ADIPOSE TISSUE: WHICH ROLE IN AGING AND LONGEVITY?

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ADIPOSE TISSUE: WHICH ROLE IN AGING AND LONGEVITY?

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EDITORIAL
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Editorial: Adipose Tissue: Which Role in Aging and Longevity?

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Editorial on the Research Topic

Adipose Tissue: Which Role in Aging and Longevity?

Since 2018, we are living in a world where there are more people over age 65 than there are children under five. Predictions indicate, if this trend continues, by the year 2050, the number of people over 65 will be double the number of people under five (1). Consequently, an understanding of the optimal physiological, endocrinological, and anthropometric conditions associated with better health during aging is to be considered a priority topic. In parallel with the increasing aging of the population, there is a parallel increase of overweight and obese individuals among older adults (2).

Normal aging involves important changes to body composition, including decreased muscle mass and increased fat mass (3). Basal metabolism, for the majority of the elderly, is the main daily energetic expenditure and its decrease with age provides one explanation for the tendency to gain weight, with age. In addition to this physiological statement, lifestyle changes in aged people and the associated reduction in physical activity level favors weight increase with age. Total body fat peaks at about 65–70 years, while in advanced old age it decreases. Aging, indeed, modifies adipose tissue accumulation and redistribution resulting in accumulation of abdominal fat. These age-related changes alter many physiological functions including inflammation and contribute to age-related diseases such as cardiovascular events, diabetes mellitus, hypertension, stroke, and several types of cancer (4). However, to what extent, the age-related adipose tissue remodeling impacts the health status in elderly is incompletely understood.

To highlight and clarify the main age-related changes in adipose tissue and discuss its implications on health status with particular regard to age-related diseases, we dedicated a Research Topic to the alteration of lipid storage, the redistribution and the types of fat, the production of different mediators contributing to a pro-inflammatory status in aging.

Conte et al. are setting the stage, discussing the evident evolutionarily advantage provided by this tissue common among all animal species. Maintaining the correct distribution of body fat seems crucial for health and longevity. Interestingly, it seems that while a lower threshold of fat mass exists, it does not appear existing an upper one. In human and in many animals, adipose tissue can be accumulated in very large amounts. Most probably, an upper limit was not established by natural selection because a large accumulation of body fat in the wild is uncommon, unlike what we are observing during modern times in our species. Although the health implication of excessive body fat is evident, as they discuss, they also propose that a suitable amount of fat is probably an important feature for reaching extended longevity (Conte et al.).

Because of its simplicity, BMI is broadly used as a surrogate for body fat, although it is highly imprecise. For example, a bodybuilder with a low percentage of body fat could fall in the obese category. Ponti et al. present how body composition is different at different ages, stressing that there is not only an increase in body fat but also a redistribution of body mass with age.

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In particular, fat mainly increases in the trunk (largely visceral fat), but not in arms or legs. A major difference also exists between male and female older adults likely contributing to the sex-difference in the prevalence of age-related diseases. An accurate assessment of body composition is critical to discriminate an increase/decrease of fat rather than muscle mass in the elderly. Ponti et al., review the most precise methods available for the clinic and for research to determine body composition [dual-energy X-ray absorptiometry (DXA), ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI)] outlining advantages and disadvantages of each technique.

Zoico et al. focus on the significance of changes happening during aging in two subcategories of body fat: brown adipose tissue (BAT) and beige adipose tissue, fat tissues rich in mitochondria with the univocal (brown) or conditional (beige) function of converting stored energy into heat.

Adipose tissue is a recognized endocrine organ, producing a variety of adipokines, whose levels tend to increase with aging. Mancuso and Bouchard have provided a comprehensive overview of adipokine functions, classifying them as pro-inflammatory (leptin, resistin, chemerin, retinol binding protein 4, lipocalin 2, CCL2, IL-1β, IL-6, IL-12, IL-18, and TNF-α) and anti-inflammatory (adiponectin, vaspin, secreted-frizzled-related protein 5, omentin-1 C1q/TNF-related proteins).

Arai et al. focus on the roles and significance of adiponectin, an adipokine whose levels are elevated in centenarians. In contrast to the majority of other adipokines, its plasma levels are inversely related to body fat. In this report, the authors describe how this adipokine is considered highly beneficial for longevity, possibly contributing to enhancing insulin sensitivity. They also describe some interesting paradoxes related to adiponectin that challenge its beneficial role: the observed association between higher adiponectin level and mortality in patients with cardiovascular disease and with frailty in elderly subjects. They propose a solution to these paradoxes introducing the concept of adiponectin resistance: higher adiponectin levels, in their view, is possibly a compensatory mechanism in response to inflammation and oxidative stress.

In light of the current SARS-CoV-2 pandemic affecting prevalently the elderly (5), an important topic is the role of the process of aging in the susceptibility to infectious diseases. Obesity, as it increases with age, exerts a cumulative effect. Obese individuals are increasingly vulnerable to fungal, bacterial, and viral infection. Frasca and McElhaney present an overview of the roles of obesity on the immune response to respiratory tract infection. Specifically, they analyze the risk for the elderly represented by pneumococcus infection, highlighting the presence of an interesting obesity paradox: it appears that obesity is protective against the more serious complications of this bacterial infection. This stresses the need to investigate further, how obesity is modulating our immune response (Frasca and McElhaney).

Salvestrini et al. look from further away at the interrelationship between excess body fat and aging. Their considerations stem from a reflection on the experimental paradigm of life span extension by caloric restriction, specifically on how best to consider control animals when translating experimental results to human (6). If a control animal, *ad libitum* fed, has to be considered an animal with no excess fat, equivalent to a normal weight human (BMI between 18.5 and 24.9) than to benefit from the lifespan-extending effect of CR, a human should approach underweight. If, instead, as many authors are proposing [reviewed in (6)], control animals in many instances should be considered the equivalent of obese humans, then the lifespan-extending capacity of CR is simply communicating that obesity has a life shortening effect, which is well-known from epidemiological evidence. From these considerations Salvestrini et al. have looked at obesity under the lens of the hallmarks of aging as listed by López-Otín et al. (7); the vast collection of literature they overviewed, demonstrates an impressive overlap between the process of aging and the metabolic consequences of excess body fat (Salvestrini et al.).

Although the increase of body fat with age remains a major risk factor for age-related diseases, several studies are needed to disentangle the complex network of metabolic, endocrinological, and immunological mediators that are involved. Moreover, the general increase of the elderly population leads to the consequent increase of 90+ elderly and centenarians. Many studies demonstrated the peculiarity of these individuals (8, 9), however little is known about the amount and kind of adipose tissue they have. Future researches are needed to investigate the age-related remodeling of body fat including also very old people.

AUTHOR CONTRIBUTIONS

AL wrote the initial draft. AS and DM implemented and revised it. All authors gave final approval of the submitted version.

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MINI REVIEW
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Influence of Obesity on Pneumococcus Infection Risk in the Elderly

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Obesity negatively affects immune function and host defense mechanisms. Obesity is associated with chronic activation of the innate immune system and consequent local and systemic inflammation which contribute to pathologic conditions such as type-2 diabetes mellitus, cancer, psoriasis, atherosclerosis, and inflammatory bowel disease. Individuals with obesity have increased susceptibility to contract viral, bacterial, and fungal infections and respond sub-optimally to vaccination. In this review, we summarize research findings on the effects of obesity on immune responses to respiratory tract infections (RTI), focusing on *Streptococcus pneumoniae* ("pneumococcus") infection, which is a major cause of morbidity and mortality in the US, causing community-acquired infections such as pneumonia, otitis media and meningitis. We show that the risk of infection is higher in elderly individuals and also in individuals of certain ethnic groups, although in a few reports obesity has been associated with better survival of individuals admitted to hospital with pneumococcus infection, a phenomenon known as "obesity paradox." We discuss factors that are associated with increased risk of pneumococcal infection, such as recent infection with RTI, chronic medical conditions, and immunosuppressive medications.

Keywords: obesity, aging, inflammation, respiratory tract infections, pneumococcus

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INTRODUCTION

The increase in the frequency of obesity is a worldwide phenomenon. Obesity is defined as a body-mass index (BMI) $\geq$ 30 kg/m^2, by both the Centers for Disease Control and Prevention (https://www.cdc.gov/obesity/adult/defining.html) and the World Health Organization (https://www.who.int/topics/obesity/en/) and is associated with several debilitating chronic diseases including cardiovascular disease (1), type-2 diabetes mellitus (T2DM) (2–4), cancer (5), psoriasis (6), atherosclerosis (7), and inflammatory bowel disease (IBD) (8). Published data indicate that high BMI negatively correlates with protective immune responses and obese individuals are highly susceptible to viral, bacterial, and fungal infections (9–11). Obesity also increases the risk of musculoskeletal disorders and chronic back/lower limb pain (12); reduces cognitive function and is considered a potential risk factor for Alzheimer's disease and dementia (13, 14); induces ovulatory infertility (15); increases the risk of early and late miscarriage, gestational diabetes and preeclampsia, and complicates labor and delivery (16); impairs respiratory function by reducing lung expansion and narrowing airways in the lung (17), leading to asthma (18), and obstructive sleep apnea (19). In general, obesity decreases both the healthspan and lifespan, increases premature

mortality and significantly increases global healthcare costs. This global obesity epidemic affects all age groups as shown in a recent survey conducted on 68 million people from 195 countries (20).

Obesity negatively affects immune function and host defense mechanisms. One of the reasons is because obesity is an inflammatory condition associated with chronic activation of the immune system and consequent local and systemic inflammation which are negatively associated with a functional immune system. It has previously been shown that systemic chronic inflammation induces intrinsic inflammation in immune cells and a status of immune activation associated with reduced immune responses. Elevated serum levels of TNF-α typical of old age negatively correlate with T cell function, due to the down-regulation of CD28 gene transcription and cell surface expression (21). B cells are also affected by inflammation. We have shown that B cells from elderly individuals spontaneously make higher amounts of TNF-α than those from young individuals (22). B cell intrinsic TNF-α levels are positively correlated with serum TNF-α and, more importantly, these B cell levels of TNF-α before stimulation are negatively correlated with the function of the same B cells after *in vivo* or *in vitro* stimulation with the influenza vaccine or with mitogens, respectively. These findings are supported by the observation that inhibition of TNF-α improves both T (23, 24) and B cell (22) function.

The adipose tissue (AT) is a major immunological tissue that contributes to systemic inflammation. AT inflammation is characterized by infiltration and activation of immune cells secreting pro-inflammatory mediators, such as cytokines and chemokines, as well as adipokines, which recruit immune cells to the obese AT. Recruited immune cells differentiate into inflammatory subsets and secrete additional pro-inflammatory molecules which contribute to the maintenance of local and systemic inflammation. Immune cells infiltrating the AT include neutrophils, macrophages, T cells, B1 and B2 cells, NK cells, and innate lymphoid cells. The cellular composition of AT is dynamic and is regulated by acute and chronic stimuli including diet, body weight, and fasting.

Aging is associated with a progressive decline in physiological functions, leading to overt chronic disease, frailty and mortality. Physiological changes include inflammation of the AT, which leads to AT dysfunction, increased secretion of pro-inflammatory mediators, immune cell infiltration and accumulation of senescent cells. These processes altogether promote low-grade chronic inflammation [inflammaging (25, 26)] and insulin resistance, and lead to transition from metabolically normal obesity to metabolic syndrome. This occurs through metaflammation (27) in which excess nutrients, due to inefficient glucose metabolism, promote chronic low-grade inflammation. Metabolic hallmarks of metaflammation are high levels of glucose, lipids, free fatty acids, and reactive oxygen species. AT dysfunction may be a fundamental contributor to the elevated risk of chronic disease, disability, and adverse health outcomes in the elderly.

This review will show the experimental evidence that obesity is linked to higher severity of RTI in individuals of different ages similar to what has been shown in older adults. Potential mechanisms responsible for these effects will be discussed. We will focus primarily on *Streptococcus pneumoniae* ("pneumococcus") infection, which is a major cause of morbidity and mortality in the US, causing community-acquired infections such as pneumonia, otitis media, and meningitis.

OBESITY AND RTI

Figure 1 summarizes major obesity-associated changes in body systems which may be responsible for reduced responses to RTI. Lung function is altered in obesity (28). Altered lung mechanics and increased airway resistance related to obesity cause an increase in work of breathing and decreased exercise capacity. Thus, increased respiratory rates and complaints of fatigue are experienced by obese vs. lean individuals. These changes in lung function are mainly due to the higher weight load on the thorax, which is independent of any underlying parenchymal lung disease, significantly contribute to physical disability and impaired quality of life. Obese individuals with chronic obstructive pulmonary disease (COPD), a leading cause of morbidity and mortality worldwide, as well as with chronic bronchitis and emphysema, require increased muscular effort needed for ventilation and exhibit greater dyspnea (29, 30). Moreover, the sedentary lifestyle of these patients leads to increased fat accumulation in the lung and consequent airway obstruction.

In general, mechanisms related to the obesity-driven, low-grade chronic inflammation may be dramatically influenced by the presence of comorbid conditions. Obesity is in fact a complex metabolic condition associated with changes in many different physiological functions of the organism, and these changes, alone or in combination, may induce, support, and exacerbate lung inflammation. These conditions include gastroesophageal reflux, a risk factor for aspiration pneumonia and asthma (31), which may be worsened by hypertension and dyslipidemia, two conditions affecting immune responses in the lungs and increasing susceptibility to asthma and aspiration pneumonia (32).

Several pro-inflammatory cytokines and adipokines are secreted by the AT. These mediators, released into the circulation, contribute to the low-grade chronic inflammation (33) and induce pulmonary inflammation. The lung is continuously exposed to insults from the air and also to toxic molecules circulating through the pulmonary and bronchial vasculature. Mouse studies have shown that different molecules, such as bacteria, ozone, allergens, and particulate matter, activate the AT to secrete pro-inflammatory mediators involved in the generation of pulmonary inflammation (34–37). In addition, mechanisms of defense against pathogens and smaller particles that have successfully penetrated the mucosal barrier, including first-line filtration, mucosal IgA, alveolar cells, and resident immune cells in the parenchyma are decreased in obese individuals leading to low-grade chronic inflammation.

Leptin is an adipokine primarily secreted by the AT (38). Its effects on systemic and pulmonary inflammation in the settings of obesity have been the focus of several studies. Plasma levels of leptin positively correlate with the amount of body fat and BMI,

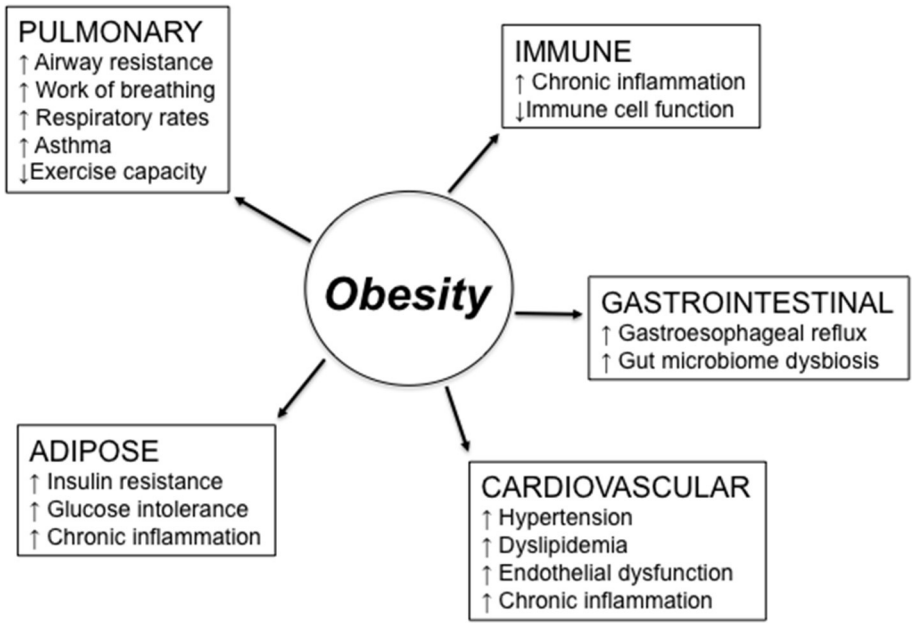

FIGURE 1 | Obesity effects on different body systems involved in the response to respiratory tract infections. Obesity-induced changes in the lung may be due to higher weight load on the thorax and lead to reduced lung function. Obesity-induced changes in the immune system lead to chronic inflammation, immune activation, and reduced clearance of pathogens. Obesity also causes gastroesophageal reflux, which is a risk factor for aspiration pneumonia and asthma, due to the excess of belly fat posing pressure on the stomach, and gut microbiome dysbiosis. Cardiovascular complications of obesity include hypertension, dyslipidemia, and endothelial dysfunction. Obesity-induced changes in the adipose tissue are responsible for increased insulin resistance and glucose intolerance, both leading to chronic inflammation.

increase with age (39), and contribute to the inflammatory status of the AT associated with obesity. Leptin induces the secretion of inflammatory cytokines by macrophages (40), T cells (41), and B cells (42, 43) *in vitro*. Leptin has also been reported to increase leukotriene synthesis by alveolar macrophages, leading to pulmonary inflammation (44). Leptin is known to down-regulate functional immune responses (45). There is evidence that cells in the lung may also be capable of secreting leptin (46, 47), although it seems more likely that leptin is found in the lung as a consequence of increased microvascular permeability associated with lung inflammation (48).

Viral RTI

Viruses causing severe RTI in elderly individuals include influenza A and B virus, respiratory syncytial virus (RSV), human parainfluenza virus (HPIVs), rhinovirus, enterovirus, human coronavirus (HCoVs). The effects of obesity have only been described for a few of these viral infections.

While many studies have investigated the effect of obesity or aging on the risk of influenza virus, only a few studies have analyzed the effect of both, likely because obesity has been shown to induce defects in peripheral immune cells similar to those induced by aging. We hypothesize that multifactorial age-associated conditions and parameters might be concomitantly associated with the predisposition of older adults to be infected with the influenza virus. During the 2009 influenza pandemic season, it was shown that obesity was positively associated with reduced pulmonary immune defenses not only against the Influenza A(H1N1)pdm09 virus but also against other pathogens (49). Several reports have clearly indicated that obese and morbidly obese individuals were more susceptible to infection with the Influenza A(H1N1)pdm09 virus, to a greater severity of illness after infection (49–51), to higher rates of hospitalization (50), admission to intensive care units (52), and death not only in the US (49) but also in many other countries (53–56).

The importance of RSV is increasingly recognized in hospitalized adults, but mainly in those 65 years and older. Vaccines for the prevention of RSV infections are not yet available, and development efforts are made more difficult in the older population due to age-associated decreases in immune responses. RSV infection in older adults causes great suffering due to hospitalization and death and is considered a social burden similar to that of seasonal influenza (57, 58). Clinical manifestations of RSV infections are similar to those caused by other viral respiratory pathogens. Most of the studies published on RSV-associated hospitalizations have been conducted in individuals ≥65 years, with 5–10% of hospitalizations for acute respiratory illnesses due to RSV infection. Older adults with COPD and/or congestive heart failure have been shown to be at higher risk (57, 59). A study conducted in middle-aged and older adults has shown that RSV infection was associated with obesity (60). Although there are no published studies on RSV infection in obese individuals, we can hypothesize that the clinical effects are similar to those observed in older adults.

The Bacterial RTI With *Streptococcus Pneumoniae*

Infection with the gram-positive bacteria *Streptococcus pneumoniae* ("pneumococcus"), a common pathogen in the nasopharynx most commonly associated with pneumonia, represents a major cause of morbidity and mortality. The risk of infection is higher in obese vs. lean individuals. Obesity has been associated with increased risk of pneumonia in young individuals (61). Studies on the effect of pneumococcus infection in obese elderly individuals are limited, but one study has reported that the incidence of community-acquired pneumonia in obese patients is directly associated with higher BMI in both age groups (62). However, other studies have conversely shown that obese compared to lean individuals are 2-fold more likely to survive after being admitted to hospital with pneumococcus infection, suggesting that extra energy may help to fight both infection and inflammation (63). After adjustment for potential confounders, morbid obesity was not associated with mortality, whereas obesity was associated with decreased mortality. Neither morbid obesity nor obesity were associated with admission into intensive care units and use of mechanical ventilation. This apparently controversial result may be due to the fact that when BMI is used as a measure of adiposity results may differ across different study populations. BMI is a crude anthropometric biomarker and it does not take into account different important measures of adiposity, such as fat mass, body fat distribution, measures of central adiposity, and nutritional status. Another reason may be due to the different inflammatory profile of the participants recruited into the studies. For example, obese individuals with high circulating levels of leptin, the adipokine secreted in large amounts during obesity, may have enhanced local immune responses against respiratory pathogens and increased host defense mechanisms in the lung (64). Leptin is a strong immunomodulator of both innate and adaptive immune responses and increases macrophage phagocytosis, neutrophils chemotaxis and natural killer cell cytotoxicity, as well as B and T cell function, leading to increased bacterial clearance. Therefore, increased leptin levels could increase immune responses of obese individuals and better protection against infection. Although a recent study of survivors of community-acquired pneumonia showed that this obesity paradox could not be attributed to differences in biomarkers of several inflammatory pathways (65), this study has only measured four markers of inflammation (not including leptin) and did not distinguish pneumonia from other causes of death, limiting the conclusions about inflammation as the pathophysiological explanation of the obesity paradox.

The risk of infection is also significantly higher in individuals aged 65 years and older as compared to younger individuals (66). **Table 1** summarizes major studies cited in this review showing the effects of age and comorbidities on mortality rates after infection with pneumococcus. Before the availability of antimicrobial treatments, >70% of patients hospitalized died of bacterial pneumococcal pneumonia and mortality rates were even higher in older adults (73). By the end of the twentieth century, mortality rates had dropped to 20% in individuals ≥65 years of age and to 40% in those ≥85 years of age (67–69). The American Centers for Disease Control and Prevention (CDC) reported that in 1995, in 4 areas of the US, the rate of invasive pneumococcal infection among older adults was 3-fold higher than infections with group B streptococcus, 10-fold higher than with *Haemophilus influenzae*, and 25-fold higher than meningococcus or *Listeria monocytogenes* infections (66). Rates of infection in elderly individuals from Asia, Africa or South America are less known.

TABLE 1 | Effect of age and comorbidities on mortality rates after pneumococcus infection.

