25-OH-D between 30–49 nmol/L) and deficiency (levels of 25-OH-D below 30 nmol/L).

Participants received vitamin D and multivitamin supplementation 3 to 6 months before surgery. Other micronutrients were supplemented if deficiencies were present at baseline to address them before surgery. Daily supplementation was then started 1 month after surgery according to the type of procedure received. The daily recommendations for SG patients were vitamin D 1000 IU and 1 multivitamin tablet (Pfizer Centrum Forte; contains, among other nutrients, vitamin D 600 IU, vitamin A 1000 IU, vitamin B12 20 µg, folic acid 400 µg, calcium 200 mg, iron 10 mg). The daily recommendations for RYGB patients were 2 multivitamin tablets, vitamin D 2000 IU, calcium carbonate 1,000 mg, ferrous sulfate 300 mg and vitamin B12 1,200 µg. The daily recommendations for BPD-DS patients were 2 multivitamin tablets, vitamin D 30000 IU, calcium carbonate 1,000 mg, ferrous sulfate 300 mg and vitamin A 30,000 IU. Supplements were adjusted during follow-up according to individual blood levels. Adherence to vitamin and mineral initial supplementation recommendations was evaluated for all patients according to supplement intake assessed in the pharmacy prescription and double-checked with patient self-reported intake at each follow-up visit. Vitamin and mineral intakes were characterized as being below, on or above target when supplement intake was inferior, equal or greater than surgery-specific initial recommendations, respectively.

2.4 Statistical analyses

Numerical data are presented as mean ± standard deviation when normally distributed and median ± interquartile range otherwise. Results of categorical variables are presented as percentages. Repeated-measures ANOVA, adjusted for age and baseline BMI, was performed to examine changes in nutrient levels 0 to 24 months after SG, RYGB or BPD-DS. Differences among surgical procedures were assessed with Tukey-HSD multiple comparisons test at each time point. To compare surgical groups on baseline categorical variables, prevalence of nutritional deficiencies and adherence to vitamin and mineral initial supplementation recommendations, Chi-squared test or Fisher's exact test were performed according to the number of observations. Changes in adherence to initial supplementation recommendations between 12 and 24 months were assessed with generalized linear mixed-effects models for binomial variables and with generalized estimating equations for multinomial variables. The study was sufficiently powered to detect a difference in the main nutritional variables or at least 25% between surgical groups, with 80% power and $\alpha < 0.05$. A p-value below 0.05 was considered statistically significant. Statistical analyses were performed with RStudio version 2022.12.0.353 (Posit Software, PBC, Boston, MA).

3 Results

Of the 215 participants recruited, 94 patients underwent SG, 48 underwent RYGB and 73 underwent BPD-DS (Figure 1). BPD-DS patients were younger than SG patients ($p < 0.05$) (Table 1). The BPD-DS group had the highest preoperative weight and BMI compared to the SG and RYGB groups ($p < 0.05$). Female and male ratios were comparable in each group. All participants had T2D and the three groups had high rates of hypertension and dyslipidemia prior to surgery.

All three groups had similar levels of vitamin D, calcium, phosphorus and PTH at baseline (Figure 2). Vitamin D levels of the BPD-DS group were higher than the SG group at 4, 8 and 12 months ($p < 0.01$) and were higher than the RYGB group only at 12 months ($p < 0.01$) (Figure 2A). However, at 24 months, vitamin D levels were similar among groups and were higher compared to baseline ($p < 0.05$). For calcium levels, BPD-DS patients had lower serum levels than the SG group from 4 to 24 months after surgery ($p < 0.001$ for all time points) (Figure 2B). BPD-DS and RYGB groups were only different at 4 and 12 months ($p < 0.001$ and $p < 0.05$ respectively), with the BPD-DS group having the lowest calcium levels. Globally, calcium levels decreased significantly during the entire follow-up for all groups. Phosphorus levels increased significantly during follow-up for all groups but started to decrease between 12 and 24 months for SG and RYGB ($p < 0.001$ and $p < 0.05$ respectively) (Figure 2C). At 12 and 24 months, the SG group had the lowest phosphorus levels of all surgical groups ($p < 0.05$). PTH levels of the RYGB and BPD-DS groups significantly increased in the postoperative period ($p < 0.01$) and there was no difference among groups for PTH levels during follow-up (Figure 2D).

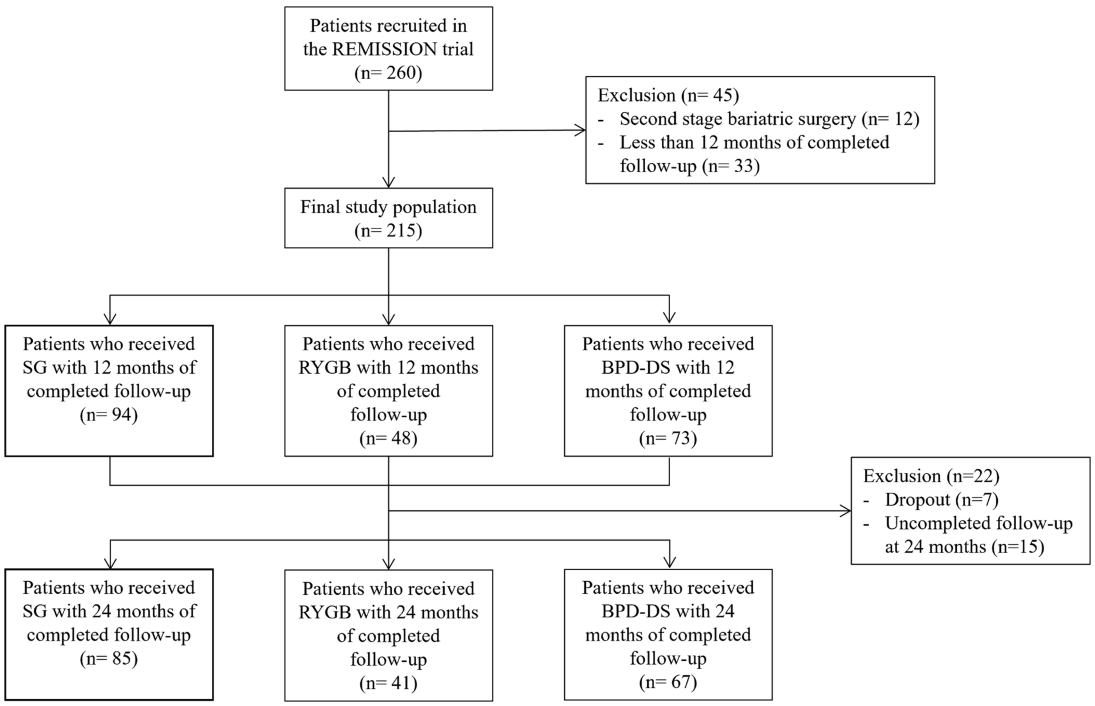

FIGURE 1
Flowchart of the study participants. Sleeve Gastrectomy (SG), Roux-en-Y Gastric Bypass (RYGB), Biliopancreatic Diversion with Duodenal Switch (BPD-DS).

TABLE 1 Preoperative characteristics of the study participants.

Variables	SG	RYGB	BPD-DS	*p*-value
n	94	48	73	
Sex (F:M)	50:44	29:19	37:36	0.5647
Age (years)	52.3 ± 10.9	51.7 ± 12.3	46.8 ± 12.0[a]	0.005625
Weight (kg)	123.1 ± 21.6	111.0±14.8[a]	135.6 ± 18.2[a,b]	< 0.001
BMI (kg/m^2)	44.3 ± 5.4	40.1±3.1[a]	47,0 ± 4.9[a,b]	< 0.001
Diabetes (%)	94 (100)	48 (100)	73 (100)	1
Hypertension (%)	74 (78.7)	34 (70.8)	59 (81.9)	0.3464
Dyslipidemia (%)	81 (86.2)	40 (83.3)	59 (80.8)	0.6399

Data analyzed with ANOVA or chi-square tests as appropriate. Results are presented as mean ± standard deviation when normally distributed and median ± interquartile range otherwise. a: different from SG ($p < 0.05$), b: different from RYGB ($p < 0.05$) after Tukey-HSD multiple comparisons. BMI, Body Mass Index.

The three surgical groups had similar levels of iron, hemoglobin, ferritin, transferrin, folate and vitamin B12 at baseline (Figure 3). Iron levels increased significantly after surgery in all groups, with BPD-DS having lower levels compared to SG from 4 to 24 months ($p < 0.05$ at all time points) (Figure 3A). Hemoglobin levels remained stable for the SG and RYGB groups during follow-up (Figure 3B). For BPD-DS, hemoglobin levels decreased in post-op so that, at 12 and 24 months, levels were significantly lower than the SG and RYGB groups. Ferritin levels of the SG group decreased during the postoperative period ($p < 0.001$) (Figure 3C). For BPD-DS participants, ferritin levels remained stable during follow-up and were significantly higher than SG and RYGB from 8 to 24 months. Transferrin levels of BPD-DS participants decreased over time to significantly lower values than the two other surgical groups from 4 to 24 months (Figure 3D). The same pattern was observed for folate levels (Figure 3E). For all groups, vitamin B12 levels increased over time (Figure 3F). However, vitamin B12 levels of the SG group remained significantly lower compared to RYGB or BPD-DS groups throughout the postoperative period.

Electrolytes, magnesium, vitamin A, albumin and prealbumin levels were also evaluated and are presented in Table 2. Sodium levels of the SG group were the highest at baseline ($p < 0.03$), though differences were minor. Sodium evolution of the three groups remained similar after surgery. For potassium, BPD-DS had higher levels compared to RYGB at baseline ($p = 0.04$). Then, at 4 and 8 months, the BPD-DS group had significantly lower levels compared to the other surgical groups but at 12 months the BPD-DS group was only different from the SG group ($p < 0.01$). Potassium levels became similar for all groups at 24 months. The BPD-DS group had higher chloride levels than the SG group from 4 to 12 months and higher levels than the RYGB group only at 12 months. There was no difference in magnesium levels among surgical groups during the entire follow-up. Vitamin A levels were similar for all groups at baseline. After surgery, vitamin A levels of the BPD-DS group decreased to become lower than the other surgical groups from 4 to 12 months and lower than RYGB only at 24 months. Albumin levels were similar among groups at baseline, but BPD-DS participants reached lower levels than SG participants 4 months after surgery. At 8 and 12 months, BPD-DS participants had the lowest levels of all three groups, but no difference was observed among groups at 24 months. Prealbumin levels of BPD-DS participants were the lowest of all three groups from baseline to 8 months after surgery. Then, from 12 months, levels of prealbumin in the BPD-DS group increased so that they were only different from SG at 12 months and similar to all groups at 24 months.

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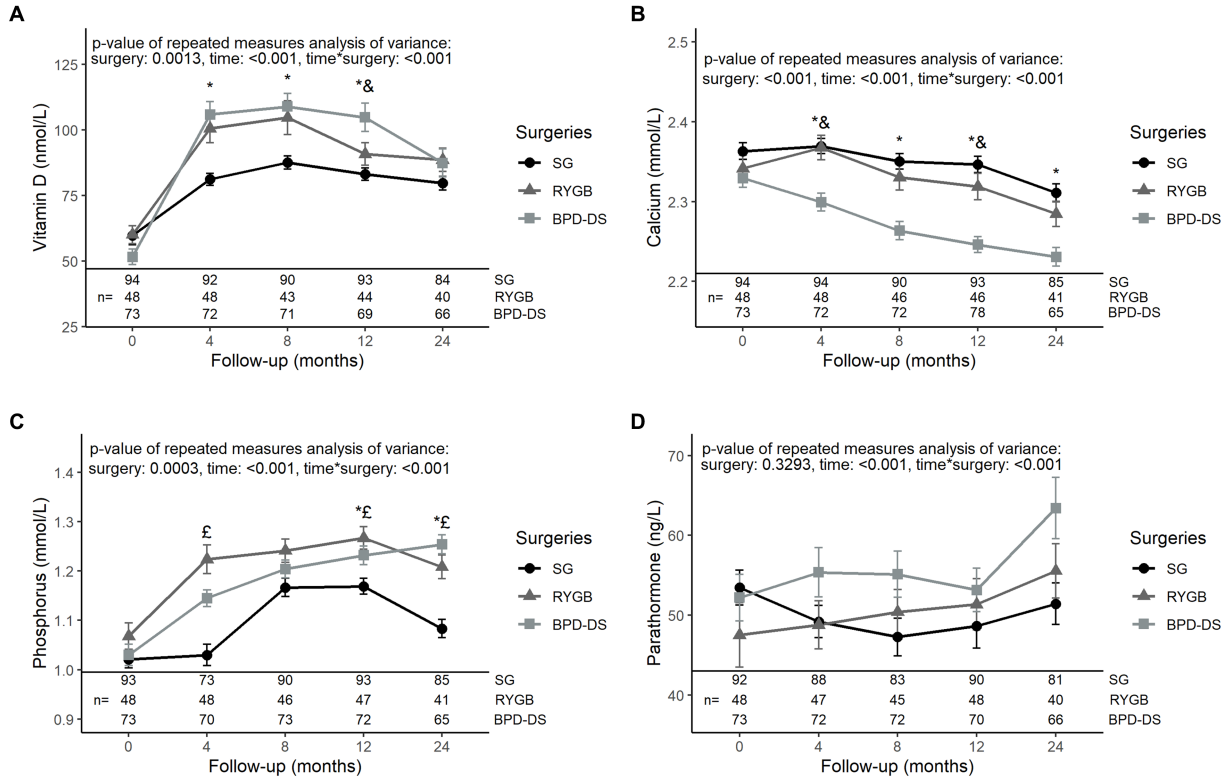

FIGURE 2
Serum levels of phosphocalcium metabolism markers in patients receiving SG, RYGB or BPD-DS from 0 to 24 months. **(A)** Vitamin D, **(B)** calcium, **(C)** phosphorus and **(D)** parathormone 0 to 24 months post-operation for SG, RYGB and BPD-DS groups. Repeated measures analysis of variance are adjusted for age and baseline BMI. Statistical tests were performed on log-transformed values for **(A,B,D)**. *: difference between SG and BPD-DS ($p < 0.05$), &: difference between RYGB and BPD-DS ($p < 0.05$), £: difference between SG and RYGB ($p < 0.05$) after Tukey-HSD multiple comparisons. Data are presented as means and standard error of the mean (SEM). SG, sleeve gastrectomy, RYGB, Roux-en-Y gastric bypass, BPD-DS, biliopancreatic diversion with duodenal switch.

To evaluate the nutritional risk of SG, RYGB and BPD-DS, nutritional deficiency rates of iron, calcium, PTH, vitamin D, vitamin A and vitamin B12 were assessed. Prevalence of nutritional deficiencies and high PTH are presented in Table 3. Before surgery, vitamin D insufficiency was the most prevalent nutritional problem in all three groups. Iron and vitamin D deficiency were also prevalent in all groups at baseline. Iron deficiency rates remained high 4 months after surgery, with a tendency for more deficiencies in the BPD-DS group ($p = 0.0537$). Then, they decreased during the rest of the follow-up to a rate of 5–6% for all groups at 24 months. The prevalence of calcium deficiency was low at baseline and during the entire follow-up. More BPD-DS patients had calcium deficiency at 8 months, but at 24 months only a tendency for more deficiency in the BPD-DS group was observed ($p = 0.0615$). Rates of high PTH were low in all groups at baseline and during the entire follow-up. No patients had high PTH at 24 months. The prevalence of vitamin D insufficiency and deficiency decreased between baseline and 24 months without statistical differences among groups. Rates of vitamin D insufficiency remained low at 12 and 24 months and vitamin D deficiency was nearly absent at the end of the follow-up in all groups. Vitamin A and vitamin B12 deficiency was almost absent in all groups during the entire follow-up.

Adherence to vitamin and mineral initial supplementation recommendations at baseline, 12 and 24 months after surgery are presented for all three groups in Table 4. At baseline, supplementation was not yet initiated for most patients. Overall, results show high adherence to initial supplementation recommendations during the first 24 months after surgery, with most patients taking adequate supplementation to prevent deficiencies. Most patients in all groups were mostly on target for vitamin B12 (>80%), iron (>50%), calcium (>60%), and vitamin A only for SG and RYGB (>80%). However, at 24 months, more than 50% of BPD-DS patients took higher doses of vitamin A and vitamin D compared to recommendations, while most SG and RYGB patients took less vitamin D than targeted doses. As for multivitamin, SG participants were mostly on target (>70%), and the RYGB and BPD-DS groups were mostly below target (>60%). BPD-DS patients were statistically given more vitamin D than RYGB and SG patients at 12 and 24 months. More RYGB patients were below the target dose for vitamin D compared to the two other surgeries at 24 months. At 12 and 24 months, the SG group had statistically more patients on target for multivitamin supplementation compared to BPD-DS and RYGB, which were mostly in the below-target category for this supplement. At 24 months, more RYGB patients were in the below-target category for iron and calcium compared to BPD-DS patients who were in higher proportions in the on-target category for these two supplements. More BPD-DS patients took calcium doses above target compared to RYGB at 24 months. Rates of adherence to initial recommendations remained stable during follow-up for all supplements except for calcium. BPD-DS and RYGB patients were

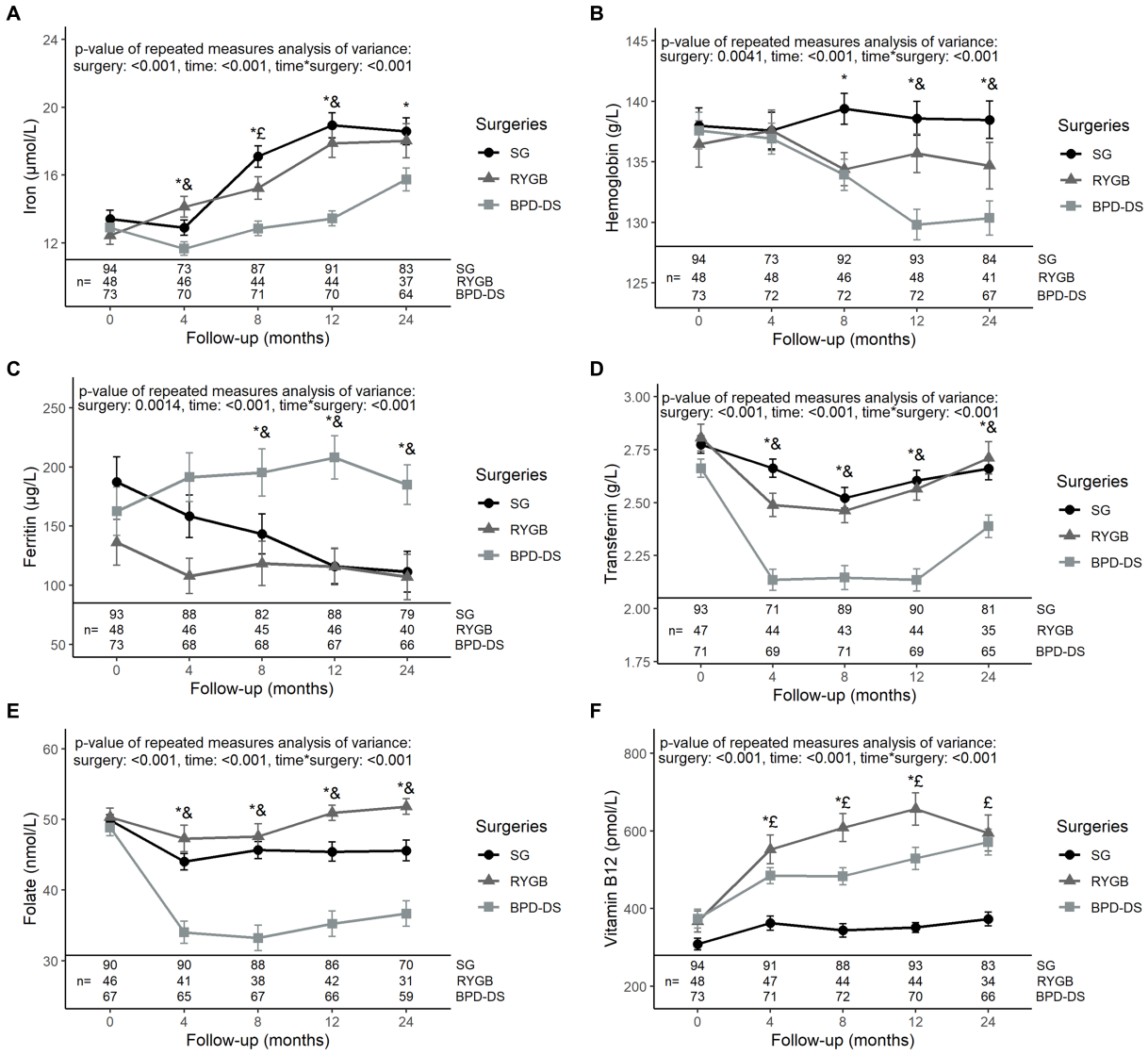

FIGURE 3
Serum levels of iron status markers in patients receiving SG, RYGB or BPD-DS from 0 to 24 months. **(A)** Iron, **(B)** hemoglobin, **(C)** ferritin, **(D)** transferrin, **(E)** folate and **(F)** vitamin B12 0 to 24 months post-operation for SG, RYGB and BPD-DS groups. Repeated measures analysis of variance are adjusted for age and baseline BMI. Statistical tests were performed on log-transformed values for **(F)**. *: difference between SG and BPD-DS ($p < 0.05$), &: difference between RYGB and BPD-DS ($p < 0.05$), £: difference between SG and RYGB ($p < 0.05$) after Tukey-HSD multiple comparisons. Data are presented as means and standard error of the mean (SEM). SG, sleeve gastrectomy, RYGB, Roux-en-Y gastric bypass, BPD-DS, biliopancreatic diversion with duodenal switch.

mostly on target for calcium at 12 months, with a significant proportion who went above target at 24 months for BPD-DS, while RYGB patients went mostly below target.

4 Discussion

The aim of the study was to examine micronutrient levels, micronutrient deficiencies and adherence to vitamin and mineral initial supplementation recommendations to characterise nutritional status over 2 years after SG, RYGB or BPD-DS. Current literature on bariatric procedures and micronutrient deficiencies mainly examined SG and RYGB in retrospective studies. To our knowledge, this is the first study to compare micronutrient status and deficiencies of patients undergoing SG, RYGB or BPD-DS in a prospective design.

4.1 Nutritional deficiencies

For all nutrients, rates of deficiency were low and similar among groups. These results differ from literature where BPD-DS is reported to cause higher deficiency rates compared to other procedures, mostly for liposoluble vitamins (24, 25). Yet, some studies reported similar or lower rates of vitamin D, vitamin B12 or iron deficiency for SG compared to RYGB (8, 26, 27). Vitamin D insufficiency was the most prevalent nutritional problem after surgery and only one patient in the sample had vitamin D deficiency at 24 months. Previous studies

TABLE 2 Evolution of electrolytes, magnesium, vitamin A, albumin and prealbumin serum levels from 0 to 24 months.

Nutrient	Group	Baseline	4 months	8 months	12 months	24 months	*p*-value of repeated measures analysis of variance		
							Surgery	Time	Time*surgery
Sodium (mmol/L)	SG	140 ± 2	141 ± 2	141 ± 1	141 ± 2	141 ± 2			
	RYGB	139 ± 2[a]	141 ± 2	141 ± 2	141 ± 2	140 ± 2	<0.001	0.1689	<0.001
	BPD-DS	139 ± 2[a]	141 ± 2	141 ± 2	141 ± 1	141 ± 2			
Potassium (mmol/L)	SG	3.9 ± 0.3	4.0± 0.3	4.1± 0.3	4.1± 0.3	4.0± 0.3			
	RYGB	3.9 ± 0.3	4.0± 0.3	4.0± 0.3	4.0± 0.3	4.0± 0.4	<0.001	0.004	<0.001
	BPD-DS	4.0 ± 0.3[b]	3.8±0.4[a,b]	3.8±0.5[a,b]	3.9±0.3[a]	4.0± 0.3			
Chloride (mmol/L)	SG	102 ± 3	104±3	104±3	105±3	105±3			
	RYGB	103 ± 3	105±3	105±3	105±3	105±3	<0.001	0.0014	<0.001
	BPD-DS	102 ± 3	106 ± 3[a]	106±3[a]	106±3[a,b]	106±3			
Magnesium (mmol/L)	SG	0.78 ± 0.09	0.80 ± 0.07	0.81±0.08	0.82±0.09	0.83±0.07			
	RYGB	0.79 ± 0.09	0.81 ± 0.06	0.82±0.07	0.83±0.06	0.83±0.07	<0.001	0.2739	<0.001
	BPD-DS	0.78 ± 0.09	0.79 ± 0.09	0.80±0.08	0.80±0.08	0.81±0.08			
Vitamin A (µmol/L)	SG	2.0±0.5	1.7±0.5	1.9±0.4	1.9±0.5	2.1±0.5			
	RYGB	2.0±0.5	1.6±0.5	1.7±0.4[a]	1.8±0.4	1.9±0.5	<0.001	<0.001	<0.001
	BPD-DS	1.9±0.5	1.3±0.4[a,b]	1.4±0.4[a,b]	1.4 ± 0.4[a,b]	1.7±0.5[a]			
Albumin (g/L)	SG	42±5	42±5	41±3	41±4	41±4			
	RYGB	41±4	42±5	40±4	41±4	40±4	<0.001	<0.001	<0.001
	BPD-DS	41±4	40±6[a]	38±4[a,b]	38±4[a,b]	40±4			
Prealbumin (mg/L)	SG	279±66	249±48	267±57	267±90	301±72			
	RYGB	270 ± 61	240±61	250±51	243±76	276±51	<0.001	<0.001	<0.001
	BPD-DS	261 ± 50[a,b]	198±41[a,b]	197±41[a,b]	215±65[a]	263±50			

Repeated measures analysis of variance are adjusted for age and baseline BMI. a: different from SG ($p < 0.05$), b: different from RYGB ($p < 0.05$) after Tukey-HSD multiple comparisons. SG: sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass, BPD-DS: biliopancreatic diversion with duodenal switch. Number of participants were as follows for SG, RYGB and BPD-DS respectively: baseline, 94,48 and 73; 4 months, 94, 48 and 72; 8 months, 94,47 and 73; 12 months, 94, 48 and 73; 24 months, 85, 41 and 67.

reported vitamin D insufficiency or deficiency as the most prevalent nutritional problem after bariatric surgery, with prevalence rates higher than our results (25, 28, 29). Less than 10% of patients from all groups suffered from iron or calcium deficiency and 2% or less of the patients presented a vitamin A and vitamin B12 deficiency or high PTH after 2 years. Prospective studies on SG, RYGB or BPD-DS showed higher rates of micronutrient deficiencies after bariatric surgery (25, 30, 31). Other retrospective studies from our group presented comparably low rates after BPD-DS (9, 32). Because of the restrictive component reducing food intake and the hypoabsorptive component bypassing major absorption sites and reducing time contact with biliopancreatic digestive secretions, micronutrient management is primordial after surgery (13, 24). Low rates of nutritional deficiencies observed in this study support the importance of a quality, long-term follow-up as offered to patients in our institution.

Before surgery, vitamin D insufficiency and iron deficiency were the most prevalent nutritional problem in all three groups. Similar or higher rates of vitamin D and iron deficiency were observed before bariatric surgery in other studies (18, 19, 33). It is not surprising that iron deficiency is prevalent in this sample since most of the participants are women, and premenopausal women are particularly affected by iron deficiency (34). For calcium, vitamin A and vitamin B12 deficiencies, rates in our groups were below 5%. While these rates are lower than those observed in other studies (19, 33), Peterson et al. observed similar rates before RYGB (18). The lower rates of deficiency present in our groups at baseline may explain why we observed less deficiencies than previous literature in the postoperative period. Indeed, nutritional deficiencies prior to surgery are an important risk factor for developing nutritional problems after surgery (12), highlighting the importance of addressing them with adequate nutritional assessment and management prior to surgery. Furthermore, rates of vitamin D and iron deficiency were lower 24 months after surgery than at baseline. Our medical and nutritional care sequence not only prevented nutritional deficiencies after bariatric surgery, but also addressed pre-existing concerns for many patients in our sample. Comparable deficiency rates at baseline were observed in a previous retrospective study by our group (30). Yet, these results are at variance with literature on SG, RYGB and BPD-DS, where micronutrient deficiency rates at baseline remained stable or increased after the procedures (25, 35, 36).

4.2 Surgical implications

Serum levels of vitamin D were higher after surgery compared to baseline in all surgical groups. Also, mean levels of all groups were in the normal range during the entire follow-up. However, a decrease in vitamin

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TABLE 3 Prevalence of nutritional deficiencies and high parathormone from 0 to 24 months after surgery.

Nutritional indicator	Group	Baseline	4 months	8 months	12 months	24 months
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Iron deficiency	SG	19 (20.9)	12 (13.5)	8 (9.2)	4 (4.4)	2 (5.4)
	RYGB	10 (20.8)	8 (17.4)	2 (4.6)	3 (6.8)	2 (5.4)
	BPD-DS	12 (16.4)	20 (28.6)	11 (15.5)	5 (7.1)	4 (6.3)
Calcium deficiency	SG	1 (1.1)	0 (0)	0 (0)	1 (1.2)	1 (1.2)
	RYGB	1 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)
	BPD-DS	1 (1.4)	0 (0)	5 (6.9)[a]	4 (5.6)	5 (7.7)
High parathormone	SG	2 (2.2)	1 (1.1)	2 (2.4)	3 (3.3)	0 (0)
	RYGB	2 (4.2)	0 (0)	0 (0)	0 (0)	0 (0)
	BPD-DS	4 (5.5)	3 (4.2)	3 (4.2)	4 (5.7)	0 (0)
Vitamin D insufficiency	SG	35 (38.8)	4 (4.3)	1 (1.1)	5 (5.4)	7 (8.2)
	RYGB	19 (39.6)	1 (2.1)	2 (4.7)	5 (11.1)	3 (7.5)
	BPD-DS	40 (54.8)	2 (2.8)	2 (2.8)	1 (1.4)	9 (13.6)
Vitamin D deficiency	SG	12 (12.8)	1 (1.1)	1 (1.1)	0 (0)	0 (0)
	RYGB	3 (6.3)	0 (0)	2 (4.7)	0 (0)	0 (0)
	BPD-DS	14 (19.2)	1 (1.4)	2 (2.8)	0 (0)	1 (1.4)
Vitamin A deficiency	SG	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	RYGB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	BPD-DS	1 (1.4)	3 (4.3)	0 (0)	1 (1.4)	1 (1.4)
Vitamin B12 deficiency	SG	4 (4.3)	1 (1.1)	0 (0)	0 (0)	0 (0)
	RYGB	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.3)
	BPD-DS	1 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)

Data analyzed with Fisher's exact ou chi-square tests as appropriate. a: different from SG and RYGB ($p < 0.05$) after Fisher's exact test. Deficiencies are determined according to references values presented in Supplementary Table S1.

D levels in the BPD-DS group was observed between 12 and 24 months. Vitamin D levels increased during the follow-up of patients correctly supplemented (37, 38). Regarding calcium, levels decreased during the entire follow-up in all groups. Even though BPD-DS had lower levels compared to SG at 24 months, rates of calcium deficiency were similar among all surgical groups at that time point. Tardio et al. showed a decrease in calcium levels 6 months after BPD-DS in a large sample (n = 1,436) (37), while a systematic review and meta-analysis reported no significant change after RYGB and an increase in calcium levels after SG (38). In our study, although elevated PTH levels were almost absent in all groups during postoperative care, PTH levels increased after bariatric surgery in our three groups. Other studies suggest that PTH levels increase after BPD-DS but remain stable after SG or RYGB (37, 39). A study by Syn et al. showed, in a large sample of Japanese men and women, that SG patients had lower vitamin D but higher calcium levels than RYGB patients at 24 months. Both groups presented similar levels of PTH in that sample at 24 months (40). Calcium and vitamin D absorption is reduced after hypoabsorptive bariatric procedures and commonly cause secondary hyperparathyroidism that can contribute to postoperative bone loss (24). Based on the low deficiency rates observed, status in vitamin D, calcium and PTH appears adequate in these groups, although evolution patterns suggest that maintaining a long-term follow-up may help prevent eventual nutritional problems and bone health deterioration.

One year after surgery, the BPD-DS group showed lower levels of hemoglobin than SG and RYGB participants and lower iron levels than SG patients only. Furthermore, iron levels increased during follow-up in all groups. Mixed results were noted regarding the effect of bariatric surgery on iron status markers with some studies showing stable levels of iron and hemoglobin after surgery (39, 41) while others found increased levels of iron and reduced levels of hemoglobin during follow-up (25, 42). In our study, ferritin levels remained stable for RYGB and BPD-DS while they decreased for SG. Some studies showed decreased ferritin levels after SG or RYGB (38, 39) but others presented increased levels after SG, RYGB or BPD-DS (41, 42). Syn et al. observed higher levels of hemoglobin in SG compared to RYGB patients while iron and ferritin levels were similar among groups at 24 months (40). Measurements of serum ferritin assess the level of iron stored in the body, dosage of hemoglobin informs on the capacity to transport oxygen in red blood cells and serum iron gives information on the adequacy of global iron supply (43). Rates of iron deficiency were low and similar among groups during the entire follow-up showing no greater risk of BPD-DS on iron status in our context of adequate supplement intake and nutritional management.

Albumin levels remained generally stable during follow-up with similar serum levels in all groups at 24 months. For prealbumin, after an early drop, levels increased in later time points to reach levels comparable to baseline for RYGB and BPD-DS or greater levels for SG. Similarly, Strain et al. observed stable albumin levels after BPD-DS (25), whereas levels were shown to decrease after SG or RYGB (30, 35, 36). Literature on

TABLE 4 Adherence to vitamin and mineral initial supplementation recommendations of SG, RYGB and BPD-DS patients 12 and 24 months after surgery.

Supplement	Group	Baseline			12 months			24 months		
		Below target	On target	Above target	Below target	On target	Above target	Below target	On target	Above target
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Vitamin D	SG	18 (19.6)	62 (67.4)	12 (13.0)	33 (35.1)	54 (57.4)	7 (7.4)[c]	39 (44.8)	39 (44.8)	9 (10.3)[c]
	RYGB	46 (95.8)	0 (0)	2 (4.2)	23 (47.0)	22 (45.8)	3 (6.3)[c]	26 (60.5)	10 (23.3)[a,b]	7 (16.3)[c]
	BPD-DS	73 (100.0)	0 (0)	0 (0)	15 (20.5)	20 (27.4)	38 (52.1)	14 (20.3)	16 (23.2)	39 (56.5)
Vitamin A	SG	0 (0)	87 (92.6)	7 (7.4)	0 (0)	85 (90.4)	9 (9.6)	0 (0)	81 (93.1)	6 (6.9)
	RYGB	0 (0)	48 (100.0)	0 (0)	0 (0)	44 (91.7)	4 (8.3)	0 (0)	38 (88.4)	5 (11.6)
	BPD-DS	73 (100.0)	0 (0)	0 (0)	5 (6.8)	33 (45.2)	35 (47.9)	8 (11.6)	24 (34.8)	37 (53.6)
Vitamin B12	SG	0 (0)	88 (93.6)	5 (5.3)	0 (0)	89 (94.7)	5 (5.3)	0 (0)	80 (92.0)	7 (8.0)
	RYGB	45 (93.8)	3 (6.3)	0 (0)	7 (14.6)	41 (85.4)	0 (0)	8 (18.6)	35 (81.4)	0 (0)
	BPD-DS	0 (0)	69 (94.5)	4 (5.5)	0 (0)	70 (95.9)	3 (4.1)	0 (0.0)	66 (95.7)	3 (4.3)
Iron	SG	0 (0)	84 (89.4)	10 (10.6)	0 (0)	85 (90.4)	10 (10.6)	0 (0)	81 (93.1)	6 (6.9)
	RYGB	36 (75.0)	9 (18.8)	3 (6.3)	6 (12.5)	40 (83.3)	2 (4.2)	12 (27.9)	24 (55.8)[a]	7 (16.3)
	BPD-DS	62 (84.9)	9 (12.3)	2 (2.7)	7 (9.6)	53 (72.6)	13 (17.8)	8 (11.6)	47 (68.1)	14 (20.3)
Calcium	SG	0 (0)	91 (96.8)	3 (3.2)	0 (0)	91 (96.8)	3 (3.2)	0 (0)	78 (89.7)	9 (10.3)
	RYGB*	46 (95.8)	2 (4.2)	0 (0)	9 (18.8)	37 (77.1)	2 (4.2)	15 (34.9)	26 (60.5)[a]	2 (4.7)[c]
	BPD-DS*	73 (100.0)	0 (0)	0 (0)	7 (9.6)	59 (80.8)	7 (9.6)	8 (11.6)	43 (62.3)	18 (26.1)
Multivitamin	SG	15 (16.0)	79 (84.0)	0 (0)	15 (16.0)	79 (84.0)[a]	0 (0)	22 (25.3)	63 (72.4)[a]	2 (2.3)
	RYGB	47 (97.9)	1 (2.1)	0 (0)	29 (60.4)	19 (39.6)[b]	0 (0)	27 (62.8)	16 (37.2)[b]	0 (0)
	BPD-DS	72 (98.6)	1 (1.4)	0 (0)	46 (63.0)	27 (37.0)	0 (0)	44 (63.8)	24 (34.8)	1 (1.4)

Below target: patients taking supplement doses below initial daily recommendations. On target: patients taking supplement doses according to the initial daily recommendations. Above target: patients taking supplement doses above initial daily recommendations. Daily recommendations for vitamin and mineral supplementation are presented in the Methods. a: different from BPD-DS ($p < 0.05$). b: different from SG ($p < 0.05$). c: different from BPD-DS between above target and cumulative proportions of on target and below target ($p < 0.05$). *: adherence significantly different between 12 and 24 months ($p < 0.05$). SG: sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass, BPD-DS: biliopancreatic diversion with duodenal switch. Number of participants were as follows for SG, RYGB and BPD-DS respectively: baseline, 94,48 and 73; 4 months, 94, 48 and 72; 8 months, 94,47 and 73; 12 months, 94, 48 and 73; 24 months, 85, 41 and 67.

prealbumin levels is inconclusive for SG and RYGB and is scarce for BPD-DS (35, 36). For both markers, levels were similar among all groups at 24 months. Albumin and prealbumin have been traditionally used as markers of nutritional status. The American Society for Parenteral and Enteral Nutrition (ASPEN) recently stated that low albumin and prealbumin serum levels are not a valid measurement of nutritional status, but rather indicators of the inflammatory status, regardless of underlying nutritional status (44). The transient reduction of prealbumin levels observed in our groups could result from acute inflammation related to surgical procedures, which is resolved in later follow-ups suggesting improved medical condition. These signs of inflammation in the early postoperative stage are only observed with prealbumin, considering its shorter half-life compared to albumin (44). Together, mean albumin and prealbumin levels were similar among groups and were in the normal range at 24 months suggesting no sign of inflammation or negative surgical evolution in the long term.

4.3 Supplementation adherence

Supplementation recommendations vary greatly across countries and to our knowledge, this is the first study to compare adherence to micronutrient initial supplementation recommendations for SG, RYGB and BPD-DS in a prospective design. Current literature on the topic is difficult to assess and there is a need for more long-term prospective studies, especially on hypoabsorptive procedures. We showed high adherence to vitamin and mineral initial supplementation recommendations in the first 2 years following bariatric surgery. This likely explains why we observed low prevalence of micronutrient deficiencies. While a prospective study on RYGB and SG showed an adherence rate of approximately 60% for calcium-vitamin D and vitamin B12 supplementation 2 years after the procedures (45), a systematic review and meta-analysis reported an adherence rate around 20% for the same procedures (38). Although literature shows a decrease in adherence to supplements within the first year (46), it remained stable in our sample for all supplements except calcium. Most RYGB patients in our sample took less vitamin D and multivitamin supplements than recommendations at 24 months. Additional analysis on vitamin D showed that most RYGB patients in the below-target category had normal serum levels. Instead of indicating low adherence, this showed that less vitamin D supplementation was enough to prevent deficiencies for most of these patients. Also, BPD-DS patients took significantly more vitamin A and D compared to recommendations at 24 months. Nett et al. also reported that 37.2 and 11.6% of BPD-DS patients, respectively, required higher doses of vitamin D and vitamin A supplementation within the five-year follow-up (47). Comparably to that group, we concluded that supplementation recommendations for patients undergoing BPD-DS should be revised, as they could benefit from higher initial doses of vitamin A and D.

4.4 Strengths and limitations

Our study has several strengths. First, we assessed for the first time the micronutrient status and adherence to vitamin and mineral initial supplementation recommendations after bariatric surgery in a prospective design and we compared 3 types of bariatric procedures: SG, RYGB, BPD-DS. Second, we evaluated the nutritional status before surgery and compared it at many time points up to 24 months. Also, the number of participants included in our study was relatively elevated in the context of a prospective study. Lastly, we presented the reference values used to determine deficiency and we evaluated the actual intake of vitamin and mineral supplements consumed by patients. Still, our study presents some limitations. This comparison of nutrient status in SG, RYGB and BPD-DS was prospective, but it was not a randomized trial due to the major differences in medical and nutritional management among procedures. Indeed, the supplementation, outcomes and risks associated with each procedure prevented randomization of the patients to the different arms of the study. Also, the data analyzed in this study are from a sample in which follow-up is ongoing. As a result, we had slightly less data available at 24 months compared to earlier time points. Our groups were also not balanced in terms of surgery type, which is representative of the proportions of the types of procedures performed in our institution. Lastly, there was a higher proportion of females in our groups and all patients were living with T2D. More studies will ascertain generalizability of our findings.

This study may help clinicians improve their practice in bariatric care. As our results showed a similar risk of developing micronutrient deficiencies for all three surgeries at 24 months, the BPD-DS appears to be a safe option regarding micronutrient status compared ot other surgeries. Also, the highest rates of micronutrient deficiencies were noted before surgery, which supports the recommendation to supplement patients in the preoperative period to prevent adverse outcomes. Using clinical experience, supplementation recommendations for patients undergoing BPD-DS should be increased, as they could benefit from higher initial doses of vitamins A and D. To improve understanding of nutritional status following bariatric surgery, micronutrient status should be evaluated for more than 24 months in a prospective design, because deficiencies may occur many years after surgery. Determinants of the nutritional risk following bariatric surgery should be investigated for early detection of patients at higher risk of developing deficiencies. Further research could also evaluate food intake to complement the characterisation of nutritional status in bariatric patients.

5 Conclusion

Vitamin D insufficiency was the most prevalent nutritional problem among patients before bariatric surgery. With appropriate medical and nutritional management, all surgeries led to similar rates of vitamin D, calcium, iron, vitamin A and vitamin B12 deficiency at 24 months. The metabolic advantages associated with BPD-DS could be offered to more patients as it appears to be safe regarding micronutrient status. Rates of vitamin D insufficiency and iron deficiency were lower at 24 months than at baseline, showing the importance of adequate supplementation to prevent micronutrient deficiencies and correct pre-existent ones. Adherence to vitamin and mineral initial supplementation recommendations was high in all groups after surgery, but most BPD-DS patients took vitamin A and vitamin D supplement doses above initial recommendations for this surgery. Initial vitamin A and vitamin D supplementation recommendations for BPD-DS patients should be revised upwards.

Data availability statement

The datasets presented in this article are not readily available. The dataset may be shared upon request with approval from the local ethics committee. Requests to access the datasets should be directed to AT, andre.tchernof@criucpq.ulaval.ca.

Ethics statement

The studies involving humans were approved by The Research Ethics Committee of the Institut universitaire de cardiologie et de pneumologie de Québec – Université Laval. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MC: Methodology, Investigation, Data curation, Conceptualization, Writing – review & editing, Writing – original draft, Formal analysis. LP: Data curation, Writing – review & editing, Writing – original draft, Formal analysis. MN: Methodology, Writing – review & editing, Project administration, Data curation. LB-B: Project administration, Investigation, Writing – review & editing, Resources. FJ: Project administration, Investigation, Writing – review & editing, Resources. AM: Writing – review & editing, Supervision, Investigation, Conceptualization. LB: Supervision, Resources, Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. AT: Resources, Methodology, Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

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Conflict of interest

AT and LB receive funding from Johnson & Johnson, Medtronic, GI Windows and Biotwin for studies on obesity or bariatric surgery. AT and LB acted as consultants for Bausch Health and Novo Nordisk.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1385510/full#supplementary-material

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Feasibility of calculating rocuronium dosage by skeletal muscle weight in patients with obesity

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This study aimed to investigate the dose–response relationship of rocuronium administered based on skeletal muscle weight and to assess the feasibility of calculating rocuronium dosage by skeletal muscle weight in short surgeries for patients with obesity. This single-center, randomized controlled clinical trial included 71 patients with obesity aged 28–70years, with body fat percentages (PBF) >20% in men and>28% in women, ASA status I-III, scheduled for tracheoscopy. Patients were randomly allocated into two groups: skeletal muscle group (SM group) received rocuronium based on the skeletal muscle content (1.0mg/kg, n=31), and the conventional administration group (conventional group) received rocuronium based on total body weight (0.45mg/kg, n=30). General anesthesia was administered using the same protocol. Parameters recorded included patients' general condition, muscle relaxant usage, onset time of muscle relaxants, non-response time, clinical effect time, 75% recovery time, and recovery index. Additionally, occurrences of body movement, choking, and incomplete muscle relaxation during surgery were recorded. Compared to the conventional group, the SM group required significantly less rocuronium dosage, resulting in significantly lower non-response time, clinical effect time, 75% recovery time, and recovery index (p<0.05), and the onset time is slightly longer. Neither group experienced body movement, choking, or incomplete muscle relaxation (p>0.05). Utilizing skeletal muscle weight to calculate rocuronium dosage in short surgeries for patients with obesity can reduce dosage, shorten recovery time, and prevent residual muscle relaxation while achieving satisfactory muscle relaxation to meet surgical requirements.

KEYWORDS

general anesthesia, obesity, body composition analysis, rocuronium, muscle relaxation monitoring

Introduction

Patients with obesity often exhibit an increased proportion of body fat and reduced blood flow through adipose tissue (1). When dosing anesthetic drugs based on actual body weight, the apparent volume of drug distribution and metabolic rate can be significantly impacted, affecting the quality and duration of awakening resulting in accumulation and prolonged

duration in clinical anesthesia for patients with obesity (2–4). Suggestions have been made to administer drugs to patients with obesity based on their defatted body weight to adjust anesthetic dosage (5). However, previous studies diagnosing obesity using body mass index (BMI) may overlook occult obesity, where body weight appears regular but excessive fat is present in body composition analysis, thus not adequately addressing drug metabolism considerations.

Direct segmental multi-frequency Bio-impedance analysis (BIA) is utilized in body composition analyzers to accurately assess the content and proportion of body components such as muscle, fat, and water, reflecting the nutritional status, obesity, swelling, and other physical health conditions of the human body (6). The body composition analyzer calculates the defatted weight of the subject based on parameters including age, gender, height, and weight. The standard percentage of body fat (PBF) is 15% for men and 23% for women, with 10–20% for men and 18–28% for women considered normal ranges. A percentage of body fat (PBF) >20% for men and > 28% for women is indicative of obesity (7, 8). Hence, in our study, obesity is based on body fat ratio, which better represents the actual body condition than solely relying on height and weight.

Simultaneously, rocuronium is a fast-acting, medium-latency non-depolarizing neuromuscular blocking agent that exerts its effect by competitively binding to N-type acetylcholine receptors at the motor end plate. Skeletal muscle content and the number of neuromuscular junctions may influence its clinical effect, leading us to speculate on the feasibility of using skeletal muscle weight to calculate rocuronium dosage (9).

In this study, we utilized a body composition analyzer to determine the skeletal muscle content of all patients with obesity, including those with occult obesity characterized by normal BMI but excessive body fat content. This served as a reference for dosing, allowing us to observe the dose–response relationship of rocuronium administered based on skeletal muscle weight and investigate the feasibility of calculating skeletal muscle relaxants by skeletal muscle weight in patients with obesity undergoing short surgeries.

Methods

This study, involving human subjects, was approved by The Ethics Committee of Henan Provincial People's Hospital [2021(160)], and all patients provided signed informed consent forms.

Seventy-one patients proposed for tracheoscopy since May 2023 in Henan Provincial People's Hospital were divided into two groups by random number table method, the skeletal muscle content administration group (SM group) and the conventional administration group (conventional group). $(N1 = N2 = 2[(t\alpha/2 + t\beta/2)S/\delta]2$, taking $\alpha = 0.05$ and $\beta = 0.1$, and using rocuronium dosage as a reference to calculate the sample size, each group needs about 28 cases).

Inclusion criteria: age 28–70 years, percentage body fat (PBF) >20% for men and > 28% for women, ASA class I-III. Exclusion criteria: abnormal liver and kidney function or disorders of water-electrolyte and acid–base balance; previous history of tuberculosis, neuromuscular disease, history of chemotherapy for oncological diseases; drugs affecting the conduction function of neuromuscular junction within the last month; expected operation time < 1 h; metal implants in the body.

After the patient was admitted to the room, monitoring the blood pressure, heart rate, pulse oximetry, and electrocardiogram. The intravenous induction of general anesthesia consisted on midazolam 0.03 mg/kg, sufentanil 0.2 μg/kg, and propofol 2–4 mg/kg. After the patient falls asleep, we performed muscle relaxation monitoring of the thumb adductor using a TOF-Watch SX muscle relaxation monitor (Organon Teknika, Netherlands). The stimulation electrodes were attached to the forearm at the location of the ulnar nerve at the wrist, with the distal electrode being placed on the radial side of the proximal flexor line through the ulnar carpal flexor and the proximal electrode 2 to 3 cm from the distal electrode. The maximum plane of the acceleration transducer was attached to the palmar root of the thumb, and the temperature sensor to the medial palmar interphalangeal area. The forearm was fixed and wrapped with gauze for insulation.

The method employed Train of Four stimulation (TOF) with specified parameters: a stimulation intensity of 50 mA, frequency of 2 Hz, pulse width of 0.2 ms, pulse spacing of 500 ms, and a stimulation interval of 12 s. The initial twitch response to the TOF was standardized to a stable 100% as the basal value (Tc). Following 3 min of continuous stimulation, rocuronium was administered intravenously. The conventional group received a dose of 0.45 mg/kg (1.5 times the ED95), while the SM group received 1.0 mg/kg based on skeletal muscle weight. For standard weight patients, approximately 45% of their total body weight was attributed to skeletal muscle, resulting in a calculated ED95 of 0.66 mg/kg administered based on skeletal muscle weight. Upon achieving a TOF ratio of 0, a laryngeal mask was placed, and mechanical ventilation initiated with specific parameters: tidal volume (VT) set at 6–8 mL/kg, ventilation frequency at 12–18 times/min, inspiratory-to-expiratory ratio (I:E) at 1:1–1:2, inhaled oxygen concentration maintained between 50 and 100%, with an inhaled oxygen flow rate of 2 L/min, and a target end-tidal CO2 (PETCO2) range of 30–45 mmHg (1 mmHg = 0.133 kPa). Anesthesia maintenance was achieved through intravenous infusion of propofol at a rate of $4 \sim 8\ mg \cdot kg^{-1} \cdot min^{-1}$ and remifentanil at a rate of $0.2 \sim 0.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$. Intraoperative blood pressure and heart rate were monitored to ensure fluctuations did not exceed 20% of basal levels. Additional inotropic drugs were not administered intraoperatively, and postoperative inotropic antagonism was avoided.

Primary observation indexes: (1) myorelaxant dosage; (2) neuromuscular function monitoring: onset of action, the duration from the termination of drug administration to the point at which TOF stimulation elicits no response (TOF = 0); non-response time, the interval from the disappearance of the first twitch response of TOF (T1) to its reappearance; Clinical action time, the period from the conclusion of drug injection to the restoration of T1 to 25% of its baseline value; 75% recovery time, the duration between drug injection cessation and the reestablishment of T1 to 75% of its initial value; recovery index, the timeframe from T1's recovery to 25% of the baseline value to its recuperation to 75% of the baseline value. These parameters collectively provide valuable insights into the neuromuscular effects and recovery kinetics following neuromuscular blockade.

Secondary observation indexes: (1) patients' basic conditions: skeletal muscle mass, age, gender, BMI, body fat ratio, ASA classification, blood potassium and sodium concentration, total plasma protein, and plasma albumin levels, and operation time; (2) occurrence of body movement, choking, and incomplete muscle relaxation during the operation.

Statistical analysis was conducted using SPSS 20.0 software (SPSS Inc., Chicago, IL, United States). Normally distributed measures were presented as mean ± standard deviation ($x \pm s$). Repeated measures design data were analyzed using ANOVA with repeated measures,

while comparison between groups was performed using the two independent samples t-test. The comparison of count data was conducted using the X^2-test. A p-value of less than 0.05 was considered indicative of statistical significance.

Results

Out of 71 screened patients, 6 declined to participate in the study, 2 had their surgery temporarily canceled, 1 underwent a change in surgical method requiring additional muscle relaxation drugs, and 1 experienced muscle relaxation monitoring failure. Ultimately, 30 cases were included in the Conventional group and 31 cases in the SM group for statistical analysis (Figure 1).

There were no statistically significant differences observed in the general condition, body composition, blood biochemistry, plasma protein levels, or surgery time between the two groups of patients ($p > 0.05$) (Table 1).

Compared to the Conventional group, the SM group utilized significantly lower rocuronium dosages, with significantly reduced non-response time, clinical effect time, 75% recovery time, and recovery index ($p < 0.05$), and the onset time is slightly longer. Additionally, there were no instances of body movement, choking, or incomplete muscle relaxation observed in either group ($p > 0.05$) (Table 2).

Discussion

Obesity induces various pathophysiological changes in the body, affecting the pharmacokinetic properties of numerous drugs due to associated physiological alterations. Recent studies have highlighted differences in the metabolism of intravenous and inhaled general anesthetics, as well as inotropic drugs, between obese and normal-weight patients (10). Many investigations have adjusted drug dosages for patients with obesity based on ideal or lean body weight. Notably, lean body weight (LBW) has been strongly associated with increased cardiac output compared to total body weight (TBW) and ideal body weight (IBW) in patients with obesity. Furthermore, clearance of most drugs increases linearly with LBW but not with TBW (5, 11–13). TBW-based calculations may lead to prolonged duration of action for muscle relaxants, necessitating dosing adjustments based on LBW rather than TBW. While succinylcholine induction doses should be calculated conventionally to ensure adequate muscle relaxation during intubation, non-depolarizing muscle relaxants such as vecuronium bromide, rocuronium, atracurium, and cis-atracurium should be dosed according to IBW to avoid fat accumulation and insufficient muscle relaxation (14, 15).