Population age	Comorbidities	Mortality rates	Reference
18–64 years	None reported[a]	19%	(67)
≥64	T2DM[b]	45%	(68)
	Chronic lung disease	33%	(68)
	Congestive heart failure	20%	(68)
	Chronic renal failure	60%	(68)
≥65	None reported	20%	(66)
≥65	AIDS[c]	69%[e]	(69)
	SLE[d]	(All comorbidities)	(69)
	Chronic lung disease		(69)
	Chronic liver disease		(69)
	Congestive heart failure		(69)
	Chronic renal failure		(69)
80	None reported[a]	71%	(70)
≥85	None reported[a]	38%	(67)
78–100 years	None reported[a]	27%	(71)
86–104 years	None reported[a]	20%	(72)

[a] *This study analyzed the total population, including healthy, and non-healthy individuals. The mortality rates due to the different comorbidities are not reported.*
[b] *T2DM, type-2 diabetes mellitus.*
[c] *AIDS, acquired immune deficiency syndrome.*
[d] *SLE, systemic lupus erythematosus.*
[e] *In this study mortality rates were calculated considering the total population (healthy and not healthy with the listed comorbidities).*

In addition to obesity and aging, several other risk factors have been identified, including previous viral RTI such as influenza and RSV (74–76) as well as chronic illnesses such as COPD, congestive heart failure, cerebrovascular diseases and dementia, cancer, and T2DM (77). Use of corticosteroids has also been shown to be significantly associated with the risk of pneumococcus infection (77).

The incidence of pneumococcal pneumonia increases with age and the number of co-morbidities; those with 2 at-risk conditions have a similar risk to those with a high-risk rheumatologic condition, and those with ≥3 co-morbidities have a 2-fold higher risk compared to those with a rheumatoid condition (78). The age-associated increase in low-grade chronic inflammation has been shown to be associated with increased susceptibility to pneumococcal infection, with higher disease severity and decreased survival in older adults (79, 80). In general, microbial dysbiosis drives intestinal permeability and translocation of bacterial components into the bloodstream, further sustaining inflammation, immune activation, and decreased immune responses (81). Increased gut permeability with age induces not only systemic but also lung inflammation and tissue damage, as

shown by increased levels of circulating bacterial toxins, leading to pulmonary endothelial damage.

Not only the gut microbiota, but also the upper RT (URT) (82) microbiota changes with age contributing to *Streptococcus pneumoniae* colonization and its inefficient clearance, as shown by studies conducted in mice (83). The URT is colonized by several different species of pathogens and is continuously exposed to bacteria present in the environment, which survive in the nasal and oral cavities of older individuals, due to loss of resistance to colonization and altered immunity. It has been shown that efficacy of intranasal vaccination with a live attenuated influenza virus, measured by mucosal IgA secretion, depends on the specific bacterial composition of the nasal cavity, suggesting the importance of nasal microbiota for nasal immunity (84). Whether the URT microbiota of obese individuals contributes to *Streptococcus pneumoniae* colonization remains to be investigated by further studies.

Obesity is associated with changes in gut microbiota at phylum-level and with reduced bacterial diversity in mice and humans (85, 86). Mouse studies have identified intestinal microbiota products that protect the host from pneumococcus infection and have shown the mechanisms involved. Briefly, it was shown that the gut microbiota increases phagocytosis of alveolar macrophages and protects from tissue damage during pneumococcus-induced sepsis (87). Human studies are necessary to confirm the positive results obtained in mice.

Nursing homes represent one of the settings for outbreaks of pneumococcal infection in the elderly. Vaccination has been reported to protect $<10\%$ of elderly individuals in nursing homes during outbreaks of pneumococcal infection (70–72).

The risk of pneumococcal infection is also higher in individuals of certain ethnic groups. Afro-American people of all ages living in the US are 2- to 4-fold more susceptible than Caucasian individuals, but rates of infection are only slightly higher in the older Afro-American population (88, 89). Native Americans and Alaskans are at higher risk of pneumococcal disease than individuals of other ethnic groups. In the population ≥ 60, Native Alaskans as well as Native Americans of the Apache tribe living in Arizona had a 2-fold increase risk of pneumococcal disease as compared to non-native populations living in the same area (90, 91). In Northern Canada as well, higher risk of pneumococcal disease has been reported for Indigenous populations (92). Higher rates of multiple chronic conditions related to the colonization of Indigenous people's diets over many generations may, in part, explain these disparities, and require further study (93).

CONCLUSIONS

Chronic activation of the innate immune system and consequent local and systemic inflammation related to obesity contributes to pathologic conditions such as T2DM, cancer, atherosclerosis, and IBD. While obese individuals have increased susceptibility to viral, bacterial and fungal infections, outcomes of these infections may be determined by a host of other factors. This is evident when comparing outcomes of influenza and pneumococcal pneumonia; while both older age and obesity contribute to the serious complications of influenza, obesity appears to be protective against the serious complications of pneumococcal pneumonia with advancing age, the so-called "obesity paradox." Future studies will need to address the significant gaps in understanding the interaction of age, obesity, multiple chronic conditions, and the microbiome, particularly related to the risk for and complications of acute RTI. Mechanistic studies are needed to move beyond what has been learned from epidemiologic studies to develop new biomarkers and related preventive and therapeutic approaches to improving outcomes of acute respiratory illness in persons with multiple chronic conditions. Future studies will also need to address prevention of obesity, by improving eating habits and increasing physical activity, as a way to fight RTI. There is indeed experimental evidence showing that weight reduction decreases systemic inflammation and improves immune responses against bacterial, viral and fungal infections. Several epidemiological studies have evaluated the effects of diet and exercise in protecting subjects from several diseases associated with chronic low-grade inflammation. This will reduce the risk for infectious diseases, will increase their responses to pathogens, and reduce the burden of illness and health-related costs.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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frontiers in Endocrinology

REVIEW
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The Dual Role of the Pervasive "Fattish" Tissue Remodeling With Age

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Human aging is characterized by dramatic changes in body mass composition that include a general increase of the total fat mass. Within the fat mass, a change in the proportions of adipose tissues also occurs with aging, affecting body metabolism, and playing a central role in many chronic diseases, including insulin resistance, obesity, cardiovascular diseases, and type II diabetes. In mammals, fat accumulates as white (WAT) and brown (BAT) adipose tissue, which differ both in morphology and function. While WAT is involved in lipid storage and immuno-endocrine responses, BAT is aimed at generating heat. With advancing age BAT declines, while WAT increases reaching the maximum peak by early old age and changes its distribution toward a higher proportion of visceral WAT. However, lipids tend to accumulate also within lipid droplets (LDs) in non-adipose tissues, including muscle, liver, and heart. The excess of such ectopic lipid deposition and the alteration of LD homeostasis contribute to the pathogenesis of the above-mentioned age-related diseases. It is not clear why age-associated tissue remodeling seems to lean toward lipid deposition as a "default program." However, it can be noted that such remodeling is not inevitably detrimental. In fact, such a programmed redistribution of fat throughout life could be considered physiological and even protective, in particular at extreme old age. In this regard, it has to be considered that an excessive decrease of subcutaneous peripheral fat is associated with a pro-inflammatory status, and a decrease of LD is associated with lipotoxicity leading to an increased risk of insulin resistance, type II diabetes and cardiovascular diseases. At variance, a balanced rate of fat content and distribution has beneficial effects for health and metabolic homeostasis, positively affecting longevity. In this review, we will summarize the present knowledge on the mechanisms of the age-related changes in lipid distribution and we will discuss how fat mass negatively or positively impacts on human health and longevity.

Keywords: adipose tissue, aging, lipid deposition, organ involution, inflammaging

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INTRODUCTION

Aging is a complex process characterized by progressive changes in body mass composition that lead to a functional decline at cellular and organ levels over time. With advancing age, lean mass and bone mineral density decrease, while total fat mass increases and changes its distribution, particularly in the abdominal region, often without concomitant changes in body mass index (BMI) (1). In mammals, fat mass accumulates as adipose tissue or ectopic lipid deposition. Adipose tissue is a dynamic organ involved in the regulation of energy homeostasis, mainly divided in three types, brown (BAT), white (WAT), and BEIGE which differ in embryogenesis, anatomy, and function (2–4). While BAT possesses high levels of mitochondria and is specialized in fat burning to generate heat, WAT is characterized by a low density of mitochondria and it is generally involved in lipid storage in two biological distinct compartments: subcutaneous (SAT) and visceral (VAT) adipose tissue. WAT is not only involved in the storage of lipids, but also plays an important role as immuno-endocrine organ (5). With advancing age, BAT mass declines, while WAT increases reaching the maximum peak by early old age and changing its distribution toward a higher proportion of VAT (2). WAT redistribution is also accompanied by an accumulation of fat mass in non-adipose tissues and organs, such as muscle, liver, heart, pancreas and others, that normally contain only small amounts of fat, stored within lipid droplets (LDs) (6). Adipose tissue shows also an extraordinary plasticity (7), in fact it can differentiate into another type of adipose tissue, such as BEIGE (8, 9) or replace the parenchyma of organs that undergo involution with age, such as the thymus.

It is well-described that increased proportions of fat mass affect body metabolism and play a central role in many chronic diseases, including insulin resistance, obesity, cardiovascular diseases, type II diabetes, and sarcopenia (1, 10, 11).

In this review, we will summarize the changes that occur in lipid distribution with increasing age, and we will propose that: (i) the generalized increased amount of fat (in form of adipose tissue or intracellular lipid droplets) should be interpreted as an adaptive response to environmental conditions and, as such, is not *per se* a detrimental phenomenon; (ii) it can be a case of antagonistic pleiotropy, *i.e.*, while it has detrimental effects at old age, it can turn to be protective in extreme longevity.

THE ROLE OF FAT MASS IN THE EVOLUTION AND DURING AGING

Body fat storage has a long evolutionary history and represents a fundamental strategy to store energy fuel that is crucial for survival in conditions where food is not continuously available (12). All living organisms, from prokaryotes to mammals, have the ability to store energy that can be mobilized in response to a need, such as growth, metabolism, and reproduction (13). While simple organisms obtain and use energy only in response to an immediate need, more complex organisms have developed a mechanism to store energy in form of adipose tissue or ectopic lipid deposition (5). In insects, fat bodies represent not only lipid deposits but also organs able to perform complex endocrine and exocrine functions similar to those of the liver (14). Fat bodies play their biosynthetic and metabolic activities by the production of circulating proteins, acting as hormones, necessary in several physiological conditions, such as morphogenesis, egg maturation, and lipid and carbohydrate metabolism (15).

In mammals, fat mass distribution has reached a quite high degree of complexity. In these organisms, fat mass is widely distributed in the whole body and it is involved in many physiological processes, *i.e.,* energy supply during periods of starvation or undernutrition, regulation of metabolic homeostasis, reproduction, thermoregulation, immune response with production of cytokines and chemokines (13, 16). However, fat mass does not remain constant during lifespan, but changes in content and distribution from birth to extreme old age (17). These changes regard both adipose tissue and intracellular lipid stores (LDs) in non-adipose sites, and some of them, as in the case of thymic involution occurring at puberty, have to be considered as physiologically programmed. Much less is known about the fat mass changes occurring at advanced age. The "thrifty genotype theory" (18) explains the accumulation of adipose tissue as a strategy of metabolic adaptation, shaped by natural selection, to survive conditions of food scarcity. However, the existence of a specific genetic program leading to lipid deposition during aging is unlikely, considering that, according to the more advanced theories, aging in mammals is neither programmed nor selected by evolution. Thus, it seems more plausible that the age-associated lipid deposition is rather a phenomenon of adaptive remodeling in response to environmental conditions. Like many other adaptive phenomena it is conceivable that it may have both beneficial and detrimental effects. A growing body of evidence demonstrates that high levels of fat mass are associated with the development of several metabolic diseases (10), for this reason very often the fat deposition is considered *tout court* purely detrimental for the organism, and every age-associated weight gain bad for health. However, several lines of evidence demonstrate that also the deficiency of adipose tissue, as observed in transgenic mice or during lipodystrophy, results in the development of metabolic dysfunctions (19–21). For example, human lipodystrophies are characterized by genetic defects in lipid storage with total or partial loss of fat mass and related metabolic abnormalities such as insulin resistance and hypertension (22). Moreover, transgenic mice expressing dominant-negative protein A-ZIP/F (19) are characterized by the absence of WAT, reduced amount of BAT, elevated serum glucose, insulin, free fatty acids (FFA), triglycerides and type II diabetes (19). Consistently, adipose tissue results to have beneficial protective effects toward metabolic syndromes (19, 23–25). We argue that also during aging fat deposition can have beneficial effects, in particular at very old age, when it can be an important reserve of strategic energy crucial for resilience and recovery from stress and, eventually, for survival.

FAT MASS DISTRIBUTION IN HUMAN AGING

In normal aging total fat mass increases over the adult lifespan with a peak at about 65–70 years, while in extreme old age fat mass decreases (26). In the following paragraphs, we will describe the different types of body fat mass (adipose tissue and ectopic lipid depots) and the re-distribution of such fat mass during aging.

White Adipose Tissue (WAT)

WAT is a complex tissue composed by unilocular adipocytes, other cellular types, such as immune and stem cells, and connective tissue (4). The main role of WAT is the storage of energy and, as such, it actively controls the energy metabolism of all organs and tissues. In fact WAT secretes cytokines and proteins that communicate with other organs, such as brain, liver, muscle, or pancreas (27). As mentioned in the introduction, the two major WAT depots are SAT and VAT. In human body, SAT is present in the hypodermis of abdominal, gluteal, and femoral districts, while the counterpart VAT resides within abdominal cavity (omental, mesenteric, retroperitoneal, gonadal fat) and mediastinum. Moreover, VAT is also present around specific organs such as heart, stomach and blood vessels. With aging WAT increases and re-distributes, in particular a relative decline of SAT in the abdomen and limb region (thigh, calve), and a concomitant increase of VAT can be appreciated (4, 28). While SAT is considered protective, being the main source of adiponectin (29), VAT is considered detrimental as it produces pro-inflammatory mediators such as leptin, that boost the status of chronic, subclinical inflammation typically found in the elderly and indicated as inflammaging (30). Aging also entails a dysregulation in WAT and a consequent excess of circulating FFA. Higher levels of circulating FFA lead to lipotoxicity and the development of metabolic disorders (31, 32).

Overall, WAT is involved in several physiological processes, as demonstrated by different studies on animal models. Studies on leptin-deficient ob/ob mice, with metabolic and immune dysfunctions, demonstrated that the transplantation of WAT normalizes high glucose levels, body weight and fertility (33), as well as thymus/spleen cellularity and inflammatory parameters like IL-6 (21). Moreover, a novel protective role for WAT in the immune response has been proposed (34). In particular, WAT from mice infected with bacteria represents a reservoir of memory T cell populations and promotes a protective memory response to infections (34). Studies in humans, and in particular in healthy centenarians, demonstrated that WAT becomes crucial in the extreme old age, as it secretes circulating factors such as adiponectin, that are associated with a protective metabolic and anti-inflammatory phenotype (35, 36).

As a whole, all these data suggest that WAT remodeling with aging may have not only negative but also positive effects on health.

Brown Adipose Tissue (BAT)

BAT is a highly vascularized, heat-producing tissue, aimed at protecting animals from hypothermia through thermogenesis. This role is prominent in small size animals and newborns. It is distributed in cervical, supraclavicular, axillary, paravertebral, mediastinal, and upper abdominal regions (4). BAT is characterized by the presence of multilocular adipocytes containing abundant mitochondria that express high levels of UCP1 through which dissipate the proton gradient across the inner membrane and produce heat (37, 38). In addition to the traditional role of BAT in thermogenesis, recent data suggest that BAT plays an important endocrine role through the release of several endocrine factors, particularly in response to thermogenic activation (39). All these signaling molecules control metabolic processes via autocrine, paracrine, and endocrine mechanisms. These factors include (i) vascular endothelial growth factors (VEGFs) and insulin-like growth factor I (IGF-I), which, respectively, favor angiogenesis and increase the number of brown adipocyte precursor cells; (ii) several bone morphogenetic proteins (BMPs), implicated in the regulation of adipocyte differentiation and energy expenditure; (iii) thyroid hormone (triiodothyronine, T3), a well-recognized regulator of thermogenesis; iv. interleukin-6 (IL-6) and fibroblast growth factor 21 (FGF21). Although IL-6 is commonly considered a pro-inflammatory cytokine, studies of BAT transplantation demonstrate the beneficial effects of IL-6 derived from BAT in the control of metabolism (40). IL-6 is a key mediator to improve glucose homeostasis and insulin sensitivity, and contributes to the increase of circulating levels of FGF21 that plays an important role in the control of glucose and lipid metabolism (41).

In humans, BAT is abundant in newborns and infants, while it gradually declines from adolescence to adulthood (42, 43). In adults the amount of BAT is modulated by several factors, such as hormones, physical activity, cold exposure, and diet (44, 45), however the responsiveness to these stimuli declines during aging (46). Due to the endocrine role of BAT, several evidences demonstrate that its induction plays a protective role in counteracting age-related metabolic diseases. While the loss of BAT predisposes to WAT accumulation and weight gain (47), the transplantation of BAT in murine models induces an enhancement of energy expenditure, weight loss and insulin sensitivity, and prevents or even reverses obesity (48, 49). It was also shown that caloric restriction is able to stimulate BAT growth, conferring protection against the major age-related pathologies, such as cardiovascular diseases, cancer, and neurodegenerative disorders (50, 51). Moreover, increased levels of BAT mass promote longevity and enhance metabolism (52).

Beige Adipose Tissue and Browning

BEIGE or BRITE ("brown in white") adipose tissue is a subset of WAT with features of BAT. In particular, BEIGE tissue is composed of adipocytes derived from differentiation of WAT pre-adipocytes or trans-differentiation of WAT adipocytes, a phenomenon known as "WAT browning" (53, 54). In adults BEIGE tissue is localized within white fat depots, at inguinal and neck levels, where acts as WAT (55), while under particular stimuli, beige adipocytes acquire brown-like functions (56). The stimuli inducing the browning are not still well-understood, however it is known that they influence several molecular factors

to orchestrate browning and thermogenesis mechanisms. Briefly, browning and thermogenesis are generally mediated by chronic cold exposure or hormones and peptide factors that activate the β-3-adrenergic receptor, an adipose tissue-selective adrenergic receptor (57). Moreover, the zinc finger protein PRDM16 and the mitochondrial protein UCP1 are considered the key contributors to prompt browning activity in the new BEIGE tissue (58). Noteworthy, a reduced expression of PRDM16 and UCP1 leads to the reversion of beige adipocytes into white adipocytes (59–61). Browning is a reversible mechanism pointing to the extraordinary plasticity of the adipose tissue. The process of browning is impaired during aging leading to a loss of BEIGE tissue and to a progressive decline in metabolic activity. This phenomenon is in part due to a reduction in the response to the β-adrenergic stimuli with aging (62). In fact, some studies have demonstrated that the loss of β-3-adrenergic receptor leads to an incapacity of white adipocytes to differentiate in beige adipocytes upon cold exposure (63, 64). Other studies in knockout or transgenic mice for different molecular regulators of browning underline the importance of this thermogenic tissue on age-associated metabolic dysregulations. As an example, in old mice the ablation of the winged helix factor FOXA3, a factor inducing the increase of adiposity and decrease of BAT mass with aging, induces browning, increases thermogenic capacity, decreases WAT expansion, thus leading to improved insulin sensitivity and lifespan extension (65). Other factors involved in the formation of brown adipocytes and in the regulation of lifespan are the BMPs. For example, BMP4, BMP7, and BMP8b control beige adipocyte development. In particular, mice treated with these factors increase browning processes and are protected from insulin resistance (29, 66).

Ectopic Lipid Depots

Several tissues, such as bone marrow, skeletal muscle, liver and pancreas, make use of fatty acids as energy source, and these fatty acids accumulate within LDs in form of neutral lipids, mainly as triacylglycerols (TAGs) and steryl esters. LDs play an evolutionarily conserved role from yeasts to multicellular eukaryotic organisms (67). The physiological role of LDs is the maintenance of cellular energy homeostasis and the protection from lipotoxicity caused by an excess of FFA accumulation (68). An alteration in LD homeostasis leads to an excess of lipid intermediates, such as diacylglycerols, which in turn perturb metabolic pathways and cellular functions causing inflammation, mitochondrial stress and increase of reactive oxygen species (ROS) (68). The amount and size of LDs increase with age and contribute to the development of several age-related metabolic diseases such as type II diabetes, obesity, hepatic steatosis, and sarcopenia (68–75). Nevertheless, the primary causes of age-dependent ectopic fat accumulation remain largely unknown. However, not only the excess but also the deficiency of LDs leads to the onset of metabolic disorders (6, 20), in fact a growing body of evidence suggests that a balance between neutral lipid accumulation and their degradation is essential for the health and longevity of the organism. Numerous studies of model organisms, such as yeasts, nematodes, insects, and mice indicate that LDs are involved in the regulation of several longevity-related mechanisms, most of which are evolutionary conserved. It has been demonstrated that LDs control metabolic and lipid homeostasis and stimulate the release of different molecular mediators, such as lipophilic hormones that act as aging regulators and promote longevity (76). As an example, LD accumulation in the intestine of *Caenorhabditis elegans* contributes to the secretion of hormonal steroid pregnenolone, also present in humans, that extends lifespan (77–79). Consistently, the accumulation of TAGs has been reported as a novel pro-longevity factor in yeast. In fact, genetic manipulations leading to an increase in TAG content (by either the decrease of TAG lipases or the increase of TAG biosynthesis enzymes), extend yeast chronological lifespan (80, 81) independently of other lifespan regulators, such as dietary restriction (82). Moreover, LDs are involved in the adaptive stress responses and cell survival by the production of signaling molecules involved in the immune response pathway (83). As an example, in humans LDs serve as main storage site for arachidonic acid, which is the precursor of signaling molecules, such as eicosanoids or retinoic acids, which regulate inflammation (84).

All these findings indicate that the balance of fat accumulation in non-adipose tissues is important for the maintenance of a healthy status, in fact, both the excess and scarcity of fat are linked to the development of pathologies (20).

THE ENDOCRINE ROLE OF ADIPOSE TISSUE DURING AGING

Adipose tissue is an important endocrine organ that controls numerous physiological functions such as appetite, body weight, insulin sensitivity, fat distribution, glucose and lipid metabolism, neuroendocrine functions. This endocrine activity influences the whole body metabolism by releasing FFA, adipokines, cytokines and other molecular factors (85) that play a pleiotropic function on different tissues such as the liver, skeletal muscle, heart, lung, blood vessels, and sensory receptors, such as olfactory ones. Recent studies demonstrate that olfactory system is closely linked to adipose tissue in the regulation of energy balance (86, 87). In particular, the olfactory mucosa and bulb are provided with receptors for adipose-derived factors, such as leptin and adiponectin through which they influence body metabolism (88). How the age-related changes in adiposity modify olfactory function remains unclear. However, it is reasonable to think that the adipose tissue dysfunction with aging may affect energy homeostasis by perturbing the olfactory system through the production of these adipokines, and, in turn, outputs from the olfactory tract are among the causes of adipose tissue modifications.

WAT regulates also immune functions. In this regards, a link between white adiposity (in particular of VAT) and immune aging was found. In WAT, there are different types of immune cells that under stress conditions, such as obesity, impair their immune capacity increasing the pro-inflammatory behaviors in adipose tissue (89). Pro-inflammatory mediators can be produced also by senescent cells that accumulate in adipose tissue

during aging (10). As for the olfactory system, the regulation of immune cell function by the adipose tissue depends on the secretion of adipokines such as leptin and adiponectin, that were originally classified as pro- or anti-inflammatory, respectively. The primary function of leptin is the regulation of appetite and energy expenditure by acting at the level of the central nervous system. It is known that higher circulating levels of leptin are present in obese and overfeeding individuals (90, 91). However, studies in ob/ob mice have demonstrated that the absence of leptin leads to obesity, hyperlipidaemia and insulin resistance, while leptin administration reverses these metabolic perturbations (92, 93). Accordingly, leptin administration has been proposed as a possible therapy to ameliorate glycemic control and dyslipidaemia in human patients affected by lipodystrophy or congenital leptin deficiency (94, 95). Likewise, adiponectin displays protective metabolic functions such as stimulating fatty acid oxidation and improving insulin sensitivity (96). High plasma levels of adiponectin are associated with low fat mass (97) and low incidence of metabolic disorders, including type II diabetes (98). Thus, leptin and adiponectin play different roles that converge on the maintenance of balanced energy levels and fat stores. Data from animal models highlight the critical functions of adipokines in metabolic homeostasis and longevity. In particular, these murine models, characterized by mutation or knockout in genes involved in metabolism, exhibit an extended lifespan associated to higher levels of plasma adiponectin, reduced adiposity, and lower-fasting insulin concentration (99–104). All these findings indicate that there is a clear association between elevated circulating levels of adiponectin and longevity, where the key mediator appears to be the maintenance of adiponectin-dependent insulin sensitivity. A recent cross-sectional study in caloric restricted mice of different age shows that longevity phenotype is linked to a specific adiponectin isoform with high molecular weight (105). This isoform was recognized as the most effective in enhancing the insulin sensitivity in humans (106). It is reported that the circulating levels of adiponectin and leptin (only in males), but not of resistin, increase with age (107). Noteworthy, also centenarians display higher levels of adiponectin associated to preserved insulin sensitivity. In particular, high adiponectin blood levels are associated with high levels of HDL-cholesterol and low levels of glycated hemoglobin (HbA1c) and C-reactive protein (35). Moreover elevated adiponectin levels are inversely correlated with the HOMA-IR, a risk factor for the onset of age-related metabolic diseases (108, 109).

Another factor secreted by adipose tissue is FGF21, an important metabolic regulator. FGF21 is in fact involved in the transcription of adiponectin in WAT, and these two factors together act to control energy metabolism and insulin sensitivity in other organs, such as liver and skeletal muscle (110, 111). FGF21 increases insulin sensitivity, energy expenditure, and weight loss also by inducing browning activity (112). Moreover, FGF21 has been also proposed as an antiaging hormone, in fact the overexpression of FGF21 in mice extends the lifespan (113). However, very recently we found that circulating levels of FGF21 in humans increase with age from 21 to 100+ years in healthy individuals and these high levels are related to worsened biochemical health parameters in old persons and decreased survival in extreme longevity (114). Accordingly, the role of FGF21 as a pro-longevity hormone has been questioned, as it appears to be responsible for the phenotype of accelerated aging in Opa1-deficient mice (115). This apparent contradiction could be explained in the framework of the hormetic paradigm. In other words, FGF21 is *per se* protective and likely able to recover a mild stress, but when the stress becomes stronger, it overcomes the beneficial effects of FGF21 and possibly an excessive production of FGF21 can have detrimental effects on the health status (114). WAT secretes also various bioactive compounds, indicated as Volatile Organic Compounds (VOCs) (116). VOCs are low-weight molecules produced by cellular metabolism that are involved in different physiological processes. VOCs mirror normal or abnormal physiological processes and reflect the metabolic condition of the organism and might have promise as diagnostic tools for a number of diseases as well as the metabolic condition of elderly people, as they seem to be characterized by a modified production of VOCs (117–119). Human fat can produce consistent amounts of VOCs detectable in breath, skin and sweat, and fluids, such as blood, urine, saliva, and in feces. It has been demonstrated that metabolic disorders or other diseases are characterized by specific VOCs profiles (120). Moreover, recent data demonstrate that the exposure to a new profile of VOCs contributes to an increase of pro-inflammatory cytokines involved in the development of metabolic diseases (116, 121). Therefore, it is reasonable to think that the age-related rearrangement of adipose tissue is at least in part responsible not only of the alteration of fat hormones production, but also of VOCs profiles, with at present unpredictable effects on the health status.

As a whole, adipose tissue and its derived adipokines have a critical role in controlling whole body energy metabolism, as well as some of the major age-related dysfunctions and longevity.

ORGAN INVOLUTION AND FAT INFILTRATION WITH AGING

One of the most universal manifestations of aging is the progressive atrophy or involution of many organs and tissues. This phenomenon is characterized by a loss of mass due to the concomitant reduction of cell proliferation and the increase of cell death rates, together with the accumulation of senescent cells (122). In some cases, this age-related loss of organ parenchyma does not lead to mere organ shrinkage, but is rather paralleled by an infiltration of adipocytes and sometimes by a complete replacement of organ with adipose tissue (122). The reasons why the age-related organ involution is accompanied by a replacement of adipose tissue remains poorly understood. As described above, adipose tissue has a crucial role in metabolic processes. Therefore, the adipose tissue substitution during organ involution is not a simple replacement with a neutral tissue, but it has to be considered as an adaptive response with dramatic biological consequences, as adipose tissue plays an active role as a source of hormones and adipokines that may regulate the homeostasis of the adjacent tissues (2, 91, 123). The substitution

of parenchyma with adipose tissue is particularly evident in thymus, bone marrow, but also in muscle and pancreas, and generally begins between 20 and 50 years of age, excepting the thymic involution that begins much earlier, around late infancy-puberty (122). However, all human organs are gradually invaded by fat cells from birth onwards.

Thymus and bone marrow are two organs highly subjected to age-associated changes. They represent primary lymphoid organs, playing a fundamental role to provide cellular components of immune system during lifespan (124). The thymus is responsible for thymocyte differentiation and maturation into T cells, while bone marrow is the main site for the generation of all blood cells and for the maturation of B cells. The thymus progressively loses its functionality with age, in a process termed thymic involution or atrophy (125, 126). This phenomenon begins relatively soon after birth and results in a significant loss in thymic mass and a replacement with WAT within the thymus but also in the peripheral areas (127, 128). The organ replacement with WAT seems to occur in all species that possess the thymus indicating that this process is not only evolutionary ancient and conserved (129) but also important to counterbalance the loss of thymus by maintaining the size of this organ throughout life (125).

Aging induces adipocyte accumulation also in bone marrow cavities resulting in a loss of hemopoietic activity and bone loss disorders. Mesenchymal stem cells (MSC) of bone marrow can give rise to adipocytes or bone-forming osteoblasts. With age, these MSC tend to differentiate more into adipocytes that can become the prevalent cellular population of the marrow. Several studies suggest that this process leads to an impairment of osteogenic and hematopoietic activities (130–132) and is associated with the development of a great number of age-related diseases, such as osteoporosis and type II diabetes (133, 134). It is however suggested that the presence of adipose tissue in the marrow is necessary and beneficial for the health of the bone, especially when it has features of BAT (135).

As previously mentioned, aging is also associated with adipose tissue infiltration at non-adipose sites that normally are not involved in the fat storage. This age-related ectopic adiposity is associated with the progressive impairment of organs and tissues. This phenomenon affects, in particular, skeletal muscle, liver, pancreas, and heart. In skeletal muscle, elevated adipose deposition is observed at both intra- and inter-muscular sites. These two types of ectopic adiposity negatively impact on muscle strength and quality, as demonstrated in previously studies from our laboratory and others (75, 136, 137). In older people intra-muscular lipid content is associated with insulin resistance and the development of metabolic disorders (138). Moreover, in skeletal muscle, a subset of stem cells indicated as fibro-adipogenic progenitors (FAPs) appears to play a major role in inter-muscular adipose tissue (IMAT) infiltration, a phenomenon linked to progressive muscle dysfunction. FAPs appear to be

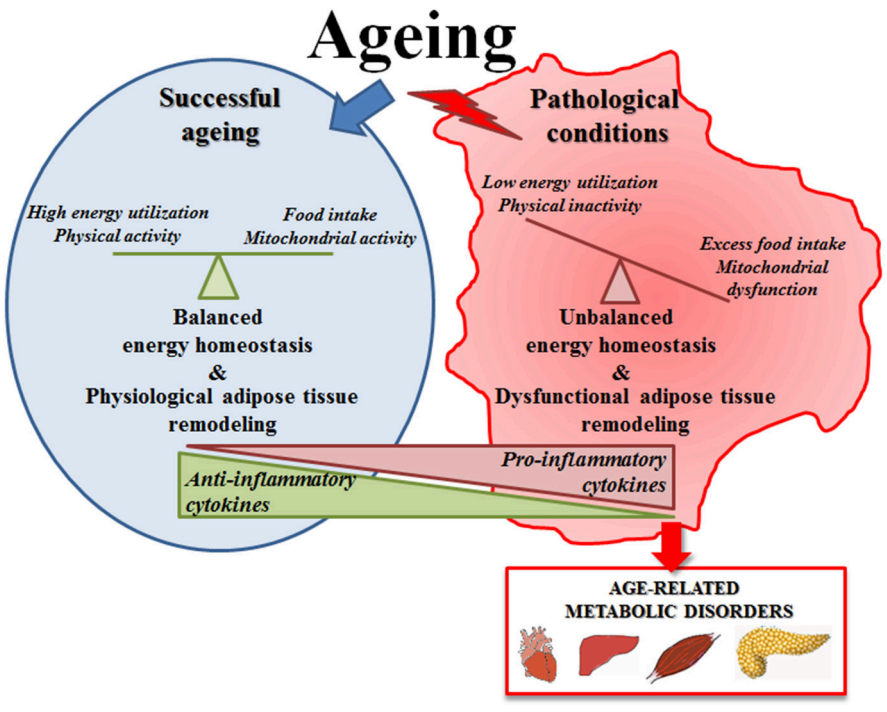

FIGURE 1 | Schematic representation of adipose tissue function in successful aging or in pathological conditions. In successful aging a preserved balanced metabolism can maintain a physiological remodeling of adipose tissue that is likely an adaptive response to environmental conditions; in pathological conditions the unbalanced energy homeostasis leads to an excessive adipose tissue hypertrophy that becomes detrimental and contributes to the onset of age-related metabolic diseases.

driven toward adipogenic differentiation by muscle inactivity (139). It is therefore plausible to consider the increased adiposity of skeletal muscle observed with age as an adaptive response to mutated organismal requests.

Pancreas undergoes several alterations with aging, not only in volume but also structure. In particular, a significant reduction of pancreatic antero-posterior diameter, an increase of pancreatic lobulation and a decline of parenchymal component with a concomitant parenchymal fat mass increase (fatty replacement or lipomatosis) have been observed. This fatty replacement in pancreas is characterized by the infiltration of adipose tissue, as interlobular fat, between pancreatic lobules, accumulating around vessels (140, 141). The increase of pancreatic fat infiltration with aging is not well-understood and is still under debate. The degree of fatty replacement varies among subjects and depends on the condition, physiological, or pathological, in which each individual is involved. However, in any case, like in other organs, also the age-related atrophy of pancreas is associated to a replacement with fat mass.

In liver, an increase of intracellular fat mass in hepatocytes appears to be associated only with a progressive dysfunction of hepatic organ. Several evidence indicate that hepatic fat infiltration is associated with an increase of oxidative stress, inflammatory response, and cellular senescence, leading to the alteration of hepatic structure and the onset of non-alcoholic fatty liver diseases (NAFLD) (142, 143). Studies on the causes or effects of aging on hepatic adiposity are still limited. However, several evidence suggest that the progression of NAFLD is associated with telomere shortening, increased p21 expression and increased M1 macrophage inflammatory responses that are considered specific markers of cellular aging (144, 145). The increased expression levels of these markers are also observed in adipocytes, indicating that adipocytes under oxidative stress exhibit increased levels of ROS, shortened telomeres and switch to senescent/pro-inflammatory phenotype with the decline in insulin sensitivity (146).

In heart, the epicardial adiposity increases in size between myocardium and pericardium (147). In healthy conditions, cardiac adipose tissue has physiological functions, including metabolic, thermogenic and mechanical functions (148). New findings demonstrate that epicardial fat is mainly composed of adipocytes with features similar to brown or beige adipocytes (149), playing a protective role against the development of metabolic diseases (150). In particular, these adipocytes act through paracrine secretion of anti-atherogenic cytokines, such as adiponectin and adrenomedullin. However, the epicardial fat is susceptible to age-associated changes. In fact, with aging brown/beige adipose tissue undergoes a brown-to-white transition becoming dysfunctional and contributing to the onset of several pathologies.

All these data suggest that the increase of fat mass with age (including the increase of volume of adipose tissue, replacement of parenchyma and ectopic lipid deposition) is an apparently universal phenomenon, linked in general (but not exclusively) to the onset of pathological conditions (**Figure 1**). In fact, it is considered that adipocytes in adipose tissue do not change in number with age but rather in size, thus resembling the phenomenon occurring in obesity (151, 152). Adipocytes from obese persons are larger and unilocular, they release high amounts of FFA, produce less adiponectin and are infiltrated with M1 macrophages and produces pro-inflammatory cytokines (152), thus representing a risk factor for many age-associated diseases. The same seems to occur with age, as the large majority of the persons show a remodeling of adipose tissue with these features. In this regard, obesity could be considered as a sort of accelerated aging of the WAT. However, adipose tissue remodeling with age is likely an adaptive response to environmental conditions, therefore is not necessarily detrimental, and a preserved balanced metabolism can maintain a physiological remodeling of adipose tissue, without excessive WAT hypertrophy, but also without excessive loss of adiposity. This could be a key feature for achieving successful aging and longevity.

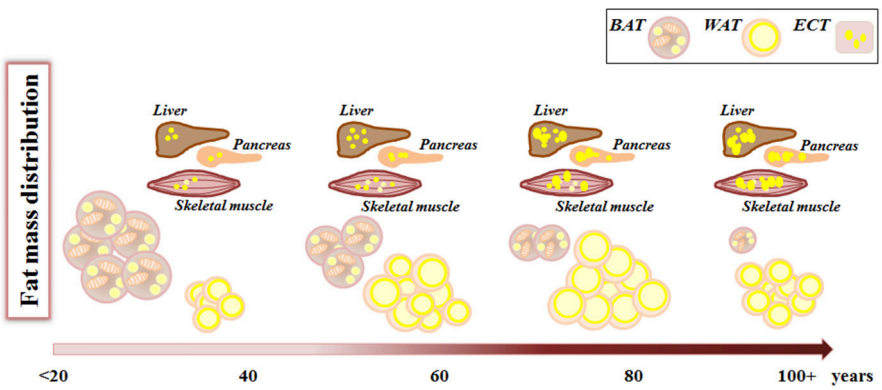

FIGURE 2 | Fat mass remodeling with aging. During aging, from birth to advanced age, fat mass changes its amount and distribution. White adipose tissue (WAT) increases both in number and volume of adipocytes, while brown adipose tissue (BAT) decreases. Concomitantly there is an increase in lipid deposition in ectopic tissues (ECT) such as liver, muscles, pancreas where lipids are stored within lipid droplets.

CONCLUSIONS

The maintenance of a balanced amount of fat mass is crucial for health and survival, as discussed above. According to the "thrifty phenotype" theory, humans were selected to accumulate fat depots to face periods of food shortage. However, while a critical lower threshold of fat content exists, an upper threshold is apparently missing, and adipose tissue can accumulate in great amounts. The absence of an upper threshold for fat accumulation is probably due to the fact that this phenomenon did not occur in the wild frequently enough to undergo selection, or, alternatively, resulted neutral for the fitness of individuals.

With aging, the "thrifty phenotype" seems to emerge more dramatically, and the balance is tilted toward an increase of fat mass, at the level of VAT and SAT as well as in ectopic sites (liver, muscles, etc.) (**Figure 2**). This increase in fat deposition at the level of SAT and VAT can be considered an adaptive response to modified health conditions interacting with contingent environmental conditions, leading eventually to decreased energy expenditure. However, in some cases the storage of surplus energy can not be claimed as the reason for fat accumulation, especially when this occurs ectopically at the expenses of other tissue types with important vital functions, as in the case of thymic involution or skeletal muscle infiltration. In this case, it seems that fat deposition in form of WAT is a sort of physiological program (genetically determined?) for organs and tissues undergoing age-related atrophy or involution. We have mentioned the fact that different stem cell subpopulations such as muscle FAPs and bone marrow MSC preferentially differentiate to adipocyte with age, therefore, we are tempted to speculate that the pathway leading to this cell type is a sort of a default choice in involution processes. Should this speculation be verified, the reasons for this choice remain elusive.

The accumulation of WAT has been for long time viewed as detrimental, being the source of pro-inflammatory mediators and other important endocrine modulators and strongly associated with metabolic diseases such as insulin resistance and type II diabetes, cardiovascular diseases and cancer. However, it is not totally clear whether this negative role is present also in extreme old age. Actually, data on body composition in non-agenarians and centenarians are largely missing, even though the BMI of these people is usually lower than that of younger (70–80 years-old) persons. It is possible that, as for other risk factors like lipid serum profile and inflammatory parameters (153, 154), also the presence of a consistent amount of WAT can be important for survival at very advanced age. Further studies are needed to verify this hypothesis.

To sum up, human aging is characterized by a general tendency to increase adiposity, a phenomenon that in industrialized Countries can synergize with obesogenic conditions and become a health-threatening phenomenon. However, low adiposity is a risk factor too, as discussed, and a qualitatively adequate amount of fat is likely a key feature of long life.

AUTHOR CONTRIBUTIONS

MC, MM and SS: concept, analysis of literature, and writing; MS and CF: analysis of literature and critical discussion.

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REVIEW
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The Impact of Aging on Adipose Function and Adipokine Synthesis

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During the last 40 years, there has been a world-wide increase in both the prevalence of obesity and an increase in the number of persons over the age of 60 due to a decline in deaths from infectious disease and the nutrition transition in low and middle income nations. While the increase in the elderly population indicates improvements in global public health, this population may experience a diminished quality of life due to the negative impacts of obesity on age-associated inflammation. Aging alters adipose tissue composition and function resulting in insulin resistance and ectopic lipid storage. A reduction in brown adipose tissue activity, declining sex hormones levels, and abdominal adipose tissue expansion occur with advancing years through the redistribution of lipids from the subcutaneous to the visceral fat compartment. These changes in adipose tissue function and distribution influence the secretion of adipose tissue derived hormones, or adipokines, that promote a chronic state of low-grade systemic inflammation. Ultimately, obesity accelerates aging by enhancing inflammation and increasing the risk of age-associated diseases. The focus of this review is the impact of aging on adipose tissue distribution and function and how these effects influence the elaboration of pro and anti-inflammatory adipokines.

Keywords: adipose tissue, adipokines, aging, menopause, cardiovascular disease, diabetes

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INTRODUCTION

The global population of individuals aged 60 years and older is expected to nearly double from 12 to 22% between 2015 and 2050 (1). Simultaneously, there has been a dramatic increase in the prevalence of obesity worldwide among developed and, more recently, low and middle income nations (2). Obesity exacerbates aging-associated inflammation by impairing insulin responsiveness and contributes to the pathophysiology of diseases frequently observed in the elderly (3). While increased weight and adiposity accompany aging, the redistribution of adipose tissue to the abdominal compartment is of greater concern. These changes occur for a number of reasons including declines in testosterone in men and estrogen in women following menopause, and alterations in the cellularity and function of subcutaneous adipose tissue (4, 5). Brown adipose tissue activity declines with age potentially as a result of reduced sympathetic nerve output and age-induced upregulation of the transcription factor FOXOA3 (6). In addition, the shift in the deposition of lipids to the abdominal adipose tissue compartment is associated with an increased risk of chronic disease (7). The ability of adipocytes to buffer dietary lipids declines with age and lipids are deposited in the liver and muscle which contributes to a low-grade state of inflammation, insulin resistance, and metabolic syndrome. Collectively, these changes in

adipose tissue function and distribution during aging affect the synthesis of adipose tissue-derived mediators, or adipokines, known to regulate many physiologic processes including inflammation. This review will briefly describe global population trends, age-associated inflammation, and changes in adipose tissue function and distribution in aging and obesity, and discuss how these factors influence the production of pro and anti-inflammatory adipokines.

AN INCREASE IN THE OBESE ELDERLY POPULATION

The number of individuals aged 65 years and older is increasing to a point where 20% of the population in the US will be 65 years or older by 2030 (1). In addition, successful public health measures have reduced the number of deaths from infectious disease in low and middle income nations raising the number of individuals who are over the age of 60 years on a global scale. Unfortunately, a transition of nutrition, where western style diets rich in calories from fat and simple carbohydrates have replaced traditional diets across the globe increasing the prevalence of obesity, defined as having a body mass index (BMI) of $\geq$30. This has coincided with an increase in chronic illnesses known to be caused by excess adiposity (7). Weight increases with age and BMI peaks occur in people aged 50–59 years and adipose tissue reaches its peak between the ages of 60 and 79 years. In total, 38.5% of persons aged 60 and older in the US were obese (8, 9). The increased prevalence of global obesity appears to have been caused by the over consumption of highly-palatable, energy dense food, and a decline in energy expenditure as a consequence of sedentary behavior (10, 11). Increased life expectancy has the potential to improve quality of life in countries with growing elderly populations. However, if life extension is associated with excess adipose tissue and altered metabolic homeostasis, the added years of life may result in diminished health status as a consequence of age-associated chronic disease, loss of physical function, and frailty (12).