However, existing weight acquisition methods overlook differences in body composition, including variations in body fat and skeletal muscle content among individuals of similar body weight (6). The pharmacokinetics of occult patients with obesity, characterized by high body fat and low skeletal muscle content despite a normal BMI, have not received adequate attention. Administering drugs at actual body weight may risk overdose and accumulation in this population. In our study, all patients with obesity with excess body fat content underwent body composition analysis, and rocuronium, a skeletal muscle relaxant, was dosed based on skeletal muscle weight, ensuring adequate muscle relaxation for surgery while reducing recovery time and minimizing residual muscle relaxation.

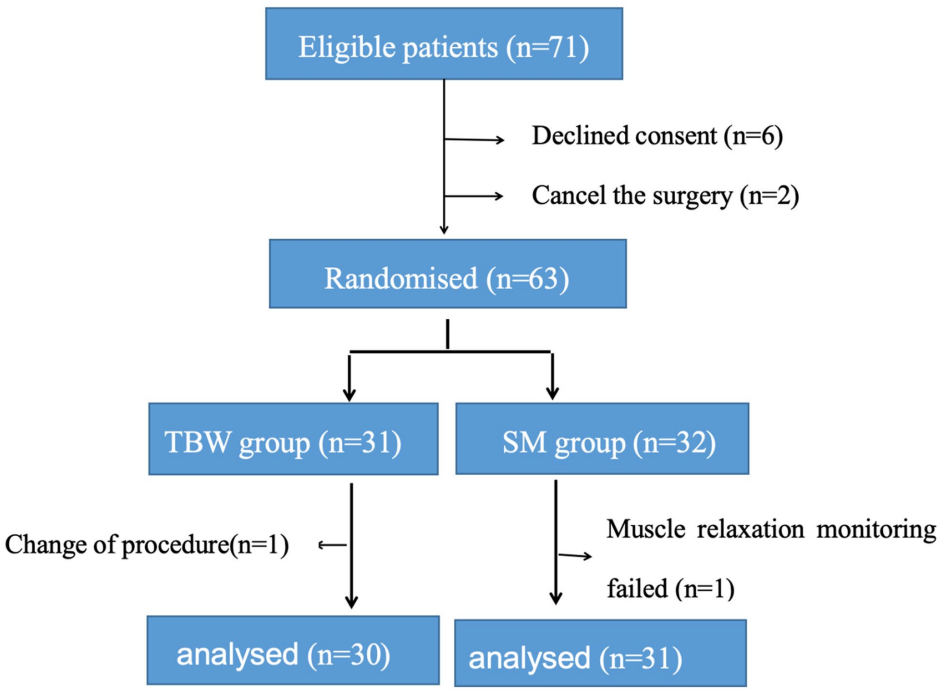

FIGURE 1
CONSORT diagram. CONSORT, consolidated standards of reporting trials.

TABLE 1 Comparison of general condition and surgery time between two groups of patients ($\bar{x} \pm s$).

Group	Conventional group ($n = 30$)	SM group ($n = 31$)	*P*-value
Gender (M/F)	20/10	18/12	0.599
Age (years)	55.73 ± 13.11	57.83 ± 11.65	0.514
Duration of surgery (min)	35.77 ± 8.73	33.68 ± 11.24	0.426
Weight (kg)	69.55 ± 11.99	72.11 ± 12.12	0.421
BMI (kg/cm^2)	28.57 ± 3.51	27.19 ± 2.93	0.891
Skeletal muscle mass (kg)	26.67 ± 4.92	25.71 ± 6.28	0.518
Body fat percentage (%)	34.94 ± 6.02	35.35 ± 6.41	0.393
Water content (L)	35.68 ± 5.94	34.39 ± 7.61	0.475
Inorganic salt	3.30 ± 0.50	3.24 ± 0.68	0.690
Protein (kg)	9.18 ± 1.65	9.52 ± 2.06	0.492
Blood potassium (mmol/L)	3.96 ± 0.42	3.98 ± 0.31	0.875
BLOOD sodium (mmol/L)	140.14 ± 2.06	135.43 ± 2.49	0.779
Plasma albumin (g/L)	37.26 ± 4.87	35.87 ± 7.04	0.391
Total plasma protein (g/L)	62.87 ± 7.47	64.89 ± 4.87	0.232

TABLE 2 Comparison of the pharmacodynamic and other indices of rocuronium between the two groups ($\bar{x} \pm s$).

Groups	Conventional group ($n = 30$)	SM group ($n = 31$)	*P*-value
Induction dose (mg)	31.37 ± 5.43	25.77 ± 6.23	<0.001
Onset time (s)	154.97 ± 24.19	174.40 ± 20.39	0.002
Non-response time (min)	21.23 ± 4.25	18.43 ± 4.48	0.018
75% recovery time (min)	31.43 ± 4.60	27.07 ± 5.28	0.001
Recovery index (min)	13.8 ± 2.18	9.43 ± 3.35	<0.001
Body movement	0	0	/
Choking	0	0	/

The primary characteristics such as sex ratio, age, weight, and BMI were similar between the SM and conventional groups. Likewise, body composition analysis results including body fat content, skeletal muscle mass, body water, inorganic salt, and protein content, were comparable. No differences were observed in plasma protein, blood potassium, and blood sodium levels, which could affect muscarinic drug metabolism and neuromuscular contractile function, ensuring comparability between the two groups.

Our findings revealed significantly lower rocuronium dosage in the SM group compared to the conventional group, accompanied by lower time to no response, recovery time, and recovery index in the SM group, its onset time was slightly higher, and no signs of insufficient muscle relaxation occurred in either group. Reduced muscle relaxant dosage and recovery time can mitigate postoperative neuromuscular residual effects and associated respiratory complications (16), particularly beneficial for short, minimally invasive outpatient procedures such as tracheoscopic consultation. Previous studies utilizing lean body weight for muscle relaxant dosing in patients with obesity under anesthesia have also reported reduced dosage and shorter recovery time, consistent with our findings (14, 17, 18). However, these studies primarily focused on patients with obesity with elevated BMI and did not consider those with occult obesity characterized by excess body fat content alone. Since non-depolarizing muscle relaxants like rocuronium competitively block acetylcholine's depolarizing effect at neuromuscular junctions, skeletal muscle content and neuromuscular junction quantity may significantly influence their clinical efficacy, warranting consideration when determining dosage.

This study has certain limitations. Firstly, in the SM group, the dose administered based on skeletal muscle mass was estimated using data on body composition and pharmacokinetics in normal populations, rather than directly determined from measured actual ED95 blood concentrations. This method of estimation assumes that neuromuscular blocking agents distribute solely within skeletal muscle tissue and not within adipose tissue. However, there may indeed be some distribution within adipose tissue in reality, potentially introducing bias into the calculated ED95. Second, we only assessed clinical effect indicators of muscle relaxants in both groups and refrained from evaluating pharmacokinetic indicators to avoid additional invasive procedures.

Conclusion

In summary, administering neuromuscular-blocking agents based on skeletal muscle weight in minimally invasive surgeries for patients with covertly obesity may reduce the required dosage, shorten patient recovery times, and mitigate residual neuromuscular blockade effects. This approach ensures satisfactory muscle relaxation while meeting surgical demands. Human body composition analysis offers a simple, non-invasive, safe, and reliable method to measure fat and skeletal muscle weight. By calculating the requirement for skeletal muscle relaxants based on skeletal muscle weight, a certain level of individualized medication can be achieved, warranting promotion to all patients requiring muscle relaxants.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Henan Provincial People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZH: Data curation, Project administration, Writing – original draft, Writing – review & editing. BL: Methodology, Writing – review & editing. ZLi: Conceptualization, Supervision, Writing – original draft. ZLiu: Methodology, Validation, Writing – original draft. SL: Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cashew nut (*Anacardium occidentale* L.) and cashew nut oil reduce cardiovascular risk factors in adults on weight-loss treatment: a randomized controlled three-arm trial (Brazilian Nuts Study)

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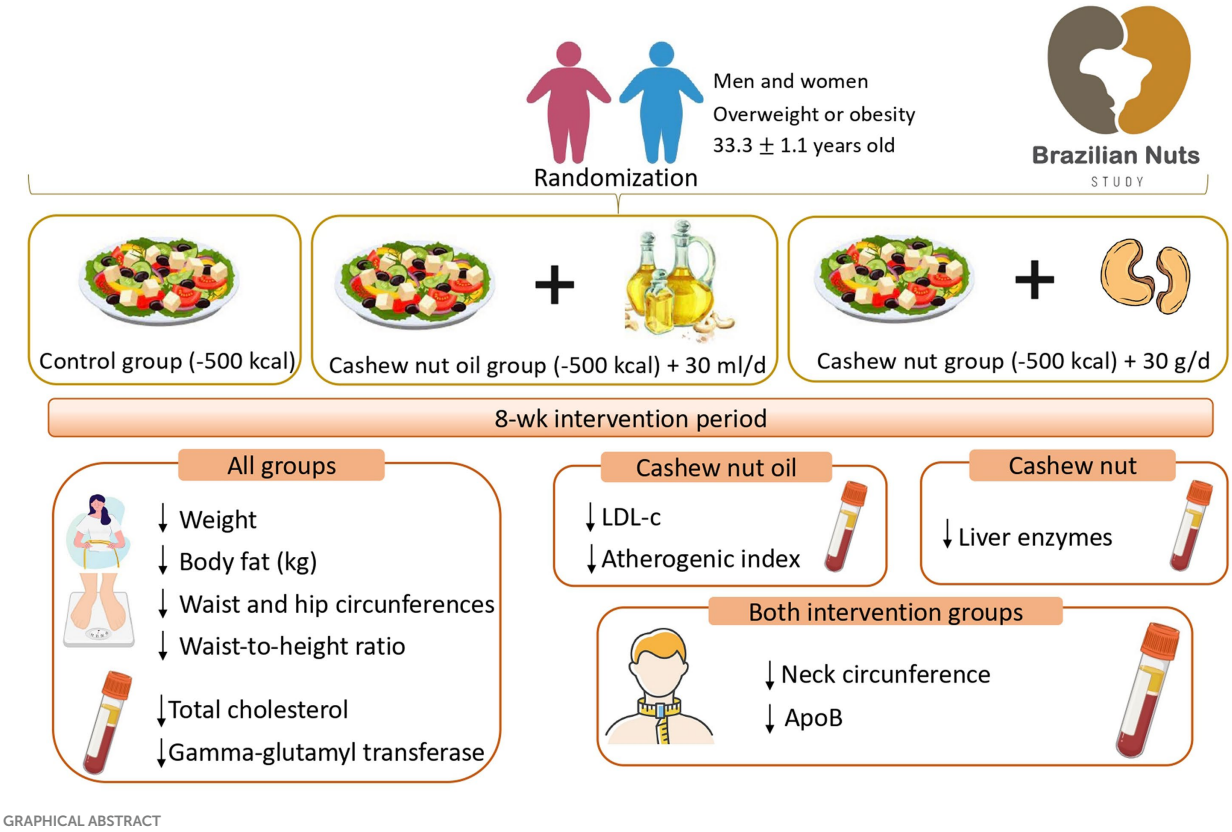
Introduction: Cashew nut contains bioactive compounds that modulate satiety and food intake, but its effects on body fat during energy restriction remains unknown. This study aimed to assess the effects of cashew nut and cashew nut oil on body fat (primary outcome) as well as adiposity, cardiometabolic and liver function markers (secondary outcomes).

Materials and methods: An eight-week (8-wk) randomized controlled-feeding study involved 68 adults with overweight/obesity (40 women, BMI: 33±4kg/m^2). Participants were randomly assigned to one of the energy-restricted (−500kcal/d) groups: control (CT, free-nuts), cashew nut (CN, 30g/d), or cashew nut oil (OL, 30mL/d). Body weight, body composition, and blood collection were assessed at the baseline and endpoint of the study.

Results: After 8-wk, all groups reduced significantly body fat (CT: −3.1±2.8kg; CN: −3.3±2.7kg; OL: −1.8±2.6kg), body weight (CT: −4.2±3.8kg; CN: −3.9±3.1kg; OL: −3.4±2.4kg), waist (CT: −5.1±4.6cm; CN: −3.9±3.9cm; OL: −3.7±5.3cm) and hip circumferences (CT: −2.9±3.0cm; CN: −2.7±3.1cm; OL: −2.9±2.3cm). CN-group reduced liver enzymes (AST: −3.1±5.3U/L; ALT: −6.0±9.9U/L), while the OL-group reduced LDL-c (−11.5±21.8mg/dL) and atherogenic index (−0.2±0.5). Both intervention groups decreased neck circumference (CN: −1.0±1.2cm; OL: −0.5±1.2cm) and apo B (CN: −6.6±10.7mg/dL; OL: −7.0±15.3mg/dL).

Conclusion: After an 8-wk energy-restricted intervention, all groups reduced body fat (kg), weight, and some others adiposity indicators, with no different effect of cashew nut or cashew nut oil. However, participants in the intervention groups experienced additional reductions in atherogenic marker, liver function biomarkers, and cardiovascular risk factors (neck circumference and apo B levels), with these effects observed across the OL group, CN group, and both intervention groups, respectively.

Clinical trial registration: https://ensaiosclinicos.gov.br/rg/RBR-8xzkyp2, identifier 8xzkyp2.



GRAPHICAL ABSTRACT

KEYWORDS

clinical trial, cashew nut, *Anacardium occidentale* L., obesity, body fat, cardiometabolic markers, liver markers

1 Introduction

Obesity is a multifactorial and complex disease characterized by excessive adiposity. It is linked to an elevated risk of developing other chronic conditions, including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, cardiovascular diseases (CVDs), and some types of cancer (1). This condition represents a burgeoning global pandemic, with estimates indicating that by 2030, over 1 billion people worldwide will be affected by obesity (body mass index (BMI) $\geq 30\,kg/m^2$). This projection translates to approximately one in five women and one in seven men (2). In 2019, obesity played a contributing role in around 5 million deaths attributed to cardiovascular diseases, diabetes, cancers, neurological disorders, chronic respiratory diseases, and digestive disorders (3).

One potential strategy for mitigating obesity involves dietary approaches aimed at achieving an optimal energy balance and energy-restriction as treatment (4, 5). Besides, a growing body of evidence from epidemiological studies and clinical trials supports the potential benefits of nuts. Not only do they avoid causing weight gain, but they also seem to contribute to improved body composition and reduced cardiometabolic risk through favorable effects on lipid profiles (6–10).

Among all nuts, cashew nut is one of the most produced and consumed globally, ranking third in both categories (11). In addition to their unsaturated fat content as monounsaturated fatty acids (MUFA) ≈ 62% and polyunsaturated fatty acids (PUFA) ≈ 18%, cashew nut are whole foods that offer supplementary non-lipid nutrients, including proteins (≈21%), dietary fiber (≈4%), and phenolic compounds (≈60 mg GAE/100 g) (12, 13). Furthermore, a derivative of cashew nut, the oil extracted from these nuts, shows promise for promoting health. Cashew nut oil contains high content of monounsaturated fatty acids (MUFA) (≈61%) (14), PUFA ≈ 19%, vitamin E (2225.93 µg/100 g), besides tocopherols and phytosterols (15). Hence, the oil can be positioned as a new product with enhanced value, attributable to its distinctive sensory characteristics, substantial nutritional advantages, and chemical stability (14). However, the combined effects of an energy-restricted diet and the dietary intake of cashew nuts has been not reported, nor has the effect of cashew nut oil on human health.

Thus, we hypothesized that cashew nut and cashew nut oil could contribute to body fat loss and further improvements in body composition, cardiometabolic and liver function markers. The objective of this study was to assess the effects of both cashew nut and cashew nut oil over an 8 week energy restriction on body fat (primary outcome) and other adiposity indicators, cardiometabolic, and liver

function markers among adults with overweight/obesity. The findings of this study can contribute to science by providing new insights into the effects of nuts on weight loss and cardiometabolic risk. This study stands out as the first to assess the effect of cashew nuts associated with an energy-restricted diet, as well as the effects of cashew nut oil on overall health. This allows us to compare the effects of cashew nuts in terms of their lipid fraction against other components, such as the whole nut. This unique approach provides a more complete and detailed understanding of the potential health benefits associated with incorporating this nut into the diet. Furthermore, the study analyzed the proximate composition, minerals, fatty acid profile, and phenolic compounds of both cashew nut and cashew nut oil.

2 Materials and methods

2.1 Cashew nut and cashew nut oil

Cashew nut (*Anacardium occidentale* L.) and cashew nut oil were produced in Brazil, coming from donation of the Brazilian Agricultural Research Corporation (Embrapa), Agroindústria Tropical, Fortaleza (Brazil).

All procedures described next were carried out at the Embrapa. Oil samples were extracted by centrifugation. For sample preparation, the cashew nut was roasted at 110°C for 15 min; cashew nut was ground in a food processor; adding water to the cashew nut (4,1 cashew nut, water w/w) and the mixture was homogenized in a processor at 90°C for 10 min. This mixture was centrifuged for 1 h at 4,500 rpm at room temperature. After centrifugation, the oil was heated in an oven at 105°C for 1 h (14). The raw material was obtained from the same crop, and its microbiological quality was analyzed and assured via reports by the supplier company until they were delivered to the Laboratory of Energy Metabolism and Body Composition of the Universidade Federal de Viçosa (LAMECC/UFV).

For the intervention, cashew nuts were portioned into laminated and vacuum-sealed packages (30 g), while cashew nut oil was fractionated and stored in 250 mL amber glass bottles. Both foods were stored in a freezer at −20°C until distribution to participants to avoid nutrient oxidation, sensory changes, and microbiological contamination. All material for consumption was handled following hygienic-sanitary standards, including the use of clean lab coats, caps, masks, and disposable gloves.

Regarding nutrients and bioactive compounds of cashew nut, moisture, ash, protein, lipids, carbohydrates, dietary fibers, amino acids, and *in vitro* digestibility were evaluated. The moisture, ash, and protein contents were performed according to the methodology indicated by the AOAC (16), the last one was obtained by combustion in the Nitrogen/Protein Analyzer equipment. Carbohydrate content was calculated by the difference of 100 and the sum of the values obtained for moisture, ash, proteins, and lipids. The energy value per 100 g of each product was calculated using the Atwater system: Caloric value = (g of protein × 4) + (g of lipids × 9) + (g of carbohydrates × 4). Total dietary fiber (soluble and insoluble fiber) was determined by the gravimetric non-enzymatic method, using the commercial kit (Total dietary fiber assay kit, Sigma®, San Luis, Missouri, EUA) (16). The amino acid contents (aspartic acid, glutamic acid, serine, glycine, histidine, taurine, arginine, threonine, alanine, proline, tyrosine, valine, methionine, cystine, isoleucine, leucine, phenylalanine, lysine, hydroxyproline, tryptophan and the sum of total amino acids) were performed based on the MA-009 R0 method (17, 18), and tryptophan by the MA-010 R.1 method (19). *In vitro* digestibility was analyzed by the previously reported method (20).

Both cashew nut and cashew nut oil underwent analysis for minerals, vitamin E and its derivatives, total phenolics, and antioxidant capacity. Mineral analyzes (phosphorus, potassium, calcium, magnesium, selenium, sodium, copper, iron, zinc, and manganese) were performed according to the methodology of the Food and Drug Administration (FDA) (21). The preparation and analysis of the vitamin E isomers (α-, β-, γ-, δ-tocopherols and tocotrienols) were extracted according to Pinheiro-Sant'Ana et al. (2011), and performed in five replicates by High-Performance Liquid Chromatography (HPLC). During analysis, the samples were protected from sunlight and artificial light using amber glassware, aluminum foil, and blackout curtains, and protected from oxygen by using lids and environments with nitrogen gas in glass bottles. The total phenolic compound content was obtained from reading of absorbance in a spectrophotometer (Thermo Scientific, Evolution 606, United States) at 765 nm. Analytical curve of gallic acid (0.005–0.10 mg/mL) was used to quantify the compounds. The results were expressed in mg of gallic acid equivalents/g of cashew nut (mg GAE/g). The antioxidant activity was determined by the sequestering capacity of free radical DPPH (2,2-diphenyl-1-picryl-hydrazil) as described before (22).

Additionally, we also performed analysis of fatty acids, acidity level, and peroxide index in cashew nut oil. Lipids were obtained using the high-pressure, high-temperature extraction system in Ankom XT-15 equipment according to the American Oil Chemists' Society (23). The fatty acid profile was determined using the procedure described by Hartman and Lago (1973). The determinations of acidity and peroxides were performed according to AOCS (2003).

2.2 Trial design

This is an 8-wk randomized controlled three-arm dietary intervention, in which subjects were assigned to receive control (CT), cashew nut (CN) or cashew nut oil (OL) plus an energy-restricted diet. This study was conducted at the Department of Nutrition and Health of the Universidade Federal de Viçosa (UFV), Brazil, between January 2022 and July 2022, according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human subjects were approved by the Ethics Committee in Research with Human Experimentation of the Universidade Federal de Viçosa (No. 4.543.541/CEPH). Written informed consent was obtained from all subjects/patients. The study is registered at the Brazilian Registry of Clinical Trials (ReBEC) with ID number RBR-8xzkyp2.

During the intervention, participants attended on three occasions at the LAMECC/UFV: initial and final days for blood sample collection, anthropometry, body composition evaluation and fill out questionnaires about physical activity practice and food record, and in the fourth week (30 days) for a face-to-face monitoring visit and anthropometric measurements. Between face-to-face visits, participants received online monitoring (Figure 1).

Compliance was evaluated during the monitoring visit to determine whether participants were adhering to the intervention. We tracked the consumption of cashew nut and cashew nut oil from the initial day of the intervention until their return. If participants in the intervention group still possessed cashew nuts or oil from the beginning of the study upon returning, they were required to surrender them for assessment, verifying whether they had indeed consumed the prescribed quantity. Additionally,

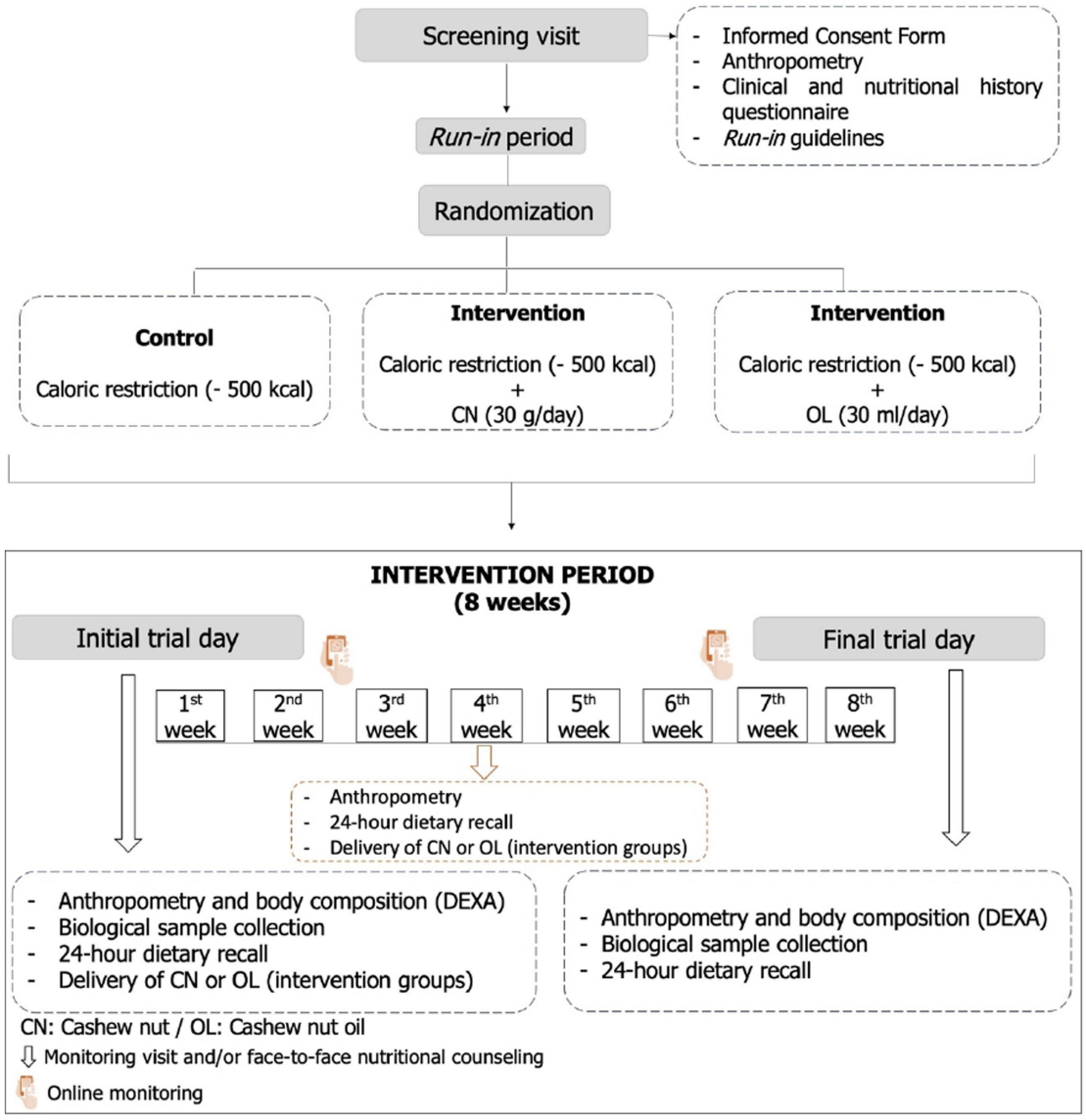


FIGURE 1
Study design flowchart. Source: own elaboration.

during the application of the return questionnaire, we evaluated whether participants had commenced any new medication or developed any illnesses. The participants who started taking any drug or developed any disease listed in the non-inclusion criteria was excluded from the study. Furthermore, compliance was gauged at the study's conclusion by monitoring weight gain. Since the intervention aimed to body fat loss by energy restriction, participants were expected to experience weight loss. Consequently, individuals who exhibited weight gain were excluded from the study due to non-compliance.

2.3 Study participants

Study participants were recruited in Viçosa, Minas Gerais, Brazil, via radio announcements, social media, and the UFV network platform. An online form assessed individuals' eligibility, with eligible candidates undergoing a face-to-face selection questionnaire to confirm eligibility. This questionnaire covered clinical, dietary, sociodemographic, and anthropometric data, along with body composition, blood pressure, and recent biochemical test results. Participants received a booklet containing guidelines about the study and were instructed to report any changes in medication or health status.

The inclusion criteria for participants in the study consisted of men or women (20–55 y); with overweight (27–29.9 kg/m^2), waist circumference (WC) ≥80 cm for women and ≥90 cm for men and with body fat percentage >30% for women and >20% for men associated with at least another component of metabolic syndrome (MS): triglycerides (TG) ≥150 mg/dL; blood pressure ≥130/85 mmHg or fasting blood glucose ≥100 mg/dL or who uses medication to control these markers; or men or women with obesity (BMI ≥ 30 kg/m^2), WC ≥80 cm for women and ≥90 cm for men, and body fat percentage >30% for women and >20% for men with or without metabolic complications.

The non-inclusion criteria included pregnant, lactating, or menopausal women; athletes; vegans; or have a diagnosis of insulin-dependent diabetes; diagnosis of HIV, digestive, hepatic, renal, cardiovascular, thyroid, cancer, inflammatory diseases and eating

disorders; history of drug and/or alcohol abuse; have an aversion or allergy to nuts; present infection in the last month; habitually consume nuts above 30 g/day; use drugs such as anti-inflammatories, corticosteroids, and antibiotics, capable of biochemical alterations; chewing difficult; weight instability (5% of usual weight) in the last 3 months; alcohol consumption >21 units (≈168 g) per week; and intake of vitamin, mineral, and omega 3 supplements.

2.4 Run-in

One week before intervention, the participants participated in a run-in period. During run-in the subjects were instructed to consume their habitual diets without nuts, dried fruits like berries (cranberry, blueberry, goji berry and raisins), açaí, cocoa, cinnamon, olive oil and alcoholic beverages, and to maintain their usual activities. Following the run-in period, individuals whose body weight fluctuated beyond ±1 kg or who consumed prohibited foods or beverages were categorized as "poor responders" and excluded from the study.

2.5 Intervention

All participants received an energy-restricted (−500 kcal/d) diet. In addition, the cashew nut group received 30 g/d of vacuum-sealed cashew nut to be consumed daily, and the cashew nut oil group received 250 mL amber glass bottles of oil along with a measuring cup to standardize the amount to 30 mL/d of cashew nut oil. All dietary advice was individualized and provided by dietitians. At the beginning, five energy-restricted diet options for all groups were designed and divided into five meals: breakfast, morning snack, lunch, afternoon snack, and dinner. All menus were calculated in an Excel spreadsheet using the Brazilian Institute of Geography and Statistics (IBGE) table. Energy requirements were calculated according to the Mifflin's formula (24). For everyone, 500 kcal were reduced from the total calculated energy requirement, considering the level of physical activity of each participant. For the interventional groups, a daily cashew nut (30 g/d) or cashew nut oil (30 mL/d) was added to the individual meal plans, and the percentage of energy from total fat was around 27% for cashew nut group, 32% for the cashew nut oil group, while the control group had around 21% (Table 1). This amount of cashew nut was based on previous studies that have used similar amounts, the PREvención con DIeta MEDiterránea (PREDIMED), which demonstrated beneficial effects in the improvement of blood pressure, lipid profile, lipoprotein particles, inflammation, oxidative stress, and carotid atherosclerosis (25, 26). For the cashew nut oil group, 30 mL/d was calculated to reach similar amounts of lipid between the two intervention groups. Moreover, most guidelines recommend a dietary intake ranging from 10 to 25% for monounsaturated fats (MUFA) and from 6 to 11% for polyunsaturated fats (PUFA) (27). As shown in Table 1 of our paper, the prescribed amounts for cashew nut group were 17.38 ± 2.71% for MUFA and 6.41 ± 1.31% for PUFA, and 14.52 ± 2.32% for MUFA and 6.01 ± 1.3% for PUFA for cashew nut oil group, including 30 g/day of cashew nuts and 30 mL/day of cashew nut oil, respectively. These values are in close alignment with the recommended doses, and people can easily consume on a daily basis. There was no statistical difference in energy calculated between the groups ($p = 0.959$).

Participants were instructed to incorporate cashew nut as a mid-morning snack, while those assigned to the cashew nut oil group were provided with recipes for incorporating the oil into shakes and salad dressings. Members of the cashew nut and cashew nut oil groups (intervention) were explicitly directed not to use the cashew nut or their oil for cooking, roasting, or frying purposes. Additionally, they were advised against consuming olive oil, avocado, or any other nuts aside from the allocated quantity of cashew nut, as well as any other foods with high unsaturated fat content. Control group participants were similarly instructed to refrain from consuming any type of nuts, olive oil, avocado, or other foods high in unsaturated fat.

2.6 Outcomes

The primary outcome of the trial was a change in body fat. Secondary outcomes were changes in the values of body weight, BMI, waist, hip and neck circumferences, waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), cardiometabolic (TG, total cholesterol, LDL-c, HDL-c, VLDL-c, ApoA1, ApoB, cortisol, total cholesterol:HDL-c, LDL-c:HDL-c) and liver function markers (AST, ALT, GGT, alkaline phosphatase) after 8 weeks of follow-up.

Body composition was assessed by dual-energy X-ray absorptiometry (Lunar Prodigy Advance DXA System, GE Lunar) and provided fat mass (FM), fat-free mass (FFM), lean mass (LM), and total mass were obtained from the total body and regions, such as trunk, android, and gynoid. The android area is between the ribs and the pelvis, while the gynoid region includes the hips and upper thighs and overlaps the leg and truncal regions. The body composition in percentages was calculated in relation to total body measurements. Body weight was assessed by a bioelectrical impedance analysis device (Inbody 230, Biospace Corp.). Height (meters), waist, hip, and neck circumferences (centimeters) were measured according to standard protocols. BMI was calculated as weight divided by squared height (kg/m^2) according to World Health Organization (WHO) (28). WHR was calculated as waist divided by hip circumference, and WHtR was calculated as waist divided by height.

Fasting (10–12 h) venous whole blood samples were collected by a registered nurse at baseline and the end of the study (8-wk) into vacuum tubes containing EDTA as an anticoagulant. Then, blood samples were centrifugated (3,500 r.p.m., 10 min, 4°C), separated in aliquots and stored until analysis. The biochemical determinations were performed by the Hemolab clinical analysis laboratory (Viçosa-MG, Brazil). Trained nursing technicians, specifically employed for this project, conducted the blood collection, obtaining samples ranging from 20 to 30 mL via vacuum. Samples were collected for evaluation of cardiometabolic risk as TG (≥150 mg/dL), total cholesterol (≥240 mg/dL), LDL-c (≥160 mg/dL), HDL-c (<40 or <50 mg/dL for men and women, respectively), and VLDL-c (≥30 mg/dL). Also, apolipoprotein-A-1 (APO-A-1), apolipoprotein-B (APO-B), liver markers such as AST transaminase, gamma GT, ALT transaminase, and alkaline phosphatase were compared as mean and standard deviation between groups. Besides, the atherogenic indices, total cholesterol:HDL-c and LDL-c:HDL-c proposed by Castelli (1988) were calculated.

TABLE 1 Macronutrients, dietary fiber, and energy distribution among dietary intervention groups.

Nutrients	Control	Cashew nut	Cashew nut oil	*p*-value
Total fat (%)	21.19 ± 1.84 [c]	27.04 ± 2.49 [b]	31.83 ± 3.87 [a]	<0.001
Saturated Fat (%)	7.87 ± 1.97 [b]	10.96 ± 1.51 [a]	7.78 ± 1.47 [b]	<0.001
Monounsaturated Fat (%)	5.97 ± 1.58 [c]	17.38 ± 2.71 [a]	14.52 ± 2.32 [b]	<0.001
Polyunsaturated Fat (%)	3.57 ± 0.86 [b]	6.41 ± 1.31 [a]	6.01 ± 1.33 [a]	<0.001
Carbohydrates (%)	55.26 ± 3.51 [a]	48.06 ± 4.17 [b]	47.17 ± 5.55 [b]	<0.001
Proteins (%)	23.55 ± 2.74 [a]	24.89 ± 3.14 [a]	20.99 ± 3.15 [b]	<0.001
Dietary fiber (g)	25.90 ± 7.69	22.62 ± 7.02	22.64 ± 8.49	0.065
Energy (kcal)	1600.83 ± 318.29	1607.40 ± 307.82	1618.05 ± 317.15	0.959

Superscript alphabets [(a–c)] not indicated by the same letter means statistical difference between groups ($p < 0.005$) according to one-way ANOVA or Kruskal–Wallis followed by post hoc tests. Letter a represents the highest value, while letter c is the lowest.

2.7 Dietary assessments

At baseline and the end of the study, we applied a 24 h recall (24HR) to monitor food consumption during the intervention. The reported intake was analyzed using the 24HR-ERICA software, adapted for the Brazilian population, and the IBGE table (29, 30).

2.8 Sample size and study power

The sample size and study power were determined using the G*Power 3.1 program. For this calculation, a total of 57 volunteers were determined, based on an average estimated effect size derived from clinical studies (0.30), considering statistical analyses for three groups, two intervention points (baseline and endpoint), an alpha value set at 0.05, and a power of 0.80. By adding 20% as a result of losses during follow-up, the total sample size was determined to be 68 participants (Supplementary Figure S1).

For the power of the study, the effect size of 0.28 was calculated from the Eta squared (0.074) based on the values of body fat from our database, an α of 0.05 was used, three groups, two intervention points (baseline and endpoint), and the total sample size of 68 individuals, whom we have information on body fat data. The calculation revealed a study power of 0.94 (Supplementary Figure S2).

2.9 Randomization

To initiate the intervention, after the run-in period, researchers performed the randomization using MinimPy 0.3 program (31). This was achieved through the stratified minimization method, accounting for sex, age, and BMI, with three levels per factor. This approach ensured a well-balanced distribution of potential factors that could interfere with the outcome variables.

2.10 Statistical analysis

Statistical analysis was conducted using SPSS version 22.0 (SPSS, Inc.), and figures displaying statistical analysis were produced using Microsoft Excel. A p-value <0.05 was considered statistically significant. The Shapiro–Wilk test was performed to check the normality of variables. Data are expressed as mean values and standard deviation. Among groups, variable changes were compared by one-way ANOVA followed by Tukey's *post hoc* test or using the non-parametric Kruskal–Wallis test followed by Dunn's *post hoc* test. To compare differences between baseline and post-intervention within the groups, pairwise tests were performed (paired *t*-test or Wilcoxon). McNemar's test was employed to analyze paired nominal data.

3 Results

3.1 Cashew nut and cashew nut oil

Regarding minerals, the content of calcium (CN: 0.37 g/kg vs. OL: 0.01 g/kg) and iron (CN: 64.00 mg/kg vs. OL: 6.10 mg/kg) was higher in cashew nut compared to the oil. Other minerals were not detected in the oil. The oil demonstrated elevated amounts of vitamin E (OL: 2225.93 μg/100 g vs. CN: 1334.02 μg/100 g) and γ tocopherol (OL: 2055.12 μg/100 g vs. CN: 1334.02 μg/100 g) compared to cashew nut. Additionally, β tocopherol, γ tocotrienol, and δ tocotrienol, which were not present in cashew nut, were found in the oil. Conversely, cashew nut exhibited higher levels of total phenolics (CN: 60.45 vs. OL: 2.25 mg GAE (gallic acid equivalent)/100 g) and antioxidant capacity (CN: 15.99 vs. OL: 9.18 uM TE/g sample) in comparison to their oil (Supplementary Tables S1, S2).

3.2 Participants and compliance

Among the participants initially assessed for study eligibility ($n = 166$), 98 were included and randomly assigned to the following groups: CT ($n = 32$), CN ($n = 32$) and OL ($n = 34$). Of these, 74 participants completed the 8-wk intervention, allocated as follows: CT ($n = 20$), CN ($n = 25$) and OL ($n = 29$). Of these 74 participants, six participants were subsequently excluded due to non-compliance with the prescribed diet as they gained weight. Since all participants were on a low-energy diet, weight loss was expected. Consequently, those who concluded the study with weight gain were excluded due to non-compliance, resulting in the following numbers for analysis in each group: CT ($n = 19$), CN ($n = 24$) and OL ($n = 25$) (Figure 2).

The study population predominantly comprised females ($n = 40$), individuals with a completed college education/incomplete postgraduate ($n = 27$), white ($n = 33$), self-reported single marital status ($n = 39$), and a family income between 2 and 3 minimum wages ($n = 23$). Regarding

lifestyle habits, the majority did not smoke ($n = 65$) and did not engage in regular physical activity ($n = 43$) (Table 2). Concerning cardiometabolic risk at baseline, 19 (79.2%), 15 (78.9%), and 23 (92%) individuals had obesity, while 13 (54.2%), 11 (57.9%), and 13 (52%) had dyslipidemia in the CN, CT, and OL groups, respectively (data not shown).

Following the 8-wk intervention, all participants in the study demonstrated a reduction in energy intake (−205 kcal; $p = 0.026$), indicating adherence to energy-restriction (data not shown). However, this reduction was not as substantial as expected (−500 kcal). When examining the groups individually, the control group exhibited a reduction in the intake of saturated fat (SFA), while the cashew nut group experienced a decrease in polyunsaturated fat (PUFA) and α-linolenic acid (Table 3).

3.3 Body fat and adiposity indicators

After 8-wk of intervention, all groups presented significant reduction in body fat (kg), with consequent weight-loss (CT: −4.4%; CN: −4.1%; OL: −3.5%). The participants also had significant reduction in other adiposity indicators as: weight-loss, WC (cm), hip circumference (HC) (cm), and WHtR. Concerning WHR and body fat (%), significant losses were observed only in the control and cashew nut groups. Both intervention groups (cashew nut and oil) exhibited a significant reduction in neck circumference. No differences were found between groups, except for android fat in the endpoint between CT and OL groups (CT: 9.5 ± 1.3%; OL: 8.1 ± 1.5%) (Table 4). Additionally, after the intervention, there was a decrease in the number of individuals with obesity among those who consumed cashew nut (19 (27.94%) vs. 13 (19.12%); $p = 0.032$) (Supplementary Figure S3).

3.4 Cardiometabolic and liver function markers

After 8-wk intervention, all groups reduced total cholesterol and GGT. In the intervention groups, both the cashew and oil groups had reductions in apo B, while those consuming only the oil experienced

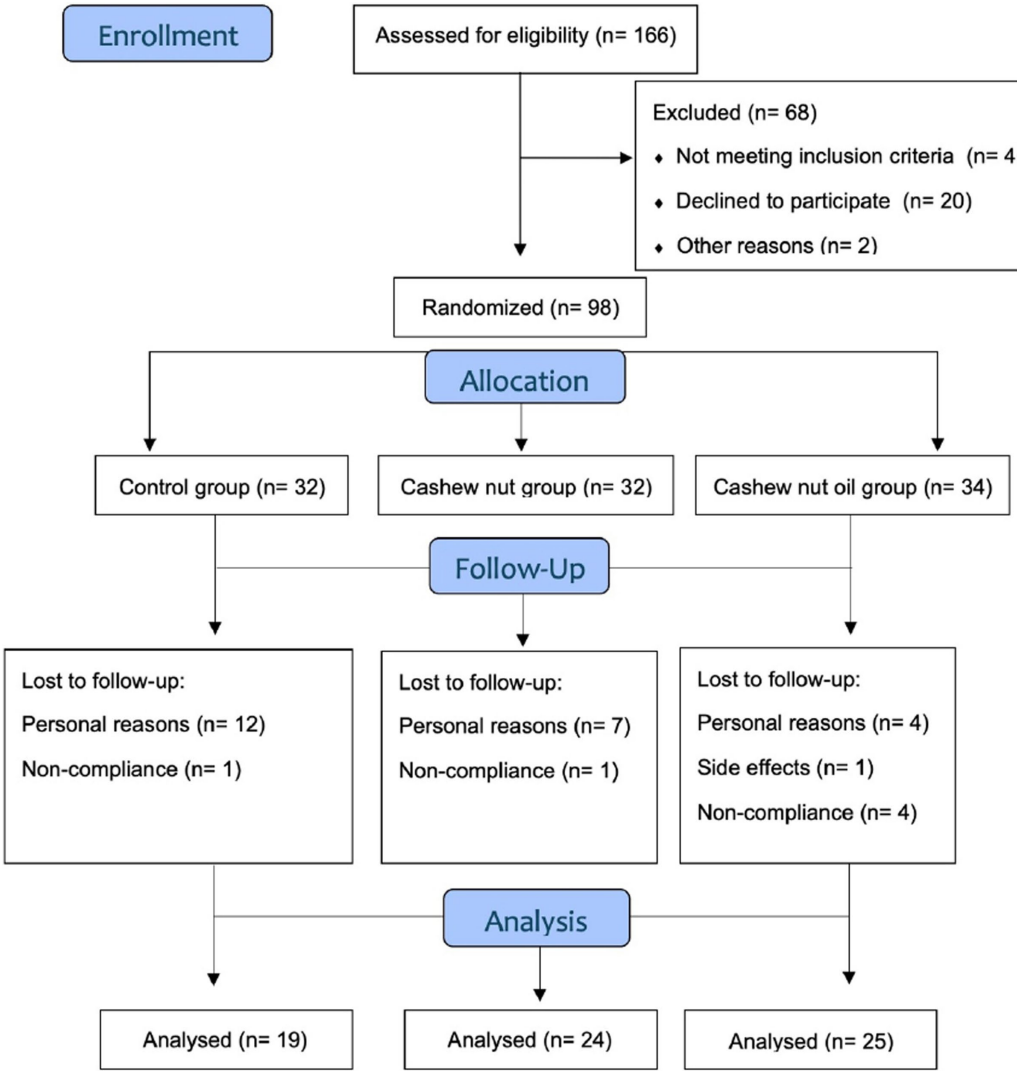


FIGURE 2
Consort statement of participants flow diagram.

TABLE 2 Sociodemographic and behavioral characteristics of the total participants according to the control and intervention groups (cashew nut and cashew nut oil).

Variables	Total	Control	Cashew nut	Cashew nut oil	*p*-value
	(*n*=68)	(*n*= 19)	(*n*= 24)	(*n*= 25)	
Age (years)	33.31 ± 8.75	34.68 ± 9.65	33.79 ±8.39	31.80 ± 8.50	0.53
Sex:					
Male	28 (41.2)	10 (35.7)	9 (32.1)	9 (32.1)	0.49
Female	40 (58.8)	9 (22.5)	15 (37.5)	16 (40)	
Smoking					
Yes	3 (4.4)	1 (33.3)	1 (33.3)	1 (33.3)	0.98
No	65 (95.6)	18 (27.7)	23 (35.4)	24 (36.9)	
Physically active					
Yes	25 (36.8)	5 (20)	10 (40)	10 (40)	0.53
No	43 (63.2)	14 (32.6)	14 (32.6)	15 (34.9)	
Schooling					
Complete primary education / Incomplete high school	2 (2.9)	0 (0)	0 (0)	2 (100)	0.09
Complete high school / Incomplete college education	23 (33.8)	7 (30.4)	6 (26.1)	10 (43.5)	
Complete college education / Incomplete postgraduate	27 (39.7)	10 (37)	8 (29.6)	9 (33.3)	
Complete postgraduate	16 (23.5)	2 (12.5)	10 (62.5)	4 (25)	
Family income					
1 minimum wage	3 (4.4)	2 (66.7)	0 (0)	1 (33.3)	0.55
1 to 2 minimum wages	16 (23.5)	4 (25)	3 (18.8)	9 (56.3)	
2 to 3 minimum wages	23 (33.8)	7 (30.4)	9 (39.1)	7 (30.4)	
3 to 5 minimum wages	15 (22.1)	4 (26.7)	6 (40)	5 (33.3)	
5 to 10 minimum wages	7 (10.3)	1 (14.3)	3 (42.9)	3 (42.9)	
> 10 minimum wages	3 (4.4)	1 (33.3)	2 (66.7)	0 (0)	
Race					
White	33 (48.5)	8 (24.2)	12 (36.4)	13 (39.4)	0.92
Black	15 (22.1)	4 (26.7)	6 (40)	5 (33.3)	
Pardo	20 (29.4)	7 (35)	6 (30)	7 (35)	
Marital status					
Single	39 (57.4)	9 (23.1)	11 (28.2)	19 (48.7)	**0.02**
Married/stable partnership	27 (39.7)	10 (37)	13 (48.1)	4 (14.8)	
Divorced	2 (2.9)	0 (0)	0 (0)	2 (100)	

For age values, one-way ANOVA followed by post hoc tests were used and the results are represented by mean ± SD (standard deviation). For all other variables, the chi-square test was used, and the results are presented in absolute and relative frequency values as shown in the table as n (%).

reductions in LDL-c and the atherogenic index (total cholesterol/HDL-c). The control and cashew nut groups observed reductions in TG and VLDL-c. In terms of liver enzymes, the cashew nut group demonstrated reductions in AST and ALT. No differences were found between groups (Table 5).

4 Discussion

In this clinical trial, all groups demonstrated a reduction in body fat (kg) and other total adiposity (body weight and BMI) and central adiposity indicators (WC, HC and WHtR), as well as in total

TABLE 3 Food consumption according to 8- wk energy-restricted intervention groups.

Daily Nutrient Intake	Control ($n = 17$)			Cashew nut ($n = 20$)			Cashew nut oil ($n = 23$)		
	Baseline	Δ	*p*-value	Baseline	Δ	*p*-value	Baseline	Δ	*p*-value
Energy intake (kcal)	1667.7 ± 560.3	−301.3 ± 692.8	0.114	1663.3 ± 592.6	−32.5 ± 685.4	0.838	1670.9 ± 671.8	−284.6 ± 660.6	0.051
Protein (% EI)	20.1 ± 6.9	−1.2 ± 5.9	0.455	20.60 ± 6.3	0.7 ± 6.4	0.640	17.7 ± 6.7	1.8 ± 8.2	0.312
Carbohydrate (% EI)	44.2 ± 10.5	6.4 ± 13.1	0.078	46.1 ± 10.3	−0.3 ± 13.5	0.920	47.2 ± 8.6	−2.4 ± 12.5	0.378
Lipids (% EI)	35.8 ± 8.8	−4.1 ± 11.4	0.186	34.1 ± 8.2	−0.2 ± 13.2	0.957	35.7 ± 8.8	1.4 ± 11.7	0.572
SFA (g)	13.4 ± 4.8	−2.5 ± 4.2	0.037	12.4 ± 3.00	0.1 ± 6.1	0.959	11.9 ± 3.5	−0.3 ± 5.6	0.819
MUFA (g)	12.3 ± 3.7	−0.9 ± 5.8	0.540	11.5 ± 3.9	1.6 ± 5.8	0.249	12.7 ± 4.4	1.3 ± 6.2	0.332
PUFA (g)	5.6 ± 1.3	−0.1 ± 2.9	0.892	6.7 ± 3.1	−2.0 ± 3.4	0.019	6.2 ± 3.00	−0.2 ± 3.8	0.799
LA (C18:2n6) (g)	9.2 ± 4.2	−1.9 ± 6.3	0.240	10.3 ± 6.7	−2.7 ± 6.7	0.100	10.1 ± 6.5	−1.7 ± 8.8	0.374
ALA (C18:3n3) (g)	0.6 ± 0.9	−0.1 ± 1.1	0.696	1.2 ± 1.7	−0.9 ± 1.8	0.037	0.9 ± 1.1	−0.3 ± 1.2	0.324
Cholesterol (mg)	387.8 ± 276.5	−137.3 ± 262.7	0.062	341.2 ± 293.8	−31.3 ± 296.4	0.651	328.6 ± 226.5	9.7 ± 304.5	0.880
Fiber (g)	17.6 ± 11.1	1.8 ± 10.9	0.522	17.3 ± 7.2	0.9 ± 8.4	0.644	15.6 ± 7.7	0.4 ± 6.7	0.786

Δ = endpoint − baseline assessment. Values are mean ± SD (standard deviation). *p*-value = intra-group comparison (paired *t*-test). According to one-way ANOVA or Kruskal–Wallis followed by post hoc tests there was no statistical difference between groups. EI, energy intake; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid. LA (C18:2n6): linoleic acid. ALA (C18:3n3): α-linolenic acid.

cholesterol and GGT. Additionally, both intervention groups (CN and OL) experienced a decrease in neck circumference and apo B, but not control group. Cashew nut group reduced liver enzymes (AST and ALT), while cashew nut oil group reduced LDL-c and atherogenic index. Furthermore, there was a reduction in the number of individuals with obesity in the group consuming cashew nut. However, no differences were found between groups.

We expected that the presence of cashew nut or cashew nut oil would exert a greater reduction in body fat, and other adiposity indicators, as well as cardiometabolic markers compared to control group. Thus, the results of this study were not consistent with our hypothesis. Several factors are crucial for contributing to weight loss, with chewing time playing a pivotal role in satiety due to its impact on neural and endocrine mechanisms. The effort involved in oral consumption and the duration spent chewing whole nuts have been linked to significant effects on satiety, the presence of fat in meals, and the stimulation of postprandial hormones such as insulin, ghrelin, CCK, PYY, and GLP-1 (32), which has previously been discussed by our research group (33). As oil has a liquid form, its digestion and absorption are quicker, abbreviating the duration of satiety. A study showed that satiety increased after chewing whole walnuts compared to walnut butter, although gut peptide concentrations remained unchanged (34). Nonetheless, although we standardized the timing of cashew nut consumption among all participants, we did not regulate the duration of chewing, which made a detailed discussion on this aspect impossible. Thus, to gain a comprehensive understanding of the effects of cashew nut consumption on satiety in future studies, it is important to incorporate a protocol that specifies chewing duration. Previous findings from our research group indicated a decrease in ghrelin hormone levels among those who consumed a mix of nuts (30 g of cashew nuts +15 g of Brazil nuts) compared to the control group (35). Confounding factors may also have affected the results, notably the inadequate adherence to the prescribed diet. Despite a prescribed caloric reduction of 500 kcal, the observed reduction was only 205 kcal, as previously demonstrated. This indicates that, overall, participants did not adhere to the diet as intended, potentially impacting the results irrespective of the interventions.

Our previous research supports the findings of this study concerning adiposity indicators and other cardiometabolic markers. We demonstrated that both the control group and the group consuming a mix of nuts (30 g of cashew nuts +15 g of Brazil nuts), alongside an energy-restricted diet for 8 weeks, experienced reductions in total and central adiposity indicators and other cardiometabolic markers, with no statistically significant differences between the groups. However, exceptions were observed in body fat (%) and VCAM-1 levels, where a statistically significant difference emerged, indicating a reduction in the group that consumed the mix of nuts compared to an increase in the control group (36).

Nuts appear to not promote an increase in adiposity markers, while the reduction of these markers is still controversy, depending on the type of nut and intervention design (37). A meta-analysis has shown that almonds were able to reduce body weight and fat mass, but not waist circumference (38). On the other hand, walnuts and cashews did not significantly modify adiposity indicators (39, 40). However, it is important to highlight that there are relatively few studies evaluating the health effects of cashew nuts compared to other nuts such as almonds, walnuts, pistachio, and peanuts (37, 40–42). Despite this, a meta-analysis presented an interesting result when comparing the duration of nut intake interventions (<12 weeks vs. ≥12 weeks), showing sustained significance in reductions of body weight, BMI, and WC in individuals with overweight and obesity when the intervention duration was ≥12 weeks, in contrast to durations of <12 weeks (37). This result leads us to consider that perhaps if the duration of our study were ≥12 weeks, we could find differences between the intervention groups compared to the control group, especially considering our target population (individuals with overweight and obesity), since the result demonstrated by this meta-analysis was for this specific group.

While our study did not uncover any statistically significant differences among the three groups, both cashew nuts and cashew nut oil demonstrated a potential in improving cardiovascular risk. This was evidenced by a statistically significant reduction in neck circumference and apo B levels observed in both intervention groups, which was not observed in the control group. The neck circumference is an indicator of subcutaneous fat

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TABLE 4 Change in body fat and other adiposity indicators according to 8- wk energy-restricted intervention groups.