INFLAMMATION IN AGING AND OBESITY

The term "Inflammaging" was originally coined by Claudio Franceschi to describe the chronic low-grade inflammation in the absence of infection driven by endogenous signals that accompany aging (3). In this scenario, the innate immune system is activated by the accumulation of cellular damage caused by reactive oxygen species (13–15). This inflammatory state increases the risk of cardiovascular disease, type 2 diabetes, arthritis, and several other ailments that compromise quality of life in the elderly (16–19). Likewise, a chronic state of low grade inflammation is observed in subjects with excess adiposity. Under these conditions, inflammation is initiated by the inability of adipose tissue to buffer dietary lipids resulting in lipotoxicity mediated by the ectopic deposition of lipids in the liver and skeletal muscle (20). Lipotoxicity in these tissues increases reactive oxygen species and activates serine threonine kinases such as c-jun N-terminal kinase (JNK), IκB kinase (IKK), and protein kinase C (PKC). These events disrupt insulin receptor signaling cascades and promote insulin resistance (15). In addition, bioactive lipid metabolites, diacylglycerol and ceramides, accumulate and negatively impact mitochondrial function, and biogenesis (21–23). These events are associated with the development of hepatic steatosis and muscle dysfunction and may trigger the development of sarcopenia (21–23). Inflammaging may also have a significant impact on the distribution and function of adipose as mentioned below.

ADIPOSE TISSUE DEPOT FUNCTION AND DISTRIBUTION

The major adipose tissue depots include the visceral, subcutaneous, bone marrow, and perivascular compartments. It is becoming increasingly clear that these depots have distinctly different functions. For example, the visceral adipose tissue depot buffers dietary lipids by storing excess calories in the form of triglycerides (20). It releases this stored energy in response to physical activity and caloric deficits in order to provide fuel for physiologic functions in the post-prandial state and during fasting. The subcutaneous compartment provides insulation, cushioning, and serves as a long-term energy storage depot (7). The function of bone marrow adipose tissue is poorly understood but this tissue replaces hematopoietic cells during aging and is the most abundant source of adiponectin in mice and humans (24). Perivascular adipose tissue, that surrounds major and small arteries and veins, regulates thermogenesis and vascular tone (25). Brown adipose tissue is closely associated with the cervical, supraclavicular, and superior mediastinal vasculature in humans (26). The deposition of lipids in various adipose tissue depots is governed by sex hormones, the location of sex hormone receptors, catecholamines, and the activity of adipose triglyceride, hormone sensitive, and lipoprotein lipases (27).

SEX DIFFERENCES IN ADIPOSE TISSUE DEPOSITION WITH AGE

Men have a lower percentage of body fat than women and tend to deposit more adipose tissue above the waist in abdominal visceral and subcutaneous compartments compared with pre-menopausal women. While visceral adipose tissue accounts for only 6–20% of total body fat, accumulation of fat in this depot is associated with an increased risk of metabolic syndrome, and cardiovascular disease (27). This is the distinguishing characteristic of the android pattern of adipose tissue deposition which is due to differences in the levels of sex hormones, testosterone and estrogen, and the adipose tissue depot specific expression of their receptors (27). In general, adipose tissue mass increases with age in response to a chronic positive calorie balance, reduced physical activity, and a lower basal metabolic rate (28). As men age, the increase in fat mass occurs predominantly above the waist with the expansion of the abdominal visceral and subcutaneous compartments and this has been attributed to declining levels of testosterone (29) Testosterone levels peak in men during puberty, begin declining

by 1% annually between the ages of 20 and 30, and reach their nadir after the age of 70 (27). In addition to a decline in testosterone synthesis, physiologically available testosterone, free testosterone and testosterone bound to albumin, also declines as a consequence of increased levels of steroid hormone binding globulin (SHBG) which binds testosterone and prevents its contribution to adipocyte fat metabolism (29). While the mechanism by which testosterone affects adipose tissue deposition has not been clearly defined, studies conducted on adipocytes obtained from human visceral adipose tissue have demonstrated that testosterone enhances lipolysis and inhibits lipid incorporation (27).

In premenopausal women, adipose tissue is distributed predominantly in the gluteal femoral subcutaneous compartment and this is associated with a lower risk of cardiovascular disease compared with abdominal fat deposition (30). This is due to estrogen receptor alpha (ERα) expression in subcutaneous gluteal femoral adipose tissue depots which mediates lipoprotein lipase activity and triacylglycerol accumulation in adipocytes this region (27). After reaching menopause, estrogen levels decline in women, and the androgen to estrogen ratio increases. Consequently, there is a redistribution of lipids to visceral adipose tissue compartment and an increased risk of cardiovascular disease, hypertension, and diabetes (5, 27, 31). The androgen to estrogen ratio is also elevated in premenopausal women with polycystic ovarian syndrome (PCOS) (32). In this a condition, lipid redistribution is also evident resulting in increased abdominal visceral adiposity and an increased risk of cardiometabolic disease (32). In addition to changes in white adipose tissue with age, a decline in brown tissue activity in older adults has also been reported (24, 33, 34).

IMPACT OF AGING ON BROWN ADIPOSE TISSUE ACTIVITY

A notable change in adipose tissue distribution associated with aging and obesity is the loss of brown adipose tissue whose function declines with advancing years and increasing body fat percentage (26). Energy is released in the form of heat from lipids stored within brown adipose tissue with the upregulation of uncoupling protein-1 (UCP-1) (26). One potential mechanism behind the loss of brown adipose tissue involves the transcription factor forkhead box protein A3 (FOXA3) which increases with aging and visceral obesity (6). Ablation of FOXA3 protects against the development of obesity and insulin resistance in aged mice on a high fat diet and improves lifespan (6). Another proposed mechanism associated with a decline in brown adipose tissue with aging is a reduction in sympathetic drive (34). Brown adipose tissue is activated and recruited to generate heat by the sympathetic nervous system. In a study by Bahler et al. sympathetic nerve activity and brown adipose tissue recruitment and activity were lower in lean older men 50–60 years old vs. lean young men aged 20–28 years (34). Finally, age may affect brown adipose tissue adipokines produced by this tissue that are known to regulate precursor cell adipocyte commitment, differentiation, and factors that promote thermogenesis (35). Brown adipose tissue adipokines have been reviewed extensively by Villarroya et al. (35).

CHANGES IN ADIPOSE TISSUE CELLULAR COMPOSITION AND DISTRIBUTION WITH AGING

Adipose tissue is composed of mature adipocytes, preadipocytes, mesenchymal cells, and various cell types that make up the stromal vascular fraction including vascular endothelial cells, smooth muscle cells, fibroblasts, and several different types of immune cells (36–40). Mature adipocytes store excess calories in the form of triacylglycerol within vacuoles to provide energy to the host in times of a negative energy balance. During weight gain, adipose tissue expands with an increase in both number of adipocytes (hyperplasia) and volume (hypertrophy). The expansion of adipocytes by hyperplasia is associated with insulin sensitivity and metabolic control, which are characteristics of subcutaneous adipocytes. In contrast, adipose tissue expansion by hypertrophy is associated with reduced triacylglycerol storage capacity, ectopic lipid deposition, and impaired insulin sensitivity (20). It also leads to adipocyte necrosis, polarization of adipose tissue macrophages that assume a classically activated or M1 phenotype, and recruitment of additional monocytes and other immune cells from the circulation in response to the elaboration of chemokines such as CCL2 and CXCL5 (41, 42). Aging has a significant impact on the lipid storage capacity and the distribution of adipose tissue in human subjects. As mentioned above, body fat percentage increases with age mostly due to increases in visceral adipose tissue expansion (43). While this is primarily due to a chronic positive energy balance, it is also influenced by a shift in lipid storage from the subcutaneous to the visceral fat depot (43). The decline in subcutaneous fat depot storage and function is thought to occur through the decline in progenitor cell function and the accumulation of senescent adipose tissue cells (44). Mesenchymal cells are progenitor cells found within the stromal vascular fraction that can undergo differentiation into preadipocytes and eventually mature adipocytes. The progenitor cell populations isolated from aged adipose tissue have reduced function and an impaired ability to incorporate lipids and potential to differentiate into preadipocytes (45, 46). In addition, there is an accumulation of senescent cells that lack the ability to divide in response to metabolic stress (47). These senescent cells express a distinguishing set of markers such as p16, p21, caveolin-1, and senescence-associated β-galactosidase (SA-β-gal). The secretion of bioactive mediators produced by these cells, referred to as having a senescent-associated secretory phenotype, is characterized by an increase in IL-6 and plasminogen activator inhibitor (PAI-1) (48, 49). Other factors that contribute to cellular senescence include telomere shortening and mitochondrial dysfunction (50, 51).

EFFECT OF AGING ON RESPONSIVENESS TO AUTONOMIC NERVE FUNCTION

Aging is associated with a decline in autonomic nervous system function which diminishes the ability of the elderly

to respond to environmental and internal stimuli (52). These impairments in autonomic system function include the loss of some autonomic nerve projections, alterations in the output and balance of sympathetic and parasympathetic outflow to visceral organs, and reduced receptor responsiveness (52). One notable example is the impact of aging on catecholamine-induced lipolysis in visceral adipose tissue (53). Under normal metabolic controls, norepinephrine released by sympathetic nerves induces lipolysis of triglycerides stored in adipocytes residing in visceral adipose tissue. Norepinephrine is metabolized by the enzyme monoamine oxidase A which is expressed in adipose tissue and sympathetic neuron-associated macrophages. In aged mice, adipose tissue macrophages are recruited to expanding visceral adipose tissue and activated in a NLRP3-inflammasome-dependent manner resulting in an increase in monoamine oxidase A and norepinephrine degradation (53). In human adipose tissue from aged humans, the import and degradation of norepinephrine is enhanced in sympathetic neuron-associated macrophages. In this circumstance, the expression of a sodium-dependent norepinephrine transporters (SLA6A2) and monoamine oxidase A are increased with aging resulting in greater clearance of norepinephrine and reduced lipolysis in visceral adipocytes (54). These changes are associated with an expansion of visceral adipose tissue, impaired insulin sensitivity, and a decline in subcutaneous adipocytes number and function with age (43, 55, 56). Ultimately, adipose tissue endocrine function and adipokine secretion are impacted as discussed below in section Effect of Aging on Adipose Tissue Adipokine Secretion.

EFFECTS OF AGING ON ADIPOSE TISSUE ADIPOKINE SECRETION

Adipose tissue is the largest endocrine gland in the human body that secretes hundreds of bioactive molecules. Among these hormones are the adipokines, proteins secreted by adipocytes and stromal vascular cells that have profound effects on several physiologic functions including appetite and satiety, adipogenesis, reproduction, glucose homeostasis, energy expenditure, inflammation, and several other physiologic functions (57). The impact of aging on adipose tissue adipokine secretion is influenced by age associated changes in adipose tissue distribution, cellular composition, local tissue inflammation, sex hormones, and cellular differentiation (43, 58–61). These combined effects alter the balance of local and systemic pro and anti-inflammatory adipokine levels. In general, the expansion of visceral adipose tissue by hypertrophy is associated with an increase in proinflammatory adipokines and a decline in anti-inflammatory mediators (42). With aging, nearly all adipokine levels are elevated in comparison with younger individuals with the same body fat percentage as mentioned below.

Pro-Inflammatory Adipokines

Leptin

Leptin is a proinflammatory adipokine best known for its role in appetite, satiety, and energy expenditure (62–64). Leptin is produced by adipose tissue and circulates in blood in proportion to total fat mass. It informs the central nervous system about the status of peripheral energy storage and contributes to the defense against weight loss. For example, when adipose tissue levels decline with weight loss, circulating leptin declines and this reduces the amount of leptin that reaches the hypothalamic nuclei in the brain that controls energy homeostasis. In response to lower leptin, appetite increases which promotes feeding. As energy intake increases, adipose tissue lipid levels rise and this restores circulating leptin and diminishes appetite to pre-weight loss levels (65). Obesity is a state of excess adipose tissue where elevated leptin levels fail to reduce appetite and increase energy expenditure. The failure of leptin to restore metabolic homeostasis in obesity is described as state of leptin resistance. Obesity induces leptin receptor induced inhibitory signals, hypothalamic inflammatory stimuli, endoplasmic reticulum stress, and gliosis. Collectively, these events promote leptin resistance in obesity (65).

In general, levels of leptin are higher in women compared with men and this difference is not only due to a higher percentage of body fat in women but is also affected by androgens (66, 67). The rate of leptin production per unit mass of adipose tissue is higher in women vs. men and this difference can be attributed to testosterone which suppresses leptin synthesis (67). Interestingly, higher leptin synthesis has been reported in subcutaneous adipose tissue compared with that observed in omental fat in overweight and obese humans (68). Despite the decline in subcutaneous fat observed in older individuals, leptin is correlated with total fat mass throughout the life course and age does not have an independent effect on leptin and adiposity in men or women (43, 61, 69–71). Therefore, the increased levels of circulating leptin in older adults is primarily due to increased fat mass in comparison with younger adults. In addition, It has been hypothesized that leptin responsiveness may be diminished with increasing age due to impaired hypothalamic leptin receptor signaling which has been demonstrated in aged rats (72, 73). While the mechanism responsible for age related leptin resistance in humans has not been demonstrated, reduced expression of the short form of the leptin receptor (LepRa) in peripheral blood monocytes has been reported in aged humans. LepRa is known to transport leptin across the blood brain barrier (71). Whether age diminishes hypothalamic leptin responsiveness in humans remains to be seen that is linearly correlated with total body fat and BMI.

Resistin

Another proinflammatory adipokine that is known to increase with obesity is resistin which was originally described by Steppan et al. as mediating insulin resistance in mice (74). Research on the role of resistin in human disease associated with obesity has been challenging due to differences between mouse and human resistin in homology and cellular sources. For example, in mice, resistin is produced by adipose tissue and monocytes. In humans, monocytes and macrophages but not adipose tissue, produce this adipokine. Resistin has been implicated as an important proinflammatory mediator in atherosclerosis since it

induces monocyte-endothelial cell interactions by increasing the expression of intracellular adhesion molecule-1 (ICAM-1) and vascular endothelial adhesion molecule-1 (VCAM-1) (75–77). While age does not appear to affect resistin levels independent of fat mass, elevated levels of this adipokine are associated with an increased risk of cardiovascular disease in elderly men and women and insulin resistance in patients with a history of coronary intervention (70, 76, 78, 79).

Chemerin

Chemerin is a hormone secreted by adipose tissue that activates the chemokine-like receptor-1 (CMKLR-1) to initiate innate and adaptive immune responses (80). It is a secreted prohormone that requires further processing by proteases in order to become biologically active (81). This proinflammatory adipokine acts as a chemoattractant for immature dendritic cells, macrophages, and natural killer cells that express CMKLR-1 (82). It is correlated with BMI and elevated in individuals with central obesity and may be an important link between excess adiposity and type 2 diabetes (81, 83, 84). It promotes the secretion of adipokines that induce insulin resistance in diabetes. Chemerin was positively associated with age but it is not clear if increased chemerin occurs as a consequence of aging or the accumulation of visceral adipose tissue with advancing years (80). In addition, there is uncertainty about a specific role of chemerin in metabolic diseases associated with excess adiposity since weight loss and improved metabolic control are associated with reduced chemerin levels. This might suggest that chemerin synthesis is responsive to metabolic status rather than it being a bioactive mediator that promotes inflammation and insulin resistance independent of other proinflammatory mediators (85). Evidence of sexual dimorphism for this adipokine is supported by increased levels of chemerin mRNA in subcutaneous vs. visceral adipose tissue compartments in women in a report by Alfadda et al. (86). In men and women with polycystic ovarian disease, a condition characterized by elevated levels of testosterone and increased visceral adipose tissue, mRNA levels of chemerin were elevated in the visceral compared with subcutaneous adipose tissue compartments (87).

Retinol Binding Protein 4 (RBP4)

RBP4 is member of the lipocalin family of proteins that binds retinoic acid and transports it to peripheral tissues and whose expression increases with BMI, total body fat, and hepatic adipose tissue (88, 89). In addition to adipocytes, it can be produced by the liver and macrophages. RBP4 may directly promote adipose tissue inflammation and insulin resistance in humans since enhanced expression of RBP4 in transgenic mice results in adipose tissue inflammation and macrophage accumulation (90). In addition, RBP4 expression is associated with the percentage of trunk fat (central adiposity) and insulin resistance in young but not elderly subjects (91). Interestingly, RBP4 levels are significantly elevated in aged individuals independent of central adiposity (91). Circulating levels of RBP4 are higher in male compared with female mice and humans (92, 93).

Lipocalin 2 (LCN2)

LCN2, also referred to as neutrophil gelatinase-associated lipocalin, is another member of the lipocalin family of proteins that transports lipid molecules such as retinoic acid, arachidonic acid, leukotriene B_4, and platelet activating factor in circulation (94). It is produced by adipocytes at high levels in mice and humans in response to inflammatory stimuli and the impact of age on this proinflammatory adipokine is unknown (95, 96). However, adipose tissue-derived LCN2 has been shown to promote the pathogenesis of renal injury, a condition that is more prevalent in aged individuals with type 2 diabetes (97, 98). In addition, it may also play an important proinflammatory role in adipose tissue remodeling during visceral fat expansion (99). Since LCN2 is from the same family of proteins as RBP4, a lipid transporter whose synthesis increases with advancing years, age may affect the expression of LCN2 and influence the progression of diseases associated with obesity (91). Like chemerin, a sexual dimorphic pattern of LCN2 mRNA expression has been observed in humans with higher levels in visceral vs. subcutaneous adipose tissue depots in men and women with polycystic ovarian disease. In women, LCN2 transcripts are higher in the subcutaneous vs. visceral compartments (87).

Classical Proinflammatory Cytokines CCL2, IL-1β, IL-6, IL-12, IL-18, and TNF-α

Age associated changes to adipose tissue increase the synthesis of classical cytokines (100–104). As noted early, aging results in the redistribution of lipids that accumulate in visceral adipose tissue (43). This results in an increase in adipocyte hypertrophy since fat mass expansion via adipocyte hyperplasia is inhibited by an age-related decline in the ability of progenitor cells to differentiate into preadipocytes. Proinflammatory cytokines also inhibit preadipocyte differentiation and maturation, and promote adipocyte senescence (44–46, 56, 60). Proinflammatory cytokines (IL-1β, IL-6, TNF-α) secreted by adipose tissue macrophages reduce PPAR-γ expression, an important transcription factor that induces adipogenesis (42). Monocytes are recruited to visceral adipose tissue in response to chemokines such as CCL2 and these cells differentiate into adipose tissue macrophages (105). These proinflammatory mediators, associated with the M1 classically activated macrophage phenotype, impair insulin sensitivity and glucose tolerance (42, 106, 107). An increase in the adipose tissue population of CD8+ T cells and a decline in regulatory T cells are thought to contribute to the promotion and maintenance of the M1 phenotype of adipose tissue macrophages with aging (107–109). In general, proinflammatory adipokines increase with age due to either increased adipose tissue mass or an enhancement of inflammation that promotes increased synthesis. In opposition to these proinflammatory bioactive molecules are the anti-inflammatory adipokines which also have been observed to increase with age. The overabundance of proinflammatory adipokines associated with excess central adiposity may outweigh the effects of the anti-inflammatory adipokines mentioned below.

Anti-inflammatory Adipokines

Adiponectin

The anti-inflammatory adipokine, adiponectin, is the most abundantly expressed adipokine found in human serum at levels in the μg/ml range (110). In contrast to all other adipokines, it is predominantly produced by bone marrow adipose tissue (24). Adiponectin forms complex aggregates that circulate in high (HMW), medium, and low-molecular weight forms with the HMW form having the greatest effect on improving insulin sensitivity and glucose tolerance (111). There are two isoforms of the adiponectin receptor (AdipoR1 and AdipoR2) that are expressed in vascular endothelial cells, monocytes and macrophages, skeletal and cardiac muscles cells, and adipocytes (60, 112). Adiponectin plays a protective role against cardiovascular disease since it inhibits foam cell formation, adhesion molecule expression, and endothelial cell-monocyte interactions (113, 114). It also inhibits the synthesis of proinflammatory cytokines such as IL-6, IL-18, and TNF-α synthesis by blocking NF-κB activation (115, 116). Adiponectin promotes adipogenesis and the expansion of adipose tissue via hyperplasia, a mechanism of fat pad expansion that reduces adipose tissue inflammation and maintains insulin responsiveness and glucose homeostasis (117). Peroxisome proliferator-activated receptor-gamma (PPARγ) agonists, such as the glitazone drugs, increase adiponectin synthesis (118, 119). Serum adiponectin levels are elevated with age, fasting, treatment with glucocorticoids, and conditions that enhance the expansion of bone marrow adipose tissue (24, 120–123). In contrast, lower levels of adiponectin are associated with obesity, cigarette smoking, and oxidative stress (124, 125). Centenarians have higher levels of adiponectin and this may be associated with longevity (126, 127). While elevated adiponectin may be associated with improved metabolic status in the elderly, it has also been associated with reduced physical functioning (127, 128). Serum adiponectin levels are higher in women than in men (129).

Vaspin

Visceral adipose tissue-derived serpin (Vaspin), a member of the serine protease inhibitor family of proteins, is expressed by visceral fat in rats and humans (130). It was originally found in Otsuka Long-Evans Tokushima rats and associated with obesity and insulin sensitivity in rats and humans (130, 131). Higher levels of vaspin have been reported in women vs. men (132). Exogenous administration of vaspin improves insulin responsiveness and glucose tolerance in mice (132). In addition, vaspin levels increase following aerobic exercise in untrained individuals (132, 133). In addition to adipose tissue, vaspin is produced by the β-cells of the pancreas, skin, and the hypothalamus in mice (133). Vaspin declines with aging and insulin sensitivity but increases following treatment with insulin or pioglitazone (130, 133). Interestingly, vaspin mRNA is undetectable in the adipose tissue of lean adults (BMI < 25) but increases in visceral and subcutaneous adipose tissue of individuals in association with BMI, body fat percentage, and insulin sensitivity (134).

Secreted-Frizzled-Related Protein 5 (SFRP5)

SFRP5 is an anti-inflammatory and insulin sensitizing adipokine that promotes adipogenesis by inhibiting wingless type MMTV integration site (Wnt) 5a/JUN N-terminal kinase (JNK) intracellular signaling events in macrophages and preadipocytes suppressing the synthesis of TNF-α', IL-1β, and CCL2 (60, 135, 136). Its production in adipose tissue promotes adipose tissue expansion via hyperplasia (42). Levels of SFRP5 are lower in individuals with obesity, diabetes, non-alcoholic fatty liver disease, and hypertension and negatively correlated with C-reactive protein (CRP) (60, 137–142). SFRP5 levels increase with age and are higher in female compared with males in both rodents and humans (143).

Omentin-1

Omentin-1 is an anti-inflammatory adipokine that is expressed in omental and epicardial fat (visceral adipose compartment) as wells as bronchial goblet cells, mesothelial cells, vascular cells, Paneth cells within the small intestine, colon, and ovaries (144). While the isoform omentin-2, has been identified, its distinct biologic function is unknown. Although the receptor and physiological functions of omentin-1 are unknown, it signals through AMP-kinase/AKT/NF-κB/MAP Kinase (ERK, JNK, p38) pathways. In general, lower levels of omentin-1 are associated with systemic inflammation and impaired metabolic control such as in obesity, type I and type 2 diabetes, coronary artery disease, metabolic syndrome, and hepatic steatosis (144–149). Omentin-1 levels increase with age, weight loss, olive oil rich diets, aerobic exercise, administration of fibroblast growth factor (FGF)-21, and following treatment with drugs used to improve insulin responsiveness (144, 150–156). Omentin-1 may be a promising treatment for atherosclerosis since exogenous administration of this adipokine prevents atherosclerosis in Apo-e deficient mice by reducing reactive oxygen species synthesis, suppression of TNF-α—induced intracellular adhesion molecule (ICAM) and vascular endothelial cell adhesion molecule (VCAM) expression, and monocyte interaction with vascular endothelium (157).

C1q/TNF-Related Proteins (CTRPs)

CTRPs are anti-inflammatory adipokines that are structurally similar to adiponectin and 15 different isoforms have been identified (158). CTRPs activate intracellular signaling events via AMP-kinase which inhibits proinflammatory cytokine production (159). CTRPS enhance insulin responsiveness and glucose tolerance after high intensity interval training (160). CTRP1, CTRP9, and CTRP12 increase with insulin sensitivity and promote glucose uptake (161–163). CTRP1 is somewhat different than other CTRP family members since it is produced by non-adipocytes within the stromal vascular fraction of adipose tissue and increases with obesity and hypertension (158). CTRP1 is associated with atherosclerosis and promotes

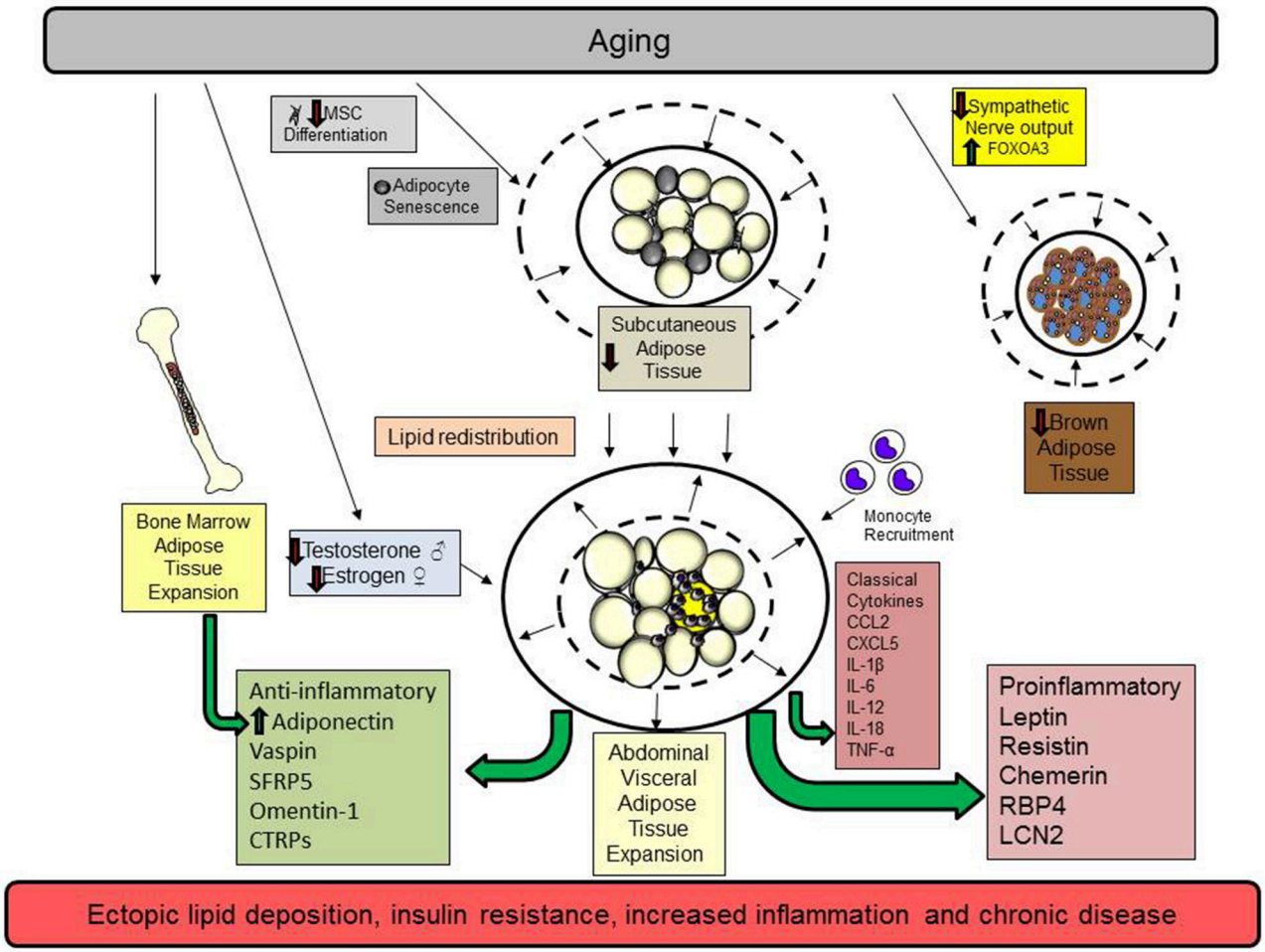

FIGURE 1 | Aging promotes the redistribution of lipids from the subcutaneous to the abdominal visceral compartment. Aging promotes cellular senescence and impairs mesenchymal stem cell (MSC) differentiation in subcutaneous adipose tissue. These changes diminish adipocyte function by reducing preadipocyte maturation, restrict adipocyte hyperplasia, and reduce subcutaneous adipocyte mass. In addition, declining sex hormones in men (testosterone) and women (estrogen) also contribute to visceral adipose tissue expansion. Brown adipose tissue declines because of reduced sympathetic output and increases in the transcription factor FOXOA3. Subsequently, lipids are redistributed to the abdominal adipose tissue depot. As adipose tissue expands in this compartment, adipocytes undergo hypertrophy, a process that contributes to adipocyte necrosis, adipose tissue inflammation, and the elaboration of proinflammatory classical cytokines and adipokines. Monocytes and other immune cells are recruited to the visceral adipose tissue depot to remove necrotic adipocytes and participate in tissue remodeling limiting lipid storage. Ultimately, these events contribute to ectopic lipid storage and insulin resistance. Bone marrow adipose tissue expands to replace hematopoietic cells and this is associated with increased adiponectin synthesis. While many pro and anti-inflammatory adipokines increase with age, the dominance of proinflammatory adipokines shifts the balance to favor a chronic state of inflammation.

monocyte-endothelial cell interactions (164). In contrast, CTRP3 has potent anti-inflammatory effects since it blocks LPS–TLR4 mediated inflammation (165). CTRP3 is lower in patients with type 2 diabetes and its levels are inversely proportional to blood glucose and insulin (166). Interestingly, serum levels of CTRP3 and CTRP5 increase following 8 weeks of aerobic training in middle-aged and older men and women and this was associated with reduced arterial stiffness (167). In liver cells, CTRP13 improves glucose uptake and insulin resistance in lipid laden hepatocytes (168). Finally, CTRP11 and CTRP14 have been shown to stimulate angiogenesis of endothelial cells and these CTRP isoforms may be important in adipose tissue vascularization (169). More research is needed to study the potential use of CTRPs known to improve insulin sensitivity and glucose tolerance in patients with type 2 diabetes.

CONCLUSIONS

There has been a dramatic increase in the number of people over the age of 60 years globally. Unfortunately, these extra years may be associated with a lower quality of life due to chronic illness and metabolic disease associated with obesity. Aging promotes the redistribution of lipids from the subcutaneous to the abdominal visceral compartment. The process is summarized in **Figure 1**. The inflammation that occurs in aging is exacerbated

by excess adiposity contributing to an increased risk of type 2 diabetes, cardiovascular disease, and many other diseases associated with obesity. To counter these events, interventions that maintain adipose tissue function during aging, such as eliminating senescent cells, exercise, weight loss, and drugs that promote insulin sensitivity, may increase life expectancy and ultimately, quality of life. More research is needed to assess the impact of sex differences and aging on adipokine synthesis and function and whether these differences contribute to or are a consequence of diseases associated with aging.

AUTHOR CONTRIBUTIONS

PM wrote and edited the manuscript. BB helped find references, edited manuscript, and provided expertise in adipokine assessment.

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REVIEW
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Adipokines and Aging: Findings From Centenarians and the Very Old

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Adipose tissue, which was once considered as a simple energy storage depot, is now recognized as an active endocrine organ that regulates the whole-body energy homeostasis by secreting hundreds of bioactive substances termed adipokines. Dysregulation of adipokines is a key feature of insulin resistance and a metabolic syndrome associated with obesity. Adipokine dysregulation and insulin resistance are also associated with energy-deprivation conditions, such as frailty in old age. Previous studies have demonstrated that preserved insulin sensitivity and low prevalence of diabetes are the metabolic peculiarities of centenarians, suggesting the possible role of adipokine homeostasis in healthy longevity. Among the numerous adipokines, adiponectin is regarded as unique and salutary, showing negative correlations with several age- and obesity-related metabolic disturbances and a positive correlation with longevity and insulin sensitivity among centenarians. However, large-scale epidemiological studies have implied the opposite aspect of this adipokine as a prognostic factor for all-cause and cardiovascular mortality in patients with heart failure or kidney disease. In this review, the clinical significance of adiponectin was comparatively addressed in centenarians and the very old, in terms of frailty, cardiovascular risk, and mortality.

Keywords: centenarian, longevity, adipokines, adiponectin, frailty

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INTRODUCTION

Advances in obesity research from the early 1990s have shed light on the prominent role of adipose tissues as an active endocrine organ that regulates energy homeostasis by secreting bioactive substances termed adipokines (1). A growing number of these adipokines have been identified, and their roles in regulating whole-body energy homeostasis via modulation of several signaling cascades in the target tissues are being increasingly discovered. Dysregulation of adipokines is regarded as a key feature of insulin resistance, hyperglycemia, and dyslipidemia, as well as the comorbidities of obesity, such as metabolic syndrome, type 2 diabetes mellitus (T2DM), and cardiovascular disease (2, 3). However, accumulating evidence signifies that adipokine dysregulation is also associated with wasting syndromes such as cachexia and sarcopenia, suggesting that adipose endocrine function is essential for maintaining whole-body energy homeostasis, which is indispensable for a multitude of physiological functions under the conditions of both energy excess and deprivation (4). Furthermore, genetic manipulation of the adipose tissue has been shown to promote longevity in mice models, denoting its possible role in regulating the lifespan (5).

Centenarians have been able to delay the onset of life-threatening diseases, such as cardiovascular diseases or cancers, or even escape from them altogether until the late years of

life, thus serving as models for healthy aging (6, 7). For more than three decades, centenarian studies have been conducted to identify biological markers conducive to healthy longevity. Several key pathways for maintaining health and longevity have been thereby discerned; of which insulin sensitivity has been recognized as one of the major pathways to healthy longevity, which is conserved right from dwarf mice to centenarians (8). In this review, we have discussed the possible roles of adipokines, especially adiponectin, in regulating longevity in humans and the possibility that this regulation may be mediated via the preservation of insulin sensitivity and compensatory mechanisms against inflammation and oxidative stress that occurs with aging.

INSULIN SENSITIVITY AS A HALLMARK OF LONGEVITY: LESSONS FROM LONG-LIVED MICE AND CENTENARIANS

Caloric restriction is one of the most replicated pro-longevity interventions across species (9). Interestingly, calorie-restricted mice and a series of long-lived rodent models, such as the Ames dwarf, Snell dwarf, and growth hormone receptor knockout, share common features, including reduced GH/insulin-like growth factor 1 (IGF-1) signaling, preserved insulin sensitivity, reduced growth, and body size (10). The precise molecular mechanism by which reduced somatotropic signaling enhances longevity has not yet been completely elucidated; however, downregulation of reactive oxygen species and increased stress resistance may be involved in the aging delay witnessed in these models (11–13). In humans, insulin sensitivity normally decreases during aging; nonetheless, accruing evidence has documented the preservation of insulin sensitivity and glucose homeostasis among the centenarians and their offspring. In the late 1990s, Paolisso et al. first reported that glucose tolerance and insulin sensitivity were better preserved in healthy centenarians than in elderly individuals aged >75 years using a euglycemic glucose clamp method (14). Subsequently, in the Leiden longevity study, Wijsman et al. revealed that the offspring of long-lived siblings had better insulin sensitivity than the controls of corresponding age and body mass index (BMI), hinting at the inheritable component of insulin sensitivity and longevity (15). Metabolic syndrome (MS) and T2DM, both of which are devastating consequences of insulin resistance, increase in older adults (16, 17). Intriguingly, the low prevalence of these metabolic diseases is reportedly observed worldwide among the centenarians. In the Tokyo Centenarian Study, Takayama et al. examined 304 centenarians living in the Tokyo metropolitan area and inferred that the prevalence of diabetes mellitus was only 6.0%, which is less than half of that in the general population of 60s (15.3%) and 70s (14.7%) in Japan (18). The Finnish Centenarians Study (19) presented a 10% prevalence of T2DM among the Finnish centenarians, which was lower than that recorded among the 65- to 85-year-old Finnish individuals. Similarly, the Italian Multicenter Study on Centenarians (20) demonstrated that 4.9% of the 602 centenarians had T2DM, and the New England Centenarian Study stated that 4% of the 424 centenarians had T2DM (21), both of which were lower upon comparison with the respective aged but younger populations. These findings collectively indicate that preserved insulin sensitivity and glucose homeostasis are the hallmarks of longevity in both rodents and humans.

ADIPOKINE PROFILES OF CENTENARIANS

To date, vigorous basic research has been conducted on the biology underlying the association between insulin sensitivity and longevity, and the adipokines have emerged as a possible mechanistic link (22, 23). Among these substances, adiponectin is one of the most potent molecules regarding insulin sensitizing activity. Unlike the majority of adipokines, plasma adiponectin levels displayed an inverse correlation with adiposity and are reduced in obese individuals (24). Adiponectin plays an anti-diabetic role within the liver and skeletal muscles by facilitating the glucose uptake at these sites, thereby enhancing the insulin sensitivity. Adiponectin also has anti-inflammatory and anti-atherogenic properties and is thus regarded as an immensely beneficial adipokine (25). Leptin is another adipokine of interest that regulates whole-body energy homeostasis by restricting food intake and stimulating energy expenditure (26). In a series of rat models, decreased visceral fat mass, obtained either by caloric restriction or surgical resection, improved age-related insulin resistance, possibly via alteration of leptin and other adipokine secretions (27, 28). Moreover, mice with fat-specific disruption of the insulin receptor gene (FIRKO) have been demonstrated to exhibit reduced adiposity, lower fasting insulin levels, and enhanced longevity (5). FIRKO mice were also characterized by elevated serum adiponectin levels. These rodent models demonstrated that reduced adiposity itself can extend the lifespan and altered adipokine secretion, especially the upregulation of adiponectin and insulin sensitivity, may be the critical mediators of this process.

On the basis of these experimental evidences from longevity model animals, centenarian studies investigated the association between adipokines and healthy longevity in humans. We used PubMed to search for relevant publications before November 2018 in English. We used the search terms "centenarians" by title/abstract screening and "adipokines," "adipocytokines," "leptin," and "adiponectin." We also checked the reference lists of the relevant publications identified in the search. We excluded articles without control groups (usually healthy, older adults), and identified seven studies as shown in **Table 1**. In the first study of its kind, Paolisso et al. demonstrated that the plasma leptin levels were higher in the 19 healthy centenarians than in adults aged <50 years, but lower in elderly aged 75–99 years (29). The levels in healthy centenarians were inversely correlated with IGF-1/IGF-1 binding protein 3 molar ratio, alluding the possible effects of the unbound form of IGF-1 on circulating leptin regulation (29). In contrast, Baranowska et al. reported that 75 female centenarians had significantly lower leptin levels than elderly females aged 64–67 years or younger females aged 20–43 years (30). Low leptin levels in

centenarians seem to be independent of BMI or fat mass, because BMI of centenarians did not differ from that of younger females. While Pareja-Galeano et al. demonstrated that 81 healthy centenarians without major disease had significantly higher leptin levels than sex-matched elderly controls aged 70–80 years, although BMI was not compared between the two groups (31). Recently, in older adults, Lana et al. demonstrated that higher leptin levels were associated with a greater risk of incident frailty, which was independent of body fat, homeostasis model assessment for insulin resistance (HOMA-IR), or CRP (32). Conflicting findings over leptin levels in centenarians may reflect multiple regulatory mechanisms of this adipokine with aging. Regarding adiponectin, Arai et al. reported that 66 female centenarians had higher plasma adiponectin levels than the BMI-matched younger females (33). In addition, the high plasma adiponectin concentrations in centenarians were associated with an advantageous metabolic phenotype, including higher high-density lipoprotein-cholesterol (HDL-C) levels and lower hemoglobin A1c, and negatively correlated with C-reactive protein and E-selectin concentrations (33). Bik et al. also testified the occurrence of hyperadiponectinemia in Polish centenarians (34); the researchers found an inverse correlation between plasma adiponectin levels and HOMA-IR, a reliable marker of insulin resistance. In addition, Atzmon et al. also claimed that 118 long-lived individuals (aged $\geq$95 years) had increased the adiponectin levels and that the levels were inversely correlated with BMI, waist circumference, and percent body fat, but positively correlated with HDL-C and the lipoprotein particle size (35). In the circulation, adiponectin has three oligomeric forms, including a trimer (low-molecular weight), hexamer (medium-molecular weight), and high-molecular weight (HMW) form. Among them, HMW adiponectin is the major active form as it displays greater insulin sensitizing and anti-inflammatory properties in experimental studies (36). Bik et al. investigated the adiponectin isoforms in 58 Polish centenarians and found that they have significantly higher levels of total isoforms, as well as all isoforms of adiponectin individually, compared with elderly individuals aged approximately 70 years (37). The investigators also proved that both total and HMW adiponectin were positively correlated with HDL-C and negatively correlated with the fasting glucose and insulin levels, HOMA-IR, and triglycerides (37). As presented in **Table 1**, most studies demonstrated a high plasma adiponectin level among the centenarians, which can be correlated with a preferable metabolic phenotype, including high HDL-C and insulin sensitivity, thereby signifying the beneficial metabolic effects of this adipokine on enhancing longevity. However, because centenarian studies on circulating adiponectin are exclusively based on cross-sectional design, whether high adiponectin levels are the cause or consequence of long life remain to be elucidated.

GENETIC DETERMINANTS OF CIRCULATING ADIPONECTIN LEVELS

There are several studies on the genetic variations that determine the circulating adiponectin level. The first genome-wide linkage study asserted that the gene (*ADIPOQ*) in 3q27 was highly associated with circulating adiponectin levels in Hispanic-Americans (39). Thereafter, the most reported single nucleotide polymorphism (SNP) in *ADIPOQ*, rs266729, located in the promoter region, was significantly linked with the circulating adiponectin level. This was demonstrated because subjects with GG genotype in rs266729 exhibited higher plasma adiponectin levels than those of other genotypes in some replicated studies, including those hailing from different ethnic backgrounds (40, 41). This SNP is supposed to be the most promising genetic variation related to adiponectin level and also the risk of MS (42), T2DM (43), and insulin resistance (41). Another SNP located in the promoter region of *ADIPOQ*, rs1656930, was highly connected with the adiponectin levels of elderly Japanese subjects (44). Another genome-wide association study (GWAS) revealed that SNP (rs4783244), located in intron 1 of the T-cadherin gene (*CDH13*) was significantly associated with the plasma adiponectin levels of Taiwanese (45), Japanese (46) subjects and the risk of MS and T2DM (45). These SNPs are also implicated in cardiovascular remodeling, such as carotid intima-media thickening (40) and cardiovascular complications (47), possibly through the modulation of circulating adiponectin levels.

The association between adiponectin genotype and longevity was tested in a cohort of Ashkenazi Jews with exceptional longevity. Atzmon et al. examined the plasma adiponectin levels and *ADIPOQ* genotypes in long-lived individuals (>95 years), their offspring and controls, and uncovered that the two common variants of *ADIPOQ* were over-represented among the male long-lived individuals compared with the corresponding controls (35). Interestingly, the findings were not observed in the female participants. Further studies with a large sample size are warranted to replicate the association between *ADIPOQ* and human longevity.

ADIPONECTIN AND CARDIOVASCULAR MORTALITY: ADIPONECTIN PARADOX

In contrast to the basic science reports and findings from centenarian studies, which collectively support the beneficial metabolic effects of adiponectin, accumulating observational studies have demonstrated an unexpected association between high adiponectin levels and increased mortality in patients with cardiovascular disease, particularly heart failure. In 195 patients with chronic heart failure, Kistorp et al. demonstrated that high plasma adiponectin levels were associated with increased mortality risk, independent of the severity of the heart failure and BMI (48). Moreover, circulating adiponectin was significantly correlated with N-terminal pro-brain natriuretic peptides (NT-proBNP), and the association between adiponectin and mortality remained significant after adjustment by NT-proBNP (48). Subsequently, the connection between adiponectin and mortality has been replicated in studies with much larger samples and other clinical settings, such as ischemic heart disease, type 1 and type 2 diabetes, end-stage renal disease, and even in the general elderly population (49–51). These findings are counterintuitive to its salutary metabolic effects and thus called

TABLE 1 | Centenarian studies reporting circulating leptin and adiponectin levels.