Outcomes		Baseline	Endpoint	Δ	*p*-value (intraindividual)
		(*n* = 68)	(*n* = 68)		
Body fat (kg)	CT	38.5 ± 7.7	35.4 ± 8.1	−3.1 ± 2.8	<0.001
	CN	41.5 ± 8.9	38.2 ± 9.1	−3.3 ± 2.7	<0.001
	OL	41.1 ± 7.9	39.3 ± 8.9	−1.8 ± 2.6	0.002
p-value (interindividual)		0.357	0.345	0.106	
Body fat (%)	CT	40.1 ± 7.8	38.5 ± 8.2	−1.6 ± 1.6	<0.001
	CN	43.6 ± 7.6	41.8 ± 8.4	−1.9 ± 1.9	<0.001
	OL	43.8 ± 7.6	43.2 ± 8.4	−0.7 ± 2.0	0.106
p-value (interindividual)		0.307	0.206	0.085	
Android fat (%)	CT	9.7 ± 1.3	9.5 ± 1.3 [a]	−0.2 ± 0.6	0.233
	CN	9.4 ± 3.4	8.7 ± 1.7 [ab]	−0.8 ± 2.6	0.169
	OL	8.5 ± 1.4	8.1 ± 1.5 [b]	−0.4 ± 1.1	0.072
p-value (interindividual)		0.122	0.022	0.579	
Gynoid fat (%)	CT	17.2 ± 1.8	17.3 ± 1.8	0.1 ± 0.7	0.463
	CN	18.9 ± 3.6	18.2 ± 1.5	−0.7 ± 3.5	0.360
	OL	17.8 ± 2.3	18.2 ± 1.9	0.3 ± 1.2	0.182
p-value (interindividual)		0.353	0.214	0.372	
Muscle mass (kg)	CT	54.3 ± 13.0	53.8 ± 12.5	−0.5 ± 1.8	0.943
	CN	50.9 ± 11.3	50.4 ± 11.4	−0.4 ± 1.7	0.241
	OL	50.2 ± 12.1	48.9 ± 11.6	−1.2 ± 2.0	0.005
p-value (interindividual)		0.753	0.472	0.582	
Body weight (kg)	CT	95.4 ± 17.2	91.2 ± 15.9	−4.2 ± 3.8	<0.001
	CN	96.1 ± 14.8	92.2 ± 13.8	−3.9 ± 3.1	<0.001
	OL	95.6 ± 14.3	92.2 ± 13.8	−3.4 ± 2.4	<0.001
p-value (interindividual)		0.982	0.944	0.852	
BMI (kg/m^2)	CT	33.7 ± 3.7	32.3 ± 3.7	−1.4 ± 1.2	<0.001
	CN	34.1 ± 4.9	32.7 ± 4.8	−1.4 ± 1.0	<0.001
	OL	33.9 ± 3.6	32.8 ± 3.8	−1.2 ± 0.8	<0.001
p-value (interindividual)		0.978	0.804	0.833	
WC (cm)	CT	109.5 ± 9.5	104.4 ± 7.7	−5.1 ± 4.6	<0.001
	CN	109.3 ± 11.7	105.4 ± 11.7	−3.9 ± 3.9	<0.001
	OL	107.7 ± 12.1	103.9 ± 10.5	−3.7 ± 5.3	0.002
p-value (interindividual)		0.838	0.884	0.612	
HC (cm)	CT	113.8 ± 5.7	110.8 ± 7.0	−2.9 ± 3.0	<0.001
	CN	116.6 ± 7.3	113.9 ± 7.4	−2.7 ± 3.1	<0.001
	OL	116.8 ± 6.6	113.8 ± 6.2	−2.9 ± 2.3	<0.001
p-value (interindividual)		0.283	0.271	0.902	
WHR	CT	0.9 ± 0.0	0.9 ± 0.1	−0.01 ± 0.0	
	CN	0.9 ± 0.1	0.9 ± 0.1	−0.01 ± 0.0	0.010
	OL	0.9 ± 0.1	0.9 ± 0.1	−0.01 ± 0.0	0.264
p-value (interindividual)		0.186	0.323	0.552	
WHtR	CT	0.7 ± 0.1	0.6 ± 0.1	−0.03 ± 0.0	0.003
	CN	0.7 ± 0.1	0.6 ± 0.1	−0.02 ± 0.0	<0.001
	OL	0.6 ± 0.1	0.6 ± 0.1	−0.02 ± 0.0	0.003
p-value (interindividual)		0.837	0.887	0.591	
Neck circumference (cm)	CT	40.6 ± 3.5	39.6 ± 3.5	−0.9 ± 2.5	0.104
	CN	39.9 ± 4.5	38.9 ± 3.8	−1.0 ± 1.2	<0.001
	OL	38.9 ± 4.4	38.4 ± 4.1	−0.5 ± 1.2	0.038
p-value (interindividual)		0.438	0.555	0.238	

BMI, body mass index; HC, hip circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; CT, control; CN, cashew nut; OL, cashew nut oil. Paired *t* test or Wilcoxon test ($p < 0.05$ within-group); Superscript alphabets ([a–b]) not indicated by the same letter in the same column means that there was a statistical difference between groups ($p < 0.05$) according to one-way ANOVA or Kruskal–Wallis followed by post hoc tests.

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TABLE 5 Change in cardiometabolic and liver function markers according to 8- wk energy-restricted intervention groups.

Biomarkers		Baseline (n = 68)	Endpoint (n = 68)	Δ	p-value (intraindividual)
Cardiometabolic markers					
Triglycerides (mg/dL)	CT	176.4 ± 98.4	124.1 ± 79.2	−52.3 ± 46.8	<0.001
	CN	127.9 ± 58.8	96.9 ± 45.6	−30.9 ± 46.2	0.003
	OL	142.2 ± 89.2	120.9 ± 74.9	−21.3 ± 48.9	0.055
p-value (interindividual)		0.119	0.284	0.052	
Total cholesterol (mg/dL)	CT	194.3 ± 30.9	181.6 ± 37.2	−12.7 ± 23.9	0.046
	CN	186.2 ± 31.6	172.4 ± 32.4	−13.8 ± 24.4	0.011
	OL	207.2 ± 46.7	190.8 ± 39.8	−16.4 ± 30.4	0.007
p-value (interindividual)		0.133	0.266	0.996	
LDL-c (mg/dL)	CT	103.1 ± 30.3	101.6 ± 31.6	−1.5 ± 25.4	0.616
	CN	105.9 ± 30.1	100.1 ± 30.9	−5.8 ± 18.5	0.141
	OL	121.4 ± 34.7	109.9 ± 30.3	−11.5 ± 21.8	0.016
p-value (interindividual)		0.119	0.357	0.316	
HDL-c (mg/dL)	CT	56.1 ± 11.1	55.1 ± 12.2	−1.0 ± 6.3	0.636
	CN	54.3 ± 9.8	52.9 ± 9.1	−1.5 ± 6.7	0.216
	OL	57.4 ± 11.5	56.8 ± 13.5	−0.6 ± 5.4	0.464
p-value (interindividual)		0.735	0.694	0.895	
VLDL-c (mg/dL)	CT	35.3 ± 19.7	24.8 ± 15.8	−10.5 ± 9.7	0.002
	CN	25.8 ± 11.4	19.4 ± 9.1	−4.3 ± 9.8	0.002
	OL	28.4 ± 17.8	24.2 ± 14.9	−3.7 ± 10.2	0.055
p-value (interindividual)		0.119	0.284	0.050	
ApoA1 (mg/dL)	CT	127.9 ± 18.8	123.8 ± 17.9	−4.1 ± 10.1	0.111
	CN	120.8 ± 12.1	117.2 ± 14.4	−3.6 ± 15.7	0.123
	OL	127.0 ± 19.6	124.6 ± 22.7	−2.4 ± 12.1	0.368
p-value (interindividual)		0.583	0.543	0.912	
ApoB (mg/dL)	CT	87.8 ± 15.1	84.4 ± 22.2	−3.4 ± 13.1	0.103
	CN	84.7 ± 17.4	78.1 ± 18.3	−6.6 ± 10.7	0.003
	OL	93.7 ± 25.1	86.6 ± 21.3	−7.0 ± 15.3	0.020
p-value (interindividual)		0.291	0.322	0.980	
Cortisol (mcg/dL)	CT	13.0 ± 3.3	13.7 ± 4.7	0.7 ± 4.7	0.546
	CN	14.9 ± 6.892	14.9 ± 5.570	0.02 ± 6.4	0.753
	OL	14.4 ± 5.9	15.0 ± 5.6	0.67 ± 5.8	0.502
p-value (interindividual)		0.899	0.664	0.909	
Atherogenic indices					
Total cholesterol:HDL-c	CT	3.6 ± 0.8	3.4 ± 0.8	−0.2 ± 0.4	0.091
	CN	3.5 ± 0.7	3.4 ± 0.9	−0.1 ± 0.4	0.076
	OL	3.7 ± 0.9	3.5 ± 0.7	−0.2 ± 0.5	0.026
p-value (interindividual)		0.833	0.742	0.741	
LDL-c:HDL-c	CT	1.9 ± 0.6	1.9 ± 0.6	0.02 ± 0.5	0.968
	CN	1.9 ± 0.6	1.9 ± 0.7	−0.03 ± 0.4	0.394
	OL	2.2 ± 0.7	2.0 ± 0.6	−0.2 ± 0.4	0.072
p-value (interindividual)		0.297	0.757	0.310	

(Continued)

TABLE 5 (Continued)

Biomarkers		Baseline (n = 68)	Endpoint (n = 68)	Δ	p-value (intraindividual)
Liver markers					
AST (U/L)	CT	26.7 ± 12.4	22.5 ± 7.5	−4.3 ± 11.7	0.098
	CN	24.7 ± 6.5	21.5 ± 5.5	−3.1 ± 5.3	0.007
	OL	25.5 ± 8.9	26.5 ± 14.9	1.0 ± 11.7	0.945
p-value (interindividual)		0.884	0.825	0.400	
ALT (U/L)	CT	25.7 ± 9.7	24.1 ± 12.6	−1.6 ± 11.7	0.314
	CN	26.8 ± 14.2	20.8 ± 8.7	−6.0 ± 9.9	<0.001
	OL	25.9 ± 12.4	25.0 ± 14.4	−0.9 ± 7.8	0.375
p-value (interindividual)		0.924	0.671	0.240	
GGT (U/L)	CT	39.8 ± 14.8	32.8 ± 13.8	−7.0 ± 10.7	0.005
	CN	42.9 ± 30.9	31.4 ± 16.4	−11.5 ± 20.3	<0.001
	OL	39.0 ± 19.1	31.4 ± 13.9	−7.1 ± 10.8	0.005
p-value (interindividual)		0.746	0.690	0.902	
Alkaline phosphatase (U/L)	CT	79.2 ± 21.0	79.1 ± 17.9	−0.1 ± 7.1	0.679
	CN	81.4 ± 23.5	82.9 ± 25.1	1.5 ± 12.1	0.661
	OL	76.9 ± 21.5	79.1 ± 19.5	2.2 ± 11.1	0.277
p-value (interindividual)		0.781	0.561	0.784	

LDL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein cholesterol; VLDL-c, very-low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CT, control; CN, cashew nut; OL, cashew nut oil. Paired t-test or Wilcoxon test ($p < 0.05$ within-group); Superscript alphabets ($^{a-b}$) not indicated by the same letter in the same column means that there was a statistical difference between groups ($p < 0.05$) according to one-way ANOVA or Kruskal–Wallis followed by post hoc tests.

distribution (43). A larger neck circumference is suggestive of higher levels of body fat, including visceral adipose tissue, which poses a risk for cardiovascular disease (44). The group that consumed cashew nuts experienced an average reduction of −1.0 ± 1.2 cm in neck circumference, while the group that consumed cashew nut oil experienced an average reduction of −0.5 ± 1.2 cm. Although these reductions may appear minor, they hold significance due to the neck perimeter's sensitivity as a health indicator. This is supported by the fact that 1 cm increase in neck circumference can lead to a rise in the risk of obesity by 1.21 to 1.73%, of systolic blood pressure (SBP) by 1.06 to 1.10%, and of diastolic blood pressure (DBP) by 1.08 to 1.06% (45). Additionally, it can elevate the risk of diabetes by 1.04 to 1.10%, hypertriglyceridemia by 1.04 to 1.10%, and metabolic syndrome by 1.08 to 1.28% (45). Thus, even modest reductions in neck circumference can exert a significant influence on decreasing cardiovascular risk. Other studies found that daily nut consumption led to decreases in LDL-c by 4.2 mg/dL and apo B levels by 4.1 mg/dL (4 and 6% reduction in coronary events, respectively) (46). Both pistachios and almonds reduced apo B levels (47, 48), while pistachios also lowered LDL-c levels (47). A meta-analysis involving twenty-five randomized controlled trials (RCTs) along with four newer RCTs and a controlled parallel trial showed that reducing SFA intake while increasing MUFA intake leads to a reduction in plasma apoB and LDL-C. However, the findings are less consistent concerning to plasma TAG, HDL-C, apoA1, and the apoB:apoA1 ratio (49). As evidenced, a decrease of 4.1 mg/dL in cholesterol levels leads to a 6% reduction in coronary events. Within the scope of our study, we observed a reduction of 6.6 mg/dL in the group that consumed cashew nuts and 7.0 mg/dL in the group that ingested cashew nut oil. This finding has significant clinical implications, suggesting a potential impact on the prevention of future coronary events.

Another important outcome of this study was the significant reduction in LDL concentrations and the atherogenic index (total cholesterol:HDL) observed in the OL-group. These markers are closely associated with cardiovascular risk (50). LDL-c, recognized as an atherogenic lipoprotein, plays a pivotal role in the development and progression of atherosclerosis. The TC:HDL-C ratio is considered a more valuable marker for determining Coronary Heart Disease (CHD) risk, being more sensitive and specific than total cholesterol as a risk predictor (51, 52).

Cashew nut, with their high content of MUFA and PUFA and low levels of SFAs, have previously been associated with LDL-lowering effects (53). Our study found a PUFA/SFA ratio of 1.04 ± 0.01 (Table 1). This ratio indicates the potential of a food to contribute to fat accumulation in body tissues when consumed. The Department of Health and Social Security advises avoiding edible oils with a PUFA/SFA ratio below 0.45 (15). Therefore, the cashew nut oil used in our clinical trial is considered beneficial for the human diet and could help reduce cardiometabolic markers.

Moreover, oleic acid, the main type of MUFA present in cashew nut, is associated with better cardiovascular health, and may have contributed to the reduction of these markers. Oleic acid exhibits several protective mechanisms in vascular cells (54). Firstly, it increases the levels of uncoupling proteins-2 (UCP-2), which are associated with vascular cell protection, preventing atherosclerosis development (55). Also, oleic acid reduces the activation of JNK1/2, crucial for cardiovascular cells, through its anti-inflammatory action. Unexpectedly, oleic acid has been found to possess anti-inflammatory properties by preventing NLRP3 inflammasome activation (56). Furthermore, oleic acid protects against vascular smooth muscle cell (VSMC) proliferation stimulated by TNF-α, Ang II, or palmitate, thereby contributing to the prevention of

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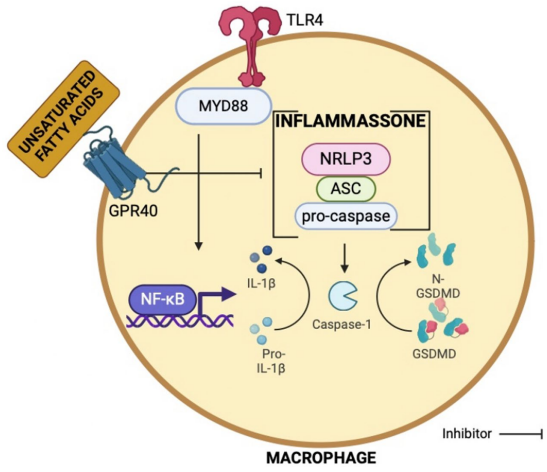

FIGURE 3
Biomechanical pathway showing the possible effects of cashew nut oil towards improving atherogenic function.

atherosclerotic plaque growth (57). Thus, a possible biomechanical pathway was proposed showing the possible effects of cashew nut oil towards improving atherogenic function (Figure 3).

Consistent with our findings, the PREDIMED study revealed that the consumption of olive oil, particularly the extra-virgin variety, was associated with reduced risks of cardiovascular disease and mortality in individuals at high cardiovascular risk. The authors attribute these benefits to components present in extra virgin olive oil (EVOO), such as the high content of MUFAs, which are less susceptible to oxidation than other types of fatty acids. Additionally, they point to other minor components with significant biological properties, including phenolic compounds, vitamin E, and other lipid derivative molecules (such as squalene, tocopherols, and triterpene alcohols), particularly abundant in EVOO (58). Cashew nut oil had significant amounts of both MUFA and vitamin E, whereas cashew nuts were rich in phenolic compounds. It is plausible that these components contributed to the reduction of markers associated with cardiovascular risk.

Another noteworthy outcome of the present study was the reductions in liver enzymes observed in the group that consumed cashew nut. Abnormal levels of liver enzymes have been linked to metabolic disorders such as insulin resistance and diabetes (59). Cashew nut contained higher amounts of magnesium, selenium, and phenolic compounds. Maybe the combination of these elements in cashew nut can contribute for these findings, as some studies indicate that supplementation with magnesium, and selenium can be beneficial to the liver (60–63). Studies have indicated that magnesium is inversely related to non-alcoholic fatty liver disease (NAFLD) (8, 9). In particular, evidence shows that magnesium influences AST and ALT enzymes, as magnesium treatment normalized AST in 87% and ALT in 91% of patients, compared to 57 and 63%, respectively, of the group treated with placebo (10). Phenolic compounds appear to act on the liver X receptor (LXR), which is found mainly in the liver (11). One of their main roles is to regulate cholesterol and lipid metabolism, which makes them ideal targets to prevent or improve dyslipidemia (11). Related to this, pecan shells have high antioxidant potential, and these phenolic compounds present in pecan shells may be involved in reduced lipid peroxidation observed in liver tissue (64). The beneficial actions of phytochemicals are acknowledged for their biologically active polyphenols, such as flavonoids and phenolic acids, which exhibit potent antioxidant activities, including the reduction of lipid peroxidation observed in liver tissue (65). However, whether cashew nuts can affect liver function is unknown. The exact mechanism by which cashew nuts influence biomarkers of liver function remains incompletely understood. Further investigations, mainly using animal models, are needed to elucidate the effect of cashew nuts on the biomechanical pathway in the liver.

Cashew nut and cashew nut oil have the potential to improve cardiometabolic markers. However, the energy-restricted diet alone has also demonstrated substantial health benefits, including weight loss, improved body composition, and lowered levels of total cholesterol and triglycerides. Therefore, when aiming to enhance health, incorporating these two foods should be complemented by a comprehensive and well-balanced eating plan, taking into account the overall nutritional quality of the diet and the bioactive compounds present in the foods. Other studies from our laboratory also demonstrated beneficial effects of nuts on health. The consumption of the mix of nuts enhanced the intestinal microbiota correlating with body fat reduction (66). In this way, our research group has demonstrated some beneficial effects of Brazilian nuts (Brazil nut and cashew nut) during energy-restriction treatment. Furthermore, when we evaluated the acute effects of these nuts, we observed a reduction in oxidative stress, as evidenced by a decrease in malondialdehyde levels, which was positively correlated with the concentrations of TG, VLDL, TG/HDL, and blood pressure (67).

The study has some limitations. First, we find a discrepancy between the planned (−500 kcal) and reported calorie restriction (−205 kcal). This variance is a common challenge in human intervention studies, especially those in free-living condition, when individuals maintain their daily life patterns, in contrast to controlled studies conducted in laboratory settings. Additionally, during the follow-up period, some participants discontinued their participation, a common occurrence in dietary intervention studies due to challenges in altering lifestyle habits and adherence difficulties, as we can see in other randomized controlled trials (68–73).

The study's strengths include its randomized controlled design, ensuring groups with similar characteristics and reducing selection bias, thereby enhancing the study's representativeness for the target population. This design also significantly improves the study's external validity. Adherence to the study protocol was diligently monitored through regular online and face-to-face visits conducted every 15 days. The inclusion of both men and women in the study enhances the extrapolation of results to real-life scenarios, increasing the applicability and relevance of the findings.

Our study contributes to the literature since there are few studies evaluating cashew nut compared to other nuts (e.g. almonds, walnuts, pistachio, and peanuts). Also, this was the first study to evaluate cashew nut oil on health, discerning the benefits of cashew nut arising from its lipid fraction or other non-lipid constituents.

5 Conclusion

Individuals in all three groups experienced reduced body weight and other indicators of adiposity over an 8-week period, with no differences between the three groups. Thus, our hypothesis regarding the potential benefits of cashew nut and cashew nut oil on body fat loss, improvements in body composition and cardiometabolic risk has not been confirmed. However, cashew nut group reduced liver enzymes, while cashew nut oil group reduced LDL-c and atherogenic index, and both the group consuming cashew nut or cashew nut oil experienced reductions in neck circumference and apo B after

intervention. All these reductions were not statistically significant in the control group. Thus, the study's findings support the incorporation of cashew nut and cashew nut oil, along with an energy-restricted diet, to have a potential to improve atherogenic and liver function biomarkers in individuals with overweight or obesity. To see differences in body fat and other adiposity as well as cardiometabolic markers between the intervention and control groups, it may be necessary to provide guidance to participants on chewing time and extend the study duration to at least 12 weeks. Since this was the first study to evaluate the impact of cashew nut oil on health, further investigations, particularly focusing on the oil, are needed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee in Research with Human Experimentation of the Universidade Federal de Viçosa (No. 4.543.541/CEPH). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

TM: Formal analysis, Investigation, Methodology, Writing – original draft. AK: Investigation, Methodology, Writing – review & editing. AW: Investigation, Methodology, Writing – review & editing. AD: Resources, Writing – review & editing. JB: Conceptualization, Writing – review & editing. HM: Writing – review & editing. ET: Writing – review & editing. HH: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

AD was employed by Brazilian Agricultural Research Corporation (Embrapa) Agroindústria Tropical—CNPAT.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1407028/full#supplementary-material

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Low muscle mass index is associated with type 2 diabetes risk in a Latin-American population: a cross-sectional study

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Objective: Diabetes mellitus is a growing disease with severe complications. Various scores predict the risk of developing this pathology. The amount of muscle mass is associated with insulin resistance, yet there is no established evidence linking muscle mass with diabetes risk. This work aims to study that relationship.

Research methods and procedures: This cross-sectional study included 1,388 employees. The FINDRISC score was used to assess type 2 diabetes risk, and bioimpedance was used for body composition analysis. Appendicular skeletal muscle mass adjusted by body mass index (ASM/BMI) was analyzed. Sociodemographic, clinical and anthropometric measures were evaluated, logistic regression models with sex stratification were conducted and ROC curves were calculated to determine the ability of ASM/BMI index to predict T2D risk.

Results: It was observed that patients with higher ASM/BMI had a lower FINDRISC score in both men and women ($p < 0.001$). A logistic regression model showed and association between ASM/BMI and diabetes risk in women [OR: 0.000 (0.000–0.900), $p = 0.048$], but not in men [OR: 0.267 (0.038–1.878), $p = 0.185$]. However, when the body mass index variable was excluded from the model, an association was found between muscle mass adjusted to BMI and diabetes risk in both men [OR: 0.000 (0.000–0.016), $p < 0.001$], and women [OR:0.001 (0.000–0.034), $p < 0.001$]. Other risk factors were having a low level of physical activity, waist circumference, age and sedentary lifestyle. A ROC curve was built and the optimal ASM/BMI cut-of value for predicting T2D risk was 0.82 with a sensitivity of 53.71% and specificity of 69.3% [AUC of 0.665 (0.64–0.69; $p < 0.0001$)].

Conclusion: When quantifying the risk of type 2 diabetes in both women and men, assessing muscle mass can help detect adult individuals with a high risk of developing type 2 diabetes.

KEYWORDS

diabetes mellitus, type 2, lean body mass, low muscle mass, sarcopenia, body mass index

Introduction

Diabetes mellitus is a significant global health issue, with prevalence rates rising dramatically over recent decades (1). Based on data from the International Diabetes Federation (IDF), about 537 million adults had type 2 diabetes (T2D) in 2021, with projections estimating this number will rise to 643 million by 2030 and 783 million by 2045 (2). The burden of T2D is not uniformly distributed, with certain regions, including Latin America, experiencing particularly high prevalence rates. In Latin America, the prevalence of T2D is estimated to affect about 32 million people, accounting for nearly 8.4% of the adult population. This increasing trend highlights the critical need for effective prevention and early detection strategies (2).

Early diagnosis of diabetes is crucial in preventing the onset of complications and enhancing health outcomes (3). Traditional diagnostic methods, such as fasting plasma glucose and oral glucose tolerance tests, are accurate but can be resource-intensive and less accessible, especially in low-resource settings (4). Non-invasive screening tools that can be easily implemented in primary care are vital for improving early detection rates, particularly in areas with limited healthcare access. These tools are essential to ensure that more individuals are identified and managed early, thereby reducing the burden of diabetes-related complications (5).

The Finnish Diabetes Risk Score (FINDRISC) is a commonly utilized non-invasive screening tool designed to estimate the risk of developing T2D (6). FINDRISC consists of a questionnaire covering factors such as age, family history of diabetes, physical activity, waist circumference, and BMI. Research has demonstrated the applicability of FINDRISC in various populations, including those in Latin America, where it has shown promise in early detection and prevention efforts (7, 8). A recent study highlighted the effectiveness of FINDRISC in identifying individuals at high risk for T2D in Latin American and Caribbean populations, emphasizing its potential utility in these regions (9).

Skeletal muscle mass has been increasingly recognized as a crucial factor in diabetes risk. Low muscle mass is associated with insulin resistance and impaired glucose metabolism, both of which are key components in the development of T2D (10). Studies have shown that maintaining adequate muscle mass can enhance insulin sensitivity and lower the risk of diabetes (11). Given the high prevalence of diabetes and muscle mass loss in aging populations, understanding the relationship between skeletal muscle mass and diabetes risk is vital for developing effective prevention strategies (12–14).

This study aims to explore the correlation between skeletal muscle mass and diabetes risk in a Latin American population using the FINDRISC tool. By establishing this correlation, we hope to enhance prevention efforts and improve early detection of diabetes, ultimately reducing the disease burden in this high-risk population. This research offers valuable insights that can provide public health strategies and clinical practices, particularly in regions with limited healthcare resources.

Materials and methods

Study design and population

This is a cross-sectional analytical study. The inclusion criteria were affiliation with the Ecuadorian Institute of Social Security (IESS) and age between 18 and 75 years. Of the 1,388 employees working in various local institutions (including educational centers, hospitals, and public and private institutions), 1373 were included. Exclusion criteria were pregnancy, a diagnosis of type 2 diabetes (T2D), and cognitive impairment. The research was approved by the Ethics Committee of San Francisco General Hospital (protocol number 031). Informed consent was obtained, and participant names were replaced with unique codes to ensure anonymity.

Sociodemographic, clinical, and anthropometric parameters

The STEPwise 3.2 method adapted to Ecuador by the Public Health Minister (MSP), National Institute of Statistics and Census (INEC), and PAHO/WHO (15), was applied in this research. Following the guidelines of this method, inquiries were made regarding sociodemographic data, tobacco and alcohol consumption. Systolic and diastolic blood pressure were measured with the participant seated using the OMRON HEM-7120 arm monitor with an accuracy of ±3% mmHg/ ± 5% pulse. Height was measured in centimeters with the patient standing erect with the head in the Frankfort plane on a portable stadiometer (Seca-217), calibrated with exact measurements in millimeters. Waist circumference was measured at the level of the navel at the end of expiration with a Cescorf tape, whose resolution is ±1 mm. BMI was calculated by bioimpedance.

Physical activity and sedentary lifestyle

Through the IPAQ questionnaire (International Physical Activity Questionnaire), the frequency, duration and intensity of weekly physical activity were measured by MET (Metabolic Equivalent of Task), with 3.3 MET per min indicating low activity, 4 MET per min moderate activity, and 8 MET per min intense activity. The time each participant spent sitting was also recorded (16, 17).

Risk of type 2 diabetes

The Latin American LA-FINDRISC score, as suggested in the MSP clinical practice guidelines, was applied. The risk of developing T2D was categorized as low (0–6 points), slightly elevated (7–11 points), moderate (12–14 points), high (15–20 points), or very high (more than 20 points). Following the MSP guideline recommendations, 12 points was the cut-off point to define high risk of T2D (7, 18).

Body composition

With a multifrequency segmental analyzer that performed 10 impedance measurements (InBody 120) which has a reliability of 98%, we obtained values for weight (kg), BMI, ASM, body fat percentage, body fat mass, and visceral fat level. Additionally, we calculated the (ASM/BMI).

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 26 and EPIDAT 3.1. After assessing normality and homoscedasticity, qualitative variables were presented in frequencies and percentages, and their associations were tested using the chi-square test. Quantitative variables were expressed as means or medians and their dispersion measures. Furthermore, a one-way ANOVA followed by Bonferroni *post-hoc* tests was performed for association analysis. A multivariate analysis with logistic regression was conducted, considering the dependent variable as having or not having diabetes risk. In the unadjusted model, the independent variable considered was ASM/BMI, classifying the participants into tertiles as follows: low (0.43–0.87), moderate (0.88–1.32), and high (1.33–1.76). The model was then adjusted for other variables, including age, sedentary hours, categorical physical activity level, BMI, waist circumference, systolic blood pressure, visceral fat level, and muscle mass. Finally, a ROC curve was built to find the cutoff point of ASM/BMI that predicts T2D risk.

Results

The characteristics of the men ($n = 557$) are summarized in Table 1. Comparative data of the variables are presented according to the ASM/BMI classified into three categories: low, moderate and high. Men with high ASM/BMI are significantly younger (32 years vs. 47 years, $p < 0.001$) and have a lower risk of T2D (6 vs. 12, $p < 0.001$). Men with high ASM/BMI have a significantly lower BMI (24.19 vs. 30.4, $p < 0.001$), smaller waist circumferences (89.4 vs. 103.5, $p < 0.001$), a significantly lower waist-hip ratio (0.90 vs. 0.97, $p < 0.001$), significantly lower systolic (121.5 vs. 128, $p < 0.02$) and diastolic blood pressure (72 vs. 79, $p < 0.001$), a lower percentage of body fat (19.2 vs. 40.2, $p < 0.001$), and a lower level of visceral fat (8 vs. 13, $p < 0.001$). Furthermore, physical activity is significantly related to moderate and high levels of ASM/BMI.

Table 2 shows the summary of women ($n = 831$) according to the proportion of ASM/BMI. In the comparative data, it is observed that women with a high ASM/BMI are significantly younger (25 years vs. 42 years, $p < 0.001$), consume less alcohol in the last 30 days (3 vs. 279, $p < 0.001$), and have significantly lower risk of T2D (4 vs. 11, $p < 0.001$). Women with high ASM/BMI have a significantly lower BMI (24.94 vs. 27.78, $p < 0.001$), smaller waist circumference (86 vs. 90, $p < 0.001$), and a significantly lower waist-to-hip ratio (0.90 vs. 0.93), a lower percentage of body fat (17.9 vs. 40.9, $p < 0.001$) and a significantly lower level of visceral fat (5 vs. 13, $p < 0.001$). Women with moderate or high ASM/BMI tend to have a greater number of hours of sedentary lifestyle, a lower level of physical activity, and slightly higher blood pressure.

In women, the risk of diabetes mellitus was statistically lower by 97% when associated with the proportion of ASM/BMI [OR: 0.003 (0.001–0.010), $p < 0.001$], while in men it was statistically lower by 94% when associated with ASM/BMI [OR: 0.006 (0.001–0.002), $p < 0.001$]. After adjusting the model for age, hours of sedentary lifestyle, level of physical activity, BMI, waist circumference, systolic blood pressure, visceral fat level, and muscle mass, no association was observed between the risk of T2D and ASM/BMI in the group of men [OR: 0.267 (0.038–1.878) $p = 0.185$], while in women it remained statistically significant [OR: 0.000 (0.000–0.900), $p = 0.048$] (Table 3).

Secondary analyses were performed in which the variable BMI was eliminated in the group of men, showing a 99% lower risk of diabetes was observed when associated with ASM/BMI in men [OR: 0.000 (0.000–0.016), $p < 0.001$]. In women, there remained a lower risk of diabetes mellitus associated with ASM/BMI [OR: 0.001 (0.000–0.034) $p < 0.001$].

Furthermore, in the adjusted model, men have a 4.9% greater risk of diabetes when associated with age [OR: 1.049 (1.023–1.076),

TABLE 1 Descriptive characteristics by ASM/BMI (males).

Variables		ASM/BMI			
		Low	Moderate	High	*p*-value
Age, years	Median (min–max)	47 (22–63)	39 (19–67)	32 (18–55)	**<0.001**
Smokers	n (%)	7 (5.3%)	108 (81.2%)	18 (22.8%)	0.999
Alcohol consumption, within last 30 d	n (%)	14 (4.3%)	270 (81.1%)	49 (14.7%)	0.322
Physical activity level, n (%)	Low	13 (6.4%)	174 (85.3%)	17 (8.3%)	**0.047**
	Moderate	10 (5.6%)	139 (77.7%)	30 (16.8%)	
	High	6 (3.4%)	139 (79.9%)	29 (16.7%)	
Sedentarism, hours	Median (min–max)	2 (0–10)	4 (0–16)	5 (0–14)	0.433
T2D risk (FINDRISC score)	Mean (SD)	12 (5)	9 (5)	6 (4)	**<0.001**
BMI, Kg/m^2	Median (min–max)	30.4 (24.4–49.9)	27.4 (16.3–42.6)	24.19 (15.3–30.8)	**<0.001**
Waist circumference (WC), cm	Median (min–max)	103.5 (78.5–126)	95.2 (60.5–164)	89.4 (71–135)	**<0.001**
Systolic blood pressure, mmHg	Median (Min–max)	128 (121–160)	126 (99.170)	121.5 (84.150)	**0.018**
Diastolic blood pressure, mmHg	Median (min–max)	79 (64–96)	77 (53–114)	72 (51–97)	**<0.001**
Waist-to-hip ratio	Median (min–max)	0.97 (0.87–1.04)	0.93 (0.79–1.04)	0.90 (0.77–0.96)	**<0.001**
Body fat percentage	Median (min–max)	40.3 (23.6–52.2)	29.6 (14.2–44.8)	19.2 (9–28)	**<0.001**
Visceral fat level	Median (min-max)	13 (5–20)	12 (5–20)	8 (1–20)	**<0.001**

$P < 0.005$. ASM/BMI, apendicular skeletal muscle mass adjusted by body mass index; WC, waist circumference; BMI, body mass index.
Bold values is that they are statistically significant, with a *p* value less than 0.05.

TABLE 2 Descriptive characteristics by ASM/BMI (females).

Variables		ASM/BMI			*p*-value
		Low	Moderate	High	
Age, years	Median (min–max)	42 (18–75)	36 (18–75)	25 (18–75)	**<0.001**
Smokers	n (%)	45 (76.3%)	13 (22%)	1 (1.7%)	<0.075
Alcohol consumption, within last 30 d	n (%)	279 (69.9%)	117 (29.3%)	3 (0.8%)	**<0.001**
Physical activity level, n (%)	Low	351 (78.2%)	98 (21.8%)	0 (0%)	**0.042**
	Moderate	192 (77.4%)	56 (22.8%)	0 (0%)	
	High	91 (67.9%)	40 (29.9%)	3 (2.2%)	
Sedentarism, hours	Median (min–max)	4 (0–16)	6 (0–12)	5 (1–11)	**0.023**
T2D risk (FINDRISC score)	Mean (SD)	11 (0.25)	8 (0.20)	4 (3–5)	**<0.001**
BMI, Kg/m^2	Median (min–max)	27.78 (18.6–53.2)	23.33 (17.1–32.0)	24.94 (23.9–27.64)	**<0.001**
Waist circumference (WC), cm	Median (min–max)	90 (11.2–129.5)	82.6 (62.2–108)	86 (82.2–102.5)	**<0.001**
Systolic blood pressure, mmHg	Median (min–max)	118 (88–193)	113 (80–172)	126 (110–131)	**<0.001**
Diastolic Blood pressure, mmHg	Median (min–max)	71 (45–104)	68 (50–95)	73 (70–78)	**<0.001**
Waist-to-hip ratio	Median (min–max)	0.93 (0.80–1.08)	0.88 (0.77–0.99)	0.90 (0.90–0.92)	**<0.001**
Body fat percentage	Median (min–max)	40.9 (25.8–55.3)	33.1 (16.2–44.4)	17.9 (16.9–27.7)	**<0.001**
Visceral fat level	Median (min–max)	13 (3–20)	9 (2–20)	5 (4–11)	**<0.001**

P< 0.005. ASM/BMI, apendicular skeletal muscle mass adjusted by body mass index; WC, waist circumference; BMI, body mass index.
Bold values is that they are statistically significant, with a *p* value less than 0.05.

$p < 0.001$], a 12% greater risk of diabetes mellitus when associated with waist circumference [OR: 1.120 (1.063–1.180), $p < 0.001$] and a 7.9% higher risk of diabetes mellitus when associated with less physical activity [OR: 1.795 (1.015–3.172), $p = 0.044$]. In the adjusted model, women have a 7.6% higher risk of diabetes when associated with age [OR: 1.076 (1.054–1.098), $p < 0.001$], an 8.8% higher risk of diabetes when associated with sedentary hours [OR: 1.088 (1.028–1.152), $p < 0.001$], a 2.49 higher risk of diabetes mellitus when associated with a low level of physical activity [OR: 2.490 (1.421–4.362), $p < 0.001$], and 6.1% higher risk of diabetes mellitus when associated with abdominal circumference [OR: 1.061 (1.028–1.096), $p < 0.001$].

Moreover, when the model was not stratified by sex, it was observed that there was a 99.99% lower risk of diabetes mellitus when associated with ASM/BMI in the adjusted model. When adjusted for other variables, a lower risk of diabetes mellitus persisted when associated with ASM/BMI [OR: 0.000 (0.000–0.147), $p = 0.010$] (Table 4).

The result of the FINDRISC score was dichotomized into those with low and slightly elevated risk versus those with moderate, high and very high risk. ROC curve was performed to determine the best ASM/BMI cut-off point that predicts having moderate or high risk in FINDRISC. Area under the curve (AUC) of 0.665 (0.64–0.69; $p < 0.0001$) was observed. With a cut-off point of 0.82 a sensitivity of 53.71% and specificity of 69.3% is obtained (Figure 1A). In men, the AUC was 0.723 (0.683–0.76; $p < 0.0001$) with a cut-off point of 1.15 with 82.94% sensitivity and 52.12% specificity. On the other hand, for women the AUC was 0.68 (0.65–0.72; $p < 0.0001$), with a cut-off point of 0.78, with 64.13% sensitivity and 64.85% specificity (Figure 1B).

Discussion

This study evaluated the association between clinical, anthropometric, and body composition measures and the diabetes risk assessed by FINDRISC score, in 1373 participants aged 18–75 years (median 40), among whom 499 (36.4%) were at high risk of T2D. The study focused on the influence of muscle mass, as a significant part of the sarcopenia concept. Higher muscle mass, defined by the ASM/BMI index, was associated with better outcomes related to T2D risk, specifically with better BMI, waist circumference (WC), waist-to-hip ratio (WHR), systolic (SBP) and diastolic blood pressure (DBP), body fat percentage (BFP) and visceral fat level (VFL) ($p < 0.001$) in both sexes. Additionally, physical activity (PA) was significantly related to moderate and high levels of ASM/BMI in men. In women, similar results were observed, but they showed more hours of sedentary lifestyle, a lower level of physical activity, and slightly higher blood pressure.

Muscle mass is a key component in measuring sarcopenia in young adults, although muscle strength and physical performance are also important factors. Most current research has focused on studying the relationship between sarcopenia and T2D in older adults, with less reported about each sarcopenic component in younger people at risk or with risk factors for this prevalent disease (19). Recent research estimating the prevalence of obesity with low lean muscle mass (OLLMM) in adults aged 20 years and older in the US has reported an association between muscle mass and T2D and its related factors. Utilizing data from the National Health and Nutrition Examination Survey (NHANES), the study found a higher prevalence of OLLMM among Mexican-American females over 60 years old. This prevalence increases with age and is higher among individuals with prediabetes, T2D, non-alcoholic fatty liver disease (NAFLD) with fibrosis, or those who have undergone bariatric surgery (20, 21). High prevalence of sarcopenia defined using height-adjusted appendicular skeletal muscle mass (ASM/h^2), with ASM calculated as the sum of the lean mass of the arms and legs has also been reported in the US, specifically in Louisiana, where Asians had a higher incidence of low muscle mass, compared to other ethnic groups (22).

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TABLE 3 Association between diabetes risk and risk factors, by sex.

	Unadjusted model		Adjusted model		Adjusted model without BMI	
	OR (CI 95%)	*P*-value	OR (CI 95%)	*P*-value	OR (CI 95%)	*P*-value
Men						
ASM/BMI	0.006 (0.001–0.002)	<0.001	0.267 (0.038–1.878)	0.185	0.000 (0.000–0.016)	**<0.001**
Age			1.058 (1.031–1.087)	<0.001	1.049 (1.023–1.076)	**<0.001**
Hours of sedentarism			1.011 (0.941–1.086)	0.770	1.002 (0.939–1.067)	0.995
Low physical activity level			1.799 (1.017–3.182)	0.044	1.795 (1.015–3.172)	**0.044**
Physical activity level, high			1.042 (0.569–1.905)	0.895	1.066 (0.584–1.946)	0.834
BMI			1.082 (1.025–2.809)	0.002		
WC			1.083 (1.026–1.141)	0.004	1.120 (1.063–1.180)	**<0.001**
Systolic blood pressure			0.998 (0.979–1.017)	0.802	1.000 (0.982–1.019)	0.966
Visceral fat level			0.973 (0.849–1.116)	0.697	0.067 (0.939–1.213)	0.320
Muscle mass			0.896 (0.523–1.535)	0.689	1.325 (1.169–1.501)	<0.001
Women						
ASM/BMI	0.003 (0.001–0.010)	<0.001	0.000 (0.000–0.900)	0.048	0.001 (0.000–0.034)	**<0.001**
Age			1.076 (1.054–1.098)	<0.001	1.076 (1.055–1.098)	**<0.001**
Hours of sedentarism			1.089 (1.028–1.153)	0.004	1.088 (1.028–1.152)	**<0.001**
Low physical activity level			2.468 (1.410–4.319)	0.002	2.490 (1.421–4.362)	**<0.001**
Physical activity level, high			1.663 (0.914–3.027)	0.096	1.688 (0.928–3.072)	0.086
BMI			1.061 (1.028–1.096)	0.459		
WC			1.061 (1.028–1.096)	<0.001	1.061 (1.028–1.096)	**<0.001**
Systolic blood pressure			1.012 (0.998–1.027)	0.096	1.012 (0.998–1.027)	0.096
Visceral fat level			0.972 (0.886–1.066)	1.066	0.975 (0.889–1.070)	0.599
Muscle mass			1.443 (0.995–2.095)	0.053	1.265 (1.117–1.433)	<0.001

P < 0.005. ASM/BMI, apendicular skeletal muscle mass adjusted by body mass index; WC, waist circumference; BMI, body mass index.
Bold values is that they are statistically significant, with a *p* value less than 0.05.

Considering all the muscle mass indexes reported in the literature [ASM alone, ASM/height^2 (ASM/h^2), ASM/BMI, ASM/weight], we did not find an association between ASM/h^2 and T2D risk, suggesting a wide divergence between the different muscle indexes. Similar results were reported in a cohort study, where absolute lower ASM was associated with incident T2D in men, but not in women (23). Another study did not find an association when analyzing both absolute ASM or ASM/h^2 but did find one when using the ASM/BMI ratio (24). In a study including older adults with hypertension, the prevalence of low lean mass with obesity by the ASM/h^2 index (9.8%) was lower relative to the ASM/weight (11.7%) and ASM/BMI indexes (19.6%), with the latter index evaluation being more efficient in showing muscle mass deficiency (25). Our results suggest that muscle mass index evaluation using ASM/BMI, stratified by sex, is useful to predict the risk of T2D in Latin Americans. However, there is little evidence among Latin American middle-aged adults regarding the influence of muscle and fat mass on the risk of developing T2D. Evidence does exist about a negative association between muscle mass and incident T2D (26, 27), for example, in diabetes-free Koreans, decreased skeletal muscle mass was significantly related to an incremented risk of new-onset diabetes in healthy middle-aged people. They found that the lowest sex-specific skeletal muscle mass index (SMI) tertile was significantly linked to an increased risk of developing T2D [adjusted hazard ratio (HR) = 1.31; 95% CI, 1.18–1.45] in a fully adjusted model. Presarcopenic obesity notably heightened the risk of incident diabetes (adjusted HR = 1.57; 95% CI, 1.42–1.73) compared to normal body composition, presarcopenia alone, or abdominal obesity alone. They concluded that low skeletal muscle mass, along with its coexistence with abdominal obesity, collectively incremented the risk of developing T2D, independent of glycometabolic parameters (27).

The prevalence of low muscle mass increases with age in most studies, which was also found in ours, making early detection an important issue for the prevention of T2D and many other diseases. In a recent review about sarcopenia in youth, investigators found that more than 10% of young adults in their 20s and 30s consistently had sarcopenia based on available data. Additionally, youth-onset sarcopenia seems to be more prevalent among Hispanics or Asians compared to white people and is least common in African Americans. Notably, when applying the strength criteria, more cases were identified in youth, underscoring the severity of sarcopenia in younger populations (21).

Research in Latin America related to association between T2D and body composition has been done in Chile. The authors concluded that in individuals with low muscle mass/high adiposity phenotypes showed an OR above 2 for diabetes, 2.7 for hypertension, 4.5 for metabolic syndrome, and over 2 for moderate-to-high cardiovascular risk, although the analysis included older aged participants with osteoarthritis (OAD) (28).

TABLE 4 Association between FINDRISC score and risk factors (overall).

	Unadjusted model		Adjusted model	
	OR (CI 95%)	*P*-value	OR (CI 95%)	*P*-value
ASM/BMI	0.048 (0.026–0.002)	**<0.001**	0.000 (0.000–0.147)	**0.010**
Age			1.055 (1.009–1.102)	**<0.001**
Hours of sedentary lifestyle			1.011 (0.941–1.086)	**0.018**
Low physical activity level			2.164 (1.463–3.202)	**<0.001**
Physical activity level, high			1.364 (0.898–2.071)	0.145
BMI			0.960 (1.025–2.809)	0.650
WC			1.057 (1.031–1.085)	**<0.001**
Systolic blood pressure			0.998 (0.979–1.017)	0.802
Visceral fat level			1.021 (0.953–1.095)	0.550
Muscle mass			1.249 (1.008–1.547)	0.042

P< 0.005. ASM/BMI, apendicular skeletal muscle mass adjusted by body mass index; WC, waist circumference; BMI, body mass index.
Bold values is that they are statistically significant, with a *p* value less than 0.05.

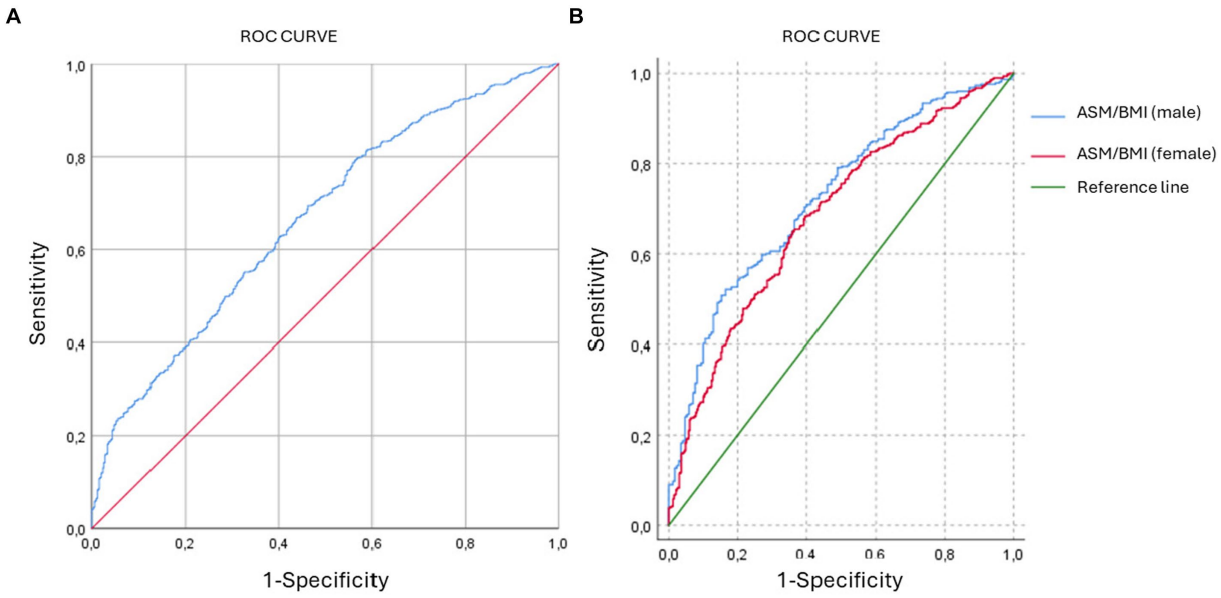

FIGURE 1
ROC curves. **(A)** ROC curve of general population. AUC = 0.665. **(B)** ROC curve of male and females. AUC = 0.723 for males and AUC = 0.684 for females.

In our study, both males and females in the low tertile of ASM/BMI index had significantly higher T2D risk. When multivariate analyses were performed, the factor that emerged as a protective predictor for the risk of T2D was having a higher ASM/BMI. Conversely, regression models identified age, waist circumference, low physical activity level, and sedentarism as risk factors for T2D. This ASM/BMI index was also reported in a study with female participants with a history of gestational diabetes (24), and in another investigation that found that unadjusted diabetes risk was lowered by 21% in men [HR 0.79 (0.62–0.99), $p = 0.04$] and 29% in women [HR 0.71 (0.55–0.91), $p = 0.008$] for higher ASM/BMI. Nevertheless, the association ceased to be significant when age, race, smoking, education, physical activity, and waist circumference were taken into account (29).

Other authors have published a synergistic effect of low-fat mass and low muscle mass together, related to T2D, expressed in exacerbation of A1C. Interesting research among females with T2D and with overweight or obesity was reported by Terada et al., in a secondary analysis of the Look AHEAD trial, that recruited participants from 16 clinical sites across the US. This study suggests that low muscle mass has a negative effect on A1C only when combined with low-fat mass in women, which is different for men, as the latter did not show a significant effect of muscle mass on A1C and high fat mass was significantly associated with higher A1C (30).

Regarding sociodemographic factors and habits, we found that among smokers, mostly men, there was no significant association with the ASM/BMI index, even though studies reinforce the relationship of tobacco use and muscle mass loss (31). In this same bivariate analysis, alcohol consumption (in women), BMI, waist-to-hip ratio, visceral fat

and fat percentage were significantly higher in people with low ASM/BMI index. Nonetheless, the association of alcohol intake with T2D risk disappeared in the regression analysis. One study reported that alcohol has no relationship with loss of muscle mass. This seems to be influenced by other factors that may intervene in the loss of muscle mass in women, such as hormonal factors (32). Furthermore, BMI has been generally reported in studies of patients with sarcopenic obesity, strengthening the relationship found in these studies, which claim that low muscle mass in populations with obesity is associated with diseases such as T2D and hypertension (33).

It is widely recognized that physical activity offers several health benefits and contributes to preventing prevalent chronic diseases while increasing muscle mass (34, 35). In this study, we identified a significant association with T2D risk, in both sexes, related to increased muscle mass. More than half of the women studied with low physical activity had low muscle mass, and in men with moderate and high physical activity levels, there was a predominance of moderate muscle mass.

In an Asian population cohort study, the authors found that predicted high lean body mass (LBM) and low fat mass (FM) were linked to a reduced risk of T2D according to anthropometric equations (36). When including patients who already have the disease, there are different analysis regarding the influence of body composition and better metabolic profiles. For example, it has been described that different combinations of fat and muscle components are associated with different outcomes, reporting that high fat and low muscle may be synergistically related to higher glycosylated hemoglobin (HbA1c) in T2D. Even with an exercise program, in participants with this profile (high fat mass, low muscle mass), exercise-induced improvements in certain cardiometabolic risk factors may be diminished (37).

In our study, higher waist circumference values are related to lower muscle mass, a result that was consistent in both sexes. Moreover, regarding body fat, we found significance in both the percentage of body fat and visceral fat in both sexes. Studies report the joint relationship of both factors with cardiovascular and other chronic diseases such as diabetes mellitus, in addition to increased mortality (38). One impact as age advances is that adipose inflammation leads to fat being redistributed toward the abdomen, infiltrating the skeletal muscles, and associated with a decrease in muscle strength, ultimately causing insulin resistance. In turn, muscle-secreted cytokines can exacerbate adipose tissue atrophy, promote chronic low-grade inflammation, and establish a vicious cycle of local hyperlipidemia, insulin resistance, and inflammation that spreads systemically, thus promoting the development of sarcopenic obesity (14, 39–41).

Additionally, the cutoff points of ASM/BMI index in identifying the risk of T2D, were higher in males than in females, with higher sensitivity in men but more specificity in women. Some previous research has developed ROC curve analysis to determine cut-off points of various anthropometric variables to predict metabolic diseases, such as type 2 diabetes mellitus, gestational diabetes or metabolic syndrome (42–44), and also using indices such as the fat-muscle ratio (FMR), among others. One of the studies that evaluated this FMR in women tried to predict the risk of gestational diabetes with a cut-off value of 1.305 (45). Another study described different anthropometric indices such as Body Roundness Index (BRI), body shape index (ABSI), and lipid accumulation product to predict metabolic syndrome among industrial workers in Russia (46). However, no cut-off points have been reported for the ASM/BMI for either sexes related to diabetes risk, as in our study, so it could be suggested as a possible anthropometric marker to predict this risk.

Finally, the ASM/BMI may serve as a convenient parameter for screening individuals at high risk for T2D, especially among males.

This study has several limitations. First, although we utilized BIA to evaluate body composition, which is not the gold standard method, it has been validated as a non-invasive method that offers precise estimates of skeletal muscle mass, which closely align with measurements obtained through DXA and magnetic resonance imaging across different ages, volume statuses, and BMI ranges (47, 48). Second, we could not assess the role of muscle strength or quality and laboratory variables such as glycemia and lipid profile to T2D risk. Additional research is needed to elucidate the connection between muscle strength, laboratory parameters, and metabolic risk in young Latin American adults. Third, because this study is observational in nature, the cross-over design does not favor causal relationships. Therefore, prospective studies would be needed for internal and external validation of ASM/BMI index and to be able to use it routinely, in that case, it would be a proposal that could contribute to the early detection of people at risk of diabetes mellitus based on novel indicators.