References	Sample size no. of centenarians (% of females)	Controls	BMI	Leptin level	Adiponectin level
Paolisso et al. (29)	19 (58% females)	30 Adults (aged <50 years) 30 elderly	↓	↔*	ND
Arai et al. (33)	66 (100% females)	66 BMI-matched young females	↔	ND	↑
Bik et al. (34)	22 (100% females)	45 young females 19 elderly females 36 obese females	↓	ND	↑
Baranowska et al. (30)	75 (100% females)	45 young females 26 elderly females 37 obese females	↓	↓	↑
Atzmon et al. (35)	118 (aged ≥95 years, 74% females) 228 offspring (50% females)	78 elderly	↓ (probands) ↔ (offspring)	ND	↓ (probands) ↔/↑† (offspring)
Meazza et al. (38)	48 (77% females)	50 elderly 62 neonates	↓	↓	↑
Bik et al. (37)	58 (86% females)	68 elderly	↓	ND	Total ↑, HMW ↑ MMW ↑, LMW ↑
Pareja-Galeano et al. (31)	81 (51% females)	46 elderly	ND	↑	↔

**Leptin levels in centenarians was higher than that in adults, but lower than that in the elderly. ↑† Adiponectin levels in offspring was lhigher than that in elderly controls when adjusted for age, sex, and BMI. ↑ Higher in centenarians compared to controls. ↓ Lower in centenarians compared to controls. ↔ No difference between centenarians and controls.*

adiponectin paradox. A meta-analysis of earlier studies, including 24 prospective studies suggested that the paradoxical association between high adiponectin levels and increased all-cause mortality risk is more significant in those with coronary heart disease (CHD) at the baseline than those without CHD (52). Sex dimorphism is also documented, and high adiponectin levels predict cardiovascular mortality in men, but not in females with T2DM (53). In contrast, recent meta-analysis, including 55 and 28 studies for all-cause and cardiovascular mortality, respectively, demonstrated that 1-SD increment of adiponectin was associated with a 24 and 28% increase in all-cause and cardiovascular mortality, respectively (54). When restricted to studies with natriuretic peptides measurement, a substantial reduction in the associations between circulating adiponectin and all-cause and cardiovascular mortality was substantially attenuated by adjustment for natriuretic peptides, denoting that the adiponectin paradox is partly mediated by natriuretic peptides (54). Interestingly, Tsukamoto et al. demonstrated that both atrial and brain natriuretic peptides enhance the production of adiponectin in adipocytes and that the intravenous infusion of ANP increases circulating adiponectin levels in humans (55). These data imply that the paradoxical association between circulating adiponectin and mortality may be indirect and mediated by coexisting cardiovascular risk factors, such as natriuretic peptides.

Another plausible mechanism underlying the paradoxical association is adiponectin resistance. Adiponectin enhances insulin sensitivity by improving glucose uptake in the skeletal muscles, inhibiting gluconeogenesis and stimulating the β-oxidation of fatty acids through adiponectin receptor 1 (Adipo R1) and receptor 2 (56, 57). In patients with chronic heart failure, Van Berendoncks et al. proved that adiponectin levels are increased, both in circulation and in their gene expression in the skeletal muscle, but also demonstrated a downregulation of Adipo R1 and deactivation of the PPAR-α/AMP-activated protein kinase pathway. Hence, increased adiponectin concentrations are not effectively connected with downstream signal transductions, resulting in functional adiponectin resistance (58). Therefore, in this context, high circulating adiponectin in heart failure represents the presence of a protective mechanism to counteract adiponectin resistance and the compromised energy metabolism.

A causal relationship between adiponectin and CHD has been addressed by genetic research. In a Mendelian randomization study, Borgers et al. examined the link between the genetic variant of adiponectin levels and CHD risk using data from GWAS consortia (59) and found no causal role of adiponectin level in CHD risk. On the other hand, Uetani et al. observed that a GWAS-based SNP in *CDH13* was associated with both circulating HMW adiponectin levels and increased all-cause mortality in the general population (60), although the researchers did not address cardiovascular-specific mortality. More experimental and epidemiological studies are needed to determine whether adiponectin has direct deleterious effects on cardiovascular pathology and mortality.

ADIPONECTIN AND FRAILTY IN THE VERY OLD: ANOTHER PARADOX

Paradoxical associations between high adiponectin levels and mortality are conspicuous in the very old even without cardiovascular disease or chronic kidney disease, indicating the potential involvement of this adipokine in geriatric syndrome, such as frailty and sarcopenia. This topic has been vigorously addressed in our longitudinal cohort study for old people, known as the SONIC (i.e., septuagenarians, octogenarians, and non-agenarians investigation with centenarians) study, which investigated the age differences and similarities in factors influencing healthy aging and psychological well-being, including psychological (i.e., cognition, change in emotion and compensation, personality, and psychological development); social (i.e., socio-economic status and social relationship); and medical, dental, and nutritional aspects (61). In 353 community-dwelling older adults of approximately 83 years, Nagasawa et al. deduced an association between circulating adiponectin and frailty status according to the cardiovascular

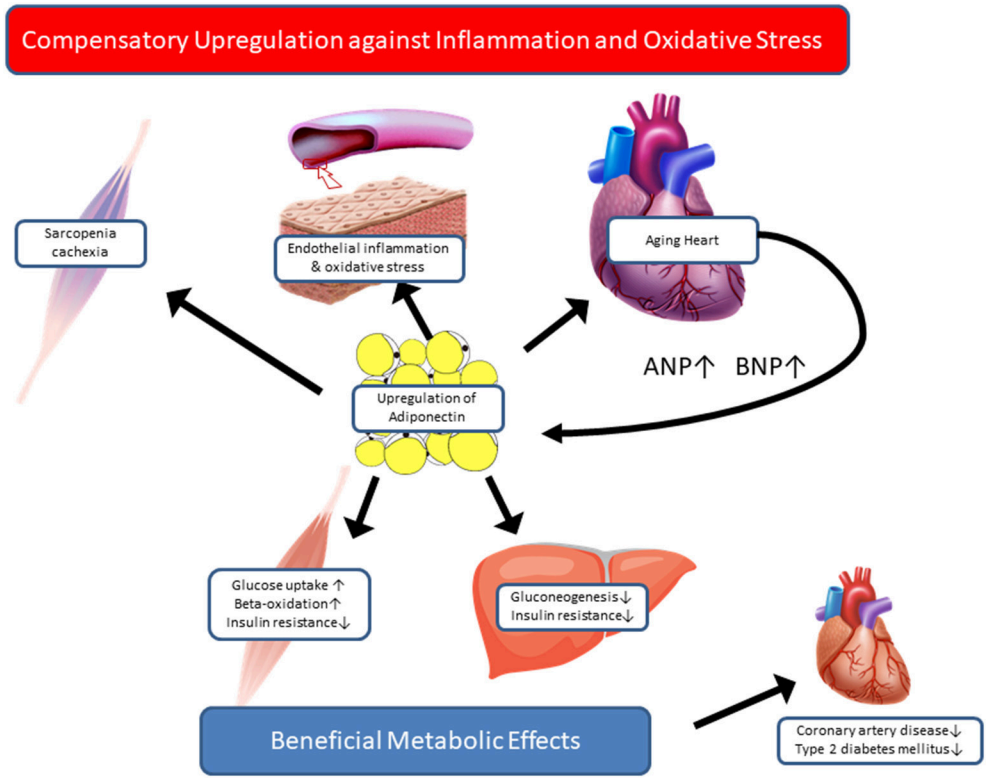

FIGURE 1 | Hypothetical roles of adiponectin in centenarians. Based on paradoxical evidence regarding the association between adiponectin and health outcomes, we propose two hypothetical roles of adiponectin in centenarians. Adiponectin is a salutary adipokine that is present at high levels in healthy and lean individuals, e.g., centenarians. High adiponectin levels are associated with low insulin levels and low HOMA-IR, and a favorable lipid profile, which is consequently associated with a low risk of coronary artery disease and type 2 diabetes. In contrast, in patients with catabolic states, such as chronic heart failure and sarcopenia, adiponectin is upregulated as a part of compensatory mechanisms against inflammation and oxidative stress in relevant organs. Once the compensation fails, in case of adiponectin resistance, high adiponectin levels predict high mortality in advanced stage of disease or aging.

health study criteria (62). The investigators found significantly higher adiponectin levels in frail subjects than in their non-frail counterparts. Moreover, a multivariate logistic regression analysis affirmed that the elevated adiponectin level, higher estimated glomerular filtration rate, and lower hemoglobin were independent determinants of the pre-frail/frail status when compared with the non-frail status. Weight loss, low muscle mass, and poor physical functioning are the core components of frailty in older adults. Among the 2,821 participants of health ABC study, who had whole-body dual-energy DXA, Baker et al. explored the independent association among circulating adiponectin, body composition, physical functioning, and mortality (63). The authors uncovered a significant relationship between high adiponectin and historical weight loss, low muscle mass, and low muscle density. Adiponectin was substantially associated with increased risk of incident disability and all-cause mortality; however, when adjusted for weight loss and physical performance at baseline, the association was attenuated and no longer significant. On the basis of these findings, the researchers suggested that the high adiponectin levels in the very old may represent a compensatory response to low energy availability in the setting of starvation. Interestingly, high adiponectin in plasma is associated with low functional capacity in patients with chronic heart failure (64), signifying that this adipokine may be a marker for wasting in CHF. Moreover, among 1,303 patients with predialysis chronic kidney disease, Hyunn et al. demonstrated that a higher adiponectin level was associated with protein malnutrition defined by hypoalbuminemia, low BMI, low urine creatinine excretion, and low protein intake (65). Collectively, these epidemiological findings suggested that circulating adiponectin may be a useful biomarker of catabolic processes, such as sarcopenia and cachexia, in the chronic conditions, which are frequently associated with weight and muscle loss as well as high mortality risk among the elderly.

HIGH ADIPONECTIN LEVELS IN CENTENARIANS: POSSIBLE COMPENSATORY RESPONSES TO MAINTAIN METABOLIC AND REDOX HOMEOSTASIS

In contrast to the beneficial metabolic and cardioprotective effects of adiponectin observed in long-lived animal models, immense epidemiological evidence supports the paradoxical

relationship between high adiponectin levels and poor outcomes in cardiovascular and geriatric conditions. If that is the case, how can we interpret the high adiponectin levels in centenarians? Most of the centenarian studies aiming at circulating adiponectin are cross-sectional and comprise a relatively small sample size, hence posing limitations in elucidating the causal relationship between high adiponectin and exceptional longevity. Recently, Sebastiani et al. assessed 38 age-related circulating biomarkers in ∼5,000 healthy, older adults of the long-life family study, aged 25–110 years, and 34 biomarkers had a statistically significant association with age at assessment (66). Among these, adiponectin and NT-proBNP showed similar correlation coefficients with age ($r = 0.3178$, $p < 0.001$; $r = 0.3793$, $p < 0.001$, respectively), although correlation between these two biomarkers are not shown. Their findings suggest that the high adiponectin levels in centenarians may be the consequence of advancing age, even without prevalent cardiovascular disease. To examine prognostic significance of adiponectin, we investigated the association between a set of adipokines and all-cause mortality in a prospective cohort study of 252 centenarians, aged 100–108 years (67). In this work, we noticed the significant association of low leptin and high TNF-alpha with higher mortality risk. Interestingly, stratified analysis by BMI revealed that the significant association of leptin and mortality was reduced in lower-BMI group, suggesting that it was mediated by low fat mass. In contrast, association between TNF-alpha and mortality was increased in lower-BMI group compared to their counterparts, suggesting that catabolic states, such as sarcopenia and cachexia, contribute to high mortality in centenarians, at least in those with low BMI. However, plasma adiponectin levels were not associated with mortality in the total sample or in the lower-BMI group; thus, our results do not support the paradoxical association between high adiponectin and increased mortality in the extreme old age. Although some aspects of the complicated relationship between adiponectin and health outcomes are still unresolved, based on the findings so far, we would like to propose a hypothesis that high adiponectin levels in centenarians might reflect the compensatory response to maintain metabolic homeostasis and to counteract oxidative stress and inflammation, which are relevant in catabolic states, such as sarcopenia and chronic heart failure (**Figure 1**). Currently, we have extended the adiponectin study to semi-supercentenarians (individuals aged >105 years) and supercentenarians (individuals aged >110 years) with various cardiovascular biomarkers to test the hypothetical roles of adiponectin in longevity. Further longitudinal research with sequential measurements of adiponectin and other biomarkers is warranted to gain a better understanding of the role played by adiponectin in promoting healthy aging and longevity.

DATA AVAILABILITY

The datasets for this study will not be made publicly available because this is not an original article, but a review summarizing previous findings.

AUTHOR CONTRIBUTIONS

YA and KK drafted the paper. NH provided critical review of the manuscript. All authors confirmed the final version of the manuscript.

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REVIEW
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Obesity May Accelerate the Aging Process

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Lines of evidence from several studies have shown that increases in life expectancy are now accompanied by increased disability rate. The expanded lifespan of the aging population imposes a challenge on the continuous increase of chronic disease. The prevalence of overweight and obesity is increasing at an alarming rate in many parts of the world. Further to increasing the onset of metabolic imbalances, obesity leads to reduced life span and affects cellular and molecular processes in a fashion resembling aging. Nine key hallmarks of the aging process have been proposed. In this review, we will review these hallmarks and discuss pathophysiological changes that occur with obesity, that are similar to or contribute to those that occur during aging. We present and discuss the idea that obesity, in addition to having disease-specific effects, may accelerate the rate of aging affecting all aspects of physiology and thus shortening life span and health span.

Keywords: obesity, overweight, aging, aging hallmarks, caloric restriction

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INTRODUCTION

The world population is aging at a rapid pace (1), we face a future where the number of elderly people will exceed that of children and there will be more people at extreme old age than ever before. The significant rise in average life expectancy during the 20th century ranks as one of society's greatest achievements. In addition, the increase in life expectancy is accompanied by a change in principal causes of disease and death, creating an "epidemiologic transition". This transition is based on a decline in infectious and acute disease and an increase in chronic and degenerative disease (2).

The question whether living longer represents more years of healthier life or an increase in years of disability is an important question (3, 4). Evidence from several studies indicate that the recent increase in life expectancy is accompanied by an increased disability rate. The net result is no net difference in the length of a healthy life span in some estimations (5–7) and potentially a decrease in other estimates (8, 9). In a large-scale study of 187 countries examining the global burden of disease, Salomone and colleagues indicated that as life expectancy rose between 1990 and 2010, the number of healthy years lost to disability has also increased (10). This trend, which is typical of industrialized countries, has a significant impact on public health, due to the cost of care imposed by the increase in years lost to disability and underscores the need to make healthy aging a priority.

A major factor contributing to the increase in disability is an increase in obesity, creating a new and pressing challenge for public health (11–17). Obesity is expanding at a worrisome rate, the frequency of overweight and obesity combined increased by 27.5% for adults and 47.1% for children between 1980 and 2013. In developing countries, the proportion of obese adults rose from about 15% in 1980 to more than 20% in 2013 (18). Obesity is associated with an increased risk of cardiovascular disease,

type 2 diabetes mellitus, cancer, osteoarthritis, work disability and sleep apnea (19).

It has been suggested that obesity not only increases the onset of metabolic imbalances, but also decreases life span and impacts cellular processes in a manner similar to aging (20).

A defining characteristic of aging is the gradual loss of physiological integrity, which results in increased vulnerability to disease and death. This loss of physiological integrity underlies multiple pathologies, including cancer, diabetes, cardiovascular disorders and neurodegenerative disease (21). Recently, nine hallmarks which define the aging process have been described (21). We will briefly discuss each of the hallmarks of aging, the potential interactions between each hallmark and obesity and, where available, the effect of caloric restriction (CR).

TELOMERE ATTRITION

Telomeres are repetitive, non-coding, chromosomal regions located at the end of each chromosome. These telomeric regions are assembled into higher order structures, which prevent both chromosomal fusions and activation of the DNA damage response. In human somatic cells, telomere erosion occurs with each cell division creating a trigger for senescence when a critical length is reached and the telomere structure is destabilized (22).

Aging and Telomeres

Telomere length is inversely correlated with lifespan (23), and telomere dysfunction accelerates the aging process (21). Telomere shortening, moreover, can be accelerated by factors that induce aging and attenuated by factors that improve health (24). On these grounds, telomere length has been proposed as marker of biological aging (21). Inflammation and oxidative stress have been associated with aging in general (25), and shortening of telomeres in particular.

Obesity and Telomeres

Obesity causes oxidative stress and inflammation, which may increase the rate of telomere shortening (24). Although the association is weak or moderate, the results of a systematic review by Mundstock and colleagues show a trend toward a negative association between obesity, in particular central obesity, and telomere length (24). Human studies indicate that telomere shortening is directly correlated to adiposity (26), and telomere length is inversely associated with BMI (19). However, this association is not linear across the age and it is stronger in younger compared to older individuals (26). Interestingly, telomere length measured from subcutaneous adipocytes was significantly lower in obese patients compared to never-obese ones (27), and it appears that physical activity may protect patients from telomere shortening due to obesity, although extended periods of overweight/obesity seem to mitigate this protection (28). It should be noted that these results are not consistent in all studies (29).

Telomere length in leukocytes is linked to both obesity and smoking. For example, telomere length was inversely correlated with serum concentration of leptin, an adipokine which may contribute to an inflammatory state and elevated oxidative stress (30). Importantly for the current discussion, leukocyte telomere length, a common aging biomarker, has been shown to negatively correlate with BMI, although the association was relatively weak and gender specific (females only) (31).

Take Home Summary

A dedicated review on the possible links between obesity, telomeres and aging concludes: "*obesity may affect telomere dynamics and accelerate the aging process*" (32). We feel that although the results cumulatively show a tendency toward an inverse correlation between obesity and telomere length; it is more prudent to conclude that the available studies are heterogeneous and show a weak statistical significance (24, 26).

EPIGENETIC ALTERATION

Epigenetic modifications such as DNA methylation, histone modification and chromatin remodeling refer to alterations in gene expression that are inherited in descendant cells or organisms (33).

Aging and Epigenetics

Epigenetic changes occur with age and there appears to be a relationship between epigenetic changes and age-related health problems (21). One of the strongest correlations between epigenetics and aging involves changes in a subset of methylation sites throughout the genome. These sites were identified as having an altered methylation pattern during aging and these changes have been proposed to represent an "epigenetic clock," that may be tied to the aging process (34).

Nutrition and Epigenetics

There is evidence that lifestyle changes, including weight loss/gain, affect gene expression by altering the DNA methylation pattern (35) and increasing the risk of developing diseases in later life. In this context, nutrition, among other environmental factors, plays a key role in inducing epigenetic changes and these changes can influence the phenotype of subsequent generations (36). Among nutrients, methyl donors play a central role. For example, folate supplementation during gestation increased DNA methylation at imprinted loci within the IGF2 gene and was associated with lower birth weight, while loss of imprinting at the IGF1 gene correlates with somatic overgrowth (36).

High fat diets (HFD) have been shown to alter the epigenome. For example, *in utero*, HFD feeding and maternal obesity alters DNA methylation patterns and histone modifications while increasing susceptibility to obesity in offspring (37). The offspring of mice exposed to a HFD exhibit modifications such as histone acetylation, in genes involved in metabolic pathways, such as glycemic homeostatic regulation. These modifications can affect the gluconeogenic capacity and potentially lead to

Abbreviations: BMI, body mass index; CR, caloric restriction; ASC, Adipose-derived stem cells; UPR, unfolded protein response; HSC, hematopoietic stem cells; BM, bone marrow; BMAT, bone marrow adipose tissue; BM-MSC, bone marrow stromal stem cell; HFD, high fat diet; GH, growth hormone; IGF-1, insulin-like growth factor; IGFBP, IGF binding protein. HSP, heat shock protein; ER, endoplasmic reticulum; UPR, unfolded protein response.

excessive glucose production and altered insulin sensitivity in adulthood (38).

Another example of epigenetic alteration due to HFD is the increased expression of the histone deacetylase HDAC5. Increased expression of this deacetylase reduces BDNF chromatin accessibility and consequently its transcription. BDNF is a key regulator of synaptogenesis, essential for learning and memory. It has been demonstrated that HDAC5 is significantly increased in the brains of diabetic patients and in the brains of mice chronically fed a HFD (39). These epigenetic changes in the brain may persist, even after a return to normal diet, leading to pathological alterations in the cognitive machinery (40). In this study, Wang and coll. demonstrated that limited, early presence of obesity and insulin resistance may have long-term deleterious consequences in the brain, leading to a more susceptible, less resilient cognitive machinery, and contributing to the onset/progression of cognitive dysfunction, such as impairment in learning and memory formation, during aging (40).

Obesity and Epigenetics

Besides the impact of nutrition, the direct role on aging and life span of BMI and obesity associated epigenetic changes, have also been studied. Several studies demonstrated that obesity is associated with extensive changes in gene expression in multiple tissues (41) and that increased BMI is associated with an altered methylation of specific genes (42–44). For instance, Nevalainen et al. showed that obesity is associated with methylation changes in blood leukocyte DNA that could lead to immune dysfunction. They also investigated the association between BMI and epigenetic age in blood cells and demonstrated that BMI is positively associated with epigenetic aging in middle-aged individuals (44). The impact of obesity on epigenetic aging is also described by Horvath et al. They showed that obesity accelerates epigenetic changes associated with aging in the human liver resulting in an apparent age acceleration of 2.7 years for a 10-point increase in BMI (45), supporting the idea that obesity may accelerate the aging process.

Caloric Restriction and Epigenetics

CR as well as overnutrition can induce epigenetic alterations, which potentially impact aging. CR clearly retarded the methylation drift, thus resulting in a significantly younger "methylation age" (46). Another example is SIRT6, a stress responsive deacetylase that represents a potentially significant enzyme for aging (47, 48). Functionally, SIRT6 plays an important role in DNA repair, telomerase function, genomic stability, cellular senescence and in regulation of the transcription factor nuclear factor-κB (NF-κB), which is involved in inflammation and aging (21, 49). SIRT6 activity is significantly modulated by CR (49). Nutrient depletion or long-term CR increase SIRT6 activity in the brain, white adipose tissue, muscle, liver and kidney in mice (49, 50).

Take Home Summary

Several reports demonstrate that nutrition and obesity are able to modulate the epigenetic signature of an individual, even during prenatal development. The observed alterations do not always overlap those seen in aging, however some studies show a close correlation between epigenetic alteration induced by obesity and an acceleration of tissue aging. This suggests that obesity could accelerate age-related dysfunction by inducing epigenetic alterations that are not necessarily the same as those observed during aging in non-obese individuals.

MITOCHONDRIAL DYSFUNCTION

Mitochondria play a central role in bioenergetic metabolism and ATP production, and maintenance of their function across lifespan is essential for general homeostasis.