Conclusion

In summary, muscle mass determined by the ASM/BMI index was associated with the risk of type 2 diabetes in middle-aged Ecuadorian men and women, and exercise appeared to be the best parameter to reduce this risk. The strongest factor associated with this risk was having a low level of physical activity, followed by waist circumference, age and sedentarism.

When quantifying the risk of type 2 diabetes in women and men, doctors may find that assessing muscle mass will help detect adults at an incremented risk of developing type 2 diabetes. Aerobic and resistance exercise can contribute to preventing diabetes by increasing muscle mass, which should be further investigated in interventional studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Human Research Ethics Committee of the San Francisco Hospital in Quito. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RS: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Data curation, Supervision, Validation. CA: Conceptualization, Formal analysis, Writing – review & editing, Validation. EB-V: Conceptualization, Data curation, Formal analysis, Validation, Writing – review & editing. YS-A: Conceptualization, Methodology, Validation, Writing – review & editing. AM: Formal

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

ANOVA	Analysis of variance
ASM	Appendicular skeletal muscle mass
ASM/h^2	Height-adjusted appendicular skeletal muscle mass
AUC	Area under the curve
BFP	Body fat percentage
BIA	Bioimpedance analysis
BMI	Body mass index
BP	Blood pressure
DBP	Diastolic blood pressure
DXA	Bone densitometry
FINDRISC	Finnish Diabetes Risk Score
FM	Fat mass
HbA1c	Glycosylated hemoglobin
IBM	International Business Machine
IESS	Ecuadorian Social Security Institute
INEC	National Institute of Statistics and Census
IPAQ	International Physical Activity Questionnaire
LBM	Lean body mass
MET	Metabolic Equivalent of Task
MSP	Public Health Minister
NAFLD	Non-alcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
OAD	Osteoarthritis
OLLMM	Obesity with low lean muscle mass
OR	Odds ratio
PA	Physical activity
SBP	Systolic blood pressure
SPSS	Statistical package for social sciences
T2D	Type 2 diabetes
US	United States
VFL	Visceral fat level
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-hip ratio

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Obesity and periodontitis: a comprehensive review of their interconnected pathophysiology and clinical implications

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Obesity and periodontitis are significant health problems with a complex bidirectional relationship. Excess body fat is linked to systemic diseases and can lead to persistent inflammation, potentially harming periodontal health. Periodontitis, a chronic inflammatory condition affecting the supporting structures of teeth, poses substantial health risks. Both conditions share pathological processes such as inflammation and oxidative stress, which aggravate health status and make treatment more challenging. Understanding this interaction is crucial for developing effective management strategies for both diseases. This study explores the multifaceted aspects of obesity and periodontitis and their reciprocal relationship.

KEYWORDS

obesity, periodontitis, oxidative stress, inflammatory response, periodontal treatment

Introduction

Obesity and periodontitis are serious public health issues that increase the burden of general health and chronic illnesses (1–3). Obesity, characterized by the abnormal accumulation of body fat, is linked to comorbidities such as insulin resistance, cardiovascular diseases, and certain cancers (1, 4). It induces a low-grade chronic inflammatory state, releasing proinflammatory mediators that may link it to periodontitis (5, 6).

Periodontitis is a chronic inflammatory disease caused by microbial-host interactions. It destroys tissue by affecting the supporting structures of teeth (7, 8) and impacts overall wellbeing (9).

The bidirectional relationship between obesity and periodontitis is complex and multifaceted. Adipose tissue functions as an endocrine organ, releasing cytokines, and proinflammatory hormones that contribute to systemic inflammation and oxidative stress—common pathophysiological mechanisms shared by both conditions (7). Epidemiological studies support the notion that obesity is a significant risk factor for the development and exacerbation of periodontitis (10–12). Likewise, several studies suggest that periodontitis may

increase obesity-related disorders such as intestinal dysbiosis (13) and insulin resistance (14, 15).

Understanding the connection between obesity and periodontitis is crucial, as both conditions are highly prevalent worldwide. Examining their relationship not only has implications for oral health but may also reveal the mechanisms underlying a variety of systemic diseases, providing opportunities for preventive, and therapeutic interventions that could significantly improve the population's overall health.

This narrative review explores the multifactorial aspects of obesity and periodontitis and their bidirectional relationship. It examines the interplay between these conditions, from inflammatory responses and oxidative stress to changes in periodontal microbiota and their impact during pregnancy or after bariatric surgery. Furthermore, the article delves into the implications of both non-surgical and surgical periodontal therapies in patients with obesity, emphasizing the need for comprehensive approaches to prevention and treatment.

Understanding the intricate connections between obesity and periodontitis is crucial for developing effective strategies to manage these interrelated conditions. As research continues to uncover the complexities of this relationship, healthcare practitioners can enhance their knowledge to provide more targeted interventions, ultimately improving the overall health outcomes of individuals affected by obesity and periodontitis.

Methods

For this narrative review, we considered publications from 1977 to 2023. The search was conducted through PubMed and Cochrane Library, using a combination of related search terms, including "periodontitis," "obesity," "oxidative stress," "inflammatory response," and "periodontal treatment." Three research team members (CR-G, JMP-V, and DS-R) reviewed the articles by titles and abstracts, selecting them for full review only if all authors agreed on their relevance. Additionally, the research team examined the references from the identified articles to incorporate additional relevant publications. Ultimately, we reviewed 33 observational studies, seven cohort studies, three case–control studies, 20 systematic reviews, eight clinical trials, 63 reviews, and 13 studies with other designs, such as animal studies or conference reports. The chosen articles underwent a comprehensive content analysis to determine evidence of the relationship between periodontitis and obesity.

Obesity

Obesity is a severe medical condition worldwide (1) characterized by excessive or abnormal accumulation of body fat, which increases the risk of several chronic diseases (3). It is primarily classified by body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters (kg/m^2), with obesity defined as a BMI of 30 or higher (16).

In the past three decades, the prevalence of obesity has increased at an alarming rate, with a 27.5% increase in adults and a 47.1% increase in children (4). The exact cause of obesity remains elusive; however, it appears to involve a complex interaction of biological, psychosocial, and behavioral factors, including genetic composition, metabolic disorders, physical inactivity, socioeconomic status, a high-calorie diet, and cultural influences (4, 17).

Obesity is associated with numerous comorbidities affecting almost all body systems, such as insulin resistance, type 2 diabetes mellitus, hepatic steatosis, cardiovascular disease, hypertension, cerebrovascular accidents, lipid metabolism disorders, gallbladder problems, osteoarthritis, sleep apnea, and other respiratory problems (1, 4, 18, 19). It is also linked to certain types of cancer, including breast, ovarian, endometrial, prostate, liver, gallbladder, kidney, colon, and thyroid cancers (1, 4, 20–23).

A key aspect of obesity is its role in inducing a state of low-grade chronic inflammation (24) and its association with inflammatory markers related to systemic disease (5, 6). In addition to storing energy, adipose tissue functions as an active endocrine organ, secreting various chemical mediators (25). These factors include leptin, cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins, adiponectin, complement components, plasminogen activator inhibitor-1, proteins of the renin-angiotensin system, and resistin (25–27). Some of these substances, like cytokines, play a critical role in systemic inflammation (5) and may serve as a link between obesity and other inflammatory conditions such as periodontitis (28).

Periodontitis

Periodontitis is a chronic, non-communicable inflammatory disease that results from the interaction between pathogenic microorganisms and the host's immune system (7). This condition destroys the tissues surrounding and supporting the tooth, including the gums, alveolar bone, and periodontal ligament (8), as a consequence of the release of proinflammatory mediators (29). The most common signs of this disease include gingival inflammation, loss of alveolar bone, dental mobility, increased probing depth, and gingival bleeding (2, 30).

The global oral health status report estimated that severe periodontal diseases affect approximately 19% of the global adult population, accounting for over 1 billion cases worldwide (9). This has made the disease a significant public health issue that causes disability, negatively impacts chewing and aesthetics, and reduces quality of life (2, 31).

According to the National Health and Nutrition Examination Survey of the United States, 42% of adults had periodontitis by 2014 (32, 33), indicating that although the disease can appear from the age of 15, its prevalence increases with age, with older adults being the most vulnerable group where more aggressive forms are presented (9, 30).

Various factors can disturb the natural balance in the mouth, leading to a shift in the biofilm beneath the gums towards proinflammatory dysbiosis. This imbalance involves excessive growth of microorganisms such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, triggering chronic inflammation (34–36).

These bacteria colonize host tissues and evade defense mechanisms. *Porphyromonas gingivalis* fimbriae binds to other bacteria, such as *Treponema denticola*, and human proteins, such as glyceraldehyde-3-phosphate dehydrogenase, to facilitate adherence and invasion of host cells (37). The macromolecules that comprise the

biofilms produced by these bacteria maintain proximity between bacterial and host cells, promoting health and disease (38).

They have also created several ways to obtain iron from the host environment, which is essential for their growth and contributes to biofilm dysbiosis (39). In addition, flagella-assisted motility allows these pathogens to seek nutrients and colonize favorable niches. At the same time, their metabolic activity and rapid growth enhance their ability to resist natural removal and mechanical debridement (38).

Another protective mechanism of these microorganisms is the production of capsules that prevent phagocytosis and release proteases that affect chemotaxis and neutrophil activation to evade host defense mechanisms. *Porphyromonas gingivalis* can also release outer membrane vesicles that scavenge interleukin-8 (IL-8), thereby protecting itself from host defense systems (40). In addition, bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans*, and *Fusobacterium nucleatum* can invade host cells and escape the immune system (38).

Finally, bacterial exotoxins and endotoxins contribute to the virulence of these pathogenic species by damaging host cells and promoting the release of inflammatory cytokines. Enzymes, such as collagenases and gingipains from *Porphyromonas gingivalis*, destroy tissue components and host defense molecules (41).

This change in the microbiome can trigger periodontitis in susceptible individuals, characterized by an inadequate inflammatory response and the consequent destruction of connective tissue and alveolar bone (42, 43).

Periodontitis is a multifactorial disease. Various risk factors are associated with the onset of periodontitis that can affect the relationship between the host and microorganisms. Smoking is the most significant risk factor (44–47), along with metabolic diseases like diabetes mellitus (48–51), obesity (7, 10, 52), stress (53, 54), genetic factors (55), and oral hygiene habits (56).

Inflammatory response

Inflammation is the immune system's biological response to organic, chemical, or physical stimuli to protect living organisms from harmful factors, including fungi, viruses, and bacteria (57). In its controlled form, as in acute inflammation, this process is crucial in eliminating pathogens, cellular debris, and inflammatory mediators while stimulating tissue repair. This leads to the resolution of inflammation and the restoration of tissue homeostasis (57, 58).

In the acute phase of the inflammatory response, immune system cells, including platelets and granulocytic cells such as basophils, mast cells, neutrophils, and eosinophils, become activated and subsequently produce and release a variety of chemical mediators, including cytokines, chemokines, and acute-phase proteins (59). These substances promote vasodilation and increase vascular permeability, facilitate the migration of immune cells to the site of inflammation, and stimulate and regulate the inflammatory response (59, 60). Depending on the extent of the injury, this acute phase may be sufficient to resolve the damage (61).

Conversely, failure to resolve inflammation and persistent inflammation, either as a result of prolonged exposure to a stimulus or a persistent pathogen, non-degradable foreign bodies, or an inappropriate autoimmune response against self-cells, can lead to the chronic phase of inflammation in which tissue damage (60, 61), fibrosis and granuloma formation can occur (60). The mechanisms involved in chronic inflammation contribute to the development of many diseases, including arthritis, asthma, atherosclerosis, autoimmune diseases, type 2 diabetes mellitus, cystic fibrosis, inflammatory bowel disease, Parkinson's disease, Alzheimer's disease, cardiovascular diseases, cancer, and conditions associated with aging (57, 61, 62).

In obesity, chronic inflammation is marked by elevated levels of pro-inflammatory cytokines such as TNF-α, interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), primarily produced by adipose tissue-derived macrophages (63), and by the adipose tissue itself, as previously mentioned (25). Furthermore, various factors currently under investigation can exacerbate the inflammatory process. Among these, non-esterified fatty acids may induce inflammation through mechanisms such as modulation of adipokine production or activation of Toll-like receptors; excess nutrients and adipocyte expansion can cause endoplasmic reticulum stress; and hypoxia in hypertrophied adipose tissue could stimulate the expression of inflammatory genes and activate immune cells (64). In contrast, in periodontitis, chronic inflammation originates from a complex immune response triggered by persistent microbial elements in the oral cavity, causing local damage and systemic effects (65), suggesting a potential interaction with the systemic inflammation observed in obesity (28).

The bidirectional relationship between obesity and periodontitis

The intricate connection between obesity and periodontitis has emerged as a crucial research area in periodontal medicine. Adipose tissue, acting as an endocrine organ, releases cytokines and proinflammatory hormones, known as adipocytokines, triggering inflammatory processes and oxidative stress disorders (7, 29, 66). This generates a shared pathophysiology between both diseases. Explored through epidemiological studies and clinical trials, this link reveals a bidirectional relationship between obesity and periodontitis (10–12), where exacerbated proinflammatory factors worsen the severity of both conditions.

Since the early reports of the relationship between obesity and periodontitis in animals in 1977 (67) and in humans in 1998 (66), numerous studies have supported the hypothesis that obesity constitutes a risk factor for the development and worsening of periodontitis. Epidemiological research results indicate that individuals with obesity show a higher prevalence of periodontal disease compared to the normal-weight population (11). Furthermore, the strength of this correlation seems to intensify with an increase in obesity (11, 12).

During obesity, adipose tissue increases, and adipocytes secrete fewer anti-inflammatory substances, such as adiponectin, while increasing the secretion of proinflammatory substances, such as leptin and chemokines (68). This leads to an infiltration of immune cells, likely early arrivals being B and T cells, influencing the secretion of proinflammatory cytokines and Interferon gamma (IFN-γ), essential for activating macrophages and inflammation. Inflammation in obesity is characterized by the abnormal presence of these cytokines, which may hinder the elimination of pathogenic microorganisms in the oral cavity (69). And induce the destruction of characteristic periodontal connective tissue and bone (70).

Inflammatory biomarkers such as IL-1, IL-6, TNF-α, and matrix metalloproteinases (MMP) (63) play a crucial role in the relationship between obesity and periodontitis (71). Elevated levels of these biomarkers, commonly associated with obesity, correlate with losing the extracellular matrix, inhibiting osteoblastogenesis, and activating osteoclasts, leading to collagen and bone destruction (8, 72).

Several studies have analyzed the cytokine profile in the crevicular fluid of patients with and without obesity and chronic periodontitis. Some have reported significantly higher levels of these proinflammatory substances in patients with obesity (73–76). Others show no differences between these two groups (77–79), highlighting the need for further analysis of the effects of obesity control on the cytokine profile in crevicular fluid and other fluids of patients with obesity and periodontal disease (71) (Figure 1).

Our understanding of these findings enables us to deduce that obesity and periodontitis are related. That being said, more research is necessary to ascertain whether these two disorders are causally related.

Obesity and bone loss

Initially, it was believed that obesity stimulated bone formation (80), but now the available evidence supports that obesity induces changes in bone density and affects periodontal health (81).

The increase of fatty tissue in the bone marrow acts as an endocrine organ that secretes various pro-inflammatory adipokines such as leptin and resistin while decreasing the secretion of anti-inflammatory substances such as adiponectin (82). These pro-inflammatory adipokines induce a chronic low-grade inflammatory state characterized by the elevation of inflammatory biomarkers such as TNF-α and IL-6, which increase osteoclastic function and reduce osteoblast formation—leading to increased bone resorption and decreased bone mineral density (83–85).

Similarly, obesity can trigger changes in the intestinal microbiota, affecting bones, including the jaw, through pathobionts or circulating metabolites that stimulate bone resorption (86).

On the other hand, studies addressing the relationship between obesity and alveolar bone loss are scarcer but also present obesity as an established risk factor for periodontitis (10). Several animal studies have reported that obesity and dyslipidemia (87), as well as a diet high in carbohydrates and palmitic acid (88, 89), contribute to increased bone loss in *Porphyromonas gingivalis*-induced periodontitis (89). This includes deterioration of trabecular bone architecture, decreased cortical bone density in the alveolar bone area, and increased serum leptin levels (90).

Another significant finding is that individuals with obesity are more susceptible to alveolar bone loss, clinical attachment loss, and, consequently, edentulism (12) compared to those without obesity (91). Obesity-induced systemic inflammation may interfere with eliminating pathogenic microorganisms in the oral cavity, promoting the destruction of periodontal connective tissue and alveolar bone. The release of proinflammatory cytokines and oxidative stress contribute to the progression of periodontitis in individuals with obesity, exacerbating the destruction of periodontal tissue (82). In addition, factors such as subgingival calculus, probing depth greater than 4 mm, and bleeding on probing are more frequent in patients with obesity (92), suggesting that obesity could be a significant risk factor, even in patients with clinically healthy periodontium (93).

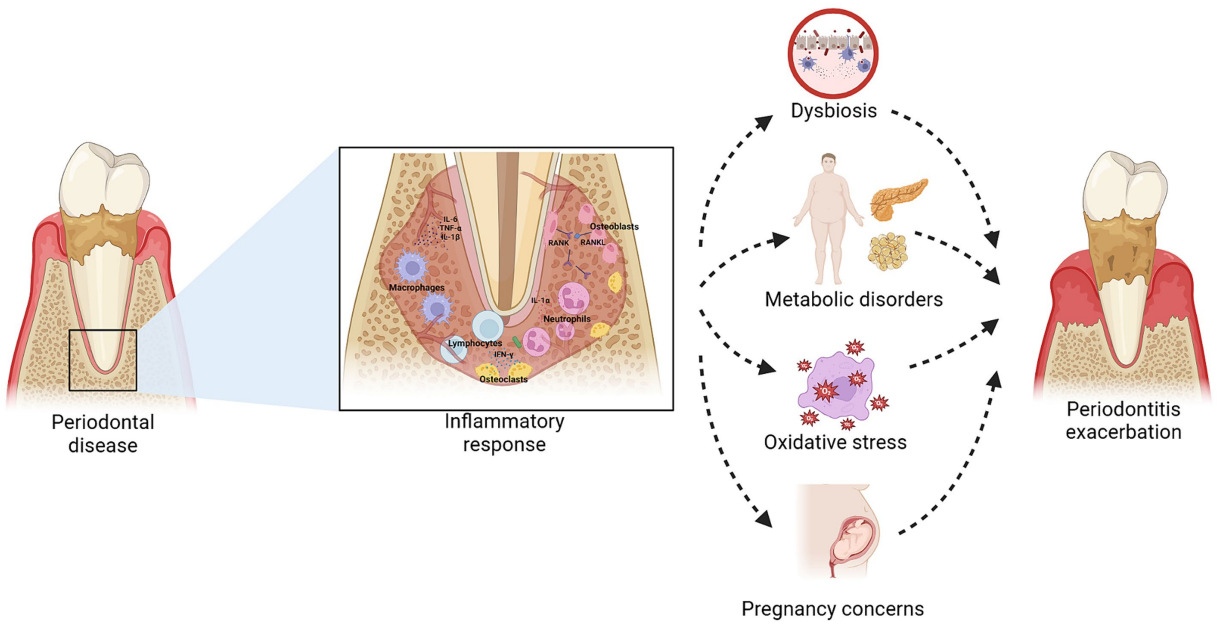

FIGURE 1
Relationship between obesity and periodontitis. Inflammation in periodontal disease, mediated by the release of cytokines such as IL-6, TNF-α, and IL-1β, can be exacerbated in individuals with obesity due to a systemic proinflammatory state. This inflammatory condition contributes to dysbiosis and oxidative stress, worsening periodontitis. Additionally, chronic periodontal inflammation can negatively influence metabolic disorders and increase the risk of pregnancy complications, perpetuating a negative feedback cycle that impacts both oral and systemic health. Created with BioRender.com.

These mechanisms underscore the need for a comprehensive approach to address obesity, bone density, and periodontal health.

Oxidative stress

Oxidative stress is an imbalance between reactive oxygen species (ROS) and the body's antioxidant systems, causing damage to proteins, lipids, and DNA (94). This condition can act as a defense mechanism of the immune system against the presence of bacteria, such as those causing periodontitis (95). After periodontal pathogenic bacteria trigger host defense responses in the biofilm, neutrophils become the most common inflammatory cells in the periodontal tissue and gingival crevice. Neutrophils are believed to be the primary sources of ROS in periodontitis (96).

The interplay between periodontitis, obesity, and oxidative stress is a significant area of study that highlights the complex interactions contributing to chronic inflammatory conditions. Oxidative stress exacerbates both conditions, leading to cellular and tissue damage (97).

Recent studies have shown that oxidative stress plays a crucial role in the pathogenesis of both periodontitis and obesity (98). Excessive adipose tissue in individuals with obesity increases ROS production, which induces oxidative damage in gingival tissues, contributing to periodontal destruction and alveolar bone loss. This oxidative damage is more pronounced in patients with obesity compared to those of average weight, indicating a strong link between obesity and periodontal oxidative stress (97, 99).

Another study highlighted higher oxidative stress markers, such as myeloperoxidase and nitric oxide, in the gingival crevicular fluid of individuals with obesity and periodontitis. These markers are associated with increased inflammation and tissue destruction in periodontal disease (97). Additionally, the study found that non-surgical periodontal therapy significantly reduced these oxidative stress markers, suggesting that periodontal treatment can mitigate oxidative damage and improve periodontal health in patients with obesity (97, 100).

Evidence also suggests that periodontitis can influence systemic oxidative stress, causing a sustained inflammatory response that may contribute to insulin resistance, a common phenomenon in obesity (99). This resistance can affect glucose metabolism and appetite regulation, contributing to weight gain (97) (Figure 2).

This interaction underscores the need for comprehensive therapeutic approaches addressing periodontal and systemic health. Periodontal therapy and lifestyle modifications can mitigate the adverse effects of these chronic conditions by reducing oxidative stress and managing inflammation.

Periodontal microbiota

The periodontal microbiota and obesity are closely related through a process of dysbiosis, an alteration in the composition of the oral microbiome that can exacerbate periodontitis and be influenced by the individual's obesity status.

Periodontitis is characterized by a dysbiotic oral microbiome characterized by an increase in periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Tannerella forsythia* (101). In patients with obesity, a higher prevalence and severity of periodontitis are observed, which is related to an altered microbial composition in the oral cavity (102, 103).

Obesity contributes to the dysbiosis of the subgingival microbiome due to several factors, including systemic inflammation and altered immune response. Excess fatty tissue in individuals with obesity produces inflammatory mediators and ROS, affecting systemic metabolism and periodontal health. Several studies have reported an increase in the proportion of *Tannerella forsythia* in subgingival plaque and *Porphyromonas gingivalis* in the saliva of patients with obesity compared to those without obesity (86), which exacerbates gingival inflammation and reduces the effectiveness of periodontal treatment in these patients (103, 104).

Conversely, periodontal inflammation can also contribute to systemic inflammation (104, 105), exacerbating obesity and its metabolic complications, such as insulin resistance and chronic inflammation, which are common in obesity (106). Periodontal inflammation can contribute to intestinal dysbiosis (107), creating a vicious cycle perpetuating poor oral and systemic health (108). This bidirectional link underscores the importance of addressing oral health and obesity in an integrated manner to improve clinical outcomes.

Interventions such as periodontal therapy and lifestyle modifications are crucial to breaking this cycle of dysbiosis and inflammation. Including dietary strategies, regular exercise, and reasonable oral hygiene control can help restore microbial balance and reduce the impact of obesity on periodontal health.

Periodontitis in pregnant women with obesity

Obesity and periodontitis are both health concerns that interact in complex ways, particularly affecting pregnant women. During pregnancy, women undergo significant hormonal, immunological, and metabolic changes essential for proper fetal development and the provision of blood, nutrients, and oxygen (109). These changes and high hormone levels impair connective tissue regeneration in the periodontium, increasing the inflammatory response in these tissues. This phenomenon may increase the proliferation of aerobic and anaerobic bacteria, thereby raising the prevalence of pregnancy-related periodontal disease (109, 110).

Maternal obesity further complicates this scenario by inducing systemic immunological and inflammatory changes that may exacerbate pregnancy's inherent inflammatory state (111). This altered immune response can increase susceptibility to infections and excessive immunological reactivity, influencing the severity of maternal periodontitis (112).

Several studies have shown a positive association between obesity and periodontal disease (109–111, 113, 114), suggesting that both conditions may synergistically increase the inflammatory and oxidative state in pregnant women. This is reflected in an increase in local and systemic biomarkers (111) and could lead to an increase in complications associated with maternal obesity, such as gestational diabetes mellitus, hypertension, placental abnormalities, pre-eclampsia, prematurity, fetal death, and spontaneous abortion (109, 111). These adverse outcomes are believed to be linked to direct and indirect mechanisms involving periodontal pathogens and systemic inflammation. Direct mechanisms involve the translocation

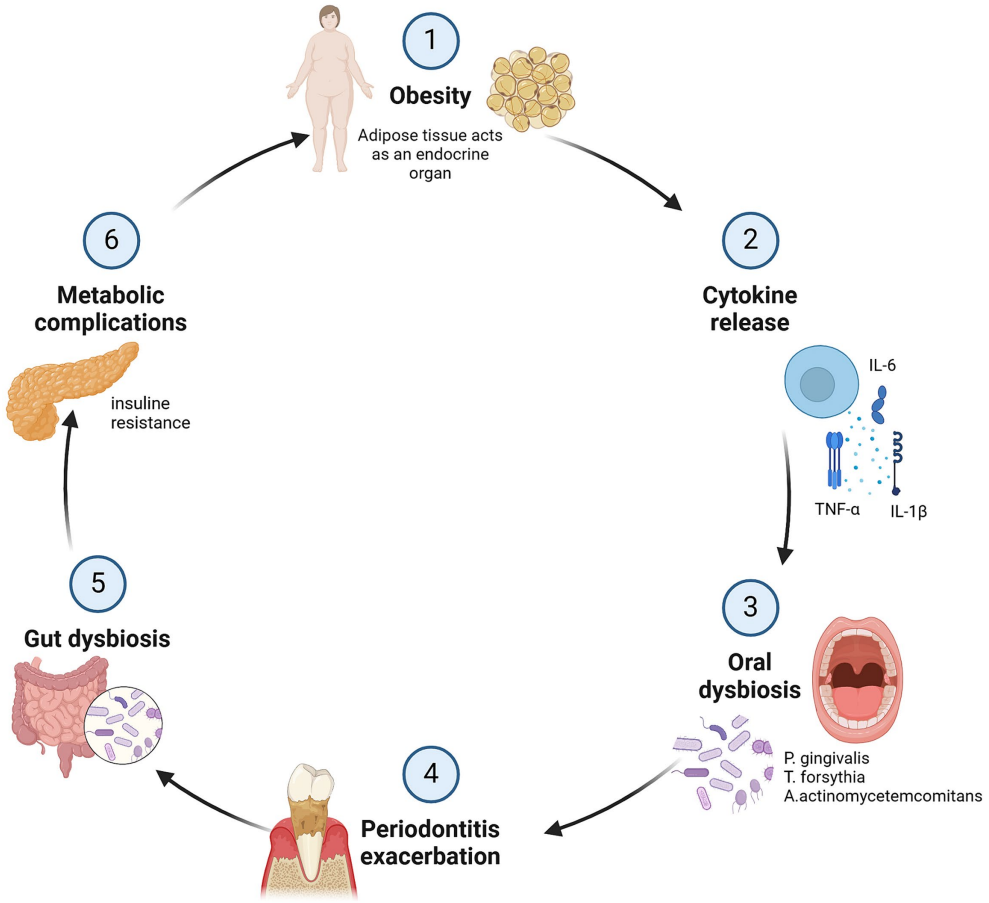

FIGURE 2
Impact of obesity on periodontal inflammation: a bidirectional cycle of damage. In obesity, adipose tissue acts as an endocrine organ releasing inflammatory substances such as TNF-α, IL-1β, and IL-6, leading a dysbiosis that contributes to periodontal inflammation and exacerbation of periodontitis, resulting in the destruction of periodontal tissue and bone loss. Chronic inflammation is also associated with metabolic complications like insulin resistance, creating a bidirectional cycle of inflammation and damage between obesity and periodontitis. Created with BioRender.com.

of oral bacteria to the placenta, triggering inflammatory responses, while indirect mechanisms involve elevated systemic inflammatory cytokines that disrupt placental function (115, 116).

Although there is evidence of an association between obesity and periodontal disease during pregnancy, the certainty of the evidence for these associations and their implications is inconclusive. This is due to current studies' methodological, clinical, and statistical heterogeneity, a potential risk of bias, and a lack of control for confounding factors. Therefore, new studies with research designs that use rigorous methods that minimize the risk of bias are needed to gain a better understanding and accuracy of these associations and their clinical implications.

Periodontitis in bariatric surgery patients

There are multiple types of bariatric surgery, the most common being gastric bypass, sleeve gastrectomy, and adjustable gastric banding (117). Regardless of the type of surgery performed, these surgical procedures are superior to non-surgical interventions in terms of weight loss outcomes and improvement in obesity-related comorbidities (118).

Studies investigating the relationship between bariatric surgery and periodontitis yield mixed results. On the one hand, some studies suggest that surgery is associated with improvements in various metabolic and physiological aspects of the body, including improvements in periodontal health due to a reduction in the inflammatory state and adipose tissue burden (119–121), as well as improved control of dental biofilm (120, 121). One study found no apparent reduction in periodontitis after bariatric surgery but noted that malabsorption of critical nutrients could affect periodontal health (122). Meanwhile, two cohort studies (123, 124) and a systematic review suggest that periodontal status may worsen in the first 6 months after bariatric surgery (125). Therefore, it is recommended to conduct periodontal evaluations and appropriately manage oral health before undergoing surgical interventions to prevent further deterioration of periodontal health post-surgery (123–125).

Non-surgical periodontal therapy in patients with obesity

The therapeutic approach to periodontitis encompasses various strategies, among which fundamental clinical interventions such as scaling and root planing stand out and are recognized as one of the

pillars of non-surgical periodontal therapy. This treatment involves the meticulous removal of tartar and impurities from the root surfaces of teeth with a probing depth ≥5 mm (126).

Several studies have evaluated the effect of periodontal scaling and root planing on gingival bleeding, probing depth, and cytokine levels in patients with and without obesity and chronic periodontitis (127). While most research reports greater probing depth and higher levels of IL-1β, IL-6, TNF-α, IFN-γ, leptin, adiponectin, and CRP in patients with obesity compared to those with normal weight (127–130), the effects of periodontal therapy are inconclusive. Subgroup analysis in specific studies has provided a deeper insight into how obesity and periodontitis interact. In some instances, treatment decreases serum levels of proinflammatory substances in patients with obesity. Still, after 3 months of follow-up, high levels of IL-6 and tumor necrosis factor-α are observed in this patient group (131). Resistin, another proinflammatory mediator, exhibits higher levels in individuals with periodontitis than those without the disease. Despite efforts of periodontal treatment, resistin shows no significant changes in serum or gingival crevicular fluid levels in individuals with and without obesity over time, indicating that its proinflammatory expression persists (127, 129, 131).

In the pharmacological realm, various studies assert that controlled administration of antibiotics can play a significant role in managing the bacterial load associated with periodontitis (132–135) and leads to significant improvement in treatment by reducing probing depth and enhancing clinical attachment (136). Specific case considerations guide the choice of antimicrobial agents, which can be administered systemically or locally (137, 138).

Long-term maintenance is an essential treatment component, involving regular clinical follow-up, periodontal evaluations, and periodic professional cleanings. Patient education, focusing on effective oral hygiene practices and understanding risk factors, strengthens the preventive component and contributes to the sustainability of therapeutic outcomes (126).

Surgical periodontal therapy in patients with obesity

Regarding surgical periodontal therapy, there are currently no studies directly comparing the outcomes of surgical periodontal therapy with non-surgical treatment in patients with obesity. However, there is evidence suggesting that patients with obesity may experience slower healing due to an exacerbated inflammatory response (63, 71), which could affect the results of surgical interventions (63), including surgical periodontal treatment.

In addition, it is common for patients with obesity to have coexisting comorbidities that may complicate surgical periodontal therapy (72, 74). This intersection of health conditions highlights the need for a comprehensive and personalized approach to the periodontal management of these patients. Based on the available evidence, non-surgical periodontal therapy may be preferable to minimize postoperative morbidity in this patient population (73, 75–77).

Discussion

The results of this review indicate that obesity and periodontitis are interrelated through inflammatory and oxidative stress mechanisms, generating a cycle where each condition may aggravate and perpetuate the other. Adipose tissue, acting as an endocrine organ, triggers inflammatory responses that affect periodontal tissues, and the chronic inflammation associated with periodontitis may contribute to the metabolic imbalances seen in obesity. However, the causal relationship between these two pathologies is unclear.

Many studies suggest that obesity is a significant risk factor for periodontitis and that there could be a dose–response relationship associated with body mass index (10, 129, 139, 140). However, other studies that consider the type of obesity only associate altered periodontal parameters with abdominal obesity and discard the relationship between general obesity and gingival attachment loss and bleeding (128, 141).

Another factor analyzed in this study was the level of cytokines present in patients with and without obesity and periodontitis. While there are studies that reported considerably high levels of IL-8, IL-1 β, TNF- α, progranulin, monocyte chemoattractant protein-4 (MCP-4), lipocalin, and resistin (73–76, 142), other investigations report no difference in the levels of these biomarkers in both subgroups (77–79). This variability in the results may be because the studies that reported comparable levels of pro-inflammatory substances in patients with and without obesity and periodontitis did not consider other factors such as systemic diseases, smoking, or the depth of periodontal probing.

It is also essential to evaluate cytokine and adipocytokine levels in different biological fluids, such as saliva, gingival crevicular fluid, and serum. While saliva and gingival crevicular fluid are more specific indicators of local periodontal conditions, serum provides a more comprehensive view of the organism (71). The choice of biological fluid can influence the interpretation of results, highlighting the need for comprehensive approaches in periodontal and obesity research.

The results related to the impact of obesity on periodontal treatment are diverse. Some authors suggest that clinical attachment levels and probing depth are comparable in subjects with and without obesity after non-surgical periodontal treatment (131, 143). At the same time, other investigations reported that patients with obesity have a lower response to periodontal therapy compared to those with normal weight (143–145), highlighting the negative effects of chronic inflammation on the periodontium. This variability calls for studies with higher methodological quality to evaluate the clinical impact of periodontal therapy in patients with obesity in the long term. Conversely, some studies indicate that periodontal treatment can improve the lipid profile (146), positively impacting obesity control.

Obesity and periodontal disease during pregnancy may also be associated. Still, the evidence is not definitive because of methodological and statistical heterogeneity, potential biases, and the inability of current research to control for confounding factors. More rigorous research is needed to clarify these associations and their clinical implications.

Regarding bariatric surgery, it has been reported that patients who lost weight after this intervention significantly improved periodontal health compared to those who did not undergo surgery (147). These results indicate that individualizing nutritional counseling, physical exercise for weight reduction, and periodontal therapy in this group of patients is imperative to improving oral and general health (147).

It should also be noted that evidence on the results of surgical periodontal therapy in patients with obesity is limited. There are no studies that directly compare the clinical effects of surgical and

non-surgical periodontal treatment in patients with obesity, but the possible exacerbated inflammatory response in patients with obesity could influence the speed of healing and the results of surgical interventions, suggesting that non-surgical therapy could be preferable in this group (63, 71).

This review had certain limitations that must be considered. Firstly, the heterogeneity of the included study designs generates variability in the results, making it difficult to generalize the conclusions. Differences in study populations, methodologies, and outcome measures contribute to this heterogeneity. Additionally, the potential for various biases exists, such as selection bias, reporting bias, and confounding factors that were not consistently controlled across studies. These biases can affect the validity and reliability of the findings. The lack of control for confounding variables in observational studies significantly limits the ability to establish a causal relationship between both pathologies. Many studies did not report controlling for confounding factors like systemic diseases, smoking, dietary habits, and physical activity, which could influence the observed relationships.

Secondly, the scarcity of longitudinal designs also represents a weakness since the temporal dynamics in the relationship between obesity and periodontitis cannot be assessed. Longitudinal studies are essential to determine the directionality and causality of the observed relationship over time.

It is important to proceed cautiously when extrapolating these results. Most evaluated investigations were carried out in particular populations, frequently in specific geographical areas or clinical situations. Diverse populations possess varying genetic, environmental, and lifestyle components, which may impact the generalizability of the findings in broader settings. For example, dietary habits, socioeconomic status, and healthcare access can all significantly impact periodontal health and obesity.

Future studies should strive to include varied populations from various socioeconomic backgrounds and geographic locations to improve the generalizability of the results. They should also look at how these correlations appear in particular subgroups, such as older people and other ethnic groups, to create tailored interventions that take into account their specific requirements.

Despite the limitations, this review presents several strengths. The breadth of the research, addressing aspects ranging from inflammatory mechanisms to outcomes in specific groups such as pregnant women and patients undergoing bariatric surgery, provides a comprehensive view of the relationship between obesity and periodontitis. Additionally, analyzing multiple factors, such as the potential causal relationship and responses to different available treatments, enriches the understanding of the interaction between periodontitis and obesity.

Several directions for future research are suggested to advance the understanding of this relationship. Prospective and longitudinal studies with long-term follow-ups are essential to establish causality and comprehend temporal dynamics. Focusing on specific populations, such as pregnant women, patients after bariatric surgery, and the younger population, will allow for more targeted therapeutic approaches. Exploration of modifying factors like genetics and the environment can provide valuable information for personalized therapeutic strategies.

In the realm of clinical practice, the analysis of the relationship between obesity and periodontitis has significant implications. A comprehensive patient assessment, considering obesity as a risk factor in periodontal evaluation, is recommended, especially in more susceptible populations such as pregnant women. A multidisciplinary approach involving healthcare professionals, including dentists, nutritionists, and surgeons, may be essential for effectively managing oral and general health in patients with obesity. Furthermore, patient education on the relationship between obesity and periodontitis and maintaining healthy habits can enhance awareness and promote prevention.

Conclusion

In conclusion, the relationship between obesity and periodontitis is multifaceted and complex, involving inflammatory and oxidative stress mechanisms. The evidence suggests that obesity significantly increases the risk of developing and exacerbating periodontitis, with elevated inflammatory biomarkers in patients with obesity, even during pregnancy. The response to periodontal treatment varies, with some improvements seen post-bariatric surgery, though evidence on surgical therapy outcomes is limited. Study heterogeneity and uncontrolled confounding factors limit the generalizability of findings. Further research is needed to understand the underlying mechanisms and develop more effective therapeutic strategies for periodontitis and obesity. Collaboration between periodontal health professionals and obesity experts is essential to moving toward integrated and personalized approaches to managing these interrelated conditions.

Author contributions

CR-G: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Investigation, Project administration. JP-V: Writing – original draft, Writing – review & editing, Methodology. NG: Writing – review & editing. AS-R: Methodology, Writing – review & editing. RZ-V: Writing – review & editing. AZ: Supervision, Validation, Writing – review & editing. DS-R: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing, Investigation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association between dynapenic obesity phenotypes and physical performance in middle-age and older women living in community

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Background: Dynapenic obesity (DO) is the coexistence of excess adipose tissue/body weight and low muscle strength. This condition is associated with an increased risk of suffering from various chronic diseases and physical deterioration in older people.

Aim: To analyze the association between DO phenotypes and physical performance in middle-aged women living in the community.

Methods: This cross-sectional study was conducted on middle-aged and older women (≥50 years) residing in Guayaquil, Ecuador. Dynapenia was diagnosticated by a handgrip strength (HGS) < 16 kg; obesity was determined based on body mass index (BMI) ≥ 30 kg/m^2. Participants were categorized into four groups based on their dynapenia and obesity status: non-dynapenic/non-obesity (ND/NO), obesity/non-dynapenic (O/ND), dynapenic/non-obesity (D/NO) and dynapenic/obesity (D/O). Physical performance was assessed by the Short Physical Performance Battery (SPPB).

Results: A total of 171 women were assessed. The median (IQR) age of the sample was 72.0 (17.0) years. Obesity and dynapenia were 35% ($n = 60$) and 57.8% ($n = 99$) of the participants, respectively. The prevalence of ND/NO was 25.1% ($n = 43$), O/ND 17% ($n = 29$), D/NO 39.8% ($n = 68$) and DO 18.1% ($n = 31$). The mean SPPB total score was 6.5 ± 3.2. Participants of D/NO and DO groups presented significantly lower mean SPPB scores ($p < 0.001$) compared to those of NO/ND and O/ND groups.

Conclusion: Women with DO and D/NO exhibited significantly lower SPPB scores, indicating poorer physical performance. These findings emphasize the importance of incorporating a comprehensive assessment of muscle strength and obesity in middle-aged and older women.

KEYWORDS

dynapenic obesity, physical performance, middle-age women, community-dwelling, dynapenia

1 Introduction

Obesity is a multifactorial, chronic, progressive disease associated with adverse health outcomes throughout the life course (1, 2). In 2022, an estimated 374 million women were identified with obesity (3), however, data on the prevalence of obesity specifically in women aged 50 and older is lacking.

In middle-aged women, several factors contribute to changes in body composition. These include age-related decline in estrogen levels around menopause (4, 5) and its impact on metabolism and related diseases (6, 7), lifestyle factors (8–10) such as diet (11), anabolic resistance associated with aging (12), among others. As a result, decreasing of muscle mass and strength, which begin to decrease around 30 and accelerate after 40 (13, 14), infiltration of fat within muscle and increasing prevalence of dynapenia (weakness) (15), sarcopenia (weakness and muscle loss), and obesity are common in this aged group (16).

Moreover, a wide range of alterations, including altered immune function, increased systemic inflammation, accumulated intracellular macromolecules, decreased genomic integrity, and changes in tissue and body composition (17), are common to both obesity and aging (18, 19).

In the last few years, the concept of dynapenic obesity (DO) has been used to describe the coexistence of excess adipose tissue/body weight and low muscle strength (20). Different criteria have been used to identify the obesity component, such as body mass index (BMI) (21), abdominal obesity (22), and fat mass percentage (23). DO is not a homogenous condition and different phenotypes might exist based on variations in factors like fat distribution and muscle quality.

Regardless of the criteria to identify obesity, DO has been associated with a higher risk of falls (24), poorer bone health (25), inflammatory biomarkers (26), and an increased risk of chronic diseases (27). Given the independent effect of obesity on muscle function (28, 29), DO could be associated with worse physical performance. In individuals with obesity have been reported impaired functional capacity (30); particularly, women with obesity exhibited slower fast gait speeds, shorter stride lengths, poorer sit-to-stand performance, and endurance (31). Nevertheless, high handgrip strength levels could attenuate the negative effect of adiposity (32).

Moreover, recent studies on the association between DO and physical performance in middle-aged women and older show conflicting results (33, 34), which might be due to population characteristics and heterogeneity in DO definitions. We previously reported the prevalence of sarcopenia and obesity in community-dwelling older adults (35), however, the current prevalence of DO in middle-aged and older women remains unknown.

Understanding different DO phenotypes can provide more specific insights into the relationship with physical performance and ultimately lead to more targeted interventions. Thus, this study aimed to assess the relationship between DO phenotypes and physical performance in middle-aged women living in the community.

2 Materials and methods

2.1 Subjects

This was an observational cross-sectional study carried out in community-dwelling, middle-aged and older women living in urban-marginal areas of Guayaquil, Ecuador from November 2019 to December 2020. The following criteria were used for inclusion: women in the ≥50 years old who agreed to participate voluntarily in the study signing an informant consent. The exclusion criteria were institutionalized individuals, those with known dementia or severe cognitive impairment, functional dependence, current cancer, chronic obstructive pulmonary disease, and musculoskeletal diseases. Figure 1 shows the sample selection flowchart.

2.2 Sociodemographic and clinical characteristics

Participants filled out a self-reported survey with a standardized questionnaire that assessed their socioeconomic and clinical characteristics. Socioeconomic variables include: age, ethnicity (mestizo, afro-Ecuadorian, Caucasian, indigenous), marital status (single, married, widowed, divorced), education level (none, primary, secondary, tertiary). Clinical characteristics were assessment by prevalent medical conditions such as type 2 diabetes, hypertension, dyslipidemia, gastroesophageal reflux disease, arthritis, constipation.

2.3 Dynapenia measurement

Dynapenia was diagnosticated by handgrip strength (HGS) using a Jamar Plus Hand Dynamometer with an accuracy of over 99% (36). HGS was evaluated in both hands, regardless of the dominant one. Subjects were advised verbally to grip the instrument and perform maximum handgrip strength. All the lectures were carried out standing, with both arms pending sideways and the dynamometer facing the evaluator. The value registered was the higher value realized by side, individuals rest 1 min at least between trials of the same hand. Dynapenia was evaluated by handgrip strength defined as HGS < 16 kg according to the European Working Group on Sarcopenia in Older People (EWGSOP2) (37).

2.4 Obesity measurement

Obesity was identified according to body mass index (BMI), calculated as weight in kilograms divided by height in meters squared (kg/m^2). Body mass (weight) was measured on a SECA 700 ® mechanical physical scale and recorded in kilograms (kg) to the nearest 0.1 decimal. Height was recorded on a SECA 213® portable stadiometer. Obesity was determined based on BMI ≥ 30 kg/m^2 (38).

2.5 Dynapenic obesity phenotypes

Participants were categorized into four groups based on their dynapenia and obesity status: non-dynapenic/non-obesity (ND/NO), obesity/non-dynapenic (O/ND), dynapenic/non-obesity (D/NO) and dynapenic/obesity (D/O) (39).

2.6 Physical performance measurement

The Short Physical Performance Battery (SPPB) was used to assess physical performance. The SPPB comprises three physical performance measures: standing balance, repeated chair stands, and gait speed (40).

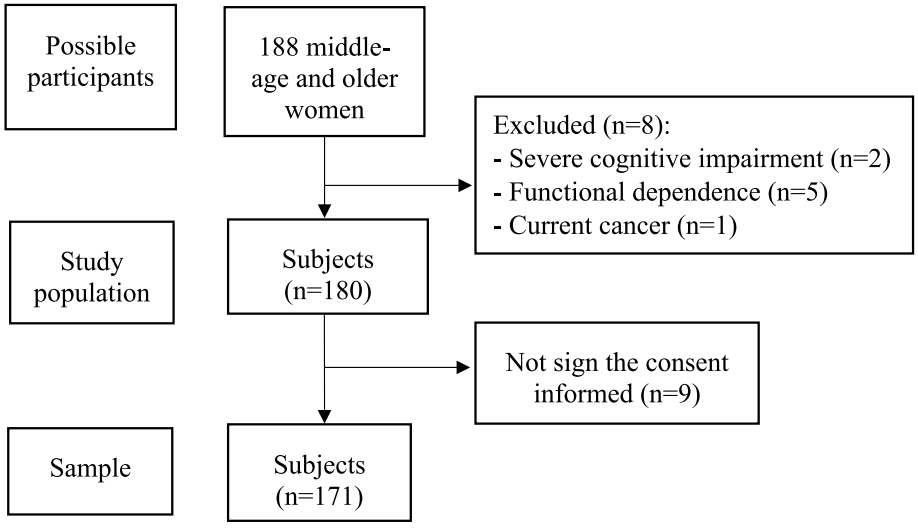

FIGURE 1
Flowchart of the recruitment process of the participants of the study.

Evaluation of balance involved hierarchical tasks consisting of side-by-side, semi-tandem, and full-tandem stands. During the repeated chair stand test, participants underwent timing while performing five sit-to-stand repetitions. Gait speed assessment was conducted by timing participants as they walked 2.44 meters at their usual pace.

Each assessment is graded on a scale ranging from 0 (indicating an inability to complete the task) to 4 points (representing the highest level of performance) on the test. The overall score for the SPPB falls within the range of 0 (indicating the poorest performance) to 12 points (indicating the best performance) and assesses performance in the various tests based on three or four distinct categories of scores: three categories include 0–6 points (indicating subpar performance), 7–9 points (indicating moderate performance), and 10–12 points (indicating good performance); while four categories consist of 0–3 points (indicating disability/very poor performance), 4–6 points (indicating poor performance), 7–9 points (indicating moderate performance), and 10–12 points (indicating good performance).

2.7 Other variables

The following body composition compartments were also measured, using a Multifrequency Segmental Body Composition Analyzer (InBody 270 DSM-BIA®): muscle mass, fat mass, and body fat percentage, as well as their index. To assess BC, participants were advised not to eat or drink 4 h before the test, consume any caffeine beverage or alcohol within 12 h of the test, use diuretic medication, perform exercise 12 h before the test, and suggest evacuating urine.

2.8 Ethical considerations

The study's approval came from the Ethics Committee for Research in Humans of the "Hospital Clínica Kennedy," Guayaquil, Ecuador (CEISH No: HCK-CEISH-19-0038, June 21, 2019) and conducted by the guidelines of the Declaration of Helsinki. All participants were informed of the study, its aims, and used instruments, following which they gave written permission to take part.

2.9 Data analysis

Data analysis was performed using IBM SPSS Statistics (version 25.0; IBM, Chicago, IL, EE. UU). Study participants were divided into groups according to DO phenotypes. Continuous variables are reported as mean and standard deviation or median and interquartile range (IQR) in the descriptive analysis, and categorical variables as frequencies and percentages. For the bivariate analysis, the numerical variables with normal distribution were compared using the Anova test; contrary to this, we used the Kruskall-Wallis test. For all analyses, a p value <0.05 was considered statistically significant.

3 Results

A total of 171 middle-aged and older women participated in this study. The median (IQR) age of the sample was 72.0 years (17.0). Obesity and dynapenia were 35.1% ($n = 60$) and 57.8% ($n = 99$) of the participants, respectively. The prevalence of ND/NO was 25.1% ($n = 43$), O/ND 17% ($n = 29$), D/NO 39.8% ($n = 68$) and DO 18.1% ($n = 31$). Subjects with D/NO were older compared with other phenotypes ($p < 0.001$).

Participants with DO had a higher BMI, waist circumference, fat mass index, and visceral fat compared with the other phenotypes. HGS and phase angel were higher in those with NO/ND and O/ND, compared with the other phenotypes, while skeletal muscle mass was higher in participants with O/ND and D/O phenotypes in contract with others groups. The sociodemographic and clinical characteristics of the participants, according to DO phenotypes, are presented in Table 1.

TABLE 1 Characteristics of the studied population according to dynapenic obesity phenotypes.

Variable	Total (n = 171)	NO/ND (n = 43)	O/ND (n = 29)	D/NO (n = 68)	D/O (n = 31)	p-value
Age (years)	72 (17.0)	72.0 ± 9.8	65.4 ± 9.3	77.4 ± 10.4	70.0 ± 12.7	< 0.001*
Ethnicity, *n* (%)						
Mestizo	119 (69.6)	24 (55.8)	24 (82.7)	47 (69.1)	24 (77.4)	0.136
Afro-Ecuadorian	24 (14)	10 (22.3)	5 (17.2)	6 (8.8)	3 (9.6)	
Caucasian	15 (8.7)	5 (11.6)	0 (0.0)	8 (11.8)	2 (6.4)	
Indigenous	13 (7.6)	4 (9.3)	0 (0)	7 (10.3)	2 (6.4)	
Marital status, *n* (%)						
Single	48 (28.1)	13 (30.2)	9 (31.0)	20 (29.4)	6 (19.3)	0.147
Married	58 (33.9)	14 (32.5)	11 (37.9)	16 (23.5)	17 (54.8)	
Widowed	48 (28.01)	12 (27.9)	6 (20.7)	26 (38.2)	4 (12.9)	
Divorced	17 (9.9)	4 (9.30)	3 (10.3)	6 (8.8)	4 (12.9)	
Education level, *n* (%)						
None	45 (26.3)	10 (23.2)	9 (31.0)	19 (27.9)	7 (22.6)	0.914
Primary	94 (54.9)	25 (58.1)	14 (48.2)	38 (55.9)	17 (54.8)	
Secondary	27 (15.8)	8 (18.6)	5 (17.2)	8 (11.8)	6 (19.3)	
Tertiary	5 (2.9)	0 (0)	1 (3.4)	3 (4.4)	1 (1.4)	
Medical conditions, *n* (%)						
None	13 (7.6)	3 (6.9)	2 (6.8)	7 (10.2)	1 (3.2)	0.468
T2D	25 (14.6)	2 (4.6)	4 (13.7)	14 (20.6)	5 (16.1)	
Hypertension	94 (54.9)	26 (60.5)	19 (65.5)	30 (44.1)	19 (61.2)	
Dyslipidemia	10 (5.8)	3 (6.9)	1 (3.4)	5 (7.3)	1 (3.2)	
GERD	2 (1.2)	1 (2.3)	0 (0)	1 (1.4)	0 (0)	
Arthritis	12 (7)	1 (2.3)	1 (3.4)	7 (10.2)	3 (9.6)	
Constipation	15 (8.7)	7 (16.2)	2 (6.8)	4 (5.9)	2 (6.4)	
Weight (kg), Median (IQR)	62 (53–71)	61 (55–66)	75 (68–82)	52.9 (45.8–60)	73 (66–86.1)	< 0.001*
Height (cm)	148 (143–153)	150 (145.5–156.9)	150 (143.5–153.7)	146.4 (141.1–151)	148.6 (144–151)	0.006*
BIM (kg/m^2)	28.4 ± 5.3	26.1 ± 2.6	34.0 ± 3.0	24.8 ± 3.5	34.5 ± 3.2	< 0.001*
Waist circumference (cm)	94.0 ± 11.7	90.2 ± 8.5	102.6 ± 7.8	87.7 ± 10.1	104.7 ± 9.6	< 0.001*
Skeletal muscle mass (kg)	15 (11.6–18.4)	14.4 (12.7–16.6)	18.9 (15.9–21.3)	12 (8.8–15.7)	18.6 (14.8–21.3)	< 0.001*
Fat mas index (kg/m^2)	11.9 (10.1–15)	11.6 (10.1–12.9)	15.6 (14–17.1)	10.5 (7.8–12)	15.7 (13.4–18.6)	< 0.001*
Visceral fat (%)	2.9 (2.4–3.5)	2.7 (2.4–3.1)	3.3 (2.7–3.7)	2.6 (2.2–3)	3.8 (3.1–4.2)	< 0.001*
Phase angle	5.2 (4.6–5.9)	5.2 (4.6–5.5)	5.7 (4.9–6.1)	4.8 (4.2–5.7)	5.7 (5–6.9)	< 0.001*
HGS (kg)	14 (10–19)	20 (18–22)	20 (17–25)	11.5 (10–12)	12 (10–12)	< 0.001*

*p value < 0.05.
Continuous symmetric variables are presented as means ± SD or median (IQR) for asymmetric variables, or numbers (percentages) for categorical variables unless otherwise indicated. ND/NO, non-dynapenic/non-obesity; O/ND, obesity/non-dynapenic; D/NO, dynapenic/non-obesity; D/O, dynapenic/obesity; IQR, interquartile range; SD, standard deviation; T2D, type 2 diabetes; GERD, gastroesophageal reflux disease; HGS, handgrip strength.

The mean SPPB total score was 6.5 ± 3.2 Participants of D/NO and DO groups presented significantly lower mean SPPB scores (p < 0.001) compared to those of NO/ND and O/ND groups (Figure 2).

Very poor performance was prevalent in 22.6% (n = 7), while poor performance, moderate performance, and good performance were prevalent in 16.1% (n = 5), 54.8% (n = 17) and 6.4% (n = 2) in the sample, respectively (Table 2).

4 Discussion

This report aims to enhance understanding of the phenotypes of dynapenia, obesity, and DO in middle-aged and older women living in the community and highlight the detrimental effect of DO on physical function, exceeding the negative effects of either phenotype alone.

To our knowledge, the only report on the prevalence of muscle weakness in older adults was published by Garces, based on the data

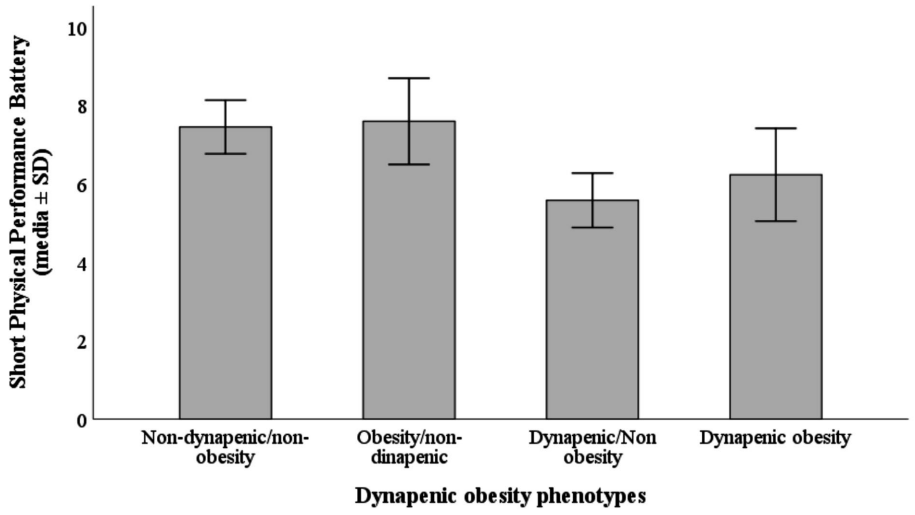

FIGURE 2
Mean Short Physical Performance Battery (SPPB) total score according to dynapenic obesity phenotypes.

TABLE 2 Characteristics of the studied population according to dynapenic obesity phenotypes.

Physical performance	Total (n = 171)	NO/ND (n = 43)	O/ND (n = 29)	D/NO (n = 68)	D/O (n = 31)	p-value
SPPB value, Media ± SD	6.5 ± 3.2	7.4 ± 2.2	7.5 ± 2.9	5.5 ± 2.7	6.2 ± 3.9	0.001*
Very poor performance	28 (16.3)	1 (2.3)	2 (6.8)	18 (26.4)	7 (22.6)	0.004*
Poor performance	45 (26.3)	12 (27.9)	7 (24.1)	21 (30.9)	5 (16.1)	
Moderate performance	80 (46.7)	24 (55.8)	13 (44.8)	26 (38.2)	17 (54.8)	
Good performance	18 (10.5)	6 (13.9)	7 (24.1)	3 (4.4)	2 (6.4)	

*p value < 0.05.
ND/NO, non-dynapenic/non-obesity; O/ND, obesity/non-dynapenic; D/NO, dynapenic/non-obesity; D/O, dynapenic obesity; SPPB, Short Physical Performance Battery; SD, standard deviation.

from the first National Health, Wellbeing, and Aging Survey (21). Later, he reported a lower prevalence of 6.8% phenotype of DO in female older adults, in comparison to 18.1% in our data. This result can be related to a more representative sample size, in contrast with our population of mostly urban-marginal middle-aged women. In other variables, the prevalence of obesity was 35.1% vs. 20%, and the prevalence of only dynapenia was significantly higher in our data with 57.8% vs. 24.7% (39).

Our main findings showed that the D/NO phenotype had the worse scores for physical performance in middle-aged women and older women in the SPPB test, followed by the DO group; we found statistical differences in the SPPB value for the four categories. Anthropometric characteristics of the population related to an increase in fat mass present statistical differences in the four phenotypic groups weight, height, BMI, waist circumference, and visceral fat. Interestingly, skeletal muscle mass was higher in participants with the O/ND phenotype compared to both DO and NO/ND groups. This suggests potential differences in body composition within dynapenic individuals.

Some reports DO have poorer physical function than individuals with obesity alone or dynapenia alone, suggesting a possible independent effect on physical performance measurements, and probably these effects are considered additive and not multiplicative (34, 41). Furthermore, based on cross-sectional and longitudinal studies that have described the mixture effect of obesity and poor muscle strength in older adults, defined as DO, this condition increases the probability of mobility disability, poor functional performance, risk of falls, hospitalization, and higher mortality (41, 42).

Low muscle mass function and obesity affect more than one in ten older adults globally (43). Our data shows that the prevalence of DO in our sample was 18.1%. Stenholm et al. evaluated 930 adults aged 65 and older in a 6-year follow-up period; obesity (cataloged with BMI), and low muscle strength (measured with knee extensor strength) registered a 17% reduction of walking speed, in comparison with 8% counterparts with only obesity and 4% individual with lower strength (44). In another study, with 2,208 adults aged 55 years and older, had been described a prevalence of walking limitations significantly higher 61% than their previous reports when DO was diagnosed (45). Additionally, a recent research suggests that diminished gait speed, an indicator of physical performance, can predict a risk of DO (46).

Regardless the relationship between muscle strength and adiposity is related to the determination of the method to diagnose body fat excess. Reports from Keevil et al. show that a larger BMI was associated with lower HGS, but a high waist circumference value has an opposite association. In addition, they found that a greater value

waist circumference HGS was lower in both sexes. These findings proposed that abdominal fat is the most metabolically active tissue with the understanding potential mechanism for the association between skeletal muscle and fat mass (47).

Finally, finding obesity phenotypes (48) could help researchers better understand how DO interacts with physical performance, which will advance the study of DO (49).

This study provides valuable insights into sarcopenia (DO) phenotypes in middle-aged and older women residing in the community. When compared to national reference data (39), our findings reveal a significant increase in the prevalence of obesity, dynapenia, and sarcopenia. This highlights the critical need for public health programs and interventions to prevent and address these conditions. The heightened prevalence of sarcopenia emphasizes the need for further research aimed at identifying associated factors and developing strategies to improve muscle health and physical function in this population.

At the national level, the high prevalence of dynapenia and obesity calls for a comprehensive approach to assessment and intervention. Potential strategies could include programs that promote physical activity through public awareness campaigns, community-based exercise and nutrition initiatives, and training healthcare professionals to manage these conditions effectively. Ensuring equitable access to care will require addressing socioeconomic disparities and improving healthcare accessibility across all sectors.

One key limitation of this study is its cross-sectional design, which does not allow for establishing causal relationships between the variables examined (e.g., obesity and dynapenia with physical performance). Furthermore, the study only included middle-aged and older women, limiting the generalizability of the results to younger populations.

5 Conclusion

In conclusion, the D/NO and D/O groups presented the worst scores in physical performance and were associated with impaired physical function. The DO group had the highest body fat percentage and worst performance on the SPPB. This suggests the DO phenotype is associated with poorer physical health. This link between the DO phenotype and functional limitations is a key finding that can help establish personalized therapeutic strategies to address the coexistence of these health problems.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee for Research in Humans of the "Hospital Clínica Kennedy," Guayaquil, Ecuador (CEISH No: HCK-CEISH-19-0038, June 21, 2019). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

CA-P: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. DF-P: Writing – original draft, Writing – review & editing. MB: Writing – original draft, Writing – review & editing. JG-C: Writing – original draft, Writing – review & editing. JE: Writing – original draft, Writing – review & editing. LÁ-C: Funding acquisition, Investigation, Project administration, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Hypovitaminosis D in university workers in Southern Ecuador: interactions between gender and lifestyle

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Background: Hypovitaminosis D may be common in tropical countries and is linked to disorders of phospho-calcium metabolism, rickets, muscle pain, immune system deficiencies, and increased susceptibility to microbial infections.

Objective: To assess the prevalence of hypovitaminosis D in apparently healthy university workers in Loja, Ecuador.

Methods: A cross-sectional study was completed in a private Ecuadorian university from May 2023 to September 2023, involving 440 participants. Data were gathered using a structured questionnaire created to assess risk factors influencing vitamin D levels. Serum 25-hydroxyvitamin D (25-OH)D concentrations were measured utilizing immunoenzymatic methods. Altered states (insufficiency or deficiency) of vitamin D were defined with serum values <30 ng/mL. Associations between vitamin D status and selected determinants were analyzed with independence tests, with significance set at $p < 0.05$. Where possible, odds ratios (OR) were calculated using logistic regression.

Results: The sample consisted of 60.9% faculty members and 39.1% administrative staff; 42.7% were men and 57.3% were women, with an average age of 41.9 $\pm$ 7.6 years. Only 2.7% of participants were aged 60 years or older. The mean serum 25-(OH)D concentration was 19.5 $\pm$ 6.8 ng/mL. Altered 25-(OH)D levels were found in 93.4% of participants, with 94.0% showing decreased serum 25-(OH)D concentrations and 1.6% displaying deficiency states. Hypovitaminosis D was associated with sex (OR = 2.40; 95% CI: 1.3–5.57; $p < 0.05$) and sunscreen use (OR = 0.36; 95% IC: 0.13–0.99; $p < 0.05$).

Conclusion: Hypovitaminosis D was almost universal among the apparently healthy university workers studied. The findings suggest that both sex and sunscreen use may independently or jointly contribute to hypovitaminosis D in these individuals. Further studies will be required to clarify this interplay.

KEYWORDS

vitamin D, deficiency, insufficiency, sun exposure, indoors, outdoors

1 Introduction

Vitamin D is a steroid-based hormone essential for regulating calcium and phosphorus balance, both of which are critical for bone formation and remodeling. Additionally, it acts an anti-inflammatory and antioxidant agent, protects the vascular endothelium, regulates immune system activity, participates in DNA repair, and promotes peripheral insulin sensitivity (1, 2). It also modulates cell growth, neuromuscular activity, and immune responses, and acts as an anti-inflamatory agent (3). It significantly influences physical performance through its involvement in muscle contraction. The extensive range of biological functions attributed to vitamin D is explained by the ubiquitous expression of its receptors across various organs and systems (4–6).

Vitamin D's potent neurotropic effects on the brain are also noteworthy, including its roles in neurotransmission, neurogenesis, and synaptogenesis (7). Equally important is its role in regulating pro-inflammatory cytokines. In the context of excess adipose tissue, the production of resistin, a proinflammatory cytokine, is exacerbated, disrupting normal vitamin D levels (6). A study involving 93 COVID-19 patients demonstrated an inverse correlation between hypovitaminosis D and inflammatory markers such as interleukins IL-1b, IL-6, IL-10, and tumor necrosis factor. Lower vitamin D levels were associated with higher mortality and longer hospital stays. Consequently, vitamin D supplementation may help prevent autoimmune and inflammatory diseases (8–11).

The link between obesity and vitamin D deficiency is intricate and involves multiple factors (7, 12). Excess adipose tissue in individuals with obesity can sequester vitamin D, decreasing its bioavailability in circulation. Additionally, reduced physical activity and lower sun exposure in this population may hinder natural vitamin D synthesis. Chronic inflammation, often associated with obesity, can also interfere with vitamin D metabolism. In turn, vitamin D deficiency can exarcebate insulin resistance, potentially leading to further weight gain and metabolic dysfunction (7, 13).

Vitamin D deficiency is universally acknowledged as a significant public health issue, with approximately one billion people worldwide affected by altered Vitamin D states (both deficiency and insufficiency). Prevalence rates of hypovitaminosis D have been estimated at 24, 37, and 40% in the United States, Canada, and Europe, respectively (14). In Lebanon, located in the Mediterranean Basin, the prevalence of vitamin D deficiency reaches as high as 83.5% (15, 16). Globally, the prevalence of hypovitaminosis D varies: North America: 78.6%; Europe: 73.6%; Africa: 86.1%; Middle East: 81.5%; and Asia: 90.4%, respectively (17).

In Latin America, Colombia reported a prevalence of altered vitamin D states (insufficiency and deficiency) of 70.6% (18). In Mexico, 63.3% of the adult population has serum vitamin D levels below 30 ng/mL (19), while Chile confirmed a prevalence of altered vitamin D states at 73.1% (20). Brazil reported a vitamin D insufficiency prevalence of 64.5% (21).

Research on hypovitaminosis D has gained particular relevance after studies indicated that decreased serum vitamin D levels could partially explain the higher mortality observed in vulnerable populations infected with SARS-CoV-2. The primary risk factor associated in reduced Vitamin D synthesis is limited sunlight exposure (22). However, vitamin D synthesis is multifactorial, influenced by both environmental and individual factors. Environmental factors include low ultraviolet B (UVB) exposure, geographical latitude, seasonal variations, pollution, and regional climate conditions. Individual factors include genetic predisposition, endocrine disruptors, toxic metal contamination, liver damage, parathyroid dysfunction, smoking (23). Other factors that inhibit vitamin D synthesis include inadequate diet, skin pigmentation, age, gender, excessive clothing, sunscreen use, work environment, and limited outdoor activity due to prolonged indoor work shifts (24) All these factors contribute to insufficient vitamin D synthesis (25, 26).

The human body synthesizes approximately 80% of its vitamin D through epidermal synthesis, facilitated by UVB light, with 7-dehydrocholesterol as a precursor (27). Despite this, controversies regarding sunlight exposure and its link to melanoma and skin cancer have led to public concern, resulting in excessive protection against sunlight. A full day of sunlight exposure can produce between 800 to over 20,000 international units (IU) of vitamin D. To maintain optimal levels, it is recommended that healthy individuals expose their forearms and legs uncovered for 30–45 min between 10 a.m. and 3 p.m. (28). Furthermore, exposing the face and arms, or arms and legs, to UVB radiation for 15 to 30 min daily from 11 a.m. to 3 p.m. can ensure adequate vitamin D levels in individuals with fair skin (29). The larger the skin area exposed to UVB rays, the higher the levels of cholecalciferol and subsequently 25 (OH)D levels produced. However, the face and hands are the most efficient producers of vitamin D (30). In summary, the benefits of sunlight in producing vitamin D are maximized when a greater skin area is exposed. Sunbathing in a bathing suit can produce a vitamin D dose equivalent to ingesting 20,000 IU daily, which is not feasible in typical work environments (28, 31). Sunlight exposure alone can produce 90% of the body's required vitamin D, compared to only 360 IU from 100 grams of salmon or other oily fish. Therefore, combining sunlight exposure with vitamin D supplementation is an effective strategy (32).

Indoor activities, particularly work shifts, may contribute to musculoskeletal conditions and other issues, especially when sunlight exposure is minimal. A strong correlation between indoor work and low serum Vitamin D levels has been well-documented (33, 34).

The angle of incidence of sunlight also impacts vitamin D synthesis, as oblique sun rays reduce the amount of vitamin D produced (35). Additionally, skin pigmentation is a critical factor: for instance, Type VI skin requires 5 to 10 times more sunlight exposure compared to Type II skin (36).

Proper sunscreen application (2 mg/square centimeter) with a sun protection factor (SPF) of 30 absorbs 97.5% of UVB radiation at the skin's surface, reducing vitamin D production by the same percentage (37). Clothing and glass block all UVB radiation, further preventing vitamin D synthesis during sun exposure (38).

Contrary to the belief that countries with year-round sunlight should not experience hypovitaminosis D, significant vitamin D deficiencies are reported in many Asian countries, particularly in the Middle East (such as Turkey, India, Iran, and Saudi Arabia) (39, 40). Conversely, countries north of the Equator experience vitamin D deficiency due to limited sunlight during extended winter periods (41).

In Ecuador, vitamin D deficiency is prevalent in 76% of the population (42, 43). A study conducted in Loja (Province of Loja) among 82 women aged 35–60 years found that 67.1% had altered vitamin D levels (Insufficiency: 23. 2%; Deficiency: 43.9%) (44).

Given these factors, it is imperative to assess serum vitamin D levels in otherwise healthy population primarily engaged in indoor work. This study aims to explore potential associations between altered vitamin D levels and selected determinants.

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2 Materials and methods

2.1 Study location

The study was conducted in Loja, a city in the southern region of Ecuador. Loja has a population of 485,421 inhabitants (51.5% women and 48.5% men) and is located in the inter-Andean region at an altitude of 3,700 meters above sea level. The climate is temperate Andean, with average temperatures ranging from 14°C and 22°C. The year is divided into two distinct seasons: winter and summer.

2.2 Study design

This research was a prospective, cross-sectional, analytical study conducted from May 2023 to September 2023.

2.3 Sample population

The total population of employees of the institution was 1,044; 988 participants were during the pilot phase. The final study sample consisted of 440 adults. Participants were selected from the university staff using non-probabilistic, convenience sampling, based primarily on individual's willingness to participate until the required sample size was reached. The study included faculty members and administrative staff aged 18 years or older, of either gender, and working full-time (8 h per day). In contrast, the study excluded pregnant or breastfeeding women and individuals taking vitamin D supplements. Figure 1 presents a flowchart illustrating the participant selection process.

2.4 Data collection

Participants were interviewed using a structured questionnaire designed to assess risk factors that might affect vitamin D levels. The questionnaire collected sociodemographic data, type of work performed (considering environmental exposure), skin type, sunscreen use, and frequency.

Data collection was supported by a trained team of five researchers from various medical specialties, all familiar with the study's objectives.

2.5 Determination of vitamin D

A blood sample was collected from each participant after fasting. Vitamin D levels were measured by qualified personnel using standardized methods and the same laboratory equipment at the institution where the study was conducted. The concentration of 25-hydroxy vitamin D in plasma was determined using an enzyme-linked immunosorbent assay (ELISA) with a Thermo Scientific Multiskan™ FC microplate photometer and DiaSource InmunnoAssays reagent kits (Belgium). Serum and heparinized plasma samples were stored at 2–8°C and processed within 24 h of collection. Analytical determinations were unaffected by hemolysis, hyperbilirubinemia, or hypertriglyceridemia. A calibration curve was included in each test run. Serum vitamin D concentrations were categorized as follows: normal (≥ 30 ng/mL), insufficient (10.0–29.9 ng/mL), and deficient (< 10 ng/mL). It should be noted that these values align with the reference literature provided by the assay kit. However, different medical societies and expert groups define different cut-off points for vitamin D insufficiency and deficiency, leading to variability in interpretating results. The same values could result in differing estimates of altered states (45).

2.6 Data processing and statistical analysis

Collected data were analyzed using descriptive statistics, including measures of central tendency (mean ± SD), dispersion (standard deviation), and frequency distributions (absolute frequencies and percentages). Altered states of vitamin D (insufficiency and deficiency)

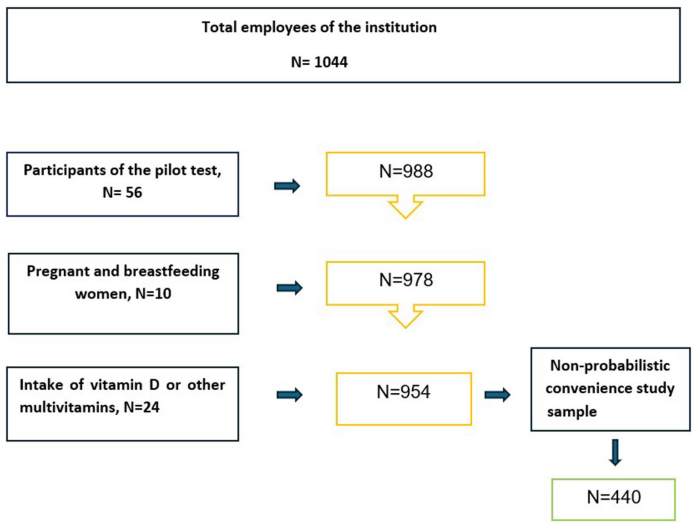

FIGURE 1
Selection of study participants.

were identified using a cut-off value of <30 ng/mL. Associations between altered vitamin D states and the determinants outlined in the questionnaire were hypothesized and tested using chi-square independence tests. A p-value of <0.05 was considered statistically significant. When applicable, odds ratios (OR) were estimated using logistic regression models (Agresti A. Categorical data analysis Volume 792. John Wiley & Sons. New York: 2012).

2.7 Ethical considerations

The study was approved by the Ethics Committee the University of Cuenca (CEISH-UC), on December 13, 2022, with the assigned code 2022-037EO-IE. All participants signed the informed consent form as part of the preliminary requirements for this study, in accordance with international bioethical standards as per the Declaration of Helsinki Statement of 2008, updated in Fortaleza, October 2013. Confidentiality of all participant data was maintained throughout the study.

3 Results

3.1 Characteristics of the participants

The study included 440 participants, with 94.5% of them working indoors. Faculty members accounted for 60.9% of the participants, while the remaining 39.1% were administrative staff. Women represented 57.3% of the participants ($p > 0.05$). The median age was 41.5 years (IQR: 10 years), with men having a median age of 41.5 years (IQR: 11 years) and women 41.0 years (IQR: 10 years) ($p > 0.05$) (Table 1).

Among the participants, 67.9% reported using sunscreen, with 40.9% of men and 88.1% of women ($p < 0.05$). The frequency of sunscreen use was as follows: Never: 32.1%; Once a day: 33.9%; Twice a day: 27.1%; and Three or more times a day: 7.0%. The sunscreen use frequency was significantly dependent on gender ($p < 0.05$). According to the Fitzpatrick skin type classification, the majority of subjects had skin types III–IV, and skin type was independent of gender ($p > 0.05$) (Table 2).

Hypovitaminosis D was identified in 93.4% of the sampled subjects. Of these, 94.0% had decreased serum 25-(OH) D concentrations (10.0–29.9 ng/mL), while the remaining 1.6% exhibited deficiency states (< 10.0 ng/mL).

Table 3 shows the associations between vitamin D status and the proposed determinants. No significant associations were found after univariate analysis.

However, given the influence of gender on other determinants, logistic regression was employed to further examine the dependencies of interest. Table 4 presents the odds ratios (OR) calculated from the logistic analyses. As anticipated, both gender and sunscreen use significantly influenced vitamin D levels. The odds of hypovitaminosis D were 2.40 times higher ($p < 0.05$) in women than in men. Conversely, the odds of hypovitaminosis D were 64% lower ($p < 0.05$) in individuals who did not use sunscreen.

TABLE 1 Sociodemographic and clinical characteristics.

Characteristic	Findings
Work category	
Faculty members	268 [60.9%]
Administrative staff	172 [39.1%]
Working conditions	
Indoors	416 [94.5%]
Indoors + outdoors	24 [5.5%]
Sex/gender	
Males	188 [42.7%]
Females	252 [57.3%]
Average age	41.5 [SD ± 10]
Age group	
< 60 years	428 [97.3%]
≥60 years	12 [2.7%]
Skin type	
Type I	6 [1.4%]
Type II	34 [7.7%]
Type III	155 [35.2%]
Type IV	186 [42.3%]
Type V	55 [12.5%]
Type VI	4 [0.9%]
Sunscreen use	
Yes	299 [67.9%]
No	141 [32.1%]
Frequency of sunscreen use	
Never	141 [32.0%]
Once a day	149 [33.9%]
Twice a day	119 [27.1%]
Three (or more) times a day	31 [7.0%]

Data are reported as numbers and percentages (in brackets).

4 Discussion

Environmental factors such as altitude and geographic location might influence the climate of Loja, where this study was conducted, potentially playing a decisive role in vitamin D synthesis. This paper reports the findings of the first-ever study completed in Loja on the prevalence of hypovitaminosis D among employees at a private university. The sample population was selected based on convenience and primarily consisted of office workers within a small, localized geographic area. These individuals generally had a comfortable socioeconomic status, high levels of education, indoor jobs, and sedentary lifestyles, all of which could contribute to altered vitamin D states, if present, could be attributed to factors like skin type, sunscreen use, and the frequency of sunscreen application. Contrary to expectations, hypovitaminosis D was found in more than 90% of the sample population, regardless of gender, age, or other determinants.

Montoya Jaramillo et al. (44) conducted a study in Loja with 82 women aged 35–60 years and found that 67.1% had altered vitamin D states. Another study revealed that vitamin D deficiency and insufficiency were present in 24.3 and 34.6% of North American women under 45 years of age, respectively (46). Additionally, a study involving 2,880 workers found that hypovitaminosis D to be more prevalent in women (71.9%) than in men (51.9%) ($p < 0.05$) (47).

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TABLE 2 Association between determinants of hypovitaminosis D.

	Sex/gender	Age	Work category	Working conditions	Skin type	Sunscreen use
Sex/Gender	1.000	0.025 (0.0006)	−0.153¶ (0.0234)	0.137¶ (0.0188)	−0.098¶ (0.0096)	0.456¶ (0.2079)
Age		1.000	−0.005 (0.0000)	−0.040 (0.0016)	0.039 (0.0015)	0.009 (0.0001)
Work category			1.000	−0.163¶ (0.0266)	0.010 (0.0000)	−0.058 (0.0033)
Working conditions				1.000	0.038 (0.0014)	0.013 (0.0002)
Skin type					1.000	0.077 (0.0059)
Sunscreen use						1.000

This table presents Spearman's correlation coefficients (r) and corresponding coefficients of determination (r^2) [in brackets]. ¶: $p < 0.05$.

TABLE 3 Distribution of vitamin D status across sociodemographic characteristics.

Characteristic	Vitamin D		All
	Expected	Diminished	
Sample size	29 [6.6%]	411 [93.4%]	440 [100.0%]
Work category			
Faculty member	15 [51.7%]	253 [61.5%]	268 [60.9%]
Administrative staff	14 [48.3%]	158 [38.5%]	172 [39.1%]
Working conditions			
Indoors	27 [93.1%]	389 [94.6%]	416 [94.5%]
Indoors + Outdoors	2 [6.9%]	22 [5.4%]	24 [5.4%]
Sex			
Males	15 [51.7%]	173 [42.1%]	188 [42.7%]
Females	14 [48.3%]	238 [57.9%]	252 [57.3%]
Age			
<60 years	29 [100.0%]	399 [97.1%]	428 [97.3%]
≥60 years	0 [0.0%]	12 [2.9%]	12 [2.7%]
Skin type			
Type I	0 [0.%]	6 [1.5%]	6 [1.4%]
Type II	4 [13.8%]	30 [7.3%]	34 [7.7%]
Type III	11 [37.9%]	144 [35.0%]	155 [35.2%]
Type IV	8 [27.6%]	178 [43.3%]	186 [42.3%]
Type V	5 [17.2%]	50 [12.2%]	55 [12.5%]
Type VI	1 [3.4%]	3 [0.8%]	4 [0.9%]
Sunscreen use			
Yes	23 [79.3%]	276 [67.1%]	299 [67.9%]
No	6 [20.7%]	135 [32.9%]	141 [32.1%]
Frequency of sunscreen use			
Never	6 [20.7%]	135 [32.8%]	141 [32.1%]
Once a day	9 [31.0%]	140 [34.1%]	149 [33.9%]
Twice a day	11 [37.9%]	108 [26.3%]	119 [27.1%]
Three (or more times) a day	3 [10.3%]	28 [6.8%]	31 [7.0%]

In our study, altered vitamin D states (deficiency + insufficiency) were similarly distributed between men and women, though women exhibited a slightly higher impairment rate (95.8%) compared to men (93.3%). The high rate of hypovitaminosis D observed is concerning and could have significant health implications for the studied population. These findings may represent a typical working population in large cities, characterized by 40-h indoor work weeks and limited sun exposure due to clothing and/or sunscreen use.

Our results contrast with those observed in a U.S. population, where vitamin D deficiency was more common in men (48). Another study conducted in China with 14,302 participants found that mean serum 25 (OH)D levels were higher in men (23.83 ng/mL) than in women (21.74 ng/mL; $\Delta = +2.09$ ng/mL; $p < 0.05$) (49). However, the literature on gender differences in serum vitamin D levels is inconsistent, varying by country and researcher (50).

Some studies report higher serum vitamin D concentrations in women, potentially due to factors like the use of estrogen-containing contraceptives, which can increase 25(OH)D levels by up to 20% (51). Additionally, endogenous steroids such as estradiol and progesterone, which are vital during reproductive stages, pregnancy, and lactation, may naturally elevate serum vitamin D levels in women. The suppression of ovarian steroidogenesis increases the risk of cardiovascular disease, osteoporosis, and fractures, partly due to its impact on vitamin D homeostasis. An interesting finding in this context is the gender-related response to vitamin D supplementation. For instance, a supplementation campaign in South Africa resulted in a 13.1% decrease in the prevalence of hypovitaminosis D among women, compared to 47.1% in men (52). It has also been suggested that women may synthesize more vitamin D in their skin due to higher levels of 7-dehydrocholesterol (7-DHC), the precursor to vitamin D (53). Moreover, a multi-ethnic study suggested that lower serum 25(OH)D concentrations are associated with reduced levels of sex hormone-binding globulin (SHBG) and elevated free testosterone in both genders (50). Lifestyle factors may also influence vitamin D status. For instance, a study in Saudi Arabia determined that although women had less sun exposure, their knowledge about the importance of vitamin D was greater than that of men (54).

Other factors must be considered when examining the association between vitamin D and gender. In a cross-sectional study of 211 healthy students (mean age: 20.1 years), women had lower vitamin D levels (12.01 ng/mL) compared to men (15.23 ng/mL; $p < 0.05$) (55). The researchers attributed this difference to factors such as low daily calcium intake, reduced muscle mass, and increased visceral fat mass (55).

Vitamin D homeostasis is also closely related to age. Serum vitamin D levels peak in adulthood but decline by about 13% per decade after age 30. This means that by the seventh decade of life, vitamin D levels may be reduced by half compared to those in

TABLE 4 Determinants of hypovitaminosis D based on logistic regression models.

	Work category	Working conditions	Sex/gender	Skin type	Sunscreen use	All the variables
Work category	1.38 0.86–2.28					1.48 0.89–2.48
Working conditions		1.23 0.29–5.11				1.23 0.26–5.67
Sex/gender			1.47 0.69–3.13			2.40¶ 1.03–5.57
Skin type				0.99 0.65–1.51		1.00 0.64–1.55
Sunscreen use					0.53 0.21–1.34	0.36¶ 0.13–0.99

Odds ratios (OR) and 95% confidence intervals (CI) are presented for each determinant. ¶: $p < 0.05$.

younger adults (56). Consequently, older adults are more susceptible to hypovitaminosis D. A study of 422 older adults found that 79.75% had vitamin D deficient (serum 25(OH)D concentration ≤ 19.9 ng/mL) (57). Similarly, a study conducted during the COVID-19 pandemic in 10 European countries revealed a strong correlation between mortality risk and vitamin D deficiency (< 10 ng/mL) (58). However, hypovitaminosis D can occur at any stage of life, including during infancy, where it can affect up to 96.0% of newborns (59).

Khazae et al. studied vitamin D levels in 102 apparently healthy adults (mean age: 42.9 years) and found mean serum vitamin D levels of 17.3 ng/mL, below the threshold for adequate vitamin D status. In this study, 73% of participants were vitamin D deficient ($r = 0.23$; $p < 0.05$) (60). A similar study from Mexico, involving 155 participants aged 18–50 years, reported that 58.1% were vitamin D deficient (serum levels <20 ng/mL) (61). In our study, the mean age was 41.9 years, with men at 41.5 and women at 41.0. This relatively young population showed a high rate of vitamin D deficiency, potentially linked to metabolic, cultural, and occupational factors, as well as changes in sun exposure patterns, as reported by other research groups (62).

Several factors, including sedentary behavior, long working hours, and diets high in ultra-processed foods, negatively impact both vitamin D synthesis and overall metabolic processes. These findings suggest that workplace lifestyle interventions can be an effective strategy for addressing obesity and sedentary behavior in working population (63).

Other contributors to reduced vitamin D levels include reduced lean body mass, increased adiposity, decreased renal 1,25(OH)2D synthesis, reduced epidermal thickness, decreased physical activity, and lower sun exposure, which become more pronounced with aging (56). The presence of 7-DHC in the skin decreases by more than 50% between the ages of 20 and 80, resulting in about 40% less vitamin D production in aging skin (64).

Skin color is another crucial determinant of vitamin D photosynthesis. While the Fitzpatrick phototype scale and melanin index are often used to classify skin types, these indicators are sometimes inconsistently associated with serum vitamin D concentrations (65). Melanin, the primary determinant of skin color, absorbs UVB rays, thereby affecting the conversion of 7-DHC to previtamin D3 in the skin (66). People with darker skin, characterized by higher melanin content, produce less vitamin D and, therefore have lower serum levels (67, 68). However, in this study, skin color as classified by Fitzpatrick, did not influence serum vitamin D levels or the occurrence of altered vitamin states.

The literature suggests that light-skinned individuals can produce >20.63 ng/mL of 25(OH)D with just 30 min of daily sun exposure, whereas those with darker skin may require over 2 h to synthesize the same amount (69). This is likely because melanin competes with 7-DHC for UV absorption, requiring more sunlight exposure to produce sufficient vitamin D (70). Furthermore, another study found that after 30 min of sun exposure, while darker skin converted only 0.3% (69). African populations tend to have a 15- to 20-fold higher prevalence of severe vitamin D deficiency (71).

A study in Saudi Arabia involving 808 children (ages 10–17 years) and 561 adults (ages 18–48 years) found significantly lower 25(OH)D concentrations in these groups (children: 16.88 ± 0.49 ng/mL vs. adults: 14.65 ± 0.74 ng/mL; $p < 0.05$). The study concluded that reduced serum vitamin D levels were associated with darker skin and reduced sun exposure (72). The authors used both the Fitzpatrick scale and melanin index to classify skin color and observed low vitamin D levels in dark-skinned women during both the summer and winter seasons (73). A study conducted in Africa involving 296 children (mean age: 12.3 years) found a strong and positive association between vitamin D levels and skin color. Of the children studied, 54% were vitamin D deficient, with skin classified as Fitzpatrick phototype IV – V (74). In our study, most participants had skin phototypes III – IV, both in males (25 and 44.4%, respectively) and females (43.8 and 39.7%). No significant statistical relationship was found between skin phototype and vitamin D status.

A study conducted in Brazil assessed vitamin D deficiency in 894 adults and found that 28.5% had serum vitamin D concentrations below 20.6 ng/mL despite high daily sun exposure (75). Similarly, a UK study with 1,000 participants found a strong negative correlation between sun exposure and vitamin D deficiency, with 60% of participants having altered vitamin D states (Insufficiency: 42.5% vs. Deficiency: 17.5%) (36). Another study involving 80 participants aged over 65 divided them into two groups: one group received 30 min of sun exposure daily for 4 weeks, while the other group had no sun exposure. Altered vitamin D states were more prevalent in the group without sun exposure, with 85% affected (Insufficiency: 55% + Deficiency: 30%) compared to 40% in the sun-exposed group ($p < 0.05$). These findings suggest that regular sun exposure reduces the frequency of altered vitamin D states, while a lack of exposure increases (76). These results highlight the importance of clear recommendations on the benefits and timing of sun exposure, especially given the increasing use of sunscreens and the isolation measures introduced during the COVID-19 pandemic.

Sunscreen use could influence vitamin D homeostasis, but the findings are contradictory. Our study identified a significant frequency

of sunscreen use in both men and women, possibly due to increased awareness of skin cancer prevention. However, sunscreen use in this study was lower than the standards prescribed by dermatologists.

We found no association between vitamin D levels and sunscreen use in our study, though sunscreen use varied by gender (Women: 87.8% vs. Men: 44.9%). The frequency of sunscreen use also differed between genders, with 39.7% of women using sunscreen twice daily compared to 30.9% of men using it once a day. These gender differences in sunscreen use may influence the risk of hypovitaminosis D, as suggested by logistic analyses, but further studies are needed to explore this relationship in. greater depth.

Short-term sunscreen use is unlikely to significantly impact serum vitamin D levels and, therefore, may not be a substantial risk factor. However, the long-term effects of chronic sunscreen use on vitamin D homeostasis remain unclear (77). It is important to note that modern sunscreens, with SPF 50+, may significantly impact UVB absorption and vitamin D cutaneous synthesis, as they can reduce vitamin D3 production by 23–26 times (77). Other factors, such as the work environment, the sunscreen SPF, topical formulations, social perceptions, self-prescribed sun exposure habits, timing of sunscreen application, exposure duration, and the amount of sunscreen used, may also affect the relationship between sunscreen use and vitamin D synthesis (37).

In a study conducted in Bangladesh, high prevalence rates of hypovitaminosis D were found in newborns, children, adolescents (21–75%), premenopausal women (38–100%), pregnant women (66.0–94.2%), adult men (6.0–91.3%), and postmenopausal women (82.0–95.8%). Hypovitaminosis D in these populations was influenced by factors such as dark skin, home confinement, sedentary lifestyle, insufficient sun exposure, air pollution, and clothing (78). Interestingly, only 3.7% of the studied population reported regular sunscreen use (78).

Several studies suggest that sunscreen use minimally impacts vitamin D synthesis (79). However, other researchers argue that because daily sunscreen use reduces UVB absorption and prevents sunburn, it may also inhibit vitamin D3 biosynthesis (68). No significant associations have been found between vitamin D deficiency and sunscreen use in healthy individuals.

A study in Egypt with 572 schoolchildren (270 boys and 302 girls) found that 99% of healthy Egyptian adolescents were vitamin D deficient. Among them, 94.8% were vitamin D deficient, and 4.2% were vitamin D insufficient. Girls had a higher prevalence of hypovitaminosis D. The report suggested that vitamin D deficiency is more influenced by clothing, such as the hijab (which covers most of the body), than by sunscreen use (80). In another study involving 441 adolescents, 30.42% reported using sunscreen only in the morning, 13.72% twice daily, and 2.76% three times daily, while 53.1% never used sunscreen (39). Serum vitamin D levels were independent of the frequency, amount, and SPF of sunscreen used, as well as season and location. The median (IQR) serum vitamin D levels was 6.1 ng/mL (3.7–9.2) in those who used sunscreen, compared to 7.3 ng/mL (4.4–10.7) in those who did not use sunscreen ($\Delta = -1.2$ ng/mL; $p > 0.05$) (39).

Several studies have examined the influence of indoor work on vitamin D homeostasis. Our study revealed a high frequency of hypovitaminosis D in a population primarily working indoors (94% of participants), though no significant relationship was established. A systematic review of 71 articles found that vitamin D deficiency was 1.7 times higher in night-shift workers and 1.6 times higher in indoor workers compared to outdoor workers (81, 82). This review also reported that 78% of indoor workers were vitamin D deficient, compared to 48% of outdoors workers (83). Another study with 1,054 manufacturing workers found mean serum vitamin D levels of 9.07 ± 3.25 ng/mL, with 68.4% of workers affected by hypovitaminosis D (84).

Working conditions can also influence vitamin D levels. A study with 213 subway workers identified a 32.9% prevalence of vitamin D deficiency (95% CI: 26.6–39.6%). The occurrence of vitamin D deficiency was 2.16 times higher in office workers (OR: 2.16, 95% CI: 1.12–4.16) and 2.25 times higher in trade workers (OR: 2.25, 95% CI: 1.05–4.81) compared to other occupations (85). Another study compared vitamin D levels in indoor and outdoor workers, finding that mean serum vitamin D concentrations were higher in outdoor workers (18.48 ± 8.08 ng/mL) than in indoor workers (12.62 ± 9.57 ng/mL; $p < 0.05$). Only 22.5% of outdoor workers were vitamin D deficient (86).

In a study involving 72 elite athletes who trained under different conditions: 50.0% trained indoors, 40.3% trained outdoors, and 19.4% engaged in mixed training. The average serum vitamin D level among all participants was 45.79 ± 15.27 ng/mL. Altered vitamin D states were observed in 19.2% of the population (Insufficiency: 15.0% vs. Deficiency: 4.2%). Athletes who trained indoors had the lowest serum vitamin D levels: Indoor training: 37.13 ± 11.55 ng/mL; Outdoor training: 131 ± 35 nmol/L; and Mixed training: 54.88 ± 11.97 ng/mL ($p < 0.05$). Altered vitamin D states were more prevalent among athletes who trained indoors. Although 69% of the athletes reported sunscreen use, it did not significantly affect vitamin D homeostasis. The authors concluded that altered vitamin D states were uncommon in elite athletes but recommended regular monitoring of vitamin D levels for those training indoors and suggested incorporating outdoor warm-up routines to increase exposure to natural light (87).

In the context of chronic comorbidities, studying vitamin D homeostasis becomes particularly important, as it is often considered an indicator of frailty (88). Vitamin D homeostasis is significantly compromised when multiple chronic conditions coexist, especially in older adults, who frequently take multiple medications. Nevertheless, our study did not evaluate the influence of comorbidities on vitamin D status.

Medications can also affect vitamin D homeostasis. Epilepsy and antiepileptic drugs induce the cytochrome P-450 enzyme system in the liver, leading to increased vitamin D elimination while inhibiting 7-DHC hydroxylation and vitamin D metabolism (89). Some anticonvulsants and antiretrovirals can precipitate vitamin D deficiency by promoting the metabolism of 25(OH)D and 1,25(OH)2D. On the other hand, ketoconazole, an antifungal, can inhibit the hydroxylation of 7-DHC. Chronic high-dose glucocorticoid use often inhibits calcium absorption, which depends on vitamin D, thereby increasing the body's vitamin D requirements (90). Nonetheless, our study did not assess the impact of medications on vitamin D status. Still, hypovitaminosis D was independent of chronic comorbidities and medication use. In contrast, a meta-analysis involving 1,150 patients with polycystic ovary syndrome (PCOS) found significantly lower 25(OH)D levels in these patients (91).

As mentioned earlier, vitamin D has multiple receptors in both male and female reproductive systems, but women tend to have lower vitamin D levels. Conditions like insulin resistance, metabolic diseases, PCOS, and altered ovarian responsiveness are more likely to affect vitamin D levels (92). A study involving 351 women with an average age of 28 years found that vitamin D levels were below 18.37 ng/mL. The study highlighted the importance of supplementation to improve endocrine status in women with hyperandrogenism (93).

The negative impact of smoking on vitamin D homeostasis has been well-documented, with several mechanisms involved. A study with 300 participants found hypovitaminosis D in 86.2% of adult patients and concluded that smoking was an independent risk factor with a detrimental effect on calcium and vitamin D metabolism (94). Tobacco smoke contains numerous chemical compounds that can interfere with the absorption of dietary nutrients. Smoking also causes oxidative stress, leading to chronic systemic inflammation that interferes with vitamin D synthesis and distribution. The higher frequency of hypovitaminosis D among smokers could also be explained by premature skin aging. Smoking affects skin health, accelerates aging, and increases the onset of wrinkles (95). As discussed earlier, aging skin (including prematurely aged skin) is a risk factor for hypovitaminosis D. Further research is needed to gain a comprehensive understanding of this influence. In a cross-sectional study of 177 apparently healthy individuals, where a 76% frequency of hypovitaminosis D was found, serum vitamin D levels were lower in smokers, with smokers being 1.8 times more likely to have hypovitaminosis D (96). A study with adolescents and children found vitamin D deficiency in 20.9% of children passively exposed to tobacco smoke and in 18.0% of young active smokers ($p < 0.05$) (97). However, the influence of smoking on vitamin D homeostasis was not assessed in the present study.

4.1 Strengths and limitations

One major limitation of this study is that it was carried out in a private institution with a population that had above-average socioeconomic status, shared low physical activity levels, and primarily worked indoors. Factors such as tobacco use, chronic comorbidities, and medication use, which could affect vitamin D levels, were not assessed and should be explored in future research. Additionally, several studies have pointed to the influence of nutritional factors and dietary habits on vitamin D status (12, 13). Diets high in ultra-processed food, excessive body weight, obesity, and "Westernized" eating patterns could be associated with lower serum vitamin D concentrations (98). Future studies should examine the influence of body weight and dietary habits on the serum vitamin D levels of the study participants.

However, this study has several strengths. We provided the first evaluation of vitamin D deficiencies in a population from southern Ecuador. The findings can serve as a reference for strengthening vitamin D supplementation practices. Additionally, the study highlights the serious situation faced by populations that work indoors without sunlight exposure. While studies on vitamin D are often controversial, it is clear that lower vitamin D levels result in increased parathyroid hormone, leading to insulin resistance, increased inflammatory cytokines, enhanced cell differentiation, angiogenesis, and mobilization of calcium from bone, ultimately reducing bone mass. Therefore, the present study, in conjunction with the clinical judgment and experience of healthcare providers, can serve as a valuable tool for preventing, diagnosing, and supplementing vitamin D in at-risk populations. Additional research is needed to determine whether comorbidities cause vitamin D deficiency, or if its deficiency causes these comorbidities. A nationwide study is recommended to confirm these findings.

5 Conclusion

The prevalence of hypovitaminosis D was remarkably high in a population of ostensibly healthy adults who generally had a comfortable socioeconomic status, high levels of education, predominantly indoor jobs, and sedentary lifestyles. Despite the sheltered nature of the population and the presence of multiple risk factors that could contribute to the low vitamin D concentrations observed, no significant statistical correlations were identified. However, interactions between sex/gender and sunscreen use may influence vitamin D homeostasis, suggesting that the co-influence of different factors likely explains the findings observed in our study.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee the University of Cuenca (CEISH-UC). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PD: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. MC: Investigation, Methodology, Writing – original draft. MM: Formal analysis, Supervision, Validation, Writing – original draft, Writing – review & editing. KG: Data curation, Investigation, Writing – original draft, Writing – review & editing. PC: Data curation, Investigation, Writing – original draft, Writing – review & editing. GC: Data curation, Investigation, Writing – original draft, Writing – review & editing. SS: Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of health at every size based interventions on health-related outcomes and body mass, in a short and a long term

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Objective: This study aims to provide rapid and up-to-date evidence on the effectiveness of Health at Every Size (HAES) interventions compared to controls or other conventional approaches in individuals with overweight or obesity, with the goal of developing more effective and body-diverse respectful strategies.

Methods: A review of literature was carried out using the following databases: PubMed, Scopus, Embase, Web of Science, and SciELO. Research articles were selected based on predefined inclusion and exclusion criteria. Extracted data included study characteristics (design, setting, population demographics, sample size, intervention characteristics, study duration, and follow-up period) and health-related outcomes.

Results: The search yielded 324 articles, of which 20 articles met the inclusion and exclusion criteria. The majority of studies focused on lifestyle improvement, particularly in nutrition, body image, and relationships with food, utilizing a HAES approach. Additionally, other studies examined outcomes such as general well-being, body weight, body composition, cardiovascular risk, and changes in physical activity. Long-term results were particularly noted in studies incorporating physical activity interventions.

Conclusion: HAES interventions appear to be a feasible strategy for promoting overall health and wellness, regardless of body size or shape. However, further evaluation is needed to assess the sustainability of these changes and their long-term impact, as current evidence suggest a they may not be maintained over time.

KEYWORDS

HAES, nutritional intervention, weight-neutral approach, eating behavior, lifestyle intervention

1 Introduction

In both clinical medicine and public health, effective weight management is essential for improving overall health and preventing chronic illnesses (1). Traditional strategies for addressing obesity typically involve weight -reduction methods, such as calorie restriction and increased physical activity (2), which can be implemented through individual or group interventions (3). These methods can offer various health benefits. For example, one study demonstrated that a low-calorie DASH diet can reduce cardiovascular risk factors, as well as lower levels of trimethylamine N-oxide (TMAO), endotoxemia, and chronic inflammation (4). Despite increased attention on obesity treatments, its incidence continues to rise. Several traditional approaches, including diet, exercise, pharmacology, and surgery, have been studied extensively in efforts to address obesity (5).

However, lifestyle change efforts and obesity treatment programs have faced significant challenges, often yielding limited success in sustaining long-term results (4, 6). For instance, while lifestyle interventions have been effective for up to 2 years in individuals with a body mass index (BMI) of under 35 kg/m^2, many participants experience weight regain, often returning to their pre-intervention weight within 3–5 years (4). Studies estimate that at least 50% of individuals with obesity will regain in the absence of sustained lifestyle changes. One factor influencing this trend is the brain-gut axis, which affects weight through the secretion of gastrointestinal hormones (7).

Furthermore, several organizations recommend intensive treatments, such as bariatric surgery, over drug therapy or lifestyle modifications for individuals with a BMI exceeding 40 kg/m^2 or between 35 and 40 kg/m^2 if obesity-related complications are present. However, uncertainties remain regarding the long-term efficacy of surgical procedures (4).

Given the challenges managing obesity, there has been a growing shift in perspective among professionals advocating for a departure from a weight-centric focus. This change has resulted in the rise of Health at Every Size (HAES) movement (8). HAES promotes a nontraditional approach to health and well-being by encouraging individuals to move away from dieting and focus instead on honoring hunger and fullness cues, following a varied, unrestricted diet, and engaging in joyful movement for health promotion—without prioritizing weight loss (9). HAES, which emerged in the early 2000s, also emphasizes mindful and/or intuitive eating, with a focus on body acceptance and overall health rather than weight loss. Key concepts associated with HAES include size acceptance, a non-diet approach, and health-focused behavior changes. The primary goal of HAES is also to reduce weight-based bias and the feelings of guilt often associated with eating and body image. Instead of emphasizing weight loss, HAES focuses on the overall health benefits of behavior changes related to eating and physical activity, highlighting size acceptance and non-dieting.

Studies have shown that implementing the HAES approach can lead to improvements in eating behaviors, such as a decrease in emotional eating, stronger reliance on internal hunger cues, intuitive eating, and improved body satisfaction (9).

Intuitive eating, which is aligned with HAES philosophy, involves responding to internal hunger and satiety cues rather than external signals (10, 11). Studies have found that body acceptance plays a crucial role in this process, with women who perceive body acceptance from others reporting higher self-esteem and better body image. Notably, BMI does not predict a positive body image, but the acceptance of one's body by significant others and society does (12). Furthermore, greater body acceptance has been linked to enhanced interoceptive awareness, which, in turn, predicts improved body appreciation and success in practicing intuitive eating (12, 13). This approach is particularly important in reducing the risk of eating disorders among adolescents with obesity or weight gain (14). Therefore, this approach can help improve quality of life in the long-term.

Systematic reviews and meta-analyses have reported that HAES interventions can lead to improvements in both total and LDL cholesterol levels in cases of obesity-related malnutrition, as well as psychological benefits like lower depression, enhanced satiety, and a reduction in disordered eating behaviors (15). This review aims to evaluate the effects of HAES intervention on body composition and compare these outcomes with conventional obesity treatments.

Other preventive approaches include the "OPERA Project," which integrates medical, athletic, gastronomic, and psychological fields to create health promotion interventions in countries with high rates of obesity and overweight (16).

On the other hand, intuitive eating has gained increasing recognition as an alternative to traditional weight-focused interventions. This approach emphasizes responding to internal cues of hunger and satiety, encouraging individuals to develop a more positive and mindful relationship with food (17). Recent studies have shown a strong association between intuitive eating and improved psychological outcomes, such as enhanced body image and reduced psychological distress, particularly in populations at risk of developing eating disorders (18) One study demonstrated that women practicing intuitive eating experienced better body image and reduced psychological distress, further supporting its potential as a viable intervention for promoting mental health and overall well-being, regardless of obesity history (19).

Research also emphasizes the interconnectedness between body acceptance, self-esteem, and intuitive eating. Higher levels of body acceptance predict greater success in intuitive eating, creating a positive feedback loop between body positivity and healthy eating behaviors (20). Moreover, individuals who perceive greater acceptance of their bodies—both from themselves and from others—tend to exhibit improved interoceptive awareness, enhanced body appreciation, and a higher likelihood of engaging in intuitive eating practices (21). These results highlight the significance of focusing on body image and self-perception in interventions aimed at promoting intuitive eating.

This review aimed to compare the effects of HAES-based interventions with those of conventional approaches in individuals with overweight or obesity.

2 Methodology

2.1 Literature research

This review was carried out according to the PRISMA 2020 statement guidelines (17). An comprehensive search was performed in PubMed, Scopus, Embase, Web of Science, and SciELO, identifying 324 articles published between January and May 2024. The search strategy was developed using the PICOS method, incorporating key

terms such as "Health at Every Size" (HAES), "intuitive eating," "non-weight-centrism," "overweight," "obesity," and "fat mass." The search syntax and controlled vocabulary for each database were adjusted accordingly, and the complete search strategy is provided in the Supplementary Table S1. This approach enabled a broad exploration of studies relevant to health and nutrition in populations with overweight and obesity.

2.2 Study eligibility, selection, and data extraction

For inclusion in the review, research articles were selected based on the following criteria: (1) BMI or Waist-Hip Index (WHI) indicative of obesity, (2) study participants over the age of 18, (3) articles written in English, Spanish, or German, (4) original research interventions primarily aimed at improving and reporting on the effects of body composition, health, or behavioral outcomes of individuals, using interventions based on the HAES (Health at Every Size) method. Eligible studies included randomized controlled trials (RCTs), quasi-experimental interventions, pre-post studies, and feasibility trials, and (5) with a publication date between 2013 and 2023.

Exclusion criteria were as follows: (1) studies that did not address the primary objective of the review, (2) articles focusing solely on hospitalized patients, (3) duplicate studies already included in another database, (4) studies using pharmacological or surgical interventions, (5) systematic reviews, narratives, meta-analyses, and protocols, and (6) interventions focused on specific diseases or health behaviors not related to body weight.

From an initial pool of 324 articles, 131 duplicates were identified and removed, along with five entries that were books and did not meet the inclusion criteria for original research. This left 188 articles for further screening. Following an initial screening of titles and abstracts, 97 articles were excluded due to study type (e.g., reviews, editorials, protocols) or lack of originality. This left 91 references for further detailed screening. During this phase, 69 articles were excluded for failing to meet the inclusion criteria: five due to involving participants under 18 years old, eight due to focusing on non-obese populations, 32 because of unsuitable study designs, and 26 because their objectives differed from the review's scope.