Aging and Mitochondria

Because of their key role in multiple cellular functions, these organelles are involved in multiple distinct processes with relation to aging, including: inflammation, mitophagy and proteolysis, the mitochondrial unfolded protein response, cellular senescence, stem cell function, accumulation of DNA mutations, and bioenergetics alterations [reviewed in (51)]. During the aging process, a reduction in the efficiency of mitochondrial bioenergetics has been observed and several involved mechanisms have been described, such as a reduced biogenesis, mutation in mtDNA, alteration in mitochondrial dynamics (imbalance fission/fusion) or defective mitophagy (52).

Both excessive nutrient consumption and obesity have been linked with mitochondrial dysfunctions.

Excessive Nutrient Consumption and Mitochondria

During excessive nutrient consumption, the metabolism shifts toward increased lipid storage and glycolytic ATP synthesis while concurrently decreasing mitochondrial biogenesis (53). Mitochondria play an essential role in nutrient adaptation; excessive consumption of nutrients affects their functions in those tissues that participate to nutrient metabolism: adipose tissue, liver, and skeletal muscle. Excessive nutrient intake also increases the concentration of free fatty acids and mitochondrial ROS production, leading to hyperglycemia and adipocyte mitochondrial dysfunction. In this tissue, mitochondrial biogenesis, mtDNA content and the rate of β-oxidation are reduced while adipogenesis, fatty acids esterification and lipolysis are altered. These modifications contribute to alteration of insulin sensitivity (54).

Obesity and Mitochondria

Obesity has also been associated with mitochondrial dysfunctions (54). CR, conversely, which increases longevity, maintains mitochondrial function (55). Several studies showed that obesity induces a reduction in mitochondrial biogenesis and a decreased mitochondrial oxidative capacity in adipocytes of both rodents (56) and humans (54). In obese individuals, reduced mitochondrial biogenesis is associated with metabolic alterations, low-grade inflammation, and insulin resistance (57). Several lines of evidence (54) suggest that obesity induces a shift toward a fission process linked to mitochondrial dysfunction in liver and

skeletal muscle. In skeletal muscle of obese mice, an increased mitochondrial fission was observed and the activity of protein involved in mitochondrial dynamic was altered (58).

Some of the adaptations observed under excessive nutrient consumption are also observed in obesity; mitochondria of obese individuals show a reduced oxidation of fatty acids, have less defined internal membranes, a lower energy generation capacity and an increased glucose dependence for ATP synthesis (59).

Mitochondria are also a central players in apoptosis (60), and the availability or ingestion of nutrients is related to the regulation of cell death. Excessive food intake impairs mitochondrial respiratory capacity and sensitizes mitochondria to apoptotic stimuli (59). Obesity upregulates apoptotic pathways proteins in rodent and humans, and increased apoptosis in adipocytes, as demonstrated by an association between body fat and a pro-apoptotic state in adipose tissue of obese patients (54).

Take Home Summary

Mitochondrial dysfunction occurs in aged tissues, in response to excessive nutrient intake, and in obesity, contributing to inflammation and insulin resistance. Aging and obesity appear superimposable in their impact on mitochondria and it is reasonable to hypothesize that they could exert additive effects.

CELLULAR SENESCENCE

Cellular senescence is an irreversible block of the cell cycle that limits the proliferative potential of cells (61). Cellular senescence, along with apoptosis, is a physiological process that plays a crucial role in the removal of damaged cells and tissue remodeling; it is a crucial mechanism for development but becomes deleterious when it affects stem and immune cell function, impacting tissue homeostasis. Senescence can be triggered by several stress stimuli, such as telomere uncapping, DNA damage and oncogene activation (62). Senescent cells have a large flattened morphology, stop DNA replication, show increased levels of proteins involved in cell cycle arrest and tumor suppression (such as the tumor suppressor p53 and cyclin-dependent kinase inhibitors [CDKi] $p16^{INK4A}$, $p21^{CIP1/WAF1}$, and $p15^{INK4B}$), and are positive for the senescence-associated β-galactosidase (SA β-gal). They also display altered histone modification profiles and an altered secretome consisting of pro-inflammatory factors, growth factors and proteases, the so called senescence associate secretory phenotype: SASP (63). SASP factors influence the behavior of neighboring cells, resulting in the paracrine induction of senescence, tissue remodeling, and recruitment of immune cells (e.g., T lymphocyte and macrophage) (63). Although senescent cells are resistant to apoptosis, their activation of immune system causes removal of nearby cells as well as the senescent cells themselves (64).

Aging and Cellular Senescence

During the initial description of replicative senescence, Hayflick proposed that the process may contribute to organismal aging (65). Although two key axioms of this idea, i.e., the relationship of replicative senescence with donor age or with species longevity are not supported by subsequent experiments [reviewed in (66)], an increase in senescent cells has been observed *in vivo* in different tissues (67, 68). Perhaps more importantly, the clearance of accumulated senescent cells in tissue during aging has been demonstrated to extend median lifespan and to attenuate age-related deterioration of organs in mice (69).

Obesity and Cellular Senescence

It has been demonstrated that SA β-gal^+ cells are more abundant in pre-adipocyte and endothelial cells isolated from obese compared to lean rats and human, moreover there is a positive correlation between BMI and adipose tissue SA β-gal activity and p53 [reviewed in (64)]. There is an accumulation of senescent T cells and an increased number of macrophages in the inflammatory foci of the visceral adipose tissue of HFD-fed obese mice (70), and obese mice accumulate senescent glial cells in the brain (71).

Adipocyte Cellular Senescence

Senescent pre-adipocytes are defective in their differentiation capacity; it has been shown that senescent adipose-derived stromal/progenitor cells express reduced levels of adipogenic regulators and altered expression of adipogenic differentiation gene patterns in response to adipogenic hormone stimuli (72). In the heterochronic parabiosis model, blood from 3 months old mice is able to reduce the levels of pro-inflammatory cytokines in the visceral adipose tissue of 18 months old mice (73).

Take Home Summary

There appears to be a strong relationship between obesity and senescence. Reports like the ones described above suggest that obesity may promote the aging process by inducing senescence. Conversely, senescence and the resulting pro-inflammatory secretory phenotype could contribute to the morbidity associated with obesity and plays a role in the development of insulin resistance and diabetes. There is vast literature in support of this view, and we refer the interested readers to gather valuable in depth reviews (74–76). Finally, Fontana et al. have proposed that CR might exert its anti-aging capacities by limiting senescent cell accumulation (77).

STEM CELL EXHAUSTION

Aging and Stem Cells

There is increasing evidence that the aging process can have adverse effects on stem cells. As stem cells age, their renewal ability deteriorates and their ability to differentiate into the various cell types is altered (78). The life-long persistence of stem cells in the body makes them particularly susceptible to the accumulation of cellular damage, which ultimately can lead to cell death, senescence or loss of regenerative function (79). These changes translate into reduced effectiveness of cell replacement and tissue regeneration in aged organisms.

Obesity and Stem Cells

Obesity is associated with a pro-inflammatory response in a wide variety of tissues. Inflammation can activate the stem cell compartment with negative consequences. For example, a

reduction in functionally active stem cells has been observed in subcutaneous adipose tissue from obese patients (80). Adipose-derived stem cells (ASC) isolated from obese patients demonstrated a reduced proliferative ability and a loss of viability together with changes in telomerase activity and telomere length (81). Moreover, their mitochondrial content and function are altered. Specifically, ASC contain a greater number of mitochondria and produce more ROS, however their mitochondria show a reduced respiration capacity, concomitant with a shift toward β-oxidation instead of glycolysis for energy production.

ASC from obese patients have reduced differentiation potential and are less proangiogenic (80), which is reflected in differences in their gene expression profile (82). Onate and colleague, demonstrated that obesity impairs the expression of genes involved in regulation of cell proliferation, differentiation and angiogenic potential of ASC, rendering them less multipotent. Moreover, obesity seems to affect ASC trafficking and homing (82), changes which may reduce the capacity of these cells for tissue repair (80).

Obesity also influences bone marrow (BM) homeostasis, increasing adipocyte formation. Bone marrow adipose tissue (BMAT) originates from bone marrow stromal stem cells (BM-MSC), which give rise to adipocyte, osteoblast and hematopoietic-supporting stroma (83). BMAT is an endocrine-active fat depot capable of influencing BM stem cells. Chronic low-grade inflammation associated with obesity is a stressor for BM stem cells due to the continuous response to inflammatory cytokines. In turn, inflammation causes alterations in the microenvironment with implications for cell production. In mice, HFD-induced obesity leads to a progenitor cell exhaustion and impairs osteoblast recruitment and bone formation, decreasing proliferative potential of progenitor cells and enhancing adipocytic differentiation of BM-MSC (83).

Obesity has a direct effect on the hematopoietic stem cell (HSC) compartment; however, obesity and aging seem to have different effects. HSC aging leads to a paradoxical increase in the stem cell pool and decline in stem cell function. One of the prominent modifications of HSC properties with age is their biased differentiation toward myeloid lineage at the expense of their lymphoid potential (84). None of these characteristics are observed in obesity. An elegant study by Lee et al. demonstrated that obesity leads to changes in the cellular architecture of the stem cell compartment. HSCs acquire an immature phenotype, remain quiescent, and are refractory to the low-grade inflammation signals, while differentiated progenitors are more greatly affected. Through the use of a genetic mouse model, the authors demonstrated that obesity affects the long-term reconstitution ability of HSC while also leading to an exacerbated proliferative response of multipotent progenitors. These effects are linked to the upregulation of Gfi1, a key regulator of HSC quiescence and self-renewal, in response to the oxidative stress associated with obesity (85). The aberrant HSCs activity is progressively acquired during weight gain but it is long lasting after weight loss, demonstrating that obesity induces lasting changes in the HSC compartment (85).

It has been demonstrated that postnatal overnutrition reduces myogenic stem cell frequency and function (86) and that HFD fed mice show a reduced number of neural stem cells in the hypothalamus with a reduced differentiation capacity (87).

Caloric Restriction and Stem Cells

Stem cells are adapting their metabolism in response to environmental changes, they skew toward a quiescent state in case of stress, or begin to proliferate-differentiate in response to injury (88). The effects of diet on stem cell metabolism and function have been assessed in response to CR. CR slows down age-related decline and enhances stem cell activity by altering their metabolic activity, promoting oxidative phosphorylation over glycolysis (88). CR potentially shifts the balance toward self-renewal while reducing the numbers of differentiated cells, thus preserving the stem cell pool and preventing stem cell exhaustion (89). In both young and old mice, CR increases the frequency and function of skeletal muscle stem cells by increasing mitochondrial content and promoting oxidative metabolism (90).

Take Home Summary

With the exception represented by the effects on the HSC compartment, both obesity and aging, negatively impact ASC, neural stem cells and BM homeostasis. In contrast, CR promotes self-renewal and prevents stem cell exhaustion. Overall, obesity does not mimic aging in terms of stem cells compartments but, similar to aging, has a disrupting influence on their tissue maintenance functions.

DEREGULATED NUTRIENT SENSING

The major signal pathways that participate in nutrient sensing are: the insulin/ insulin-like growth factor (IGF-1) signaling (IIS) pathway which informs the cell of the presence of glucose (and IGF-1); mTOR, for sensing amino acid concentrations (and integrating this information with growth factor signals from the IIS); AMPK which senses low-energy state by detecting low level of ATP; and sirtuins which sense nutrient scarcity by detecting high NAD+ levels.

Aging and Nutrient Sensing

Trophic signals that activate IIS or the mTOR pathways are now considered major accelerators of aging. Multiple studies in mutant mice show that a reduction in the growth hormone (GH)/ IGF-1 signaling extends life span [reviewed in (91)] and at least one study points to an IGF-1 independent role of GH (92). mTOR activity is now regarded by many as a central player in dictating the pace of aging (93). On the opposite side, upregulation of the AMPK and sirtuins pathways may mediate lifespan extension (21).

Obesity and the Insulin/ IGF-1 Signaling (IIS) Pathway

Mediators of inflammatory signals such as c-Jun NH2-terminal kinase (JNK) and kB kinase-B (IKKβ) impair insulin signal pathways, in turn interfering with the phosphorylation of receptor substrate 1 (IRS1), reducing the interaction with PI3K

and consequently reducing glucose uptake (94). In obesity, altered insulin action and the consequental PI3K/Akt signaling pathway alteration in skeletal muscle, liver and adipose tissue may cause systemic insulin resistance (95). In skeletal muscle, insulin resistance leads to a decreased glucose transport, and a reduction in glycogen synthesis. In liver, insulin resistance results in a failure of gluconeogenesis suppression, however it stimulates fatty acid synthesis. Adipose tissue shows altered insulin-stimulated glucose transport and lipolysis. However, not all insulin signaling is diminished. For example, in liver tissue, the gluconeogenic pathway becomes insulin resistant, although insulin dependent lipogenesis stays sensitive (96).

When caloric restriction is present, the liver produces less IGF-1 and it is refractory to GH stimulation (97). While it has been clearly demonstrated that hyperinsulinaemia in obesity leads to significantly reduced GH secretion, which affects insulin's ability to maintain normal glucose homeostasis (98). The effects of obesity on IGF-1 levels are more controversial. Chronic hyperinsulinemia is associated with increased circulating IGF-1 levels. Insulin suppresses IGF binding protein (IGFBP)-1 and -2, which reduce the bioavailability of IGF-1 in the peripheral tissues (98). Increasing BMI is associated with a reduction of IGFBP-1 and IGFBP-2 expression and consequently with high circulating free IGF-1 levels (98). However, while it has been reported that IGF-1 levels are high in obesity, other studies show that it is not increased or may even be decreased (98). These differences may be due to methodological challenges associated with IGF-1 measurements.

Diet and surgical induced weight loss can revert the defects in the GH/IGF-I axis in obesity (99).

Obesity and the mTOR Pathway

Obesity promotes mTOR activity in adipose tissue, leading to exacerbated hyperlipidemia and insulin resistance (100). For example, mTORC1 is hyperactivated in tissue of obese and HFD fed rodents (101) and genetic variation in Raptor, an mTOR-interacting partner, is associated with overweight/obesity in American men of Japanese ancestry (102). High adiposity is closely associated with development of insulin resistance, and it has been demonstrated that in the state of overnutrition, one of the molecular factors involved in insulin resistance is the ribosomal protein S6 kinase 1 (S6K1), a downstream target of mTOR signaling (103).

Decreased activation of mTOR/S6K1 has been associated with increased insulin sensitivity (104). S6K1 is hyperactivated in the adipose tissue, liver and muscle of different genetic mouse model of obesity. It has been described that HFD fed *s6k1* deficient mice are protected from developing obesity and insulin resistance (103). Chronic activation of the mTOR/S6K1 pathway by insulin, TNF-α and amino acids promote insulin resistance in obese mice and primary cultures of skeletal muscle cells from patients with type 2 diabetes through increased IRS1 serine phosphorylation and degradation (105). The HFD fed *s6k1* deficient mice show a strong reduction of phosphorylation of these sites; suggesting that S6K1 inhibits insulin signaling by mediating IRS1 phosphorylation (104). Moreover, obese patients express increased levels of *RPS6KB1*, the human gene encoding S6K1, in visceral fat compared to lean volunteers (103). Fat mass reduction after CR is associated with adipose tissue mTOR inhibition. Accordingly, pharmacological inhibition of mTORC1 pathway is associated with a reduction of both adipocyte size and number (106). Deletion of the mTORC1 target p70S6K protects against age- and diet-induced obesity (104).

Obesity and the AMPK Pathway

Obesity induces a broad, non-tissue, or isoform specific decrease in AMPK activity (107). HFD substantially inhibits AMPK activity in white adipose tissue, heart and liver, and this reduced activity is associated with systemic insulin resistance and hyperlipidemia (107). It has been reported that AMPK activity is lower in morbidly obese humans who are insulin resistant than in comparably obese individuals who are insulin sensitive (108). AMPK activity is also reduced in the paraventricular nucleus of mice with diet-induced obesity (109). In addition, some studies demonstrated the impairment of AMPK activation in skeletal muscle of individuals with obesity and diabetes (110, 111), and in visceral adipose tissue of centrally obese humans with Cushings syndrome, a disorder associated with insulin resistance (112).

Obesity and Sirtuins

There is a correlation between obesity and reduced Sirt1 levels. Adipose tissue from HFD fed mice (113) and db/db leptin resistant obese mice (114) show a significant reduction of Sirt1. Lower levels of Sirt1 have been reported in obese pigs compared to lean ones (115), and Choi et al. demonstrated that microRNA mir34a, which is elevated in obesity, reduces NAD+ levels and Sirt1 activity (116). Observational studies demonstrated the association between changes in sirtuins and obesity in human. Reduced mRNA levels of Sirt1 were observed in adipose tissue from obese women compared to lean women (117) and in peripheral blood mononuclear cells of diabetic subjects with insulin resistance (118). Furthermore, an increased expression of Sirt1 and Sirt3 was observed in adipose tissue of severely obese patients who experienced weight loss after gastric banding surgery (119).

Take Home Summary

In biogerontology, the IIS and mTOR pathway are considered "accelerators" of the aging process. There is accumulating literature suggesting that in obesity, these pathways are over-activated. In contrast, there is also accumulating literature showing that pro longevity pathways, such as the AMPK and sirtuins pathways are dampened by obesity. In conclusion, there is solid evidence that obesity deregulates cellular mechanisms related to nutrient sensing.

ALTERED INTERCELLULAR COMMUNICATION

It is accepted that aging impacts the organism at the cellular level, but also decreases the capacity of cells of an organism to interact.

Aging and Intercellular Communication

During aging, there is a decreased communication at the neuronal, neuroendocrine and endocrine levels. Two of the most compelling examples of impaired communication are inflammaging and immunosenescence (120). Inflammaging refers to the concept that aging is accompanied by a proinflammatory state, which is the consequence of multiple conditions, SASP, defects in autophagy and mitophagy, an enhanced activation of the inflammatory mediator, NF-κB. This phenotype results in elevated cytokines such as: IL-1b, tumor necrosis factor, and interferons. These cytokines can accelerate and propagate the aging process. Immunosenescence refers to the decreasing efficiency of the adaptive immune system with aging.

Obesity and Pro-inflammatory Cytokines

With obesity, the adipocyte secretome changes toward greater secretion of pro-inflammatory mediators and reduced production of anti-inflammatory or insulin sensitizing factors (121). More precisely, hypertrophic conditions induce adipocyte stress, activating Jun N-terminal kinase (JNK), NF-κB, Ask1, and MKK4. Activation of these pathways induce adipocytes, endothelial cells and immune cells to produce pro-inflammatory cytokines, endothelial adhesion molecules, proatherogenic and chemotactic mediators [IL-6, tumor necrosis factor- α (TNF-α), IL-1β, MCP-1, PAI-1, Csf-1, progranulin, chemerin, and others] in adipose tissue (122). These changes impact both number and function of immune cells, increasing the number and the activity of a subset (macrophages, neutrophils, mast cells, B, and T lymphocytes) and other subtypes [eosinophils, T helper 2, Treg and natural killer T cells (NKT)] (123, 124).

It has been demonstrated that macrophage number increases with adiposity, and the accumulation is greatest in visceral fat in humans (124). Chemoattractant molecules, such as MCP-1, secreted by adipocytes, recruit monocytes from peripheral blood to adipose tissue, where they differentiate into macrophages (125). Moreover, MCP-1 promotes the local proliferation of adipose-resident macrophages. Monocytes migrate in adipose tissue in response to adipocyte-derived cell stress markers, including CCL5, IL-6, IFN-γ and TNF-α which enhance macrophage accumulation and their polarization toward a pro-inflammatory M2 phenotype (124). The increased number of macrophages has a positive correlation with the degree of insulin resistance in both mice and humans (124). Elevated chemokine ligand (CXCL)-2 release by adipose tissue promotes neutrophil infiltration, which are 20-fold more abundant in adipose tissue from HFD fed mice compared to chow-fed ones (124). On the contrary, obesity decreases AT eosinophil numbers leading to reduced insulin sensitivity while an increase in eosinophils in response to IL-15 overexpression improves obesity-induced insulin resistance (123).

CD4+ Th1 cells increase in human subcutaneous adipose tissue with obesity and exhibit an activated CD25+ phenotype. HFD fed mice show an increased IFN- γ secretion, that impaired insulin signaling and promoted macrophage infiltration, as a consequence of Th1 cell predominance (124). As with CD4+, obesity also increases CD8+ T cell levels along with their products, granzyme B and IFN-γ. In obesity, Treg cells, suppressors of inflammatory reactions, are decreased both in their proliferative capacity and in number. Dendritic cells accumulate in AT of HFD fed mice, and induce a pro-inflammatory microenvironment by secreting IL-6 and promoting macrophage recruitment/proliferation, following enhanced INF signaling and MCP-1 production (124).

The resulting imbalance in immunological phenotypes leads to development of local inflammation that further spreads into systemic circulation affecting other organs. For example, the adipokine Haptoglobin (Hp), a clinical marker of inflammation increased in the cerebral spinal fluid of patients with neurodegenerative disorders, has an abundance positively related to body fat in adipose tissue and plasma (126, 127).

Because inflammaging contributes to immunosenescence, the obesity-derived inflammatory status reduces the efficiency of the immune system, consistent with the observation that obese people are more susceptible to infection from bacteria, fungi or viruses [see an article part of this Research Topic, (128)]. For a more in depth discussion of the interconnections between adipokines and aging we refer the reader to two additional articles which are part of this Research Topic (129, 130).

Obesity and Extracellular Vesicles

Extracellular vesicles (EV, micro-vesicle and exosomes) are nanoparticles that contain protein and nucleic acids, which interact with target tissues. Exosomes are increased in many inflammatory conditions (131), and increased numbers of microvescicles have been associated with obesity (132), while a significant reduction occurs in CR or following bariatric surgery in obese patients (133).

Several studies have demonstrated that EVs collected from adipose tissue of *ob/ob* obese mice induce, in a target cell population, changes consistent with the obese phenotype (134). EV treated monocytes were more activated, secreted more IL-6 and TNF-α compared to those treated with EV from wild type mice, and macrophages were more activated and had an increased homing capacity to adipose tissue and liver (134). In humans, EVs isolated from adipose tissue induced monocytes to adopt properties characteristic of adipose tissue macrophages (135).

Finally, it has been demonstrated that obesity reduces the pro-angiogenic potential of adipose tissue stem cell-derived EV by reducing VEGF, MMP-2 and miR-126 content (136).