The final selection of articles was carried out through a comprehensive review process conducted by three independent reviewers. All selection discrepancies were addressed through discussion and agreement. Throughout the review, Zotero software was used for reference management. Data extraction was conducted by two reviewers and verified by all authors to ensure consistency and accuracy. The data extracted included study design, population characteristics, intervention details, and health outcomes.

3 Results

Twenty articles that satisfied the inclusion criteria were selected for this report and are shown in Table 1. The screening process is illustrated in Figure 1, which provides a flow diagram of the search strategy.

Characteristics of included studies are summarized in Table 1.

Of the final articles included, twelve described programs focused on lifestyle improvements, specifically related to nutrition, body image, or the relationship with food, all framed within a HAES perspective (1, 18–28). Eight studies adopted the same perspective or intervention but included physical activity (2, 4, 9, 29–33). In addition, eight studies investigated overall well-being (1, 2, 4, 9, 20, 21, 31, 33), ten focused on body weight, body composition, and body image (4, 9, 18–21, 29, 33), five examined cardiovascular risk impacts (1, 9, 19, 26, 33), two explored changes in eating behaviors (28, 30) and three analyzed physical activity outcomes (27, 29, 30).

Furthermore, eight studies evaluated the long-term effects of lifestyle changes in participants undergoing these interventions (1, 4, 18, 19, 21, 22, 25, 26).

These findings will be analyzed in detail in the following section, comparing them to similar studies for further insights.

4 Discussion

This review aimed to explore the feasibility and effectiveness of HAES interventions for individuals with obesity, focusing on their impact on various health-related outcomes. We reviewed 20 articles; while preliminary findings indicate promising short-term outcomes across various health domains, our analysis focuses on long-term effects.

4.1 Effects on overall well-being

Eight studies evaluated the effects of HAES on quality of life or overall well-being using different tools such as validated instruments, focus groups, and interviews. One consistent finding across these studies is that strategies aimed at enhancing overall well-being can positively affect health outcomes, irrespective of significant weight loss.

In the study by Ulian et al. (9), both the intervention group (I-HAES®) and the control group (CTRL) showed significant improvements in quality-of-life parameters. The I-HAES® group demonstrated increases in the "physical" ($p = 0.05$), "psychological" ($p = 0.03$), and "quality of life" ($p = 0.02$) domains, while the control group improved in the "psychological health" ($p = 0.04$) and "perception of quality of life" ($p = 0.01$) domains. These results were achieved as participants worked to change their routines.

In a follow-up study conducted in 2022 with the same population, weight loss was associated with improved quality of life ($\beta = -1.05$, $p = 0.007$), as measured by the World Health Organization Quality of Life—BREF questionnaire (WHOQOL-BREF). This intervention primarily focused on nutritional counseling without a diet prescription (33).

The results suggest that the positive changes in body image observed in the traditional control group were expanded in the interdisciplinary intervention group, which likely fostered an empathetic atmosphere, increased self-esteem, and improvements in body attitudes and perception, all of which contributed to an enhanced quality of life, which might be a result of these improvements. In contrast, Brown et al. (34), highlighted the negative effects of stigma and lack of support in primary care settings on access to healthcare services for patients with obesity, emphasizing the importance of including nutritional counseling in obesity treatment programs.

TABLE 1 Results summary.

Autor (year)	*n*	Design	Objective	Intervention	Time	Results	Conclusions
Carbonneu et al. (2017) (22)	Intervention: 216 women, Observational: 110 women	Longitudinal	Investigate the effects of a HAES® program on intuitive eating and diet quality in women.	Program with an emphasis on body acceptance and intuitive eating: thirteen 3 h weekly meetings and a 6 h intensive day in groups	16 months	HAES® program ↑ score at $T = 4$ months in quality. The daily consumption of high-fat/ high-sugar foods did not differ between the two groups	Improved the quality of their food intakes at short but not long term, and that their diet quality was positively related to intuitive eating score.
M. Punna et al. (2021) (27)	$N = 177$	Longitudinal	Discover whether an ACT (acceptance and commitment therapy)-based peer-tutored online intervention can increase self-reported physical activity.	Program provided by health services, including three online modules of ACT of six week each, and via five group meetings and four phone calls.	24 months.	Baseline: • High profile group: ↑ physical activity, psychological flexibility and ↓ thought suppression, psychological symptoms measured by DASS. • During the intervention: • Low profile group: ↑ Physical activity • High profile group: ↑ Psychological flexibility (AAQ-II) • ↓ thought suppression (WBSI) in both profiles	Intervention was effective for participants with low physical activity participation.
Dimitrov Ulian, M et al. (2022) (33)	*N*: 55	Randomized controlled trial.	Investigate the association between weight loss resulting from Health at Every Size (HAES®)-based interventions and changes in cardiometabolic risk factors.	HAES®-based interventions	7 months	Weight loss was associated ↓ in waist circumference, fasting glycemia, total cholesterol LDL cardiometabolic risk, ↑ quality of life	Improvements in cardiovascular risk factors and quality of life regarding the change of weight.
Carroll et al. (2007) (20)	$N = 31$	Secondary analysis of a randomized, controlled trial.	Examined the short-term effects of a non-dieting lifestyle intervention program, within the theoretical psychological framework of self-determination theory (SDT)	Non-dieting lifestyle intervention	3 months.	↑ Metabolic improvements: diastolic blood pressure and high-density lipoprotein cholesterol in both groups. The lifestyle intervention group: ↑ general psychological well-being	Improvements of psychological well-being improved cardiorespiratory fitness and psychological well-being.
Borkoles et al. (2016) (4)	$N = 31$	RCT	Examine the effects of a non-dieting lifestyle intervention designed in the frameworks of Health at Every Size and self-determination theory on weight maintenance and psychological well-being.	2 h orientation session on weight management, healthy eating, and physical activity	12 months.	↓ weight at 3 months for IG. SPP showed significant interaction effects; **12 months** Significantly improved ↑ psychological functioning in autonomy ↓ Chance Subscale from baseline to 12-month follow-up Perceived stress ↓ 12 months	The role of a non-dieting weight management approach by including several important psychological dimensions such as general well-being and a multidimensional measure of self-esteem.

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TABLE 1 (Continued)

Autor (year)	*n*	Design	Objective	Intervention	Time	Results	Conclusions
Mensinger et al. 2023 (28)	*N* = 40	Longitudinal.	Effectiveness of a weight-inclusive health intervention aimed at reducing disordered eating through the promotion of intuitive eating	Face-to-face group sessions in the weight-inclusive health program.	6 months.	The total effects of the weight inclusive health program ↓ uncontrolled eating, and ↓ emotional eating	Importance of minimizing the self-shame and blame that is inherent in internalized weight stigma and fuels maladaptive eating behavior.
Scagliusi F et al. (2020) (31)	*N* = 39	RCT.	Describe qualitatively the responses to weight stigma and body acceptance issues from urban Brazilian gorda women.	HAES® program.	24 months.	The I-HAES®-group: ↑ body acceptance, well-being, CTRL-group internalized and accepted stigma.	HAES® could meaningfully address weight stigma and promote body acceptance
Dimitrov Ulian M et al. (2018) (9)	*N* = 58	RCT	Investigate the effects of an intensive, interdisciplinary HAES® -based intervention on multiple physiological aspects.	HAES® program	7 months.	HAES® group: ↑ maximal oxygen uptake and better performance on the timed stop test ↑ dietary attitudes and practices. ↑ Body Attitude improvement ↑ physical health ↑ psychological health ↑ quality of life	HAES® improved participants dietary attitudes and practices, body image perception, physical capacity, and health-related quality of life, despite a lack of change in body weight and physical activity levels.
Gagnon-Girouard MP (2010) (21)	*N* = 107	RCT	To compare the effects of a HAES intervention with and a no-intervention control group	HAES intervention (*N* = 48), (2) social support (SS) group intervention (*N* = 48), and (3) waitlist (WL) (*N* = 48).	12 months.	↑ psychological improvement	HAES improved with psychological variables and body weight maintenance
Mensinger et al. (2016) (1)	*N* = 80:	RCT	Compared the effectiveness of a weight-neutral versus a weight-loss program for health promotion.	HUGS Program for Better Health LEARN Program for Weight Management	24 months	↓ Weight loss, BMI and LDL cholesterol levels = Blood pressure Fasting blood glucose, and triglyceride	Provides novel evidence supporting an alternative approach to weight loss in the promotion of health for high BMI individuals.
Cloutier-Bergeron (2019) (26)	*N* = 210	Multicentric quasi experimental study.	Identify trajectories of responses to a non-diet intervention for adult overweight/obese women.	13 weekly sessions of 3 h plus an intensive 6 h day led by a social worker or psychologist and a dietitian.	16 months.	Non-responders: ↑ weight gain in the three months ($p = 0.03$); ↑ depressive symptoms, ↓ quality of life and self-esteem.	There is a need to consider psychological characteristics to move towards personalized healthcare in obesity management.

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TABLE 1 (Continued)

Autor (year)	*n*	Design	Objective	Intervention	Time	Results	Conclusions
Provencher et al. (2009) (18)	*N* = 144;	RCT	To assess the effects of HAES intervention on eating behaviors, appetite sensations, metabolic and anthropometric variables, and physical activity levels in women.	The HAES: 14 weekly sessions. The SS intervention: The control group: usual lifestyle habits for the duration of the study.	12 months.	Situational susceptibility to disinhibition and susceptibility to hunger: ↓ in both groups ↓ in both groups ↓ weight at 16 months HAES	HAES approach could have long-term beneficial effects on eating behaviors.
Bacon et al. (2005) (19)	*N* = 78	RCT	Examine a model that encourages HAES as opposed to weight loss.	HAES program or diet program	24 months	The 92% of the HAES group completed the program. The diet group: ↓ weight posttreatment and maintained the weight loss. ↓ BP posttreatment and post aftercare. The HAES group sustained change at follow-up	HAES could maintain long-term behavior change
Jospe et al. (2017) (23)	*N* = 250	Exploratory secondary analysis from RCT	Examine the adherence to "hunger training" influenced weight loss and eating behavior	Hunger training, which monitoring blood glucose levels before eating to teach individuals to eat only when truly hungry. Participants received diet and exercise counseling in a face-to-face session.	6 months.	Hunger training ↓ weight over a 6-month period.	Hunger training is a feasible and effective method for weight loss and improving eating behaviors in adults, provided that adherence guidelines are met.
Begin et al. (2019) (25)	*N* = 216	Quasi-experimental	To assess the effects of HAES intervention on eating behaviors, psychological factors, and BMI	The Health at Every Size (HAES) intervention = 14 weekly meetings provided by health professionals, the program focused on promoting healthy lifestyle habits, self-acceptance, and intuitive eating.	16 months	HAES group: ↑ intuitive eating scores, ↓ obsessive-compulsive eating scores, ↑ the flexible restraint scores, ↓ disinhibition and susceptibility to hunger scores at 4–16 months.	HAES intervention led to significant improvements in psychological outcomes such as self-esteem, body esteem, and depressive symptoms, as well as positive changes in eating behaviors like intuitive eating, disinhibition, and susceptibility to hunger; and was effective in improving eating-, weight-, and psychological-related variables in the short and long term.

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TABLE 1 (Continued)

Autor (year)	*n*	Design	Objective	Intervention	Time	Results	Conclusions
Mensinger et al. (2016) (1)	*N* = 80	RCT	Examine the impact of internalized weight stigma on eating behaviors in women with high BMI	HUGS Program for Better Health and Health at Every Size®.	24 months.	Effect of restraint: ↑ weight control program. Internalized weight stigma: ↑ in both groups at 6–24 months	Incorporate more innovative and direct methods to reduce internalized weight stigma for women with high BMI in order to enhance the overall benefits of weight-neutral approaches.
Ulian et al. (2015) (30)	*N* = 30	Prospective	To evaluate the effects of a non-prescriptive multidisciplinary intervention based on the Health at Every Size® philosophy in obese women	Weekly physical activity sessions, five philosophical workshops, and bimonthly individual nutritional sessions.	12 months	↑ attitudes towards eating, body image perception, and physical activity, empowered to make changes, and exercise	Non-prescriptive multidisciplinary intervention based on the Health at Every Size® philosophy was effective in improving various aspects of participants' well-being, including blood pressure, lipid profile, physical activity levels, eating behaviors, self-esteem, and body image perception, despite no significant weight loss.
Berman M. et al. (2022) (32)	*N* = 19	RCT	Comparing AY to a more commonly used and widely disseminated group-based behavioral weight loss program, WW.	Group-based behavioral weight loss program	12 months.	Fitness ∅ groups ↑ eating disorder symptoms and ↑ in WW.	AY appeared safe, feasible, and offered initial evidence of efficacy for depression.
Sabatini F. et al. (2019) (2)	*N* = 43	RCT	Investigated the perceptions of obese women about eating pleasure before and after an intervention based on the HAES approach.	HAES intervention	7 months.	The HAES group: ↑ autonomy regarding eating, pleasure in shared meals, familiarity with cooking practices, ↓ automatic eating.	The HAES- enhance appreciation for physical activity, and stimulation of pleasure eating without leading to indiscriminate eating.
Mensinger J. and Meadows A. (2017) (29)	*N* = 80	RCT.	To investigate the influence of internalized weight stigma (IWS) on physical activity (PA) outcomes among women	Health-at-every-size vs. weight-loss-focused group-based healthy living program.	6 months	↑ enjoyment of moderate physical activity ↑ reduced internalized weight stigma	Self-directed stigma and holding negative attitudes about one's weight interferes with positive changes in PA outcomes.

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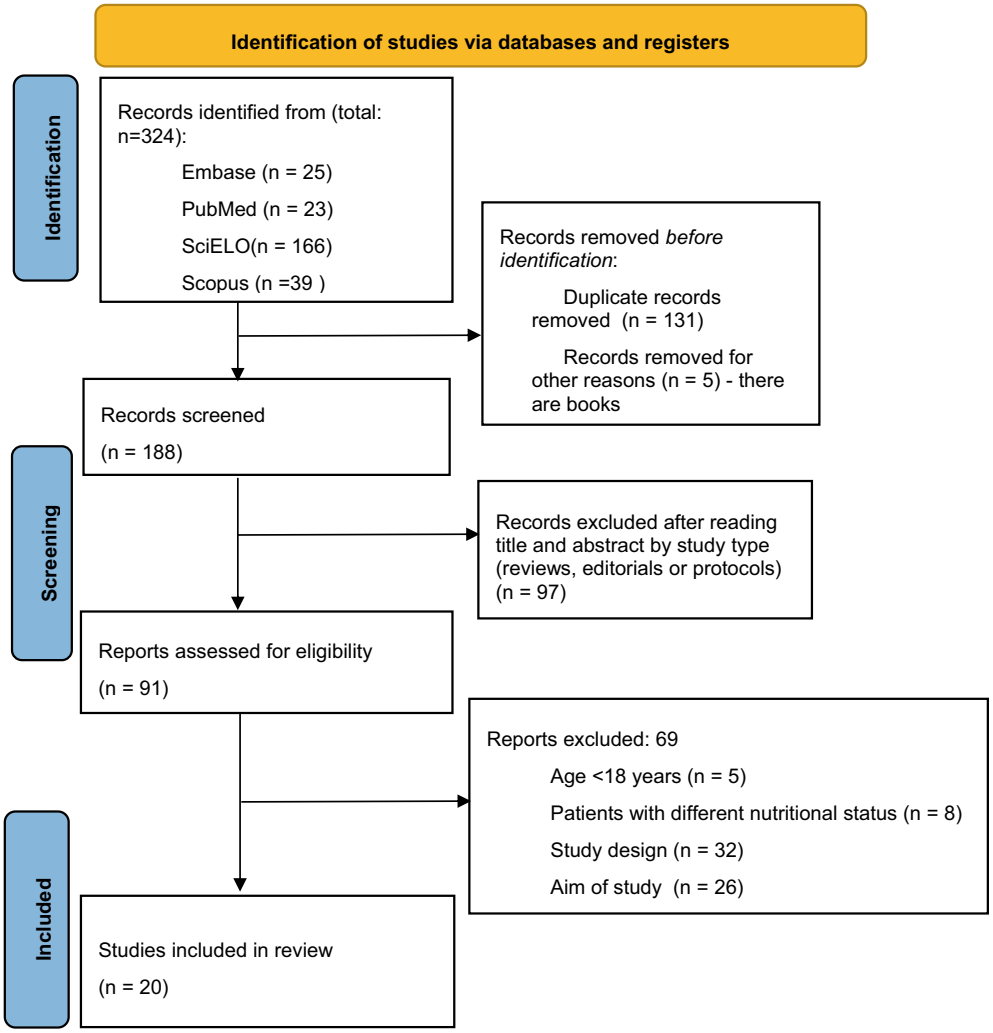

FIGURE 1
Study data collection: authors' own creation.

Scagliusi et al. (31), did not present comparative data due to their study design, which did not account for time effects versus intervention impacts. However, Sabatini et al. using a case–control design and focus groups, found that both intervention groups reported improvements in eating pleasure, a decrease in guilt around eating, and enhanced experiences of commensality. The I-HAES group also reported reductions in emotional eating, greater confidence in food choices, improved cooking skills, and less mindless eating. These studies underscore the need for standardized tools to measure quality-of-life outcomes.

Carroll et al. (20) reported significant improvements in psychological well-being compared to the control group (test for interaction, $p = 0.0005$) in absence of significant changes in body mass or composition. Similarly, Borkoles et al. (4) assessed well-being using the General Well-Being Schedule (GWB) and found significant improvements across all subscales from baseline to 12-month follow-up, despite the absence of significant weight loss. Similarly, The Healthy Weight in Lesbian and Bisexual Women study ($n = 266$ LB women age ≥ 40) conducted by Ingraham (35), assessed the effects of mindfulness interventions on health outcomes. Although weight loss was not a primary outcome, increased mindfulness was associated with significant improvements in mental health and quality of life.

Gagnon-Girouard et al. (36) observed no significant short-term changes in well-being but reported that HAES interventions could lead to sustained long-term improvements in mood, self-esteem, quality of life, body dissatisfaction related to appearance, body dissatisfaction—weight, body dissatisfaction—attribution, binge eating, and body weight. These improvements are directly targeted by the HAES intervention, suggesting that achieving self-acceptance, enhanced quality of life, and positive body image may require a longer duration to manifest.

Finally, Mensinger et al. (24) found sustained improvements in psychological well-being, such as enhanced quality of life and self-esteem, over 24 months, though there were not significant differences between the intervention and control groups. Bruce and Ricciardelli (37) reviewed the growing body of literature supporting a positive correlation between intuitive eating and emotional well-being in women. Similarly, Tribole and Resch, in their book on intuitive eating, they associated restrictive eating behaviors with an increase in depressive symptoms and poor emotional regulation (38).

4.2 Effects on body weight, body composition and body image

Several authors have reported the impact of the HAES intervention on body weight after. Ulian et al. (33) noted that after 7 months of intervention, weight loss was significantly related to improvements in waist circumference ($\beta = 0.83$, $p < 0.001$). Similarly, Borkoles et al. (4) also found a modest weight reduction after 3 months of lifestyle intervention.

Other authors reported that improvements in body esteem during the intervention phase suggested the likelihood of maintaining body weight during follow-up phase ($p = 0.011$) (21). Mensinger et al. (1) observed reductions in weight, BMI, and LDL cholesterol from baseline to post-intervention ($p = 0.003$), with greater reductions in the weight-neutral program. Provencher et al. (18) found that 63.4% of women in the HAES group maintained a lower weight at 16 months compared to baseline (mean BMI 30.10.4 at baseline vs. 29.50.5 at 16 months; 2% difference from the initial weight).

In contrast, Bacon et al. (39) reported significant weight loss in the diet group post-treatment (−5.2 kg ± 7.3 from baseline), with participants maintaining a 5.2% reduction in weight after follow-up (−5.3 kg ± 6.7 from baseline). However, most studies noted weight maintenance or even weight gain over time (1, 4, 19, 33). Additionally, some authors using HAES methods reported no significant changes in body weight (9, 20, 23, 26, 29).

Despite these findings, several reviews highlight that HAES and other non-weight-centric interventions lead to significant and sustained changes in dietary behaviors and practices (up to 2 years), although these changes are not reflected in anthropometric measurements (9, 40). These results suggest that weight is not the sole indicator of overall well-being.

4.3 Impact on cardiovascular risk

Analyzing the results of the aforementioned studies reveals a variety of findings concerning the HAES approach and its impact on cardiovascular health. Ulian et al. (33) found that weight loss was associated with significant improvements in waist circumference ($B = 0.83$; $p < 0.001$), fasting blood glucose ($B = 0.45$; $p = 0.036$), total cholesterol ($B = 1.48$; $p = 0.024$), LDL ($B = 1.33$; $p = 0.012$), and pooled cardiometabolic risk ($B = 0.18$; $p = 0.006$). In contrast, Mensinger et al. (1) observed no significant changes in systolic or diastolic blood pressure, fasting blood glucose, or triglyceride levels over time. Cloutier-Bergeron et al. (26) identified significant differences when comparing non-responders to other groups, finding higher rates of cardiovascular disease (x2 (1, $N = 205$) = 6.232, $p = 0.013$, n2 = 0.03) and dyslipidemia (x2 (1, $N = 199$) = 5.471, $p = 0.019$, n2 = 0.028). Bacon et al. (19) reported a significant decrease in systolic blood pressure but no significant changes in diastolic blood pressure. In addition, Ulian et al. (9) showed that although fat-free mass (FFM) increased and waist and hip circumferences slightly decreased, these changes were not statistically significant.

Recent studies support the complexity of the relationship between the HAES approach and cardiovascular risk. For example, Schaefer and Magnuson (41) revealed significant improvements in health-related quality of life ($B = 0.72$; $p = 0.021$) and a reduction in anxiety ($B = -1.25$; $p = 0.038$) in individuals who adopted a HAES approach. Similarly, Bacon and Aphramor (42) found a significant decrease in perceived stress ($B = -0.56$; $p = 0.017$) and improved body image in participants following a health-focused approach rather than a weight-loss-centered one.

Gagnon-Girouard et al. (21) reported that the HAES approach improved self-esteem ($B = 0.72$; $p = 0.021$) and reduced depressive symptoms ($B = -1.25$; $p = 0.038$) in women with overweight or obesity. Mensinger et al. (1) also found significant improvements in physical activity ($B = 0.56$; $p = 0.017$) and life satisfaction in participants following the HAES approach.

These results emphasize the importance of considering comprehensive approaches, such as HAES, to promote cardiovascular health and overall well-being. They highlight the need to personalize health strategies to address cardiovascular risk effectively in diverse populations, focusing on improving health and quality of life rather than just weight loss.

4.4 Impact on eating behaviors

Mensinger et al. (28), provide significant statistical supporting the importance of addressing maladaptive eating patterns in women with high BMI. Their study demonstrated a 25% decrease in emotional eating scores ($b = -1.79$, $SE = 0.34$, $p < 0.0001$), and a 20% reduction in uncontrolled eating behaviors ($b = -3.76$, $SE = 0.64$, $p < 0.0001$), following 6 months of participation in a HAES-based program, showing a statistically significant improvement in dietary patterns ($p < 0.05$) (28).

Moreover, each reduction in weight stigma was associated with a corresponding 0.75-point increase in intuitive eating behavior score ($r = -0.60$, $p < 0.01$), highlighting that reducing weight stigma is crucial for fostering a healthier relationship with food, an essential aspect of the HAES intervention.

Ulian et al. (30) also demonstrated the impact of the HAES approach by showing a 13% decrease in body fat mass, an 11.1% reduction in body fat percentage, a 3.6 kg reduction in weight, and a 3.2 -point reduction in BMI, all of which were statistically significant. Additionally, binge eating behaviors improved; initially, 57.1% of participants exhibited moderate binge eating, but by the end of the study, 78.6% exhibited no binge eating behaviors, while only 14.3% continued to display moderate levels of such behaviors.

Both studies highlight the importance of comprehensive approaches that address both physical and psychological aspects of health during interventions. Mensinger et al. (28) provide evidence of reduced uncontrolled and emotional eating, while Ulian et al. (30) show reductions in binge eating. These findings suggest that reducing weight stigma and promoting intuitive eating can lead to improved health outcomes and greater body acceptance.

4.5 Effects on physical activity

Punna et al. (27) investigated the effects of an online peer-mentored intervention based on acceptance and commitment therapy. The study found that participants with low baseline physical activity levels significantly increased their participation in physical activity, highlighting the importance of personalizing interventions to maximize effectiveness.

Ulian et al. (9) also reported significant improvements in body composition following an exercise program, nutritional counseling, and philosophical workshops. After the intervention, there were significant reductions in weight, BMI, body fat mass, and fat mass percentage (−3.6, −3.2%, −13.0%, and −11.1%, respectively; $p \leq 0.05$), all of which positively impacted cardiovascular and metabolic health. Similar findings were reported by Schaefer and Magnuson (41), who found that participants adopting a HAES approach, including physical activity, experienced significant improvements in health-related quality of life (B = 0.72, $p = 0.021$) and reduced anxiety (B = −1.25, $p = 0.038$). Bacon and Aphramor (42) similarly found that combining physical activity with nutrition education led to significant reductions in perceived stress (B = −0.56; $p = 0.017$) and improvements in body image. Gagnon-Girouard et al. (21) also showed that health promotion strategies incorporating physical activity increased self-esteem (B = 0.72; $p = 0.021$) and reduced depressive symptoms (B = −1.25; $p = 0.038$) in women with overweight or obesity.

These results highlight the importance of adopting a holistic approach that integrates physical activity with other wellness factors to foster positive changes in health and quality of life. More recently, Mensinger et al. (1) demonstrated that a "weight neutral" approach, which emphasizes physical activity and overall health, was associated with greater body satisfaction (B = 0.72; $p = 0.021$) and a reduction in eating disorder symptoms (B = −1.25; $p = 0.038$) in women with overweight or obesity. These findings further support the value of prioritizing health and wellness over weight loss.

Schaefer and Magnuson (41) supported these findings, reporting significant improvements in self-efficacy for exercise ($\beta = 0.72$; $p = 0.021$) and increased physical activity adherence (β = −1.25; $p = 0.038$). These results underscore the importance of fostering self-efficacy and intrinsic motivation to promote the adoption and long-term maintenance of an active lifestyle.

In contrast, Mensinger and Meadows (29) observed that the effect of internalized weight stigma on moderate-intensity physical activity was not statistically significant (b = 0.22, SE = 0.11, 95% CI, $t(132) = 1.89$, $p = 0.061$). However, they noted a significant increase in moderate-intensity physical activity over time (b = 0.80, SE = 0.14, 95% CI [0.51, 1.08], $t(71) = 5.54$, $p < 0.001$), emphasizing the importance of considering psychological factors such as weight stigma to promote long-term physical activity adherence.

Bacon et al. (19) further revealed that the HAES approach, which combines physical activity and nutrition education, significantly improved diet quality (B = 0.72; $p = 0.021$) and reduced cardiometabolic risk (B = −1.25; $p = 0.038$) in adults with overweight or obesity. These findings highlight the value of adopting a holistic approach to promote cardiovascular and metabolic health.

4.6 Results at long term

A very relevant question regarding health interventions, especially those addressing cardiovascular, metabolic, or nutritional health, is whether the results are maintained in the long term. In other words, do individuals continue adhering to the changes implemented during the intervention? This question has been extensively explored in the articles included in this review, and the findings are discussed below.

The average duration of the interventions analyzed ranges from 4 to 6 months, while long-term analysis typically take place 12 months after the intervention's completion (4, 18, 22, 25, 26, 36), or in some cases, up to 24 months (1, 19).

Some interventions showed that changes in eating behaviors, dietary quality, or weight were not maintained over the long term (18, 24), or that the differences between control and intervention groups were no longer significant after the intervention period (1, 4, 18). However, results in areas like autonomy and other psychological functions remain significant ($p < 0.001$) (4), and improvements in depression symptoms were observed ($p < 0.05$) (25, 26). Additionally, changes in individual's relationships with food, such as reduced compulsive eating ($p < 0.0001$), were sustained (25). In contrast, studies focusing on quality-of-life improvements found that these effects were not maintained long-term (30). Cloutier-Bergeron et al. (26) also highlighted the existence of a group classified as "non-responders," who exhibited worse psychological function, less adaptation to changes in eating behavior, and higher rates of clinical depression. These individuals struggled to adjust to the behavioral changes introduced during the intervention.

While interventions based on this methodology can have a significant effect in the short-term impact, they seem to be less effective in the long term. Research evaluating HAES interventions, which emphasize healthy behaviors, size acceptance, and non-dieting approaches, has demonstrated health benefits regardless of weight loss. Nevertheless, as mentioned in previous sections and corroborated by other literature from the last twenty years (33, 43, 44), the long-term effectiveness of these interventions remains in question. Available data and findings from other authors suggest the long-term (>12 months) may not be sustained (45, 46). More long-term data are needed to support the use of these interventions.

It is important to acknowledge both the strengths and limitations of this review. One limitation is that some studies were carried out by the same research teams, meaning more studies from various regions are needed to strengthen the evidence. While interventions have been carried out in Canada, Brazil, the UK and the USA, which provides some diversity, more information is needed on the application of HAES across different cultural contexts. The increasing number of participants in these studies makes the data more robust, but it should also be noted that the majority of these studies have focused exclusively on women. This gender bias indicates that more research is needed on the effects of these interventions on men. Furthermore, few studies evaluate body composition or weight measurements, aligning with HAES principles of weight-neutrality. Nonetheless, this approach complicates comparisons between clinical outcomes.

Future research should include men and older populations, have longer follow-ups (>12 months), extend the intervention duration (>6 months), and involve larger population groups. Additionally, more detailed data on food intake is needed to understand what nutritional changes lead to improved health outcomes and, where applicable, reduced weight or body fatness in intervention groups. Factors such as energy-balance, food intake, and overall well-being, should be more thoroughly examined.

In conclusion, available data suggest that HAES interventions have positive effects on body composition, cardiovascular health, and psychological factors related to food and well-being. However, these long-term effects (particularly in studies lasting a minimum of 2 years)

require further verification, as current evidence suggests that some benefits may not be sustained. More extensive and longer-term studies are needed to clarify these findings.

Author contributions

RS: Writing – review & editing, Writing – original draft. GC: Writing – review & editing, Writing – original draft. CH: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. MaM: Writing – review & editing, Writing – original draft. JQ: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. MM: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. YS-A: Writing – review & editing, Writing – original draft. LC-A: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Protein supplementation preserves muscle mass in persons against sleeve gastrectomy

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Introduction: Sleeve gastrectomy surgery can lead to deficiencies in both macro and micronutrients, with protein being particularly crucial due to its role in muscle mass, physiological, and metabolic functions. Inadequate protein intake due to physiological, psychological, or financial reasons may prevent achieving the recommended intake levels. The significance of this issue is often underappreciated.

Aim: This study evaluates the impact of protein supplementation on muscle mass in individuals undergoing sleeve gastrectomy and emphasizes the need for more comprehensive dietary training by expert dietitians.

Method: Data were collected from 60 participants (15 male, 45 female, aged 20–54) who visited the surgery clinic. Participants were divided into two groups: those receiving the recommended protein supplement (15 g/day) with post-bariatric surgery diet training (BSD + PS), and those receiving only the post-bariatric surgery diet (BSD). A pre-surgery questionnaire gathered health and general information. Daily energy and nutrient intakes were recorded using 24-h food consumption logs on the day before surgery and at 7 days, 1 month, and 3 months postoperatively. Anthropometric measurements, including muscle and fat mass, and International Physical Activity Questionnaire (IPAQ) data were also collected.

Findings: The characteristics of participants in both groups were similar, although there were more females in the BSD + PS group (86.7%) compared to the BSD group (63.3%). Despite an increase in energy and nutrient intake over time, levels remained below the recommended amounts in both groups. A significant difference was found in protein supplement consumption between the groups ($p = 0.000$). Repeated measures showed significant differences in body muscle mass percentage over time ($F = 202.784$; $p = 0.000$).

Conclusion: In individuals who underwent sleeve gastrectomy surgery, deficiencies in macro and micronutrient intake were observed below reference levels. For this reason, the first approach in the treatment of obesity should always be medical nutrition therapy accompanied by a dietician. When designing post-bariatric surgery nutrition programs, it should be taken into consideration that nutrition protocols and trainings should be followed more closely and given in more detail under the supervision of a specialist before supplements are considered.

KEYWORDS

muscle mass, protein supplementation, sleeve gastrectomy, protein intake, postbariatric surgery diet

1 Introduction

Obesity is defined as a chronic and inflammatory disease that develops due to excess fat accumulation in the body, which can disrupt health and cause disease (1). The body mass index (BMI) used in the classification of obesity is calculated as the body weight in kilograms divided by the height in meters squared (2). According to BMI values, individuals over 25 kg/m^2 are classified as having excess body weight, and individuals over 30 kg/m^2 are classified as obese (1). Excess energy taken from food accumulates in many different parts of the body such as the liver and muscles and can cause diseases (3). The main ones of these diseases are metabolic diseases, heart diseases, psychosocial, central nervous system, reproductive system and pulmonary diseases (4). There are many different treatment options for obesity. These are grouped under 5 different headings: nutritional therapy, physical activity, lifestyle and behavioral changes, drug therapy and surgery (5). Treatment should always start with medical nutrition therapy, which is shown as the safest method. However, surgery should be considered in individuals who do not respond and meet the treatment criteria (6). The criteria that individuals who are considered suitable for surgical procedures will have are BMI > 40 kg/m^2 or BMI 35–39.9 kg/m^2 and obesity-related (prediabetes, diabetes, dyslipidemia, obstructive sleep apnea, asthma, polycystic ovary syndrome, infertility, sexual dysfunction, hypertension, atherosclerosis, impaired kidney function) having at least one concomitant disease or BMI 30–34.9 kg/m^2 and concomitant diabetes and it is indicated in the form of metabolic syndrome (7).

The most basic purpose of surgical procedures is to reduce body weight and the health risks associated with obesity (8). There are 3 main procedures of bariatric surgery (BS): restrictive, absorbent and both restrictive and absorbent (9). Sleeve gastrectomy (SG), one of the surgical methods, is the vertical division of the stomach volume, leaving approximately one-fourth of it. In this process, the pyloric structure, gastric functions and digestive processes are not damaged (4). Reducing visceral fat in the body, accordingly, it is aimed to increase insulin sensitivity, reduce the amount of free fatty acids and interleukin-6 level (10). It has also been observed that their quality of life and psychosocial status have improved (11). However, there are also disadvantages. The most common complications are; leakage, hemorrhage, kidney stones, cholecystectomy, insufficient weight loss, liver or spleen injury, portal vein thrombosis, venous thromboembolism, breathing difficulties, abscess, stomach stenosis, venous thromboembolism, choledocholithiasis, pneumonia, sepsis, infection, minor complications and deaths. It can also cause macro and micronutrient deficiencies (12). It has also been observed that individuals regain weight after surgery due to the main reasons such as increasing the amount of energy consumed over time, choosing high-energy beverages, having five or more meals, insufficient activity level, advancing age, drug use or hormonal changes, increase in stomach volume, and high-carbohydrate diet (13).

When observational studies were examined, it was stated that the energy consumed should be similar to the general nutrition recommendations. It should be planned that 35–48% of the total energy should be met from carbohydrates, 37–42% from fat. Adequate and balanced nutrition recommendations should be determined by experienced dietitians during the day, the importance of high protein foods should be explained, and protein supplementation recommendations should be made if necessary (14). The most common macronutrient deficiency in all BS methods, especially in absorption-disrupting procedures, has been identified as protein (15). Protein deficiency is observed within the first month after surgical procedures, and the sensitivity to protein foods develops at the same rate (16). Protein deficiency is seen within the first month after surgical procedures, and sensitivity to protein foods develops at the same rate (16). This situation can occur in 3 main ways. The first is an aversion or feeling of nausea that develops against protein-rich foods due to changes in taste and smell. The second is the decrease in the amount of food taken due to the removal of a large part of the stomach volume. Finally, it is a decrease in the secretion of digestive enzymes, especially stomach acid and pepsinogen, and the passage of food through the digestive lumen very quickly (15, 17, 18). In addition, most patients after bariatric surgery are subjected to a solid liquid diet in the early period after surgery. They cannot consume a large amount of food at one meal or get solid protein in the first months. This indicates that there is a higher risk of developing protein malnutrition (19). It has been observed that inadequate protein intake can cause problems such as decreased skeletal muscle mass, low serum albumin level, endocrine imbalances, acceleration of the aging process, anemia, low immune system, bone and calcium losses, decrease in metabolic rate and failure to reach the target weight (20). A small amount of muscle mass loss can be expected in weight losses, but maintaining metabolic balance and muscle integrity is of vital importance (21).

Protein is an essential nitrogenous element necessary for all living life. It forms the building block of cells and enzymes that catalyze the metabolic reactions that take place (22). Protein is an essential nitrogenous element necessary for all living organisms. It is the building block of cells and enzymes that catalyze metabolic reactions (22). It is recommended as 0.8 g/kg/day for adults. The amount of intake can be changed during pregnancy and lactation, in growing children and in pathological conditions (23). Current guidelines recommend that patients consume 60–80 g protein per day or 1.2 g/kg of ideal body weight (24, 25). However, it has been reported that 45% of BS patients have problems in complying with these guidelines (26). A significant prevalence of lean body mass loss has been described in BS patients. Patients have been found to lose approximately 22% of their lean body mass within the first year after Laparoscopic Roux-en-Y gastric Bypass (RYGB) (27, 28). Moderately high protein diet intake has been found to preserve muscle mass and basal metabolic rate. However, it has also been found to support weight loss (29, 30). Considering these considerations, bariatric guidelines recommend the adoption of a relatively high protein intake in the first months after surgery, when the risk of energy restriction and associated loss of lean mass is higher (31, 32). During this period, the use of high-quality protein sources with high leucine content is of vital importance for many tissues and organs, especially muscle mass (33). When the literature was reviewed, it was observed that the number of studies on this subject was insufficient. The aim of the study was to evaluate the effect of protein supplementation recommended in addition to medical nutrition therapy on the muscle mass of patients after BS. To emphasize the importance of more comprehensive nutrition education before supplementation is considered.

2 Materials and methods

2.1 Selection criteria of individuals

It has been observed in general nutrition education after surgery that protein intake of individuals is inadequate due to reasons such

as changed gastric capacity after surgery, development of food intolerances, difficulty in consuming supplements, difficulty in meeting protein requirements, unwillingness to continue supplementation routine and even refusal to use additional supplements. This study is a prospective study with follow-up aiming to evaluate the effect of protein supplementation in addition to post-bariatric surgery diet on muscle mass measurements in individuals undergoing sleeve gastrectomy (SG) surgery. The primary endpoint is to evaluate the effect of protein supplementation on the existing lean body mass due to protein deficiency in patients who underwent SG surgery. The primary outcomes were weight loss and body composition at days 7, 30 and 90 after SG. Variables assessed included weight, BMI, muscle mass, fat mass, fat percentage, percentage of muscle mass loss, and percentage of fat loss. Secondary outcomes were changes in macro- and micronutrient status at days 7, 30 and 90 after SG. As a result of the power analysis using the G*Power 3.0.10 program, the sample size was determined as at least 59 people in total with 80% power, 5% type 1 margin of error and $d = 0.7500000$ effect size. The study was conducted by collecting data from a total of 60 individuals, aged between 20–54 years, who received 30 post-bariatric surgical diet (BSD) and 30 post-bariatric surgical diet + protein supplements (BSD + PS) on the day before surgery (pre-op 0) and 7, 30 and 90 days after surgery (post op). The patients who have been decided to undergo SG surgery have been divided into two groups, consisting only of BSD and BSD + PS, due to their inability to comply with the use of protein supplements. Participants received verbal and written diet instructions during their hospital stay, as well as at 7, 30, and 90 days following their bariatric surgery. They were advised to strictly adhere to the post-bariatric diet guidelines provided by the ASMBS Allied Health Nutrition Committee. This ensured that both groups consumed a similar, safe diet throughout the study period. The study was approved by the Ethics Committee of Ankara Yildirim Beyazit University with the decision number 40 dated 08.12.2020, permission was obtained from the clinic where the study was conducted, and a voluntary consent form was obtained from the participating patients. The study was conducted in Ankara General Surgery Clinic between January and June 2021.

All individuals scheduled for surgery were evaluated multidisciplinary by physicians, dietitians, and anesthesiologists according to their comorbidities. All procedures were performed by a single physician in accordance with the relevant guidelines and regulations. Individuals with body mass index BMI $\geq 40\,kg/m^2$ or BMI $\geq 35\,kg/m^2$ and at least one comorbidity associated with obesity (prediabetes, diabetes, dyslipidemia, obstructive sleep apnea, asthma, polycystic ovary syndrome, infertility, sexual dysfunction, hypertension, atherosclerosis, impaired renal function) were included in the study. Individuals who had not achieved body weight loss for at least 6 months on various diet programs and had the capacity to understand the surgical procedure and its effects were selected. The exclusion criteria for this study are as follows;

- Under 19 or over 64 years old
- Having uncontrolled endocrinological diseases
- Pregnancy
- Having uncontrolled mental health problems or depression
- Having substance addiction
- Having problems that cannot follow the guidelines and recommendations regarding nutritional status
- Having eating disorders
- Having cancer
- Having coagulation disorders
- Having contraindications that prevent surgery (cardiovascular disease, anesthesia-related risks, etc.)

Demographic characteristics, general and health information (gender, age, education level, family history of obesity, consumption of beverages with added sugar, tea consumption, use of added sugar, sleep duration, alcohol consumption, chronic disease status, methods used to reduce body weight, night eating habits, water consumption) were questioned with a questionnaire.

When the studies conducted on this subject are examined, it is seen that a follow-up period of up to 3, 6, 12, or 36 months is planned (32). However, due to the pandemic experienced worldwide, the study was continued for 3 months in order to complete the process (34).

2.2 Protein supplement

It is known that individuals develop many macro and micronutrient deficiencies due to stomach capacity and possible physiological changes, and protein is defined as the most important nutrient (16). Considering the importance of protein intake, recommendations are made by the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery (ASMBS). It is emphasized that these recommendations should be individualized, evaluated, and recommendations should be made by a dietitian who is an expert in the field, recording the gender, age, and current body weight of the individuals. Protein intake should be a minimum of 60 g per day (35).

Individuals who complete the surgical process stay in the hospital for 2 nights and 3 days. In the clinic routine, post-bariatric surgery diet education is started to be given (by the dietitian) in the morning visits. These medical nutrition programs are created specifically for individuals in accordance with the literature and necessary recommendations are made (36). 24-h food consumption records were evaluated using a food photo catalog in the pre-op 0 and post-op control periods. These data were analyzed using the "Computer-Assisted Nutrition Program, Nutrition Information System" (BeBis) (37). The nutrient values calculated via BeBis were classified according to the 'Dietary Reference Intake Level' (DRI) recommendations according to age and gender % ≤67 of the reference values were categorized as inadequate, % 67–133 as sufficient and ≥ %133 as excessive intake (38). In addition to the nutrition programs, the recommended protein supplement was planned to be consumed without cooking by adding it to foods in liquid form with the help of a scale once a day. Those who consumed less than 80% of the supplement were excluded from the study. A similar study was taken as an example and 15 g/day whey protein supplement was added (39). Because individuals who have undergone bariatric surgery may develop an aversion to protein-rich foods due to changes in taste and smell. In addition, removal of a large portion of the stomach volume may reduce the amount of food taken in and the release of enzymes that help digestion and may cause physiological changes that reduce the amount of food intake (17).

2.2.1 Educational content of post-bariatric surgery diet

The content of the nutrition education provided to postoperative patients is as follows (40):

2.2.1.1 Post-op 1–2, day (hospital admission process)

- To begin with, clear liquids (sugar, carbohydrate and caffeine-free) should be consumed.
- It should be switched to liquid intake as sipping and as tolerance is achieved, it should be ensured to consume liquid in a way that can be approximately 1,400 mL per day.
- The use of straws should always be avoided to prevent the formation of air bubbles.

2.2.1.2 Post-op 3–7, day (discharged)

- The consumption of clear liquids (sugar, carbohydrate and caffeine-free) should be maintained.
- However, approximately half of the recommended daily consumption of 1,400 mL-1800 mL of liquid should consist of clear liquid.
- It should be switched to full liquids (skimmed milk, lactose-free milk, soy milk, plain yogurt or grain-free soup).
- However, whey or soy-based protein powder can be added to complete liquids (<20 g/meal).
- A chewable multivitamin and mineral supplement should be started, such as a tablet twice a day.

2.2.1.3 Post-op 2–3, week (puree diet)

- Clear liquids can be increased up to a daily amount of 1,400–1800 mL.
- Soft, pureed, ground solid foods with a low fat and high protein content should be added instead of full liquids (eggs, cheese with a low-fat content, fish, poultry, lean meat, boiled beans).
- It should be consumed with 4 or 6 meals during the day, and the meal portion should be approximately <60 mL/meal planned.
- First of all, protein should be consumed. Daily protein consumption of 60 g and above should be targeted.

2.2.1.4 Post-op 4–6, week

- As long as tolerance is achieved, the nutritional steps should progress. Well-cooked vegetables, soft or crushed, peeled fruits can be included in nutrition programs.
- 4–6 meals can be consumed daily, and the meal portions should be approximately 120 mL/meal.
- First of all, meals should be started by consuming protein foods.
- To avoid the risks of dehydration, 1,400–1,800 mL of clear liquid should be consumed daily.
- Drinks should not be consumed for 30 min before meals and for 30–60 min after meals.
- Besides, food should be chewed well.

2.2.1.5 Post-op 7, the week and beyond

- Height length, body weight and age factors should be planned by evaluating daily energy requirements.
- A balanced nutrition program should be established in which lean meat products, fruits, vegetables and whole grains are added.
- The consumption of vegetables and fruits with high fiber density should be avoided. These products can be consumed well-cooked or mashed.
- A daily nutrition plan should be created so that three main meals and two intermediate meals are consumed. The serving size should not be over 240 mL.
- The daily consumption of clear liquid in the amount of 1,400–1,800 mL should be ensured.
- A Drink should not be consumed 30 min before meals and should be planned to be consumed 30–60 min after.
- On the other hand, it is planned that foods should be chewed well (26).
- Any diet application before surgery is not recommended, but nutrition education based on literature is provided. After the surgery, face-to-face nutrition education is repeated practically during the visiting hours of the patients.

2.2.2 General nutrition education

Important points to be considered in the nutrition of postoperative patients are explained below (36).

- It is recommended to reach a protein amount of 60–120 g/day in order to maintain body muscle mass. This value is for RYGB; 1.1–1.5 g/kg/day and for BPD; care should be taken to take the amount of 120 g/day,
- To avoid simple sugar (sucrose) products and foods with low nutrient content and high energy content in order to prevent dumping syndrome that may occur after absorbent or restrictive procedures, avoid simple sugar (sucrose) products and foods with high energy content,
- Avoiding caffeinated and acidic drinks, fried foods, alcohol, foods containing high saturated fat,
- They should consume 3–6 meals daily, take small bites, chew well before swallowing, and meals should last about 30 min,
- It is in the form of taking multivitamin supplements in chewable or liquid forms for at least 6 months after surgery.

2.3 Anthropometric measurement analysis

Body composition was evaluated with bioelectrical impedance (TANİTA 780 MA) analysis under the supervision of a dietician. The individuals who will be measured were informed about the points they should pay attention to before coming for measurement. The main points are; not to consume food and beverages including coffee and tea with diuretic effects for 2 h before the measurement, not to do intense physical activity, not to consume alcohol, not to have any metal objects in contact with their skin during the measurement (41). Anthropometric measurements, mainly body weight, muscle and fat mass, were repeated in appropriate forms at the end of the pre-op and post-op 7 days, at the end of the 1st and 3rd months.

2.4 Assessment of physical activity

The International Physical Activity Questionnaire (IPAQ-Short Form), which was developed by the International Physical Activity Assessment Group and whose Turkish validity and reliability was performed by Öztürk (42) in 2005, was used to determine the physical activity status of individuals. IPAQ includes subheadings that

determine the MET score by evaluating the frequency, duration and physical intensity levels of physical activity performed in the last seven days. The short form is calculated by multiplying the duration minutes and frequency data of walking, moderate activity and vigorous activity.

2.5 Statistical evaluation

In order to compare quantitative variables, it was first investigated whether parametric test conditions were met. In the comparison of quantitative data with normally distributed data, independent *t* test analysis was applied for the difference between two independent groups. Mann Whitney U test was applied for the difference between two independent groups that did not show normal distribution. Chi-square analysis was used to measure the relationship between categorical variables. In our study, qualitative variables were summarized by number and percentage, and measurements related to quantitative variables were summarized by mean and standard deviation. The obtained measurements were analyzed by repeated measures analysis of variance (ANOVA). These models were tested for main effects (group and time) and interaction effect (group*time). In such models, a significant interaction effect is interpreted as evidence that time-dependent changes differ across groups and main effects are not interpreted. In cases where the interaction effect is not significant, the results regarding the main effects are interpreted. In all analyses, the significance level was accepted as 5% and all analyses and graphs were performed using "IBM SPSS v25 for Windows (IBM Corp, Armonk, NY, USA)" software.

3 Results

3.1 Sociodemographic conditions

This study was conducted with a total of 60 individuals who received protein supplementation in addition to post-bariatric surgery diet (BSD + PS) and post-bariatric surgery diet alone (BSD) after bariatric surgery. In the BSD + PS group, 26 (86.7%) were female and 4 (13.3%) were male, while in the BSD group, 19 (63.3%) were female and 11 (36.7%) were male. In both groups, it was observed that the majority of those who wanted to have surgery were women. The mean age of those in BSD + PS was 33.6 ± 10.4 years, while the mean age of those in BSD was 36.3 ± 9.9 years. When the education levels were analyzed, 16 (53.3%) of the individuals in BSD + PS were undergraduates and 16 (53.3%) of those in BSD were high school graduates. The educational level of individuals in BSD + PS was found to be higher ($p < 0.05$). The majority of those in BSD + PS and BSD had a family history of obesity. Eighteen (69.2%) of those in BSD + PS and 17 (75.0%) of those in BSD were obese. The distribution of the patients included in the study is shown in Table 1.

3.2 Nutrition habits

According to the answers given to the question about eating speed, it was found that fast eating habits were common in 26 (86.7%) and 27 (90%) individuals in BSD + PS and BSD. When sugary drink consumption was analyzed, 22 (73.3%) of the individuals in BSD + PS and 19 (63.3%) of those in BSD answered yes to the question. The majority of individuals in both groups consume tea. The difference between the frequency of tea consumption and BSD + PS and BSD groups was statistically significant. When the consumption of added sugar was questioned, it was found that 6 (20.0%) individuals in BSD + PS and 9 (30.0%) individuals in BSD consumed 1–5 pieces of added sugar daily. However, the majority of individuals in BSD + PS and BSD did not use added sugar.

3.3 Medical history conditions

The mean sleep duration of the individuals in BSD + PS was 7.3 ± 1.8 h, while the mean sleep duration of those in BSD was 7.8 ± 2.1 h. The majority of the individuals in both groups did not smoke. When alcohol consumption was analyzed, it was found that 10 (33.3%) of the individuals in BSD + PS and 7 (23.3%) of those in BSD consumed alcohol. The majority of the individuals belonging to both groups, 25 (83.3%) of the individuals in BSD + PS and 20 (66.7%) of those in BSD, had at least one chronic disease. Individuals belonging to both groups made attempts to reduce their body weight before surgery. However, these interventions differed between the groups. Among the individuals in BSD + PS, 30 (100.0%) diet, 25 (83.3%) exercise, 8 (26.7%) acupuncture and among those in BSD, 30 (100.0%) diet, 23 (76.7%) exercise and 10 (33.3%) acupuncture were used to reduce or control their weight. The majority of the individuals belonging to both groups stated that they applied diet 1–10 times (Table 1).

3.4 Evaluation of anthropometric measurements

It was observed that the mean percentages of muscle mass before surgery decreased at the end of the 7th day (50.4, 53.8%) in BSD + PS (51.7%) and BSD (54.5%), respectively, and the mean percentages of fat mass increased in BSD + PS (45.6%) and BSD (42.7%), respectively, compared to the beginning (46.9, 43.4%). These percentage changes indicate the changing percentages in the current weight due to sudden muscle loss in the first seven days. However, the mean percentage of fat mass decreased, and the mean percentage of muscle mass increased in the current weight of the men and women belonging to the groups over time (Table 2). Individuals belonging to both groups had a high mean percentage of muscle mass within their current body weight at baseline. There was a statistically significant difference between BSD and BSD + PS at pre-op and post-op 7th, 30th and 90th days ($p < 0.05$). The mean percentage of available muscle mass of individuals in BSD + PS (58.2%) was lower than those in BSD (61.4%). When women and men were evaluated, the percentage of fat mass in the current weight of women in both groups was found to be higher in all periods compared to men (Table 2).

3.5 Evaluation of lost anthropometric measurements

There was high muscle mass loss in the first seven days after surgery. The average percentage of muscle mass lost within the weight loss decreased from the 7th postoperative day to the 90th day.

TABLE 1 Distribution of sociodemographic, health, and nutritional status of individuals.

Gender sex, *n* (%)	BSD + PS *n* (%)	BSD *n* (%)	*p*
Woman	26.0 (86.7)	19.0 (63.3)	**0.037***
Male	4.0 (13.3)	11.0 (36.7)	
Age (year)			
Avrg. ± Std. deviation	33.6 ± 10.44	36.3 ± 9.95	
Education level *n* (%)			
Middle School	3.0 (10)	7.0 (23.3)	**0.025***
High School	9.0 (30.0)	16.0 (53.3)	
License	16.0 (53.3)	5.0 (16.7)	
Postgraduate	2.0 (6.7)	2.0 (6.7)	
Family history of obesity *n* (%)			
There is	26.0 (86.7)	24.0 (80.0)	0.488
No	4.0 (13.3)	6.0 (20.0)	
Sugary drink consumption (330 mL) cans/day			
Yes	22.0 (73.3)	19.0 (63.3)	0.405
No	8.0 (26.7)	11.0 (36.7)	
Tea consumption (120 mL)/ medium-sized tea cup			
Yes	21.0 (70.0)	27.0 (90.0)	**0.053***
No	9.0 (30.0)	3.0 (10.0)	
Frequency of added sugar consumption (qty/cube/day)			
Does not consume	16.0 (53.3)	17.0 (56.7)	0.462
1–5 pieces	6.0 (20.0)	9.0 (30.0)	
6–10 pieces	4.0 (13.3)	1.0 (3.3)	
11 Pieces and above	4.0 (13.3)	3.0 (10)	
Sleep Duration (hours)			
Mean ± Std. deviation	7.3 ± 1.80	7.8 ± 2.19	0.482
Alcohol consumption			
Yes	10.0 (33.3)	7.0 (23.3)	0.390
No	20.0 (66.7)	23.0 (76.7)	
Chronic disease status			
Yes	25.0 (83.3)	20.0 (66.7)	0.136
No	5.0 (16.7)	10.0 (33.3)	
Previous methods to reduce body weight**			
Diet	30.0 (100.0)	30.0 (100.0)	0.076
Exercise	25.0 (83.3)	23.0 (76.7)	0.519
Acupuncture	8.0 (26.7)	10.0 (33.3)	0.573
Gastric balloon	-	1.0 (3.3)	0.313
Stomach Botox	1.0 (3.3)	1.0 (3.3)	0.754
Diet implementation			
Nothing	-	-	0.238
1–10	21.0 (70.0)	21.0 (70.0)	
11–20	7.0 (23.3)	5.0 (16.7)	
21 and above	2.0 (6.7)	4.0 (13.3)	
Method of providing dietary support**			
Dietitian support	22.0 (73.3)	24.0 (80.0)	0.542
Internet book recommendations	15.0 (50.0)	11.0 (36.7)	0.297
Individual effort	20.0 (66.7)	20.0 (66.7)	0.608
Medication or supplements	8.0 (26.7)	14.0 (46.7)	0.108
Night eating habits			
Yes	21.0 (70.0)	18.0 (60.0)	0.417
No	9.0 (30.0)	12.0 (40.0)	
Types of food consumed at night**			
Cheese and derivatives	2.0 (9.5)	1.0 (5.6)	0.643
Meat products	1.0 (4.8)	9.0 (50)	0.348
Bakery products	9.0 (42.9)	-	0.656
Nuts	3.0 (14.3)	1.0 (5.6)	0.370
Drinks with added sugar	1.0 (4.8)	2.0 (11.1)	0.458
Processed convenience foods	5.0 (23.8)	8.0 (44.4)	0.173
Water consumption (200 mL) cups/day			
Mean ± SD deviation	1146.6 ± 1164.04	1253.3 ± 1147.93	0.442

Chi-square analysis. *p values considered statistically significant are indicated in bold ($p < 0.05$), Post-bariatric Surgery Diet Group (BSD), Post-bariatric Surgery Diet Group + Protein Supplement Group (BSD + PS) **more than one option is marked.

It was found that the average percentage of fat mass lost increased. In individuals in BSD + PS, a weight loss of 6.1% was found on the 7th postoperative day and 22.8% at the end of the 90th postoperative day. The percentage of fat mass within the average weight lost up to the 90th day was 68.3% and the percentage of muscle mass was 29.9%. In individuals in BSD, 22.6% of the current weight was lost after the 90th day. In individuals in BSD, the percentage of fat mass lost within the weight lost at the end of the 90th day was 66.7% and the percentage of muscle mass was 31.5%. It was found that women in BSD + PS (40.2%) lost a higher percentage of muscle mass within the weight lost in the first month compared to men (31.7%) (Table 3). No statistically significant difference was found between the groups in terms of lost body weight, muscle mass and fat mass measurements ($p > 0.05$). Time-dependent changes and comparisons of body composition measurements are shown in Figure 1.

3.6 Daily energy and macronutrient intake averages and percentage of DRI coverage

It was found that the averages of energy and macronutrient intake in both groups decreased in the first seven days and increased again over time. In addition, the mean daily energy intake of individuals in BSD + PS was found to be significantly higher than that of BSD on the 90th post-op day ($p < 0.05$). The mean daily protein intake of individuals in BSD + PS was 72.8 ± 31.42 grams (g) in the pre-op period, 25.7 ± 8.53 g on post-op day 7, 33.1 ± 11.95 g on post-op day 30 and 39.5 ± 17.66 g on post-op day 90. Those in BSD were 78.4 ± 34.04 g pre-op, 12.0 ± 12.36 g post-op day 7, 16.2 ± 9.06 g post-op day 30 and 19.5 ± 10.12 g post-op day 90. In addition, the mean protein intake of

TABLE 2 Mean and standard deviation (X ± SS) values of anthropometric measurements for general and gender.

		BSD + PS (*n* = 30)	BSD (*n* = 30)	*p*	BSD + PS (*n* = 30)	BSD (*n* = 30)	*p*	BSD + PS (*n* = 30)	BSD (*n* = 30)	*p*
		X ± SS	X ± SS		X ± SS	X ± SS		X ± SS	X ± SS	
		General			Female			Male		
Body weight (kg)	Pre-Op	111.6 ± 19.77	119.4 ± 24.01	0.178	106.9 ± 16.11	111.5 ± 18.21	0.375	142.7 ± 11.25	133.1 ± 27.38	0.512
	Post Op 7. Days	104.8 ± 18.87	112.3 ± 22.82	0.170	100.3 ± 15.47	105.8 ± 17.94	0.286	134.2 ± 10.95	123.6 ± 26.65	0.462
	Post Op 30. Days	98.9 ± 16.98	105.2 ± 19.51	0.189	94.8 ± 13.41	99.3 ± 17.61	0.334	125.3 ± 14.67	115.3 ± 19.22	0.362
	Post Op 90.Days	86.4 ± 16.09	92.2 ± 17.81	0.187	82.3 ± 12.73	87.7 ± 15.56	0.206	112.7 ± 9.25	100.0 ± 19.49	0.239
BMI (kg/m^2)	Pre-Op	41.1 ± 4.97	42.8 ± 6.35	0.245	40.4 ± 4.95	42.3 ± 5.65	0.252	45.1 ± 3.18	43.7 ± 7.61	0.733
	Post Op 7. Days	38.5 ± 4.84	40.3 ± 6.10	0.218	37.9 ± 4.83	40.2 ± 5.55	0.157	42.4 ± 3.16	40.5 ± 7.24	0.635
	Post Op 30. Days	36.3 ± 4.28	37.8 ± 5.43	0.260	35.9 ± 4.34	37.8 ± 5.56	0.224	39.4 ± 2.29	37.9 ± 5.22	0.589
	Post Op 90. Days	31.7 ± 4.09	33.1 ± 5.08	0.234	31.1 ± 3.93	33.3 ± 4.98	0.105	35.6 ± 3.05	32.8 ± 5.48	0.365
Current fat mass (kg)	Pre-Op	50.9 ± 10.66	51.0 ± 13.83	0.982	50.1 ± 11.01	53.3 ± 12.68	0.380	56.1 ± 6.86	47.1 ± 15.43	0.287
	Post Op 7. Days	49.2 ± 10.22	49.0 ± 14.44	0.963	48.6 ± 10.61	51.8 ± 13.13	0.367	53.0 ± 7.04	44.2 ± 15.94	0.313
	Post Op 30. Days	43.3 ± 9.59	43.2 ± 13.10	0.968	43.2 ± 9.61	46.1 ± 12.85	0.390	44.2 ± 10.8	38.2 ± 12.52	0.414
	Post Op 90. Days	33.7 ± 8.84	33.1 ± 12.28	0.846	33.4 ± 8.88	37.0 ± 11.48	0.240	35.6 ± 9.58	26.5 ± 11.1	0.170
Percent fat mass (%)	Pre-Op	45.6 ± 4.34	42.7 ± 7.44	0.073	46.5 ± 3.63	47.3 ± 4.22	0.520	39.3 ± 3.50	34.7 ± 4.34	0.080
	Post Op 7. Days	46.9 ± 4.53	43.4 ± 8.07	**0.043***	48.0 ± 3.42	48.3 ± 4.55	0.823	39.5 ± 4.10	34.9 ± 5.14	0.133
	Post Op 30. Days	43.8 ± 5.36	40.8 ± 8.29	0.105	45.1 ± 3.95	45.6 ± 5.19	0.714	35.0 ± 5.28	32.4 ± 5.47	0.442
	Post Op 90. Days	38.7 ± 5.87	35.2 ± 10.16	0.103	39.9 ± 5.02	40.8 ± 7.34	0.644	31.4 ± 6.28	25.5 ± 6.31	0.133
Current muscle mass (kg)	Pre-Op	57.7 ± 11.49	65.0 ± 15.71	**0.043***	53.8 ± 5.56	55.2 ± 6.07	0.437	82.6 ± 8.13	82.0 ± 12.28	0.930
	Post Op 7. Days	50.1 ± 10.31	60.2 ± 14.29	**0.031***	49.1 ± 5.30	51.3 ± 5.31	0.184	77.4 ± 8.44	75.7 ± 11.21	0.787
	Post Op 30. Days	52.8 ± 10.87	59.0 ± 30.286	**0.049***	49.0 ± 4.36	50.5 ± 5.07	0.284	77.4 ± 7.38	73.5 ± 7.86	0.412
	Post Op 90. Days	52.9 ± 11.29	56.2 ± 20.059	**0.043***	46.5 ± 4.26	48.2 ± 4.87	0.228	73.5 ± 5.77	70.2 ± 8.71	0.496
Percent muscle mass (%)	Pre-Op	51.7 ± 4.17	54.5 ± 7.19	0.071	50.8 ± 3.44	50.0 ± 3.98	0.511	57.8 ± 3.33	62.2 ± 4.16	0.081
	Post Op 7. Days	50.4 ± 3.95	53.8 ± 6.97	0.313	49.3 ± 3.27	49.1 ± 4.33	0.314	57.7 ± 3.86	62.1 ± 5.96	0.664
	Post Op 30. Days	53.4 ± 5.13	56.3 ± 8.01	0.100	52.1 ± 3.73	51.6 ± 4.91	0.713	62.0 ± 5.97	64.5 ± 5.27	0.065
	Post Op 90. Days	58.2 ± 5.76	61.4 ± 9.61	0.124	57.1 ± 4.96	55.8 ± 6.11	0.850	65.4 ± 6.00	71.1 ± 6.01	0.309

The "Independent Sample-*t*" test (*t*-Chart value) statistics were used to compare two independent groups with normal distribution. *The *p* values considered statistically significant are indicated in bold ($p < 0.05$). BMI, Body Mass Index; BSD, Post-bariatric Surgery Diet Group; BSD + PS, Post-bariatric Surgery Diet Group + Protein Supplement Group.

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TABLE 3 The mean and standard deviation (X ± SD) values of the general and gender-based anthropometric difference measurements of individuals.

		BSD + PS (*n* = 30)	BSD (*n* = 30)	*p*	BSD + PS (*n* = 30)	BSD (*n* = 30)	*p*	BSD + PS (*n* = 30)	BSD (*n* = 30)	*p*
		X±SS	X ±SS		X±SS	X ±SS		X±SS	X ±SS	
		General			Female			Male		
Lost body weight (kg)	Post Op Day 7	6.8 ± 2.13	7.0 ± 3.50	0.766	6.6 ± 1.97	5.6 ± 2.48	0.176	8.5 ± 2.64	9.5 ± 3.78	0.661
	Post Op Day 30	12.8 ± 4.65	14.2 ± 6.87	0.341	12.0 ± 4.41	12.1 ± 3.23	0.940	17.4 ± 3.61	17.8 ± 9.78	0.940
	Post Op Day 90	25.3 ± 6.41	27.2 ± 9.1	0.358	24.5 ± 6.39	23.7 ± 5.33	0.652	30.0 ± 4.78	33.1 ± 11.30	0.473
Body weight lost (%)	Post Op Day 7	6.1 ± 1.64	5.9 ± 2.79	0.714	6.2 ± 1.65	5.2 ± 2.24	0.088	6.0 ± 1.79	7.2 ± 3.24	0.476
	Post Op Day 30	11.3 ± 2.94	11.7 ± 3.72	0.677	11.1 ± 2.86	11.0 ± 3.13	0.914	12.4 ± 3.63	12.8 ± 4.53	0.889
	Post Op Day 90	22.8 ± 4.15	22.6 ± 4.7	0.865	23.1 ± 4.31	21.4 ± 3.89	0.198	21.0 ± 2.55	24.6 ± 5.45	0.235
Fat mass lost (kg)	Post Op Day 7	1.8 ± 2.29	2.0 ± 2.49	0.719	1.6 ± 2.37	1.5 ± 1.87	0.891	3.1 ± 1.07	2.9 ± 3.20	0.902
	Post Op Day 30	7.7 ± 3.8	7.8 ± 3.25	0.910	7.1 ± 3.21	7.2 ± 2.57	0.886	11.9 ± 5.14	8.9 ± 4.10	0.254
	Post Op Day 90	17.2 ± 4.56	17.9 ± 5.3	0.634	16.7 ± 4.46	16.3 ± 3.76	0.711	20.5 ± 4.37	20.6 ± 6.57	0.977
Percentage of fat mass lost in weight lost (%)	Post Op Day 7	31.9 ± 29.3	26.1 ± 25.1	0.564	25.2 ± 39.45	27.5 ± 37.20	0.311	36.6 ± 5.48	29.8 ± 29.25	0.663
	Post Op Day 30	56.7 ± 10.2	55.8 ± 54.1	0.842	58.9 ± 22.42	59.1 ± 14.58	0.971	66.5 ± 14.68	52.9 ± 9.80	0.056
	Post Op Day 90	68.3 ± 8.54	66.7 ± 8.22	0.448	68.4 ± 7.99	68.9 ± 8.65	0.837	68.2 ± 10.98	62.9 ± 7.20	0.290
Muscle mass lost (kg)	Post Op Day 7	4.8 ± 2.66	4.8 ± 3.05	0.993	4.7 ± 2.81	3.9 ± 2.49	0.332	5.1 ± 1.63	6.2 ± 3.47	0.552
	Post Op Day 30	4.6 ± 3.2	5.0 ± 3.8	0.496	4.8 ± 2.66	4.7 ± 2.29	0.833	5.1 ± 1.52	8.4 ± 5.67	0.289
	Post Op Day 90	7.6 ± 2.86	8.8 ± 4.53	0.221	7.4 ± 2.79	7.1 ± 3.07	0.732	9.0 ± 13.28	11.8 ± 5.16	0.260
Percentage of muscle mass lost in weight lost (%)	Post Op Day 7	65.0 ± 5.1	69.6 ± 31.2	0.589	70.7 ± 37.41	72.2 ± 38.54	0.314	60.2 ± 4.67	66.8 ± 28.82	0.664
	Post Op Day 30	39.0 ± 15.98	40.6 ± 12.66	0.673	40.2 ± 16.27	38.5 ± 13.83	0.713	31.7 ± 13.45	44.3 ± 9.83	0.065
	Post Op Day 90	29.9 ± 8.02	31.5 ± 8.07	0.457	29.9 ± 7.86	29.4 ± 8.15	0.850	30.2 ± 10.38	35.0 ± 6.88	0.309

The "Independent Sample-*t*" test (*t*-Chart value) statistics were used to compare two independent groups with normal distribution. The *p* values considered statistically significant are indicated in bold ($p < 0.05$). BMI, Body Mass Index; BSD, Post-bariatric Surgery Diet Group; BSD + PS, Post-bariatric Surgery Diet Group + Protein Supplement Group.

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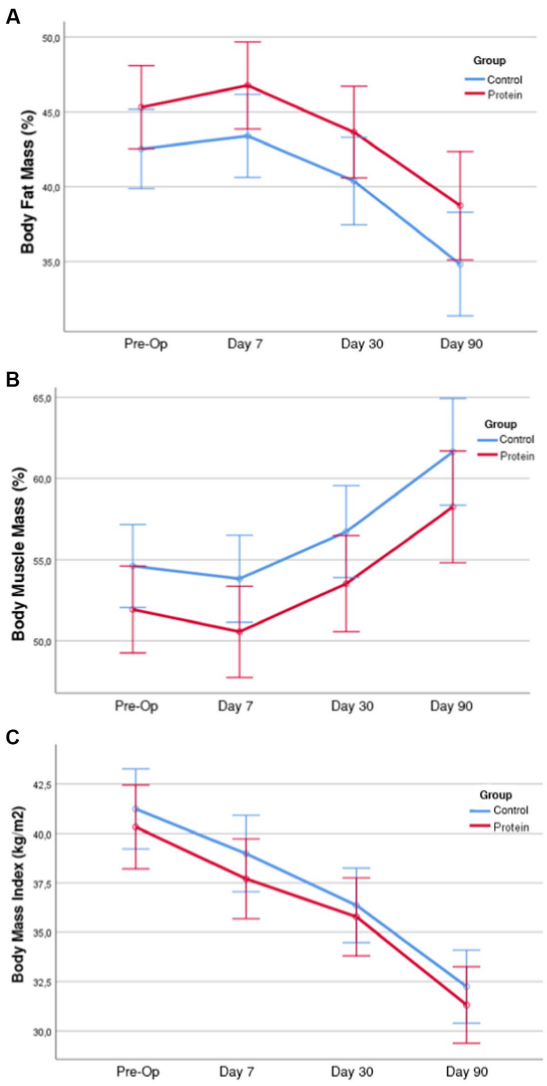

FIGURE 1
Time dependent changes and comparisons of body fat mass (%), muscle mass percentage, body mass index in groups, body fat mass (%) measurement averages of the groups by time (with 95% Interval). **(A)** According to the results of the analysis of variance of the body fat mass (%) variable, the group-time interaction effect was not significant (F=0.692; p=0.558). Therefore, the time-dependent changes in body fat mass (%) were similar in the groups. When the main effects were analyzed, the difference between the groups was not significant (F=2.586; p=0.115) and the time-dependent changes were significant (F=173.34; p<0.001). In short, while the time-dependent changes in Body Fat Mass (%) were significant in both groups, the difference between the groups was not significant. **(B)** According to the results of the analysis of variance of the body muscle mass (%) variable, the group-time interaction effect was not significant (F =0.339; p =0.754). Therefore, the time-dependent changes in body muscle mass (%) were similar in the groups. When the main effects were analyzed, the difference between the groups was not significant (F =2.452; p =0.125) and the time-dependent changes were significant (F =192.10; p <0.001). In short, in the variable body muscle mass (%) of the groups, the time-dependent changes were significant in both groups, but the difference between the groups was not significant. **(C)** According to the variance analysis results of the BMI variable, the group-time interaction effect was not significant (F =0.917; p =0.435). Therefore, the time-dependent changes of BMI variables in the groups were similar. When the main effects were analyzed, the difference between the groups was not significant (F =0.468; p =0.498) and the time-dependent changes were significant (F =667.85; p <0.001). In short, while time-dependent changes were significant in both groups in the BMI variable of the groups, the difference between the groups was not significant.

the BSD + PS group was significantly higher than the BSD group on post-op day 7, 30 and 90 ($p < 0.05$). The mean protein intake of both groups decreased after surgery. The mean intake increased with time but remained below the targeted amount (Table 4).

3.7 Mean daily vitamin and mineral intake of individuals and percentage of DRI coverage

It was observed that the average daily dietary vitamin and mineral intake of the individuals decreased at the end of the 90th day post-op compared to the beginning. However, the average intake increased over time (Table 5). When the difference between the groups was examined, the average potassium mineral, riboflavin, folic acid, vitamin A and C intakes of the individuals in BSD + PS were significantly higher than those in BSD on the 90th day post-op ($p < 0.05$). The percentages of meeting the DRI according to the groups differed depending on time. The percentage of meeting the vitamins of the individuals in BSD + PS was found to be higher than those in BSD. However, it was observed that the vitamin and mineral intake rates of the individuals in both groups could not be met according to the DRI. When the difference between the groups was examined, the average A, C vitamin and calcium, potassium mineral intakes of the individuals in BSD + PS were significantly higher than those in BSD on the 90th day post-op ($p < 0.05$).

4 Discussion

Our study, which aimed to evaluate the success of protein supplements recommended in addition to postoperative nutrition education and their effect on muscle mass, was conducted with 60 individuals aged 19–60 years who underwent sleeve gastrectomy (SG) surgery and had similar characteristics. The groups were divided into two groups as protein supplement users (BSD + PS) and non-users (BSD). There was no significant difference between the groups in terms of muscle mass in the postoperative period. Although supplementation increased protein intake, we found that it caused compliance difficulties due to different reasons. In addition, we observed that not all individuals were able to complete the targeted daily intake. We determined that more comprehensive, strictly monitored and nutrition education prepared by expert dietitians is required before protein supplementation is considered.

High weight loss in postoperative processes may lead to undesirable loss of muscle mass (43). Since it has a great effect on the regulation of metabolic balance, preservation of skeletal muscle integrity and functional capacity according to age, precautions should be taken (21). Surgery can realize the expected weight loss with new arrangements in the anatomical structure (44). However, the intake, digestion and absorption of many nutrients, especially amino acids, change due to these new arrangements and cause nutritional deficiencies. One of the major reasons for this has been defined as a decrease in gastric volume and inadequate release of digestive enzymes, especially hydrochloric acid (15). It has also been observed that taste and odor sensitivity may develop in the postoperative period, especially in the first month (13).

In a study by Andreu et al. examining the effect of protein intake on muscle mass and blood parameters, it was found that supplement use

TABLE 4 Mean daily energy and macronutrient intake of individuals and percentage of DRI coverage.

		Pre-Op	Post Op Day 7	Post Op Day 30	Post Op Day 90
Energy (kcal)	BSD + PS ($n = 30$)	2555.7 ± 806.24	418.2 ± 273.39	439.8 ± 210.71	**549.5 ± 238.06**
	BSD ($n = 30$)	2457.8 ± 913.92	361.7 ± 208.80	384.9 ± 205.93	**392.3 ± 186.67**
Protein (g)	BSD + PS ($n = 30$)	72.8 ± 31.42	**25.7 ± 8.53**	**33.1 ± 11.95**	**39.5 ± 17.66**
	BSD ($n = 30$)	78.4 ± 34.04	**12.0 ± 12.36**	**16.2 ± 9.06**	**19.5 ± 10.12**
Protein (TE %)	BSD + PS ($n = 30$)	11.4 ± 9.00	**24.0 ± 11.44**	**33.5 ± 10.20**	25.9 ± 39.35
	BSD ($n = 30$)	11.9 ± 11.95	**12.5 ± 8.54**	**17.7 ± 5.87**	18.9 ± 1.76
Protein content per weight (g/kg)	BSD + PS ($n = 30$)	0.6 ± 0.70	**0.2 ± 0.11**	**0.3 ± 0.12**	**0.4 ± 0.21**
	BSD ($n = 30$)	0.6 ± 1.10	**0.1 ± 0.11**	**0.2 ± 0.13**	**0.2 ± 0.12**
Carbohydrate (g)	BSD + PS ($n = 30$)	268.6 ± 102.56	34.9 ± 154.50	20.2 ± 48.90	38.2 ± 20.32
	BSD ($n = 30$)	260.6 ± 105.74	40.0 ± 144.45	26.3 ± 102.75	28.5 ± 19.00
Carbohydrate (TE %)	BSD + PS ($n = 30$)	42.0 ± 8.87	**36.7 ± 14.65**	**20.8 ± 9.76**	**28.0 ± 7.65**
	BSD ($n = 30$)	43.2 ± 11.34	**55.7 ± 20.23**	**33.2 ± 15.65**	**32.8 ± 12.66**
Fat (g)	BSD + PS ($n = 30$)	122.7 ± 42.47	12.4 ± 19.05	23.6 ± 13.62	**26.5 ± 14.57**
	BSD ($n = 30$)	118.8 ± 52.39	10.7 ± 29.05	19.9 ± 10.09	**19.6 ± 11.49**
Fat (TE %)	BSD + PS ($n = 30$)	43.4 ± 8.03	30.9 ± 13.23	46.7 ± 13.89	40.8 ± 13.03
	BSD ($n = 30$)	43.0 ± 9.87	30.8 ± 15.32	47.9 ± 13.43	45.7 ± 15.05
Energy (DRI coverage)	BSD + PS ($n = 30$)	103.8 ± 32.1	17.5 ± 11.9	18.1 ± 9.2	**22.7 ± 10.3**
	BSD ($n = 30$)	102.1 ± 38.6	16.0 ± 39.3	16.0 ± 8.7	**17.1 ± 8.0**
Protein (DRI coverage)	BSD + PS ($n = 30$)	150.8 ± 61.5	**53.3 ± 19.0**	**63.5 ± 24.7**	**68.6 ± (30.4–182.6)***
	BSD ($n = 30$)	159.2 ± 65.0	**25.4 ± 27.0**	**33.6 ± 17.1**	**34.6 ± (9.1–103.8)***
Carbohydrate (DRIcoverage)	BSD + PS ($n = 30$)	206.6 ± 78.9	23.7 ± (6.6 + 117.3)*	15.5 ± (4.9 + 70.3)*	29.4 ± 15.6
	BSD ($n = 30$)	200.5 ± 81.3	30.8 ± (5.2 + 207.1)*	20.2 ± (2.9–155.2)*	21.9 ± 14.6
Fat (DRIcoverage)	BSD + PS ($n = 30$)	122.73 ± 42.47	13.93 ± 8.14	30.00 ± 11.03	26.45 ± 14.54
	BSD ($n = 30$)	118.76 ± 52.39	13.20 ± **11.80**	36.87 ± 17.56	19.56 ± 11.49

The "Independent Sample-*t*" test (*t*-Chart) is used to compare two independent groups with a normal distribution. *The "Mann–Whitney U" test (Z Chart value) for comparing two independent groups that do not have a normal distribution. Statistics were used. The *p* values considered statistically significant are indicated in bold ($p < 0.05$). BSD, Post-bariatric Surgery Diet Group; BSD + PS, Post-bariatric Surgery Diet Group + Protein Supplement Group; TE, Total Energy; g, Gram; kg, Kilogram.

despite recommendations was 63.4, 50.5, and 33.7% at 4th, 8th, and 12th months, respectively. In addition, 45, 35, and 37% of the targeted protein intake was <60 g/day at 4th, 8th, and 12th months, respectively. Male gender and weight loss were significantly associated with muscle mass independent of protein intake. It was emphasized that compliance with targeted protein supplements was poor (14). Another study supporting this situation was revealed in a study conducted by Bertoni et al. (45). Assessed protein intake in the first three months after sleeve gastrectomy (SG) in 47 patients with severe obesity. It found that protein intake from foods was insufficient, averaging 30.0 g/day in the first month and increasing to 34.9 g/day ($p = 0.003$) by the third month, both below the recommended 60 g/day. The use of protein supplementation significantly increased total protein intake to 42.3 g/day ($p < 0.001$) in the first month and 39.6 g/day ($p = 0.002$) in the third month, but compliance with supplementation was low, dropping from 63.8 to 21.3%. Overall, the study concluded that despite dietary guidance and supplementation, protein intake remained inadequate in the early post-operative period (45). In our study, there was a significant increase in the protein intake of both groups at the end of 3 months, but the recommended protein intake was not reached. Literature data support our study.

In a 2016 study by Schollenberger et al. (39) researchers examined the effect of 15 g/day protein supplementation in addition to standard nutritional therapy on body weight, fat mass loss, and muscle mass preservation after surgery. The results showed that protein intake amounts were significantly higher in the protein supplementation group compared to the control group ($p < 0.001$). At the 6-month follow-up, fat mass loss was found to be significantly greater in the protein supplementation group (79%) compared to the control group (73%) ($p = 0.02$). Additionally, muscle mass loss was less significant in the protein supplementation group (21%) compared to the control group (27%) ($p = 0.05$). However, when analyzing overall body weight loss, the results were similar between the protein supplementation group (25–7.2%) and the control group (20.9–3.9%) ($p > 0.05$).

In a study examining the effects of high protein (2 g/kg/day) and standard protein (1 g/kg/day) diets on anthropometric measurements after surgery, the high protein group showed a significant decrease in fat mass from the 3rd month ($p < 0.01$), while muscle mass and basal metabolic rate were preserved ($p < 0.01$). Another study also found that protein supplementation prevented muscle loss. In the group receiving 1.2 g/kg/day protein supplementation in the 1st month, muscle mass at the end of the 6th month was similar to the control group (46). In our study, we also found a significant decrease in muscle loss over time with protein supplementation, but no difference between the groups (Group: $F = 3.297$; $p = 0.075$, time: $F = 202.784$; $p < 0.001$, group*time; $F = 0.317$; $p = 0.743$).

TABLE 5 Mean daily vitamin and mineral intake of individuals.

Micronutrients		Pre-Op	Post Op Day 7	Post Op Day 30	Post Op Day 90
Thiamine vit. (B1) (mg)	BSD + PS ($n = 30$)	1.4 ± 0.81	0.2 ± (0.76–0.08)	0.2 ± 0.17	0.3 ± 0.16
	BSD ($n = 30$)	1.2 ± 0.63	0.1 ± (0.00–0.70)	0.2 ± 0.14	0.2 ± 0.11
Riboflavin vit. (B2) (mg)	BSD + PS ($n = 30$)	1.5 ± 0.48	0.4 ± (0.00–1.30)	0.5 ± 0.34	**0.6 ± 0.38***
	BSD ($n = 30$)	1.5 ± 0.55	0.4 ± (0.00–1.90)	0.4 ± 025	**0.5 ± 0.23***
Pantothenic acid vit. (B5) (mg)	BSD + PS ($n = 30$)	4.8 ± 1.67	1.0 ± 0.67	1.3 ± 0.77	1.3 ± 0.78
	BSD ($n = 30$)	4.5 ± 1.72	1.0 ± 0.64	1.1 ± 0.54	1.2 ± 0.64
Pyridoxine vit. (B6) (mg)	BSD + PS ($n = 30$)	1.4 ± 0.58	0.2 ± (0.00–1.10)	0.3 ± 0.18	0.3 ± (0.10–0.90)
	BSD ($n = 30$)	1.3 ± 0.57	0.2 ± (0.10–0.70)	0.2 ± 0.18	0.4 ± (0.00–1.40)
Biotin vit. (B7) (mcg)	BSD + PS ($n = 30$)	48.8 ± 24.72	10.3 ± 6.94	15.8 ± 9.68	14.8 ± 10.67
	BSD ($n = 30$)	49.4 ± 24.88	12.2 ± 7.92	12.3 ± 7.01	13.4 ± 8.48
Cobalamin vit. (B12) (mcg)	BSD + PS ($n = 30$)	4.4 ± 1.90	0.9 ± (0.00–2.60)	1.4 ± (0.00–4.00)	1.2 ± (0.20–8.90)
	BSD ($n = 30$)	4.4 ± 2.19	0.6 ± (0.00–4.30)	1.0 ± (0.00–9.40)	1.2 ± (0.10–8.80)
Total folic acid vit. (B9) (mcg)	BSD + PS ($n = 30$)	283.6 ± 110.09	32.9 ± (6.60–74.70)	57.2 ± (5.80–273.90)	**66.4 ± (24.70–259.30)***
	BSD ($n = 30$)	255.9 ± 110.92	26.6 ± (9.10–161.20)	54.3 ± (14.80–321.90)	**61.5 ± (9.60–188.60)***
Vit. C (mg)	BSD + PS ($n = 30$)	79.7 ± 52.35	14.2 ± (0.20–36.60)	21.9 ± (0.30–88.00)	**35.3 ± (1.40–134.30)***
	BSD ($n = 30$)	76.3 ± 56.24	13.5 ± (2.00–130.30)	15.3 ± (1.00–62.10)	**15.6 ± (0.00–113.30)***
Vit. A (mcg)	BSD + PS ($n = 30$)	1373.5 ± 638.62	195.8 ± (17.70–4219.00)	300.1 ± 159.05	**355.0 ± 197.79***
	BSD ($n = 30$)	1286.7 ± 667.24	106.3 ± (18.1–1208.90)	248.7 ± 144.02	**266.8 ± 133.13***
Vit. K (mcg)	BSD + PS ($n = 30$)	97.0 ± (24.5–959.1)	16.7 ± (2.40–123.20)	13.1 ± (0.00–213.10)	17.6 ± (0.30–238.80)
	BSD ($n = 30$)	75.4 ± (12.1–959.1)	12.0 ± (0.00–389.80)	13.6 ± (0.90–165.50)	14.5 ± (0.00–65.10)
Iron (mg)	BSD + PS ($n = 30$)	15.1 ± 7.90	1.2 ± (0.20–9.40)	1.9 ± (0.50–6.10)	2.9 ± 1.87
	BSD ($n = 30$)	14.5 ± 7.32	1.3 ± (0.20–5.60)	2.0 ± (0.60–8.90)	2.3 ± 1.54
Calcium (mg)	BSD + PS ($n = 30$)	736.9 ± 274.18	167 ± (13.9–869.5)	252.0 ± 222.32	227.8 ± (30.9–1193.7)
	BSD ($n = 30$)	688.1 ± 319.28	174.3 ± (21.00–1450.0)	136.5 ± 119.92	207.4 ± (26.90–420.40)
Zinc (mg)	BSD + PS ($n = 30$)	13.3 ± 5.42	1.3 ± (0.10–4.90)	2.8 ± 1.77	2.9 ± (0.40–15.60)
	BSD ($n = 30$)	13.3 ± 6.26	1.5 ± (0.20–12.80)	2.8 ± 1.96	2.9 ± (0.40–15.50)
Sodium (mg)	BSD + PS ($n = 30$)	4501.0 ± 1682.49	531.1 ± 26.58	591.9 ± 30.07	681.1 ± 30.93
	BSD ($n = 30$)	4353.7 ± 2196.61	297.8 ± 34.42	458.7 ± 27.65	628.4 ± 33.35
Potassium (mg)	BSD + PS ($n = 30$)	2544.2 ± 1095.72	450.5 ± (80.8–2087.0)	535.2 ± 374.60	**642.4 ± (198.9–2117.8)***
	BSD ($n = 30$)	2433.7 ± 1045.01	502.0 ± (24.20–2208.0)	419.9 ± 271.71	**589.1 ± (87.00–957.70)***

(Continued)

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TABLE 5 (Continued)

Micronutrients		Pre-Op	Post Op Day 7	Post Op Day 30	Post Op Day 90
Magnesium (mg)	BSD + PS ($n = 30$)	383.7 ± 212.79	51.5 ± 37.43	59.4 ± 45.8	73.0 ± 45.8
	BSD ($n = 30$)	358.6 ± 203.40	53.0 ± 43.12	55.6 ± 26.7	59.0 ± 32.9
Micronutrients Percentage of DRI coverage		*Pre-Op*	*Post Op Day 7*	*Post Op Day 30*	*Post Op Day 90*
Thiamine vit. (B1) (mg)	BSD + PS ($n = 30$)	122.4 ± 69.96	12.8 ± (0.00–45.45)	19.8 ± 14.72	23.4 ± 14.56
	BSD ($n = 30$)	105.6 ± 53.71	9.0 ± (0.00–63.64)	17.2 ± 12.19	19.3 ± 10.09
Riboflavin vit. (B2) (mg)	BSD + PS ($n = 30$)	128.5 ± 41.14	34.8 ± (0.00–118.18)	44.2 ± 30.68	**50.6 ± 33.70***
	BSD ($n = 30$)	129.2 ± 49.44	31.8 ± (0.00–172.73)	35.4 ± 21.89	**40.5 ± 20.01***
Pantothenic acid vit. (B5) (mg)	BSD + PS ($n = 30$)	4.8 ± 1.67	1.0 ± 0.67	1.3 ± 0.77	1.3 ± 0.78
	BSD ($n = 30$)	4.5 ± 1.72	1.0 ± 0.64	1.1 ± 0.54	1.2 ± 0.64
Pyridoxine vit. (B6) (mg)	BSD + PS ($n = 30$)	108.2 ± 44.88	15.3 ± (0.00 ± 84.62)	21.4 ± 13.80	23.0 ± (7.69–69.23)
	BSD ($n = 30$)	100.1 ± 44.07	15.3 ± (7.69 ± 53.85)	15.4 ± 13.89	26.3 ± (0.00–107.69)
Biotin vit. (B7) (mcg)	BSD + PS ($n = 30$)	162.7 ± 82.40	34.2 ± 23.12	52.5 ± 32.26	49.2 ± 35.58
	BSD ($n = 30$)	164.6 ± 82.93	40.6 ± 26.41	41.1 ± 23.35	44.3 ± 28.25
Cobalamin vit. (B12) (mcg)	BSD + PS ($n = 30$)	184.8 ± 79.03	37.5 ± (0.00–108.33)	56.2 ± (0.00–166.67)	50.0 ± (8.33–370.83)
	BSD ($n = 30$)	182.7 ± 91.36	25.0 ± (0.00–179.17)	41.0 ± (0.00–391.67)	50.6 ± (4.17–366.67)
Total folic acid vit. (B9) (mcg)	BSD + PS ($n = 30$)	70.8 ± 27.52	8.2 ± (1.65–18.68)	14.3 ± (1.45–68.48)	**16.5 ± (6.18–64.83)***
	BSD ($n = 30$)	63.9 ± 27.77	6.6 ± (2.28–40.30)	13.3 ± (3.70–80.48)	**15.5 ± (2.40–47.15)***
Vit. C (mg)	BSD + PS ($n = 30$)	100.1 ± 65.79	17.8 ± (0.27–48.80)	21.0 ± (0.33–117.33)	**46.6 ± (1.87–179.07)**
	BSD ($n = 30$)	99.2 ± 75.73	16.1 ± (2.22–173.73)	20.8 ± (1.33–82.80)	**18.0 ± (0.00–151.07)**
Vit. A (mcg)	BSD + PS ($n = 30$)	1373.5 ± 638.62	195.8 ± (17.70–4219.00)	300.1 ± 159.05	**355.0 ± 197.79***
	BSD ($n = 30$)	1286.7 ± 667.24	106.3 ± (18.1–1208.90)	248.7 ± 144.02	**266.8 ± 133.13***
Vit. K (mcg)	BSD + PS ($n = 30$)	99.5 ± (20.42–799.58)	17.2 ± (2.67–136.89)	12.2 ± (0.00–225.67)	19.2 ± (0.33–265.33)
	BSD ($n = 30$)	75.7 ± (13.44–1065.67)	12.3 ± (0.00–433.11)	13.8 ± (1.00–183.89)	13.5 ± (0.00–72.33)
Iron (mg)	BSD + PS ($n = 30$)	123.4 ± 87.07	10.0 ± (1.11–52.22)	17.3 ± 12.46	18.3 ± (6.67–85.00)
	BSD ($n = 30$)	109.7 ± 76.06	8.9 ± (1.11–31.11)	13.9 ± 15.61	18.9 ± (3.89–81.25)
Calcium (mg)	BSD + PS ($n = 30$)	72.9 ± 27.40	16.7 ± (1.39–86.95)	25.0 ± 22.27	**22.8 ± (3.09–119.37)***
	BSD ($n = 30$)	68.8 ± 32.01	17.4 ± (2.10–145.00)	13.7 ± 12.04	**20.0 ± (2.69–42.04)***
Zinc (mg)	BSD + PS ($n = 30$)	149.2 ± 56.4	14.3 ± (1.25–61.25)	32.2 ± 22.19	34.9 ± (5.00–182.50)
	BSD ($n = 30$)	153.7 ± 67.42	16.9 ± (2.50–160.00)	31.5 ± 21.91	33.6 ± (5.00–140.91)
Sodium (mg)	BSD + PS ($n = 30$)	300.1 ± 112.17	35.4 ± 26.58	39.4 ± 30.07	45.5 ± 27.65
	BSD ($n = 30$)	290.3 ± 146.44	19.9 ± 34.42	30.9 ± 30.93	41.6 ± 33.35

(Continued)

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TABLE 5 (Continued)

Micronutrients		Pre-Op	Post Op Day 7	Post Op Day 30	Post Op Day 90
Potassium (mg)	BSD + PS ($n = 30$)	90.1 ± 38.03	17.3 ± (2.57–80.27)	19.2 ± 13.82	**23.2 ± (7.52–81.45)***
	BSD ($n = 30$)	88.8 ± 38.72	19.3 ± (0.93–84.92)	14.3 ± 9.09	**21.05 ± (3.35–35.60)***
Magnesium (mg)	BSD + PS ($n = 30$)	110.5 ± 57.31	15.5 ± 11.96	17.5 ± 13.89	22.0 ± 15.13
	BSD ($n = 30$)	106.1 ± 54.42	16.2 ± 13.63	16.9 ± 7.99	18.8 ± 10.56

The "Independent Sample-*t*" test (*t*-Chart) is used to compare two independent groups with a normal distribution. *The "Mann–Whitney U" test (Z Chart value) for comparing two independent groups that do not have a normal distribution. Statistics were used. The *p* values considered statistically significant are indicated in bold ($p < 0.05$). BSD, Post-bariatric Surgery Diet Group; BSD + PS, Post-bariatric Surgery Diet Group + Protein Supplement Group; vit, Vitamin; mg, Milligram; mcg, Microgram.

Supplements may be considered to have an indirect effect by helping to support reaching the targeted intake, but the expected adequate protein intake (<60 g/day) could not be reached in nutritional therapy due to reasons such as the 3-month follow-up of the study due to pandemic conditions, the possibility of food intolerance in individuals, gastrointestinal complaints caused by some foods, shrinking stomach volume and changing hormonal systems.

In the study conducted by Dagan et al. (47) in 2016, when the average energy intake of all individuals followed up was examined, it was found to be 2117.6 ± 920.9 kcal in the preoperative period, 838.9 ± 348.5 kcal in the 3rd month, 1105.9 ± 453.7 kcal in the 6th month and 1296.5 ± 496.5 kcal in the 12th month. When the daily carbohydrate intake values were examined, it was found to be 222.2 ± 125.8 g in the preoperative period, 90.8 ± 47 g in the 3rd month, 121.1 ± 67.2 g in the 6th month and 142.3 ± 69.8 g in the 12th month. When the average daily fat intake was examined, it was found to be 90.4 ± 43.9 g in the preoperative period, 32.7 ± 16.9 g in the 3rd month, 43.9 ± 19.4 g in the 6th month and 52.4 ± 22.6 g in the 12th month. When the daily protein intake was examined, it was found to be 93.5 g in the preoperative period, 41.4 ± 18.5 g in the 3rd month, 51.7 ± 18.9 g in the 6th month and 58.1 ± 22.9 g in the 12th month.

In a study conducted by Giusti et al. (48) in 2015, the average daily energy intake of 16 women decreased from 2072 ± 108 kcal preoperatively to 681 ± 58 kcal in the 1st month, then gradually increased to 1.448 ± 57 kcal by the 36th month. Average daily protein intake declined from 87 ± 4 g preoperatively to 29 ± 2 g in the 1st month, later reaching 57 ± 3 g at 36 months. Carbohydrate intake dropped from 231 ± 11 g preoperatively to 76 ± 8 g in the 1st month, then increased to 144 ± 6 g by 36 months. Similarly, fat intake decreased from 89.7 ± 7 g preoperatively to 29 ± 3 g in the 1st month, before rising to 76 ± 5 g at 36 months. Overall, significant decreases in energy, protein, carbohydrate and fat intake were observed in the early postoperative period, with gradual increases over the long-term.

In the study conducted by Gobato et al.'s (49) in 2014, study found that pre-operative daily energy intake was 1812.2 ± 767.52 kcal, decreasing to 1610.3 ± 322.25 kcal by the 6th month. Daily protein intake also decreased from 96.2 ± 36.13 g pre-operatively to 47.1 ± 17.70 g at 6 months. The average daily energy intake was higher at 2555.7 ± 806.24 kcal in the BSD + PS group and 2457.8 ± 913.92 kcal in the BSD group, compared to other studies. Daily zinc intake decreased from 10.0 ± 4.01 mg pre-operatively to 6.9 ± 3.25 mg at 6 months. Intakes of vitamins and minerals like vitamin B12, iron, calcium, magnesium, and folic acid also decreased significantly from pre-operative to 6-month levels. In our study, it was determined that the iron, calcium, zinc, magnesium and potassium mineral intake averages were below the targeted values in all periods, and similarly, vitamins, especially vitamin A, vitamin C, thiamine and riboflavin, fell below the targeted values in the 1st and 3rd months after surgery.

The existing literature supports that protein intake is inadequate in the postoperative period and adherence to protein supplementation is low. The most important limitations of our study are the small sample size and the relatively short follow-up period. We focused our attention on the first period after surgery, when the protein intake issue is more important and weight loss is faster. In order to better evaluate the clinical impact of our results, they can be supported by further studies with longer follow-up and body composition data. However, our sample was mostly limited to female gender and adult patients, and the physical activity levels recorded in the first three

months after surgery were very low. In our study, we evaluated only patients treated with SG, and we can assume that postoperative protein intake may vary in different types of bariatric surgery.

5 Conclusion

In post-bariatric surgery patients, muscle mass preservation is highly related to protein intake. However, in our prospective study, the targeted daily minimum protein intake level could not be reached even with protein supplements. No effect of daily protein intake with protein supplements on the decrease in muscle mass loss or increase in fat mass loss was detected during the 3-month follow-up period. In addition, undesirable reasons such as the fact that protein supplements consumed by individuals may cause gastrointestinal complaints, the feeling of boredom caused by daily use of these flavors, and the inability to maintain consumption discipline made it difficult to comply with the targeted protein intake recommendations. For this reason, it was observed that the targeted daily intake amounts of other food groups could not be reached. In addition to the protein malnutrition experienced by post-bariatric surgery patients, vitamin and mineral losses were found to be significantly low. This study also raises awareness among existing healthcare providers who need to encourage adequate protein intake in post-bariatric surgery patients. It was concluded that new postoperative diet models that include more rigorous and intensive training programs that take into account all food groups, especially protein, are needed before considering supplements to minimize muscle mass losses. Studies investigating the quantity (g/day) and quality (whey, casein or soy) of protein supplements or high-protein diets in these models in larger study populations are needed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ankara Yildirim Beyazit University Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NA: Writing – review & editing, Writing – original draft. YO: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Methylphenidate can help reduce weight, appetite, and food intake—a narrative review of adults' anthropometric changes and feeding behaviors

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Introduction: Obesity constitutes a complex global health that carries several comorbidities that include cardiovascular disease, diabetes, and cancer. Current treatments, such as lifestyle modifications and bariatric surgery, are often difficult to implement or carry risks, creating a need for alternative approaches. Methylphenidate (MPH), a drug commonly used to treat Attention Deficit and Hyperactivity Disorder (ADHD), has shown potential in regulating dopamine levels to modulate appetite and feeding behaviors.

Methods: This narrative review evaluated the effect of MPH in reducing food intake, body weight, and anthropometric indicators in adults with obesity or overweight. Using the PICO method, 39 studies were selected, including 14 randomized controlled trials and 3 observational studies.

Results: MPH canblead to modest weight loss of 1–2% and significant appetite suppression, with stronger effects observed in women, who reported greater reductions in appetite and food cravings. Studies could remain underpowered to detect consistent effects in men.

Discussion: Even if these results suggest MPH could be an option for treating obesity, concerns regarding its safety profile and long-term efficacy persist. This review underscores the need for further investigation to confirm MPH's therapeutic potential, particularly through studies that address gender-specific responses and evaluate its sustainability as a weight management tool.

KEYWORDS

methylphenidate, obesity, feeding behaviors, appetite, weight

Introduction

Obesity has become a major pandemic of the 21st century (1, 2). Being overweight leads to being in a chronic state of inflammation, which increases the risk of many serious health problems, including heart disease, stroke, diabetes, and cancer (3, 4). Obesity also takes an economic toll, with billions spent each year on obesity-related medical costs (1). Despite this, obesity can be categorized as one of the most refractory conditions since lifestyle changes like diets and exercise are challenging to maintain long-term in the actual fast-paced world (5–7). Irreversible treatments such as bariatric surgeries are effective. Still, they carry risks and are only suitable for selected patients (8). There is an urgent need for additional interventions to aid individuals in achieving and maintaining a healthy body weight. Pharmacological

treatments targeting the biological mechanisms of obesity could serve as a critical enhancement to the existing therapeutic arsenal.

The Mesolimbic Dopaminergic Pathway, established in the ventral tegmental area (VTA), is a fundamental regulator of the brain's reward system, coordinating pleasure and reinforcement learning through various other neural pathways (9). Its primary neurotransmitter, dopamine, transmits signals associated with reward-related stimuli from the VTA to crucial brain regions such as the nucleus accumbens (NAc), amygdala, and prefrontal cortex (10). When individuals participate in pleasurable activities, for example, consuming food, dopamine is released in the NAc, triggering the feeling of satisfaction, reinforcing positive feedback for motivation, and a sense of reward. This process enhances motivation and facilitates learning by associating specific actions with positive outcomes, thus shaping future behaviors (11). In individuals with obesity, the mesolimbic dopaminergic system may be dysregulated. Naef et al. explained that these individuals showed reduced dopamine D2 receptor availability in the striatum, suggesting a hypodopaminergic state and resulting in overconsumption of food to compensate for reduced dopamine signaling (12). Drugs that modulate dopamine neurotransmission could help restore normal function in this system, consequently eating less and losing weight (13).

Methylphenidate (MPH) is a central nervous system stimulant that increases levels of dopamine and norepinephrine in the brain by inhibiting its reuptake in the presynaptic neuron. In so doing, MPH increases dopaminergic transmission in the mesolimbic (ML), mesocortical (MC), mesostriatal (MS), and infundibular (IN) pathways. Methylphenidate is metabolized in the liver and is readily eliminated through the kidneys (14) (Figure 1). MPH is primarily used to treat attention-deficit hyperactivity disorder (ADHD). Still, it has also been investigated for its potential weight loss effects by increasing dopaminergic activity in the ML, MC, and MS pathways and, ultimately, the reward system (15).

Lifestyle changes should remain the primary line of obesity treatment. However, medications could play a crucial role in aiding appetite control. Drugs that target the dopaminergic reward system could help people lose weight and maintain their long-term health (16). As mentioned before, MPH is one potential candidate; nevertheless, more research must be done to be approved by the FDA (17, 18). Other drugs that modulate dopamine, such as antidepressants and anxiolytics, are also being investigated (16). Ultimately, lifestyle changes, behavioral therapy, and pharmacotherapy may be the most effective approach to the obesity pandemic (19). Medications could be an essential tool to help people lose weight and improve their

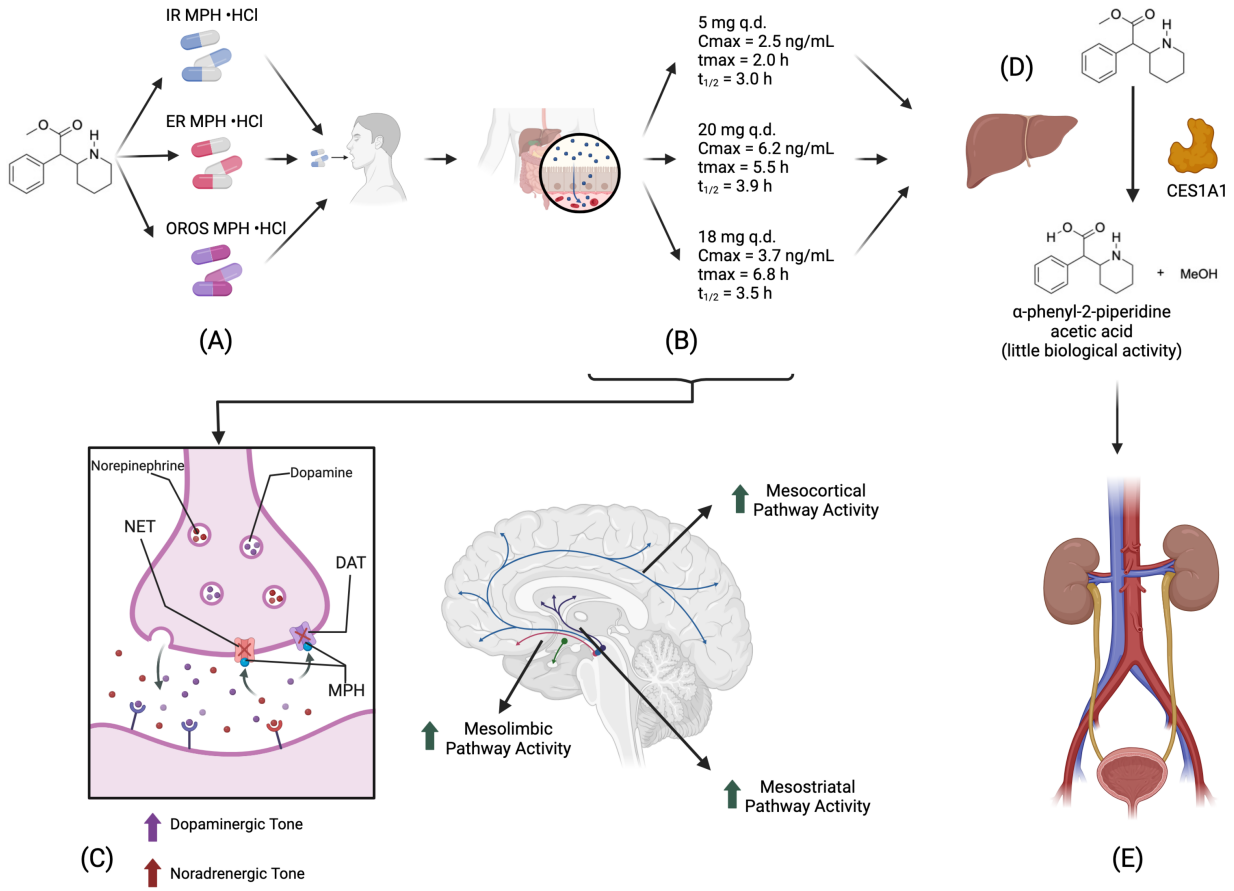

FIGURE 1
Pharmacokinetics and pharmacodynamics of MPH. **(A)** MPH exists in immediate (IR), extended-release (ER), and osmotic release oral systems (OROS). **(B)** MPH is readily dissolved in water. It is not absorbed in the stomach but absorbed in the intestine. IR requires to be given tid to have pharmacokinetics similar to ER and OROS. **(C)** Once distributed, MPH can cross the blood–brain barrier (BBB). It inhibits Dopamine (DAT) and Norepinephrine (NET) transporters, thus increasing the activity of noradrenergic and dopaminergic pathways. **(D)** MPH is metabolized into α-phenyl-2-piperidine acetic acid by Carboxylesterase-1 (CES1A1). This metabolite has deficient biological activity and has renal elimination (12).

health (20). With further research and development, we may see more anti-obesity drugs approved in the coming years. The main objective of this narrative review is to examine the current literature on the effects of methylphenidate (MPH) on appetite suppression and weight regulation in adults with obesity or overweight.

Methods

To perform this review, a Participant-Intervention-Comparison-Outcome (PICO) approach was followed to answer our research question. A methodological roadmap is shown in Figure 2. We present a decision tree in Figure 3 to show how the search queries were built. Six different search queries (Figure 3) were used in 4 databases: PubMed, Scopus, Web of Science, and EBSCO. These databases were chosen because of the scope and breadth of journals they cover. We included only articles published in English after 2010 to cover all the relevant publications in the last 10 years. Studies had to be experimental and observational studies in human adults that reported objective anthropometric, appetite, or dietetic indicators or that reported weight loss as a side effect of MPH. MPH dosage had to be disclosed. Reviews, meta-analyses, conference papers, animal models, *in-vitro* studies, studies in children, articles published before 2010, articles without relevant outcomes, with patients receiving a mix of medications, or where participants had any condition that could produce weight loss were excluded.

A total of 39 articles were selected (Figure 4). Articles could be grouped into two categories: category 1 had articles that addressed our research question directly, and category 2 had articles that reported weight loss, appetite changes, and other side effects related to nutrition status because of MPH when used for other purposes. Out of the 39 articles, 17 met the inclusion and exclusion criteria to different extents. Of the 39 selected articles, 33 (85%) were experimental or observational, 34 (90%) were carried out on human adults, all of them were published after 2010, 26 (67%) had a relevant anthropometric or appetite outcome, 32 (82%) had a methylphenidate dose declared, all of them were in English or Spanish (100%), 3 (8%) used different medications. In none of the articles did participants have other weight loss predisposing conditions. The most common reason for rejecting an article was that articles did not declare anthropometric or appetite outcomes. The studies varied in design and size, but the majority (83.3%) were randomized controlled trials (RCTs). The remaining articles were all cohort studies. Seven studies (41.2%) were grouped in category 1, while the remaining 10 (58.8%) could be grouped in category 2.

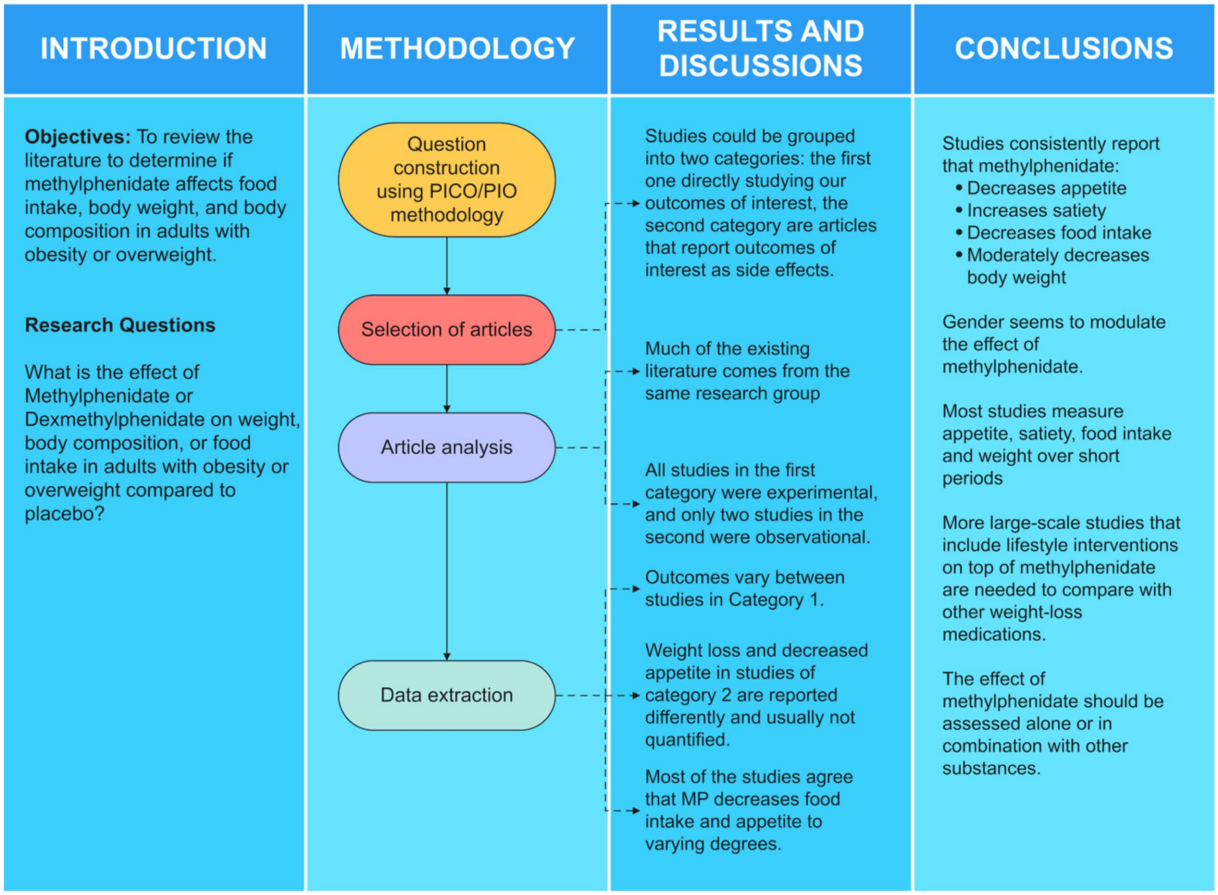

FIGURE 2
Methodology roadmap—this study followed the steps above to answer our research question. The results can be analyzed at different descriptive levels: the type of articles found, including their design, and the actual data in the literature.

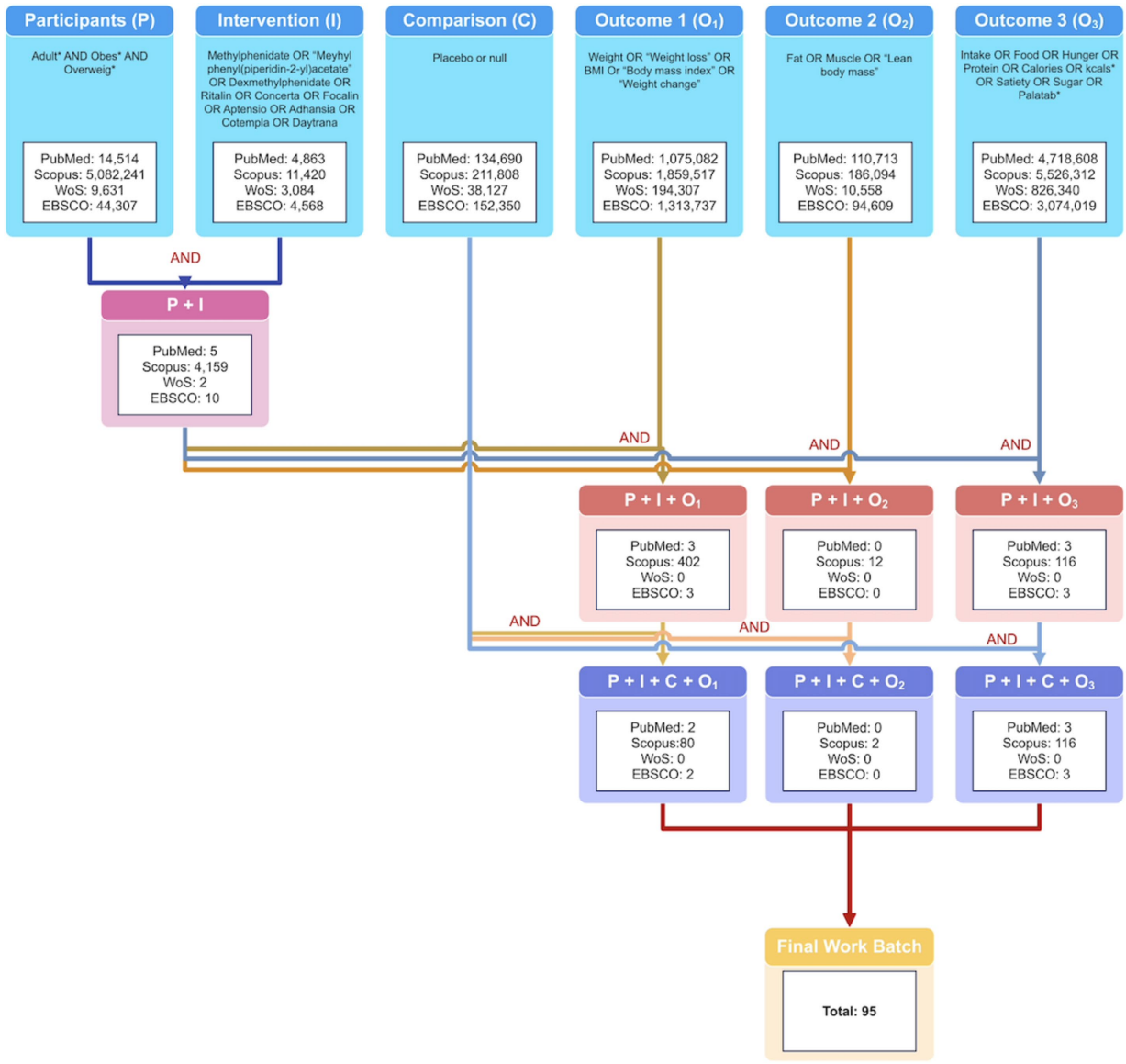

FIGURE 3
PICO/PIO methodology decision tree—several search queries were built using Boolean operators to reach a final work batch of 95 further screened articles.

Results

Effects of MPH on body weight, eating behaviors, and appetite

The present review looked at studies assessing the effects of methylphenidate (MPH) on various anthropometric and behavioral outcomes related to weight management, including body weight, eating behaviors, and appetite in adults. Only half (n = 741.2%) of the selected studies belonged to category 1 (18, 21–26). Weight and Body Mass Index (BMI) and waist circumference were the only studied anthropometric outcomes. Weight was an outcome in 4 studies (57.1%) (18, 24, 26), BMI was an outcome in 2 studies (28.6%) (24, 25), and waist circumference was an outcome in only one study (14.3%) (24). Only two studies (28.6%) found that MPH had a significant effect on anthropometric indicators: Heffner et al. (26) found a 1.6% weight decrease in participants who were trying to quit smoking and took MPH versus a 1.3% weight increase in participants who were trying to quit smoking in the placebo group ($p < 0.001$); on the other hand, Quilty et al. (25) showed that when compared to cognitive behavioral therapy (CBT), treatment with MPH produced a more considerable decrease in BMI ($p = 0.01$) (Table 1).

All the articles measured at least one appetite/dietetic indicator as an outcome. Three crossover randomized studies evaluated the effect of MPH on food consumption, food cravings, and appetite variables and how this effect interacts with BMI (21), food addiction (23), and binge eating disorder (BED) (22). People with a normal BMI had a significant consumption reduction in snack consumption ($p = 0.017$), appetite ratings ($p = 0.017$), and food cravings

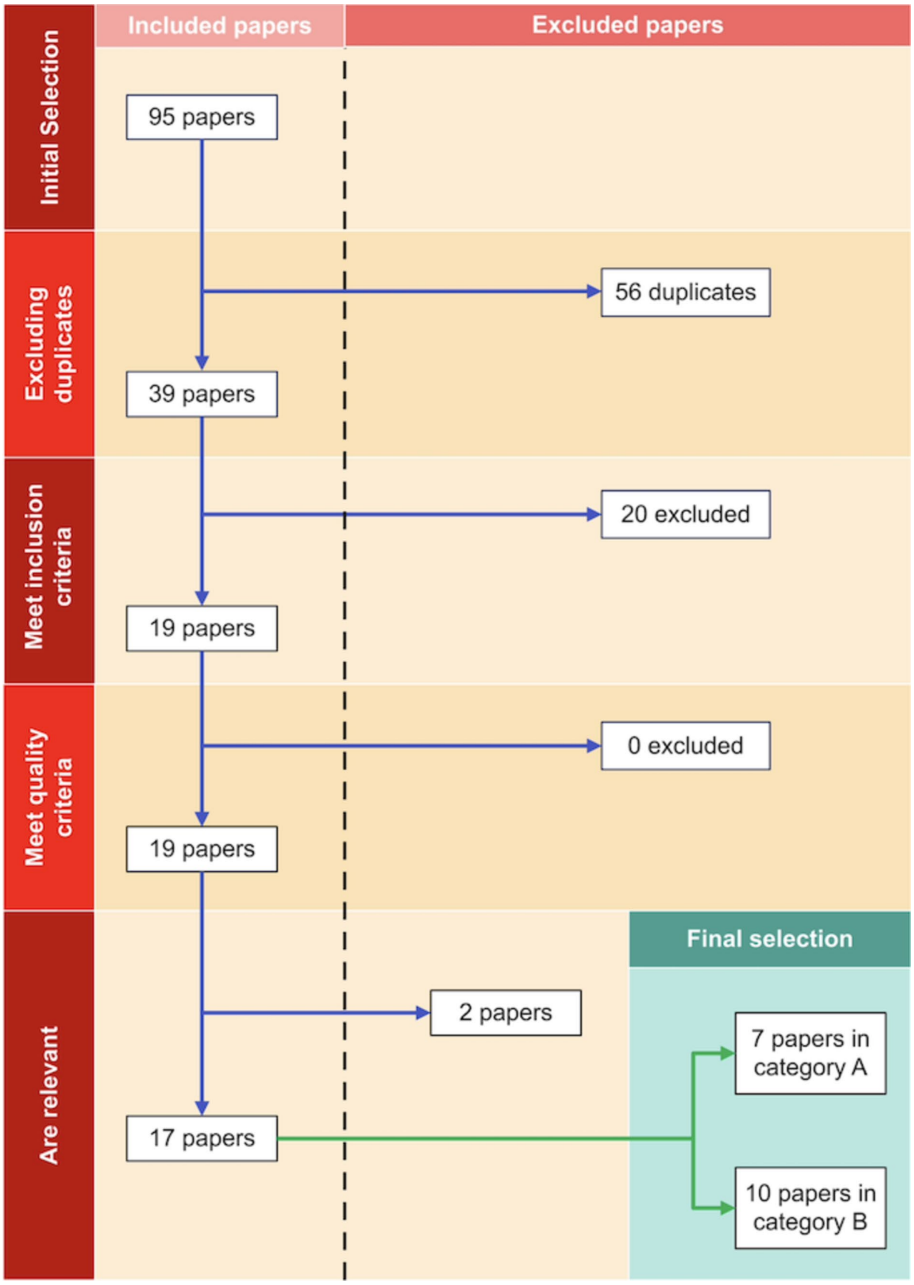

FIGURE 4
PRISMA flowchart depicting the process of article selection.

($p < 0.0001$) when receiving MPH compared to placebo. In contrast, in people living with obesity, there was only a snack consumption reduction ($p < 0.0001$), appetite ratings ($p < 0.007$), and food cravings ($p = 0.008$) in women when receiving MPH but not in men (21). Participants with food addiction had higher baseline food cravings and appetite than participants without good addiction ($p < 0.0001$ for both). Regardless of food addiction status, all participants showed a significant decrease in appetite ratings ($\eta^2 = 0.157$, $p = 0.031$) y and food cravings ($\eta^2 = 0.128$, $p = 0.006$) when given MPH compared to placebo. There was only a significant interaction between food addiction and MPH for snack consumption, where participants without food addiction reduced their intake when receiving MPH ($\eta^2 = 0.276$, $p < 0.0001$) (23). In Davis et al. (22), there was a significant decrease in appetite ratings ($p = 0.002$), food cravings ($p = 0.023$), and snack consumption ($p = 0.002$) when participants took MPH, regardless of whether they had BED or not. There was no effect of BED on any of the variables studied. In contrast, Quilty et al. (25) found that the frequency of binging episodes decreased when taking MPH in comparison with CBT ($F = 11.9$, $p < 0.001$) and that this effect had a significant interaction with time ($F = 2.10$ $p < 0.02$).

Other studies replicate similar results. El Amine et al. (18) found that desire to eat ($p = 0.001$), hunger ($p = 0.001$), and prospective food consumption ($p = 0.003$) decreased, and satiety increased ($p = 0.028$) in people with obesity receiving MPH when compared to placebo. Moreover, another study reported a gender x MPH interaction for

TABLE 1 Summary of articles that looked at dietetic or anthropometric as a function of MPH use.

Article	Country	Design	Objective	Sample characteristics	Intervention	Relevant outcomes	Main findings	Methodological remarks
Davis et al. (21)	Canada	Cross-over Randomized Controlled Trial	To assess the effect of BMI and gender on food consumption, food cravings and appetite after administering Methylphenidate (MPH)	n = 132 Adults between 24–45 years old. 73.5% female No history of DSM IV Axis I disorders (except unipolar depression). No history of serious medical illness. Not taking medications contraindicated against methylphenidate. 44% of the sample had BMI < 25. 56% had BMI >30. 19% smoked tobacco.	Patients were given short-acting 0.5 mg/kg of MPH as intervention. After 1 h, they were presented with their favorite snack in two occasions (one placebo, one MPH).	Appetite Rating: validated own instrument with 3 questions. Food Cravings: General Food cravings questionnaire %Snack Food Consumption: In-lab feeding test.	Snack consumption was equivalent among both genders, BMI categories, and their interactions. Normal weight individuals significantly decreased their appetite rating (p = 0.017), food cravings (p < 0.0001), and snack consumption (p < 0.017) regardless of gender. In individuals with obesity, there was a significant gender x day in appetite ratings (p < 0.007), food cravings (p = 0.008), and snack consumption (p < 0.0001). No changes in appetite ratings, food cravings, or snack consumption were seen in males, but they were seen in females (p < 0.0001 for all).	While the study has a large sample size. Most participants were females, so the male group may be underpowered to find statistical significance.
Davis et al. (23)	Canada	Cross-over Randomized Controlled Trial	To assess whether food addiction status and gender modulate food consumption, food cravings and appetite after administering MPH	n = 136 Adults between 25 and 50 years old. Predominantly overweight or with obesity. 67.7% female 17% met criteria of food addiction according to YFAS. Mean BMI of food addiction group did not differ from that of the rest of the group. No history of serious medical illness, psychotic disorders, or substance abuse disorders. Not taking medications contraindicated against methylphenidate. 26 and 20% of the participants with food addiction and the general group smoked tobacco, respectively.	Patients were given short-acting 0.5 mg/kg of MPH as intervention. After 1 h, they were presented with their favorite snack in two occasions (one placebo, one MPH)	Appetite Rating: validated own instrument with 3 questions. Food Cravings: General Food cravings questionnaire %Snack Food Consumption: In-lab feeding test. Food addiction: YFAS questionnaire.	Participants in the food addiction group had higher baseline food craving scores and appetite ratings (p < 0.0001 for both). There was a decrease in appetite ratings and craving scores between placebo day and MPH Day (η^2 = 0.157, p = 0.031) and (η^2 = 0.128, p = 0.006 respectively). The interaction between placebo/MPH and food addiction was not statistically significant. The interaction between placebo/MPH and food addiction was significant for food consumption (p = 0.018). The food addiction group did not decrease their food consumption, but the general group did (η^2 = 0.276 p < 0.0001). Women also tended to consume less of their snack than men (η^2 = 0.039, p = 0.022).	It is possible that the food addiction group was underpowered to produce significant differences in variables, so results must be interpreted with caution, even if the study itself has a large sample size.

(Continued)

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TABLE 1 (Continued)

Article	Country	Design	Objective	Sample characteristics	Intervention	Relevant outcomes	Main findings	Methodological remarks
Davis et al. (22)	Canada	Cross-over Randomized Controlled Trial	To assess whether having binge eating disorder (BED) modulates food consumption, appetite, and food cravings after administering MPH	n = 198 Adults between 24 and 50 years old. All of them with overweight or obesity. 76.8% female 96 participants had binge eating disorder (76 females). No history of serious medical illness, psychotic disorders, or substance abuse disorders. Not taking medications contraindicated against methylphenidate (MPH).	Patients were given short-acting 0.5 mg/kg of MPH as intervention. After 1 h, they were presented with their favorite snack in two occasions (one placebo, one MPH).	Appetite Rating: validated own instrument with 3 questions. Food Cravings: General Food cravings questionnaire %Snack Food Consumption: In-lab feeding test.	Self-reported appetite (p = 0.002), food cravings (p = 0.023), and snack consumption (p = 0.002) decreased significantly between placebo day and MPH Day. There was also a significant day x sex interaction (p = 0.007, p = 0.048, and p = 0.032 respectively), showing only a decrease in female participants (p < 0.0001 in all cases). BED status did not modulate the response.	While the study has a large sample size, most participants were females, so lack of significance in the male population should be taken with caution due to possible underpowering.
El Amine et al. (18)	Canada	Randomized Controlled pilot Trial	To determine the effect of short-acting MPH at 0.5 mg/kg during 2 months on appetite sensations, olfactory threshold, energy intake, and body weight in individuals with obesity	n = 12, randomized into a placebo group with n = 7 (3 males and 4 females), and an MPH group with n = 5 (2 males and 3 females). Adults between 18 and 40 years old with BMI > 30 kg/m^2 but body weight below 200 kg so as not to surpass the maximal dose of MPH (100 mg/d). All had a stable weight for the past 6 months. None of them smoked, had ADHD, used MPH, had history of mental health or substance abuse disorders, took any medication that could affect appetite, had any major health problem, or reported any food allergy	Patients received short-acting 0.5 mg/kg of MPH or placebo divided twice daily 1 h after lunch and dinner. One initial appointment and two measuring appointments were scheduled monthly.	Appetite: Visual Analog scale (desire to eat, hunger, prospective food consumption, and fullness). Olfaction: Sniffin' sticks®. Bodyweight Height Body composition: DXA. Energy intake: In-lab feeding test.	For olfaction, there is a significant interaction in group x time (p = 0.029), where participants receiving MPH increased their olfaction threshold (M = −3.8, p = 0.017). There was a significant decrease in the areas under the curve for desire to eat (p = 0.001), hunger (p = 0.008), and prospective food consumption (p = 0.003); and an increase in fullness (p = 0.028) in the MPH group when compared to placebo. Changes in olfaction and appetite variables were not correlated with anthropometric variables.	Sample size is small and thus not generalizable; however, these results look promising for a larger scale study.

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TABLE 1 (Continued)

Article	Country	Design	Objective	Sample characteristics	Intervention	Relevant outcomes	Main findings	Methodological remarks
Goldfield et al. (24)	Canada	Cross-over Randomized Controlled Pilot Trial	To estimate if there is gender modulates the effect of short-acting 0.5 mg/kg MPH on energy intake, macronutrient consumption, food preferences, appetite sensations and relative reinforcing value of food.	n = 120 Adults between 18 and 40 years old with BMI larger or equal than 20 kg/m^2 but body weight less than 120 kg to not surpass maximal dose of MPH. 50% female All non-smokers and non-tobacco users.	Patients received short-acting 0.5 mg/kg MPH at sessions. One initial appointment, and two subsequent monthly (for females) or weekly (for males) appointments for measurements. Participants had to eat from a standardized mixed meal buffet 1 h after taking the pill.	Appetite variables: Visual analog scale (desire to eat, hunger, prospective food consumption, and fullness) Buffet Energy and micronutrient Intake Weight Height Waist Circumference BMI Red button pressing for relative reinforcing value of food.	Significant gender x drug interaction for energy intake (F = 4.9, p = 0.01) and carbohydrate intake (F = 8.2, p = 0.02) with a greater reduction in men than in women relative to placebo. No significant gender x drug interaction for macronutrient preferences. No drug x gender interaction for food hedonic ratings, relative reinforcing value of food, and water intake in the buffet test. No drug x gender interaction for satiety quotients of appetite sensations. Hunger ratings between MPH and placebo groups were not statistically different before or after drug administration.	This trial has a large sample size with equal gender representation.
Heffner, 2013 (26)	USA	Randomized Controlled Trial	To study the effect of Osmotic Release Oral System (OROS)-MPH on weight gain of quitting smokers with ADHD.	n = 215 Adults 18–55 years old. Smoking at least 10 cigarettes/day, expired CO level ≥ 8 ppm, DSM-IV ADHD Rating Scale score > 22. In good physical and mental health; no narrow angle glaucoma, tics, seizure disorder, Tourette syndrome. Non-nicotine substance abuse, mood/anxiety disorders, antisocial personality disorder, psychosis. Without recent treatment for smoking or ADHD	OROS-MPH was titrated to a dose of 72 mg/day over the first 2 weeks and continued at the maximum tolerated dose until the end of the 11-week treatment period. Participants had 11 appointments once every week. In each visit, participants received counseling and a nicotine patch. Weight assessments were conducted at baseline, week 6, and week 11.	ADHD diagnosis or severity: Adult ADHD Clinical Diagnostic Scale and the DSM-IV ADHD Rating Scale. Nicotine dependence: Measured by the Fagerström Test for Nicotine Dependence (FTND). Smoking abstinence: self-report confirmed with CO measurement of <8 ppm. Nicotine withdrawal: Withdrawal Scale for Tobacco (WST), Weight	Participants in the OROS-MPH group lost an average of 1.6% of their body weight, while those in the placebo group gained an average of 1.3%. Difference was statistically significant (p < 0.001). No significant drug x gender interactions percent weight change. The group receiving OROS-MPH had a lower severity of hunger (M = 1.1) compared to the placebo group (M = 1.6). Difference was statistically significant (p < 0.001).	The study did not do an intention-to-treat analysis along with the completing sample analysis. The use of the nicotine patch may introduce some further bias to the study.

(Continued)

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TABLE 1 (Continued)

Article	Country	Design	Objective	Sample characteristics	Intervention	Relevant outcomes	Main findings	Methodological remarks
Quilty, 2019 (25)	Canada	Randomized Controlled Trial	To compare the effect of methylphenidate versus cognitive behavioral therapy (CBT) on reducing binge eating episodes in women with BED, as well as the modulating effect of impulsivity	$n = 49$ randomized into CBT group ($n = 27$) and MPH group ($n = 22$). Adult women 19–51 years old. All with BED. BMI larger or equal than 25 kg/m^2. One third either a mood or an anxiety disorder. None were currently pregnant or breastfeeding, had undergone recent psychotherapy or behavioral treatment for eating/weight, had taken psychotropic medication recently, had severe mental disorders or uncontrolled medical conditions, taking medications affecting weight or contraindicated for methylphenidate.	Patients on the MPH group had weekly appointments for the first 4 weeks, then twice a week for8 weeks. MPH doses were increased from 18 mg/day to 72 mg/day by week 4, and adjusted for side effects, with discharge to a family physician after 12 weeks. Patients on the CBT group had a weekly for 12 weeks lasting 50 min each. Sessions focused on eliminating binge episodes, reducing intake, restructuring cognitions, and preventing relapse.	Binge Eating Behaviors: Frequency of objective binge episodes per week, assessed by a daily binge diary. Quality of Life: QoL inventory Impulsivity: Impulsive Behavior Scale (UPPS-P) BMI	There was a significant decrease in binge episodes in both treatment groups ($F = 11.9$, $p < 0.001$). BMI over time significantly decreased in both treatment groups ($F = 4.4$, $p < 0.001$), but there was a significant difference in BMI between treatment groups at Week 12 with a larger weight loss in the MPH group ($t = 2.73$, $p = 0.01$). There was a significant time × perseverance interaction that modulated objective binge episodes ($F = 2.10$, $p < 0.02$); and a significant time × negative urgency interaction modulating subjective binge episodes ($F = 1.79$, $p = 0.049$).	The sample size is good and supposedly well powered, but subgroup analyses that are non-significant must be analyzed with caution. The sample does not represent males.

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energy ($F = 4.9$, $p = 0.01$) and carbohydrate ($F = 8.2$, p = 0.02) intake, where males had more considerable reductions than females (24).

In nine out of 10 articles in Category 2 (27–35), weight changes were studied as a side effect. Weight loss is reported in eight articles studying weight loss, while the remaining article reports no changes in weight (27–29, 31–35). In only one article, weight loss was measured and reported in kilograms (35). In this study, the mean weight loss in the MPH group was 0.8 kg versus no weight loss in the placebo group ($p < 0.05$). One study measured the proportion of participants with a weight loss larger than 10% of their baseline body weight (27). The remaining seven articles reported the proportion of participants with any weight loss (28–34). The number of participants who lost weight followed a dose–response pattern. In RCTs, at doses of 54 mg, 0.0–10.1% reported any weight loss, and at doses of 72 mg, the interval of participants losing weight was between 0.0 and 23% (28–32). Adler et al. (27) showed that the number of participants losing over 10% of their initial body weight was 11.1% at any MPH dose (Table 2).

Regarding other relevant effects, nausea was reported in 7 studies (27, 29, 31–34). Adler et al. (27) reported nausea in 11.1% of the patients at any dose with no dose–response effect. Casas et al. (29) also found no dose–response effect with nausea in 17.4–18.0% of the participants. In cohort studies (33, 34, 36), the rate of nausea was between 0.43–6.5% (Table 2). Three studies reported decreased appetite as a side effect (29, 32, 36). Two were RCTs (29, 32), and one was a cohort study (36). Casas et al. (29) found a dose–response trend in reduced appetite. In this study, the prevalence of decreased appetite was 19.1% at 54 mg MPH and 28.3% at 72 mg MPH. Kis et al. (32) found a prevalence of decreased appetite at 54 mg MPH of 22.4%. The prevalence of decreased appetite in the cohort study was 28% (36). Anorexia was reported in only one article (31). The prevalence of anorexia in this study was 7.5% at a dose of 54 mg (Table 2).

Some of the reviewed studies found slight differences in this response between genders. Women showed more significant reductions in appetite, food cravings, and food consumption in response to MPH than men. This effect is consistent regardless of the presence of BED (22) and food cravings (21, 23). The differential expression of dopamine receptors in distinct brain areas can explain these sex-specific susceptibilities. Women tend to have more D2Rs in the frontal cortex and striatum than men, making them more sensitive to dopamine's effect on eating behaviors and, therefore, more prone to reduce their food intake due to MPH.

Conversely, males have more dopamine-1 receptors (D1R) in reward-processing areas such as the NAc (37) and probably overeat. Moreover, when depressed, women tend to show more dopamine transporter (DAT) binding, probably making it more susceptible to being inhibited by MPH (37). It is essential to mention that males seem underrepresented in most articles that reach these conclusions. For this reason, more studies in males with well-powered sample sizes are required.

The mechanism of action of MPH and its effect on eating behaviors and body weight

Research has shown that food intake regulation comprises two mechanisms—a homeostatic hunger-satiety mechanism to regulate energy balance controlled in the hypothalamus and a mechanism that is not driven by energy needs (sometimes called hedonic) that includes hypothalamic control but is mainly regulated in the neocortex and limbic system (38). In addition, a decrease in Dopamine 2 receptors (D2R) expression in the dorsal striatum and NAc has been associated with compulsive food intake in animal models and humans (38, 39).

In addition, the VTA in the midbrain projects neurons to the NAc, forming a complex network that will regulate food's motivational saliency. Food cues are categorized and prioritized as pleasurable and compelling in these brain areas. According to Nicola (38), food's rewarding effect can be classified into three different components: the motivational component (wanting), the hedonic component (liking), and the learning component (reinforcement). The motivational component of eating has been related to the dopaminergic pathways, while there is evidence that the hedonic component has an opioergic regulation (38, 40).

The brain's dopaminergic systems and conditioned learning drive food-seeking behaviors in humans. This means that even without hunger, different stimuli (i.e., smells, memories, or the sight of food) can motivate an individual to look for food, even when it implies a significant effort. In addition, dopaminergic neurons in these circuits appear to be regulated by hormones that regulate energy balance (homeostatic mechanisms). Neuropeptide Y (NPY), ghrelin, orexins, and agouti-related peptide (AgRP) have been seen to increase dopamine release, while glucagon-like peptide 1 (GLP-1), insulin, and leptin decrease it (38, 40).

In rodents, Sucrose has been shown to stimulate dopamine transmission in the ventral striatum and olfactory bulb—cues paired with sucrose stimuli condition dopamine release in these brain regions. The effects of sucrose in the dopaminergic pathways have been compared to the effects of several drugs on the same areas. The effects appear to differ in the higher speed at which dopamine activity subsides after sucrose is used (39).

Pleasurable stimuli activate the opioid system. Consuming palatable and calorie-dense foods stimulates μ-opioid receptors in the NAc. Activating the opioid system increases the motivational salience of food through a Pavlovian conditioning mechanism. Cues that remind the individual of a pleasurable eating experience can further reinforce dopamine release (38, 40). Figure 5 depicts the mechanisms mentioned above.

Disrupted dopaminergic signaling, including decreased D2R expression in areas of the reward network such as the dorsal striatum, the VTA, and the NAc, translates into reduced activity in the orbitofrontal cortex and the cingulate gyrus. Since these systems regulate compulsive eating (39), their dysregulation can lead to overeating highly palatable foods (39, 40). Given that MPH inhibits dopamine reuptake, it follows that enhancing dopamine's action in these areas could modulate compulsive eating behaviors. Notably, MPH has been shown to decrease the intake of dietary fats and carbohydrates, suggesting a shift in macronutrient preference toward lower-fat options (24). This effect could help people struggling to lose weight to improve their food choices and modify their food composition. While this review focuses on the effects of MPH in adults, literature has also found similar effects on teenagers (41).

As previously mentioned, MPH inhibits dopamine and norepinephrine synaptic reuptake and is available in various pharmaceutical presentations (Figure 1). The literature shows that

TABLE 2 Effect of MPH on weight, and hunger studied as a side effect.

Article	Country	Design	Objective	Sample characteristics	Intervention	Relevant side effects reported
Adler et al. (27)	USA	Open label Randomized Controlled Trial	To assess the safety of OROS-MPH in the long-term treatment of ADHD in adults.	*n* = 540 Adults between 18–65 years old with ADHD. 48% females	MPH dose was titrated starting at 36 mg/d and escalated up to 108 mg depending on safety. There were two groups: one received the drug for 6 months, and the other for 12 months.	**Weight changes.** Proportion of participants exhibiting more than 10% weight loss increased in a dose–response pattern (1.3% of participants at 36 mg, and 18.1% at 108 mg. 11.1% at any dose). Only 0.9% of the sample gained more than 10% of their initial weight at any dose. This variable did not exhibit a dose–response pattern. **Nausea.** 11.1% of the sample presented with nausea at any dose. This variable did not exhibit a dose–response pattern.
Bron et al. (28)	The Netherlands	Cross-over Randomized Controlled Trial	To evaluate the effect of OROS-MPH in adult executive functions.	*n* = 22 (12 allocated to MPH first and 10 to placebo first). Mean age 30.5 with SD 7.4 years. All adults with ADHD. 22.7% females	For 6 weeks, participants received a titrated MPH dose starting at 36 mg/d for 7 days. 36 mg weekly increments were done until reaching 72 mg for 3 weeks.	A non-quantified weight loss rate of 23% was reported in this study.
Casas et al. (29)	42 European locations (Managed in Germany and Spain)	Randomized Controlled Trial (Phase III)	To determine the efficacy and safety of two doses (54 and 72 mg/d) of OROS-MPH in adults with ADHD.	*n* = 279, (90 in MPH 54 mg, 92 in 72 mg and 97 in placebo)- Adults 18–56 years old with ADHD 45.7–51.1% females	Dose was titrated to 54 or 72 mg according to group starting in 36 mg/d. There was also a placebo group. Dose was increased 7 days after initiation to the required dose. Trial lasted 13-week	**Weight changes.** Dose – response weight-loss was observed (4.1% of participants in placebo group, 10.1% in 54 mg group, and 18.5% in 72 mg group). It was not quantified. **Anorexia**. Dose—response self-reported anorexia was observed (4.1% in placebo, 6.7% in 54 mg group, and 13.0% in the 72 mg group). **Nausea.** Nausea was seen in 8.2% in placebo, 18.0% in the 54 mg group, and 17.4% in the 72 mg group. **Appetite.** Dose – response trend in decreased appetite (5.2% in placebo, 19.1% in the 54 mg group, and 28.3% in the 72 mg group).
Edvinsson and Ekselius (36)	Sweden	Cohort Study	To determine the safety profile of MPH in adults with ADHD over a long period of time.	*n* = 112. 51% of them in treatment. Mean age was 35 years old at the beginning and 42 years old at the end of the study. 46 were taking MPH, 3 were taking MPH and Atomoxetine, and 8 were taking dexamphetamine. 37% females	No actual intervention. Participants with ADHD were followed for 6 years.	**Appetite** In the group taking MPH (n = 46) 28% of the participants reported decreased appetite **Nausea/Vomiting** In the group taking MPH (n = 46), 6.5% reported nausea or vomiting.

(Continued)

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TABLE 2 (Continued)

Article	Country	Design	Objective	Sample characteristics	Intervention	Relevant side effects reported
Ginsberg et al. (30)	Sweden	Randomized Controlled Trial	To assess the long-term effectiveness and persistence of OROS-MPH related side effects on cognition, motor activity, institutional behavior and quality of life of male adult prison inmates with ADHD.	$n = 30$ ($n = 15$ for placebo and $n = 15$ for MPH group) Adult males between 21 and 61 years old. High prevalence of comorbidity such as substance abuse, antisocial personality disorder, mood and anxiety disorders.	This was a 52-week trial. Dose started at 36 mg for 4 days, then increased to 54 mg for 3 days, and finally to 72 mg for 4 weeks. Those who completed the 4 weeks, entered an open-label extension with a dose of 1.3 mg/kg based on response and tolerability.	No effect on body weight was observed in this study.
Hurt et al. (31)	USA	Randomized Controlled Trial	To explore the effect of OROS-MPH on smoking cessation in adults.	$n = 80$ (40 randomized to each group). Mean age was 38 years in the placebo group and 35.6 years in the OROS-MPH group. 57.8% female	This was a 6-month study comprised by 1 telephone pre-visit, 11 clinical visits and 1 telephone follow-up. Participants were titrated to a dose of 54 mg/d for 2 weeks, and this maximum dose was maintained for 8 weeks with weekly assessments.	**Anorexia** 7.5% of the participants in the MPH group presented anorexia vs. 0.0% of the participants in the placebo group. **Weight changes** 2.5% of the participants in the MPH group lost an unknown amount of weight vs. 0.0% of the participants in the placebo group. **Nausea** 5.0% of participants in the MPH group presented nausea, while only 2.5% of the participants in the placebo group did.
Kis et al. (32)	Germany	Randomized Controlled Trial	To compare the effectiveness and safety of MPH and CBT in adults with ADHD over a 1-year period.	$n = 419$ (randomly assigned to 4 groups: MPH + CBT, MPH + Clinical Management (Clin), Placebo (Pl) + CBT, Pl + Clin). Mean age 35 years old (range of 18–56) Females from 45.3 to 56% depending on group	OROS-MPH dose was titrated to 54 mg/d during a 2-week period and maintained for 8 weeks. Participants attended the clinic weekly for counseling sessions.	**Decreased appetite** Occurred in 22.4% of the MPH group vs. 3.8% of the Pl group ($p < 0.05$) **Nausea** 12.2% of the participants in the MPH group reported nausea vs. 9.6% in the Pl group. Not statistically significant. **Abdominal discomfort** 6.3% of participants in MPH group vs. 2.9% of participants in Pl group. Not statistically significant. **Weight changes** 6.3% of participants in MPH group decreased their weight, while only 1.9% of participants in Pl group. ($p < 0.05$)
Michelsen et al. (35)	The Netherlands	Cohort Study	To assess the cardiovascular side effects of stimulant medications in older adults with ADHD.	$n = 113$ (89 had some pharmacological treatment) age was between 55 and 79 years 57% female	No actual intervention. 44% of the patients had extended release (ER) MPH, 9.7% were taking dexmethylphenidate (DMP), and 7.1% were taking Dexamphetamine (DAM). The observational study lasted 1 year.	**Weight changes** A significant 0.8 kg weight decrease was observed in patients taking MPH ($p < 0.05$). No significant weight changes were observed in other medications.

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TABLE 2 (Continued)

Article	Country	Design	Objective	Sample characteristics	Intervention	Relevant side effects reported
Retz et al. (34)	Germany	Randomized Controlled Trial	To determine if ER MPH reduces ADHD symptoms and psychopathology in adults with ADHD.	*n* = 162 (84 randomized to MPH ER, and 78 to placebo). Age between 18 and 56 Females 54.8% in MPH ER group, and 43.6% in placebo	MPH ER dose was titrated up to 40–120 mg/d (1 mg/kg maximum) for 2 weeks and then brought up to maximal dose for 6 weeks.	**Weight changes** 48% of participants in MPH group decreased their weight at the maximal dose tolerated, while only 10% of participants in Pl group. **Nausea** 17% of the participants in the MPH group reported nausea vs. 4% in the Pl group.
Retz et al. (33)	Germany	Cohort Study	To describe the safety profile of MPH in adults with ADHD attending a real-world clinic.	*n* = 468 from 126 sites. Age between 18 and 71. Females 42.1%	No actual intervention. Dose was started at 0.23 mg/kg and increased to 0.45 mg/kg as per the clinic protocol.	The study reports weight loss rate of 1.71% and nausea rate of 0.43%.

MPH can reduce food intake and weight. This effect is seen in articles that aim to determine if MPH can help adult patients lose weight and reduce their intake (Category 1) and in articles that evaluate different research questions regarding the use of MPH in adults (Category 2). Further exploring its potential effects on weight, body composition, and food intake could help increase the availability of safe and tolerable pharmacological interventions to treat obesity or excess weight.

MPH's effect of increasing dopaminergic activity in the ML, MC, and MS pathways can suppress appetite and reduce food intake. Increased dopamine release in these brain areas implies that the motivational salience of food will be reduced (39, 42). As a result, people with obesity or overweight taking MPH could reduce their energy intake and improve their food choices (18, 41).

MPH also appears to reduce appetite and food intake by modulating olfactory sensitivity (18). These findings are interesting because the literature on obesity and olfaction has shown that individuals with obesity seem to discriminate smells less than their normal-weight counterparts. Impaired olfaction may delay satiety cues, and olfactory cues could influence food choices. It is essential to mention that it is impossible to establish a causal relationship between olfaction and obesity because there may be a bidirectional association – impaired olfaction may alter intake and metabolism. Still, obesity may, in turn, affect how the brain perceives smells and detection thresholds (43, 44).

Olfactory cues seem tightly linked to dopaminergic processing in different brain regions. Sorokowska et al. (45) have shown that food odors can increase dopaminergic activity in reward circuits such as the anterior cingulate cortex, the putamen, and the insula, thus influencing eating behaviors. These results seem to be supported by Rampin et al. (46), who show that food odors can further increase dopaminergic transmission in the ventral striatum.

Interestingly, the results on olfactory sensitivity in participants with ADHD seem to be discrepant. Some studies have replicated olfactory impairment in children with ADHD (47). However, another study even showed that MPH cessation in children with ADHD improves olfactory discrimination (48). More work in this area is needed to determine the role of olfaction in developing unwanted eating behaviors. As it is, MPH's dopamine reuptake inhibition could reinforce increased olfactory detection and thus improve eating behaviors. Also, while MPH seems to have a dose–response effect on appetite, all doses used in the reviewed studies decreased appetite. This means that moderate and high doses of MPH reduced energy intake, with a notable reduction in the consumption of highly palatable foods. This effect is replicated in older literature (49).

Clinical considerations and safety issues

While promising as a potential weight-loss intervention, it is important to mention that MPH has been associated with increased cardiovascular risk in patients who are susceptible to heart conditions (50). Moreover, some studies in children with ADHD have shown that MPH has proarrhythmic properties (51). A prospective cohort study with a three-month follow-up in 100 Iranian children with ADHD between 6 and 11 years old found that children taking MPH had significantly higher systolic and diastolic blood pressures and increased heart rates. There were no significant differences in the

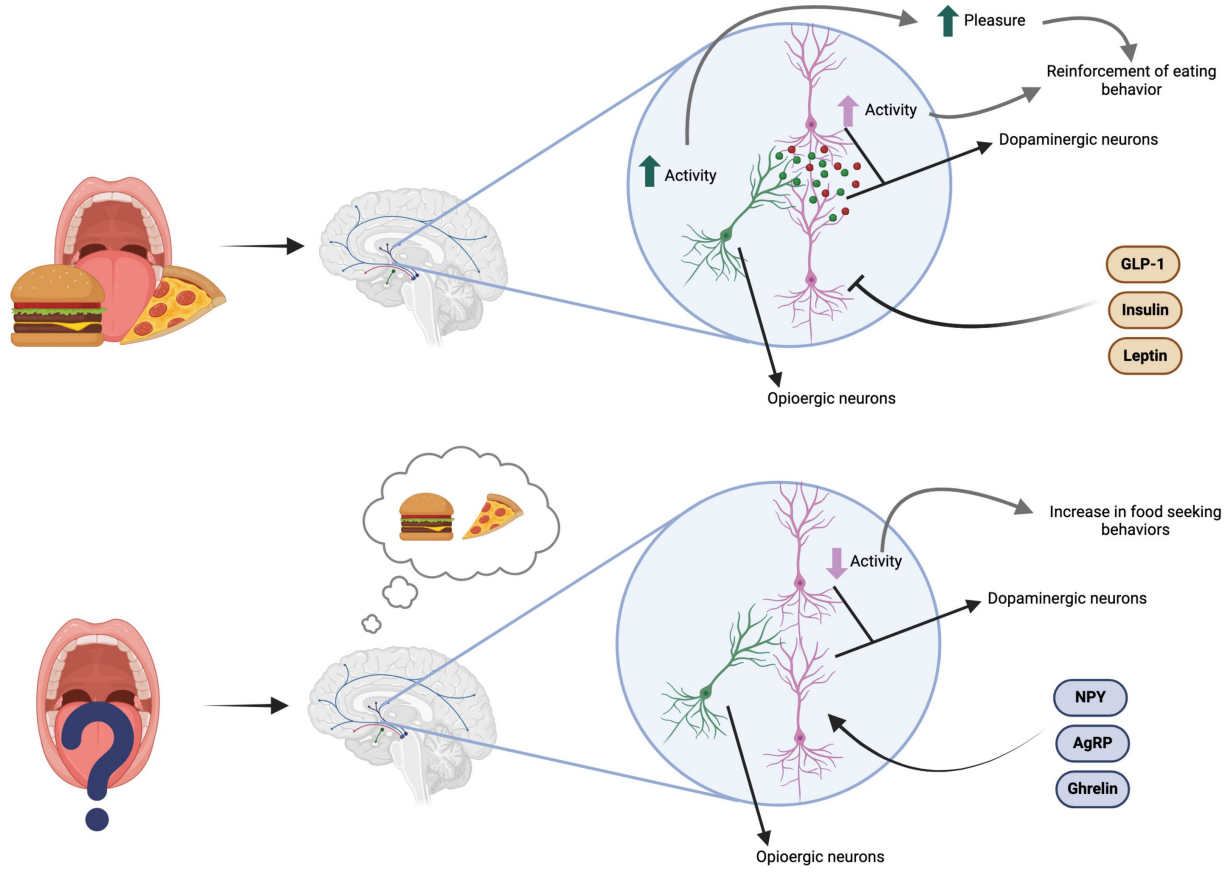

FIGURE 5
The dopaminergic model of appetite regulation explains how the brain responds to food. After consuming a palatable meal, opioid and dopaminergic activity in the mesolimbic pathway increase, enhancing pleasure and reinforcing eating behavior. Anorexigenic peptides inhibit this dopamine activity. In the absence of palatable food, dopamine levels remain low, but the sole thought of pleasurable food can trigger food-seeking behaviors to restore dopamine levels. Orexigenic peptides stimulate dopamine activity (38–40).

cardiac output, QT interval, and left ventricular mass. Clinically irrelevant changes in systolic and diastolic functions were also seen in children taking MPH, but the drug was determined to be safe (52).

A retrospective study on 26,710 individuals between 12 to 60 years without ADHD using MPH matched to 225,672 controls found that there was a 41% increased risk of cardiovascular events in the group using MPH (50). Another retrospective study on 43,999 new MPH users matched to 175,955 non-users found an 84% increased risk for sudden death or ventricular arrhythmia and a 74% risk of all-cause mortality in MPH users. There was no significant risk of stroke or myocardial infarction, and there was no significant dose–response effect or extended vs. immediate release effect (53).

In addition, a systematic review and meta-analysis analyzing the cardiovascular risk associated with medications used in ADHD gathered 19 observational studies and nearly 4 million participants from different age groups. The risk of cardiovascular events was not significant in stimulant users, non-stimulant users, or users of any age group, suggesting that the risk of cardiovascular events in stimulant users is the same as the risk in the overall population (54).

The literature shows mixed results regarding the cardiovascular risks linked to MPH. Since people with obesity have a higher rate of heart comorbidities than their normal-weight counterparts, further studying the safety profile of MPH in people with obesity and overweight is of prime importance before considering it a therapeutic option in this population. It is also important to consider gender and ethnic differences in dopamine receptor expression to fully understand the plausibility of using MPH as a treatment for obesity and overweight.

Discussion

Since the early 2000s, several studies have found that MPH can lead to weight loss in individuals. A meta-analysis in 2007 of 8 randomized controlled trials found that methylphenidate treatment resulted in an average weight loss of 2.03 kg compared to placebo (55). These effects appear to be mediated by reduced appetite and food intake, a competitive regulation of dopamine without the action of eating (49, 55). This review has found similar effects in newer studies. The selected studies indicate that the use of MPH can produce a modest weight loss and appetite suppression, particularly through its effects on the brain's hedonic and sensory processing pathways and that this effect appears more pronounced in women. Side effects, such as nausea and anorexia, may also contribute to these outcomes.

The interpretation of these findings is limited by several factors: study heterogeneity, small sample sizes, and lack of long-term data make it challenging to generalize results. Additionally, none of the reviewed studies evaluated MPH in combination with lifestyle or dietary interventions, which are commonly prescribed together with weight-loss drugs in clinical practice. MPH's association with cardiovascular risks highlights the need for caution, especially in patients with obesity who may already have an elevated risk of heart disease. While MPH shows potential as an adjunct therapy for weight management, further research is essential to confirm its safety and efficacy in broader, more diverse populations and to determine its suitability for long-term use.

Some examples of real-world include one using a Phentermine + Topiramate combination for the treatment of obesity in adolescents included a lifestyle intervention for both placebo and experimental groups. This study showed a maximum BMI loss of 10.44% after 56 weeks of treatment (56). Another trial using glucagon-like peptide-1 (GLP-1) agonists in patients with type-2 diabetes in the "real world" found that over 67% of the participants lost more than 5% of their initial body weight at 72 weeks without explicitly offering lifestyle interventions, and mean weight loss was 2.2% (57). This is comparable with the magnitude of weight loss found in the articles in this review, which was around 1.6% (26). Also, the proportion of participants losing over 10% of their initial body weight was around 11% in Adler et al. (27). However, another article using GLP-1 agonists plus lifestyle interventions found that an exercise intervention increased the number of participants losing weight 3.7 times compared to the control group and that exercise protected participants from regaining weight after treatment (58).

Another area that limits discussion is that it is difficult to compare the selected studies given their heterogeneity and that three articles appear to come from the same cohort (21–23). Furthermore, measurements, doses, and MPH presentations are not standardized across the studies. Also, it is essential to remember that none of the studies in Category 1 addressed any adverse effects of MPH that may become relevant in people with obesity.

MPH is not the first drug with noradrenergic/dopaminergic activity to be considered to promote weight loss in individuals with obesity or overweight. Amphetamine derivatives, phentermine, bupropion (all enhancing norepinephrine and dopamine activity through different mechanisms), and sibutramine (a serotonin and norepinephrine reuptake inhibitor), among others, have been used alone or in combination to promote weight loss. Similar drugs that are currently approved for weight loss come in combination. Examples include Phentermine + Topiramate (an antiseizure drug with multiple targets) and Bupropion + Naltrexone (a μ-opioid receptor antagonist used in higher doses to treat alcohol cravings) (20). Given its similar pharmacodynamic profile and moderate weight-loss-inducing properties, MPH could be a good candidate for further study. While MPH does enhance dopamine activity in reward-processing brain areas and the evidence does show that MPH can decrease weight and promote anorexia, more studies are needed to fully uncover adverse effects in people with obesity who may be at risk of cardiovascular events, the optimal doses to promote weight loss in different populations, and its potential to be combined with other drugs.

Conclusion

Methylphenidate appears to suppress appetite and reduce food intake in adults with obesity or overweight. This effect appeared to be more pronounced in women. Given the current state of the evidence, it is not possible to determine if men are less sensitive to the anorexigenic effects of MPH or if the sample was underpowered. MPH also seems to influence macronutrient preferences, reducing fat and carbohydrate intake. These effects could be mediated by increased dopamine levels, which affect the reward value of food. Overall, MPH shows promise as a potential pharmacological intervention for weight management in obese and overweight individuals.

Current studies are limited by small sample sizes, design heterogeneity, short follow-up periods, and lack of integral accompanying interventions. To build a robust evidence base, future research should prioritize large-scale randomized controlled trials focusing on the long-term efficacy and safety of MPH in diverse populations. Studies assessing cardiovascular risks in individuals with obesity and MPH's impact over extended periods are especially important. Furthermore, analyzing the effect of MPH in combination with lifestyle modifications or other anorexigenic/weight-loss medications could provide further answers into its possible role within a comprehensive weight management strategy. Understanding optimal dosing and the role of gender differences in MPH's effects on appetite and weight regulation also remain unanswered issues that need future addressing.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

FV-G: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. SY: Writing – original draft, Writing – review & editing. AO-M: Writing – original draft, Writing – review & editing. VF-T: Conceptualization, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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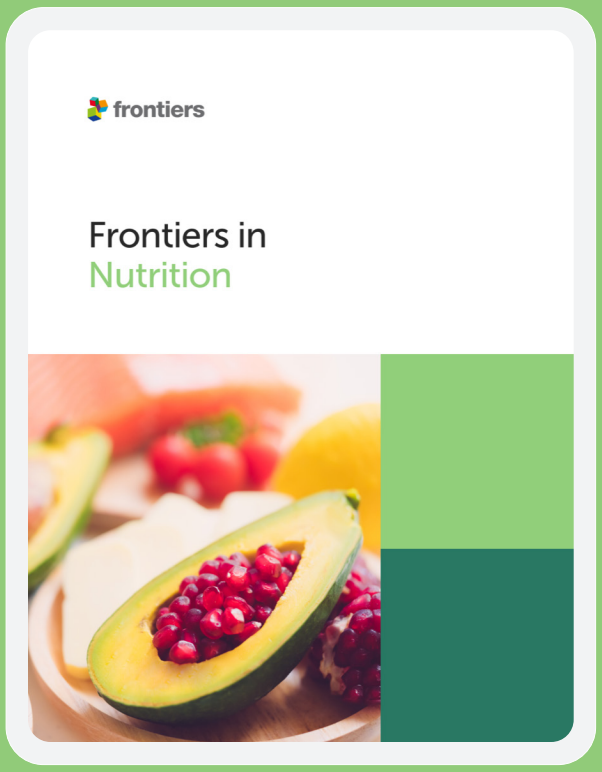

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