Take Home Summary

The literature persuasively suggests that the accumulation of pro-inflammatory cells, in the adipose tissue of obese patients, through cytokines and extracellular vesicles, accelerates the rate of aging both in the adipose tissue itself and the entire organism.

GENOMIC INSTABILITY

Aging and Genomic Instability

The hypothesis that aging may result from the accumulation of DNA damage is one of the classical theories of aging (137), and is supported by considerable evidence. For example, accumulation of DNA damage (138) and mutations (139) with

increasing chronological age. Longevity differs by several orders of magnitude among animals and long life spans seem to associate with a greater capacity to detect the presence of DNA damage at the cellular level [reviewed in (140)]. Enhanced recognition of damage should allow enhanced DNA repair. In mammals, there is an exponential relationship between longevity and the capacity to perform the first step of non-homologous end-joining, i.e., the recognition of linear DNA ends (141), resulting in improved genomic stability (140, 142).

Obesity and Genomic Instability

The impact of obesity on genomic instability has been analyzed in a recent review by Setayesh et al. (143). Results from animal studies and from 39 studies in humans, monitoring DNA damage in lymphocytes and sperm, were analyzed. However, heterogeneity in the study design, methodology, and confounding factors, preclude the conclusion that an association exists between obesity and DNA damage. Nevertheless, the causal relation between excess of body weight and genomic instability is supported by mechanistic studies.

Several molecular mechanism may cause genetic instability in overweight/obese individuals; one of them is oxidative stress. Oxygen derived free radicals may act as potential cytotoxic intermediates inducing inflammatory and degenerative processes, or as signal messengers for the regulation of gene expression. Many articles show evidence for the induction of oxidative DNA damage and a decreased antioxidant capacity in obesity. High glucose levels directly, and high insulin levels, through the over activation of its signaling pathways, could be responsible for increased ROS formation. Othman et al. demonstrated that insulin causes DNA damage in kidney cells (144); it has been demonstrated that insulin and glucose blood level correlate with DNA damage in Korean men (145), as well as DNA damage in sperm in a mouse model (146). Other studies provide evidence for a reduction of antioxidant enzymes and a subsequent oxidative stress as a consequence of obesity, in human and mice (143).

Oxidative stress leads to oxidation of fatty acids, and some metabolites of lipid peroxidation are molecules that attack DNA and are involved in the etiology of cancer. Elevated levels of lipid peroxidation markers are observed in blood, muscles and adipose tissue of obese individuals. Excess body weight causes hormonal imbalance and it has been demonstrated that alterations of hormonal status plays a role in some cancers, including breast and endometrial cancer (143). Hormones increase the mitotic activity of breast cells, leading to accumulation of errors in DNA replication that are frequently converted in persistent mutations (147). Some products of estrogen metabolism cause direct DNA damage. Metabolites of estradiol are mutagenic in rat and human cells, and the association between genotoxic estrogen metabolites and breast cancer is well documented (143). Another mechanism by which ROS are generated is glycation. Glycation end products cause DNA damage directly and *via* interaction with signaling pathways. They bind specific receptors and activate NADH-oxidase to induce ROS formation (148). Elevated concentrations of glycation end products have been observed in adipose tissue and the livers of HFD fed mice (149), as well as human adipose tissue (150). In patients with metabolic syndrome, elevated serum levels of glycation end products correlate with markers of insulin resistance and inflammation (151).

The persistent production of ROS by inflammatory cells present in adipose tissue damages macromolecules (DNA, RNA, lipids, carbohydrates and proteins), induces genomic instability and tips the balance from an antitumor activity of ROS to a tumor promoting one (152).

Obesity is strongly associated with an increased incidence of cancer both in humans (153) and in rodents (143). An impact of obesity has been described also on infertility, and some studies (154, 155) demonstrated an increase in DNA damage in the sperm of obese men.

Obesity, moreover, impacts the DNA repair process. For example, the offspring of mice fed a low folate diet showed a reduced base excision repair capacity in several brain regions when exposed to HFD (156). There is an inverse association between adiposity and nucleotide excision repair (157), while some studies demonstrate an altered methylation pattern of genes involved in DNA repair in overweight individuals (143). Significantly, HFD reduces the expression of MLH1, a protein involved in DNA mismatch repair, and elevate CpG methylation in mice (158).

Caloric Restriction and Genomic Instability

Several studies demonstrated a beneficial impact of CR on genomic stability. CR slows down the rate of DNA damage by decreasing the levels of oxidative stress and by increasing the expression of stress response genes to enhance DNA repair (159). Although the vast majority of available studies are on rodents, there is also evidence in humans; for example, after 12 months of bariatric surgery, using the comet assay, a significant reduction in DNA damage is observed in peripheral blood cells (160).

Take Home Summary

Although much research has been performed, the assumption of a relation between obesity and genomic instability is not supported unequivocally. Oxidative damage seems as the one mechanism regarded as the most relevant (161).

LOSS OF PROTEOSTASIS

Proteins represent a key components of cells and tissues, and protein quality control and homeostasis are critical to the organism. Proteostasis is maintained through multiple mechanisms ensuring stabilization of correctly folded proteins and degradation of misfolded proteins. The first task is performed by chaperones, most prominently the heat shock protein (HSP) family, and the second task is performed by proteasome and lysosome mediated degradation (162). Proteins are synthetized in the endoplasmic reticulum (ER) where unfolded proteins are bound by the ER stress sensor Binding immunoglobulin protein (BiP/GRP78) to trigger the unfolded protein response (UPR). The existence of this evolutionarily conserved mechanism provides evidence of the critical role of proteostasis.

Aging and Loss of Proteostasis

With age, the ability of many cells and organs to preserve proteostasis under resting and stressful conditions is gradually compromised (162). Key pathways affected by the aging process alter components of the proteostasis machinery, e.g., by inducing reduction of chaperones or proteasomal degradation (163, 164). The consequent increase in misfolded or degraded proteins can lead do the development of age-related pathologies such as Alzheimer and Parkinson diseases (165).

Obesity and Loss of Proteostasis

Obesity can induce prolonged or chronic UPR response (166) possibly mediated by proteasome dysfunctions (167). In the livers of mouse models of obesity and in HFD fed mice, proteasome activity is reduced and polyubiquinated proteins accumulate. In these mice, impaired proteasome function leads to hepatic steatosis, hepatic insulin resistance, and UPR activation. Treatment with chemical chaperones partially reverted this phenotype (168). Elevated free fatty acids in obesity activate the UPR in both adipose tissue and liver (167). It has been demonstrated that ER protein folding is impaired in the liver and within adipose tissue of obese mice. Overexpression of the chaperone BiP/GRP78 in the liver of *ob/ob* mice reduces UPR activation markers, hepatic steatosis, and improved insulin action (169). Obesity-induced changes in ER calcium store can induce a reduction in chaperone-mediated protein folding activity, ER stress and UPR activation (167). Cholesterol and free fatty acids induce ER stress via increased reactive oxygen species, and ER Ca^{2+}depletion from sarco/endoplasmic reticulum calcium ATPase (SERCA) dysfunction. Diminished SERCA expression and activity were observed in livers and macrophages of obese and insulin resistant mice, which also have higher level of ER stress (170). Overexpression of SERCA in obese mice reduced UPR activation and improved glucose homeostasis (167).

Other key regulators of ER homeostasis are the three luminal sensor inositole, requiring protein 1 (IRE1α), protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6). Obesity leads to a disproportionate production of these key molecules. A reduction of ATF6 in the presence of a sustained PERK activation was observed (171). Hyperactivation of the IRE1α-XBP1 pathway has been documented in the adipose tissue of obese human (172). Shan *et al.* found that IRE1α was activated in adipose tissue macrophages and adipocytes of HFD fed mice (172). Their observations are consistent with other studies showing that in genetic and diet-induced models of obesity, IRE1α undergoes prominent activation (173).

A link between HSPs and obesity was suggested by observations that HSP70 was reduced in muscles of insulin-resistance obese patients with type 2 diabetes (174). Subsequently, several studies confirmed an altered expression of HSPs in obese humans and animals (94). Binding of extracellular HSP60 to TLR4 triggers a proinflammatory response and promotes insulin sensitivity (175). Obese subjects with or without type 2 diabetes have high HSP60 plasma levels. Interestingly, a reduced expression was observed in morbidly obese individuals after weight loss due to bariatric surgery (94).

Upregulation of HSP72 and HSP25 was previously shown to inhibit JNK and IKK-β activation, improve glucose tolerance, restore insulin-stimulated glucose transport, and increase insulin signaling in skeletal muscles from rats fed at high-fat diet (176).

Misfolded proteins can also be removed through autophagy, which is enhanced by CR (177). Autophagy is regulated by the integrated action of insulin and mTOR, both altered in obesity (178). Bugliani et al. have recently reported that promotion of autophagy increases survival of human pancreatic beta cells under ER stress and in type 2 diabetes (179). Yang et al. demonstrated that defective autophagy is causal to impaired hepatic insulin sensitivity and glucose homeostasis (178). Persistent IIS signaling in cell culture decreases autophagy and cell viability (164). Significant autophagy defects are observed related to ER stress in the liver tissue of HFD fed mice, and restoration of autophagy reduced ER stress (178).

Take Home Summary

Here we have briefly reviewed the abundant literature indicating that obesity significantly decreases mechanisms associated with proteome maintenance.

CONCLUSIONS

Two, Not Mutually Exclusive, Hypotheses

We have reviewed and organized the literature with the intent of showing the existing parallels between excessive fat accumulation and the aging process. We have categorized these reports following what have been proposed to be the nine hallmarks of aging (21) (**Figure 1**). Based on the evidence, two distinct hypotheses can be proposed. One is that the cellular responses provoked by an excess of nutrients cause obesity, and that obesity is responsible for accelerating the pace of aging. Supporting this hypothesis are the observations that knocking out the fat-specific insulin receptor, to produce extremely lean mice (180), and removal of visceral fat in rats (181) increased life span; additionally, CR on lean strains of rats, had only a minor effects on lifespan (182, 183). The alternative possibility is that the cellular responses provoked by an excess of nutrients are responsible for increasing the pace of aging. This common soil shared by both aging and obesity has been named "adipaging" (184), and there is some evidence of commonalities: hyperglycaemia, for example, induces senescence and the SASP in endothelial cells and macrophages (185) while glucose reduction prevents replicative senescence in human mesenchymal stem cells (186). The more abundant macronutrients (by weight and by calories) in the diet are usually carbohydrates and lipids, and specific reviews are available that focus on the possible toxic effects of their respective excess: carbotoxicity (187) and lipotoxicity (188). In this second scenario, obesity represents only a side effect of the excess nutrient status and the fulcrum are the cellular nutrient sensing pathways; see for example the possible central role of mTOR (189, 190). Whether adipose tissue hyper-function/dysfunction is causative of aging functional decline or whether it represents simply a marker of the advancing aging process will become clearer with future studies. In addition, not all fat depots are equal

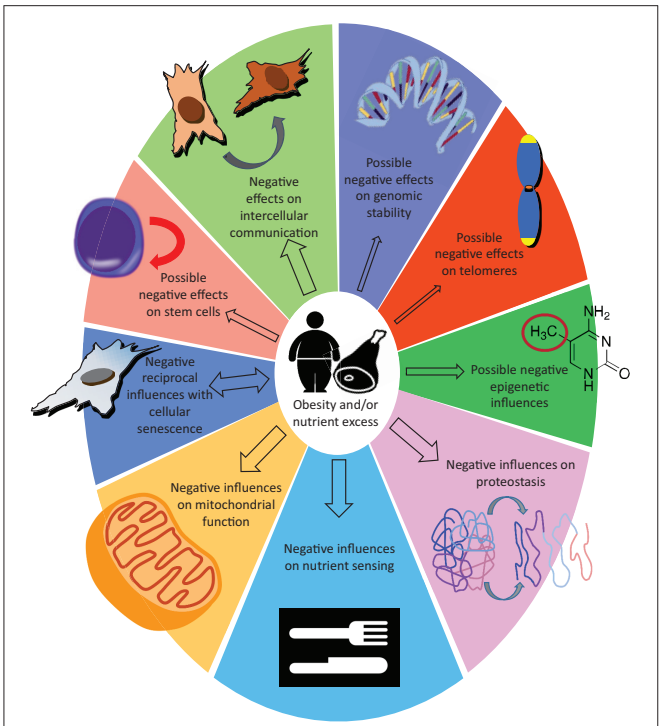

FIGURE 1 | Effect of obesity or nutrient excess on the hallmarks of aging. The size of the arrows indicate how solid are the evidences, see "take home summaries" in the text. The double-headed arrow for cellular senescence indicate that detrimental influences can feedback from senescence to obesity.

in their impact to health (191) and it could also turn out that both hypotheses are concurrently true (192).

Will Caloric Restriction Work on Humans?

While large epidemiological analyses indicate obesity will threaten any future gains in life expectancy (193), caloric restriction is considered a powerful tool to slow down the pace of aging. The effect of CR on increasing life span were first observed in rodents in 1935 (194). Although there are important differences between mouse, rat and human fat depots (195), the CR regiment has a clear impact in reducing fat mass in all these species (196). Caloric restriction studies are undoubtedly highly valuable for understanding the aging process; however, how to translate the data on animal models to human is a highly debated issue (197–204).

One caveat is that the response of our species could not be as strong as the one observed in experimental species. In fact, although the extension of life span with CR seems a universal biological response, this response is particularly evident in model species (*Saccharomyces cerevisiae, Caenorhabditis elegans, Drosophila melanogaster* and Rodents) suggesting involuntary selection caused by human husbandry (205). Additionally, while wild-*Drosophila* respond to CR (206), wild-mice do not (207).

Moreover, it is not clear if all humans will benefit from CR. Data on diets mimicking fasting (208), a more recent approach to caloric restriction, suggest that this approach is effective, particularly on subjects at risk for metabolic disease (209). Additionally, while extreme obesity consistently increases all-cause mortality, overweight and even mild obesity appears protective toward cardiovascular disease. A phenomenon well described and referred to as the obesity paradox (210). This stresses the importance of carefully considering the starting BMI level before suggesting CR to people. Lorenzini has proposed that initial BMI levels could be the main reason why the two larger CR studies on rhesus monkeys gave discordant result on longevity (201).

If the possibilities raised in this review are correct, we will have to conclude that it is not CR that is slowing down aging but it is the *ad libitum* feeding, coupled with the lack of physical activity (the typical condition of laboratory animals) that are actually accelerating aging (181). If this is true, we should call *ad libitum* feeding "overfeeding," an insight that has profound implications well beyond geroscience (211), and translating to humans the evidence from CR on animals will be as simple as to say: "avoid obesity".

AUTHOR CONTRIBUTIONS

VS and AL wrote and revised the article. AL wrote Introduction and Conclusions. VS wrote all the other paragraphs. CS implemented and revised each section. All authors gave final approval of the submitted version.

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REVIEW
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Brown and Beige Adipose Tissue and Aging

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Across aging, adipose tissue (AT) changes its quantity and distribution: AT becomes dysfunctional with an increase in production of inflammatory peptides, a decline of those with anti-inflammatory activity and infiltration of macrophages. Adipose organ dysfunction may lead to age-related metabolic alterations. Aging is characterized by an increase in adiposity and a decline in brown adipose tissue (BAT) depots and activity, and UCP1 expression. There are many possible links to age-associated involution of BAT, including the loss of mitochondrial function, impairment of the sympathetic nervous system, age-induced alteration of brown adipogenic stem/progenitor cell function and changes in endocrine signals. Aging is also associated with a reduction in beige adipocyte formation. Beige adipocytes are known to differentiate from a sub-population of progenitors resident in white adipose tissue (WAT); a defective ability of progenitor cells to proliferate and differentiate has been hypothesized with aging. The loss of beige adipocytes with age may be caused by changes in trophic factors in the adipose tissue microenvironment, which regulate progenitor cell proliferation and differentiation. This review focuses on possible mechanisms involved in the reduction of BAT and beige activity with aging, along with possible targets for age-related metabolic disease therapy.

Keywords: brown adipose tissue (BAT), beige adipose tissue, aging, inflammaging, metabolic disease

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INTRODUCTION

Aging is considered a common and a well-established risk factor for several chronic diseases, as well as for decline in physical function and frailty (1–3). Moreover, aging is associated with increasing prevalence in obesity, dyslipidaemia, type 2 diabetes, glucose intolerance and other comorbidities.

In recent years, the adipose organ has assumed considerable importance in aging and age-related metabolic dysfunction. Important and profound changes in the adipose organ occur with aging in terms of adipose tissue distribution and composition, and it has been suggested that progressive dysfunction of AT may represent an important hallmark of the aging process. AT dysfunction represents a process responsible for the metabolic alterations, the multi-organ damage and the systemic pro-inflammatory state ("inflammaging") typical of aging itself (4). Data in the literature support the idea that adipose tissues are organized in a large adipose organ with discrete anatomy, vasculature and innervation, specific cytology and high plasticity (5). AT is distributed in several depots, localized into two main compartments: subcutaneous (SAT) and visceral (VAT) adipose tissue with different compositions and functions. The main cells of AT are represented by adipocytes, defined as white and brown adipocytes in relation to their different morphology, which

reflects their different functions (5) (**Table 1**). Both types of cells are present within multiple sites of adipose organ in discrete depots and are named white and brown adipocytes.

At the morphological level, the main characteristic of white adipocytes is their single large intracellular lipid droplet (LD), while the brown adipocytes are characterized by the presence of multiple small cytoplasmic LDs (**Table 1**). White adipocytes have the function of storing excess lipids in the form of triglycerides (TG) and releasing free fatty acids (FFA) in periods of body energy demand; white adipocytes also synthesize and release adipokines which regulate metabolic homeostasis (**Table 1**). The main function of brown adipocytes is the dissipation of energy through uncoupled respiration so as to produce heat; this mechanism is mediated by a protein called the uncoupling protein-1 (UCP-1), present in the inner membrane of mitochondria (6) (**Table 1**).

A third type of adipocyte with an intermediate morphology between that of white and brown adipocytes, also referred to as beige, "brite" (brown-like-in-white) or "inducible brown" adipocytes, was firstly described in mouse WAT and then found in various human WAT depots (7, 8). Despite similarities to brown adipocytes, beige adipocytes can undergo a thermogenic or storage phenotype depending on environmental conditions (**Table 1**).

Across aging, AT undergoes changes in quantity and distribution, with an increase in total AT and VAT up to 65 years, as well as of ectopic fat deposition, and a decrease in SAT (9–11). Across aging, BAT declines, even if BAT activity may be identified in some rodents models and, under certain conditions, in human beings. However, the relevance and potential role of BAT decline with aging has still not been fully explored and determined.

BROWN ADIPOSE TISSUE: ANATOMICAL DECLINE WITH AGING

The main deposits of brown adipose tissue in the mouse are located around the spinal cord in the paravertebral area and in the mediastinum (12), especially in the para-aortic area and around the heart, at the apex. Infradiaphragmatic deposits have also been described, in particular in the perirenal area, which occur in smaller quantities than the supra-diaphragmatic deposits (13).

Most of available information on BAT has been obtained from rodents because a carcass evaluation can be performed. In mice, white, brown, and mixed areas are present in discrete depots; some subcutaneous and visceral depots are clearly partitioned into WAT and BAT (14, 15). Under physiological conditions, the exposure of mice to cold increases the amount of BAT depots. After cold exposure, UCP-1-dependent pathways are also activated in subcutaneous WAT (sWAT), and in brite adipocytes through the activation of the sympathetic nervous system (16–18).

In adult humans there are functionally active areas of BAT, more frequently in women than in men, in particular in the cervico-supraclavicular region; however, the study of human BAT is difficult (19). In humans, the 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET-CT) computed tomography is the most common method for the measurement of metabolically active BAT, by the identification of AT regions that have a high assimilation of 18F-FDG on the PET scan. It is important to point out that the BAT detected using 18F-FDG PET-CT has been demonstrated to correspond histologically to BAT (20). [18F] FDG PET reveals glucose metabolism in tissues; in detail, active BAT of mice and humans preferentially combusts fatty acids derived from plasma triglycerides after lipolysis, which is fueled by glucose. Indeed, [18F] FDG PET does not detect directly metabolically active BAT, but it is still a reliable indicator of activated BAT (21, 22).

In humans, BAT changes during the various stages of life (**Figure 1**). BAT begins to form during gestation, and it has a critical role in thermoregulation in the first phases of human life because newborns do not possess the ability to shiver yet. In infants, the large bilateral supraclavicular depot represents the most metabolically active form of BAT, which can be rapidly activated to heat production (**Figure 1**). During childhood, adolescent BAT is found mainly in the supraclavicular region but, although active BAT is present in every child, metabolically active BAT is detected only in about half of adolescents after cold exposure (23–25).

Moreover, other evidence suggests that there is an increase in BAT activity during adolescence, especially during sexual maturation and musculoskeletal development. Studies with FDG-PET/TC scans indicate that there is a synchronized growth of BAT and skeletal muscle during puberty and the development of these tissues is related (24, 25).

BAT function and mass decline with aging. Anatomical distribution of BAT is similar between adolescents and adults: most of the depots are located in the cervical-supraclavicular region and other depots are in axillary, mediastinal, paravertebral, epicardial and abdominal regions (26, 27) (**Figure 1**). Peripheral depots, such as interscapular one, are the first to lose BAT with increasing age, whereas deeper BAT depots, in particular perivascular or perikidney ones, decline in later stages of life (28–30) (**Figure 1**).

Non-stimulated BAT can be identified in people under the age of 50 years at a rate of three times more than in individuals older than 64 years old (26–31). Through the use of FDG-PET/TC to visualize BAT in living subjects, it has been shown that cold-stimulated BAT activity decreases with age (26, 27, 29). Loss of BAT may plateau around the sixth decade of life and then decrease in later years, and cold-stimulated BAT activity is rarely detected in individuals over the age of sixty; this could explain why there is a decrease in the ability of the elderly to tolerate cold temperature and to control body temperature (29). However, FDG PET/TC studies measure only activated BAT, which may or may not reflect changes in mass (29). The decline in BAT activity with age in humans is consistently supported by findings from rodents: in fact, the interscapular BAT depot in rats becomes infiltrated by white adipocytes with age, with an important decline in UCP1 activity and function (30). A significant loss of UCP1 with age is also observed in rats subcutaneous WAT, confirming the findings

Abbreviations: BAT, brown adipose tissue; WAT, white adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

TABLE 1 | Main morphological and functional characteristics of white, brown, and beige adipocytes.

Characteristics	White adipocytes	Brown adipocytes	Beige adipocytes
Morphology	Spherical cells with a single cytoplasmatic lipid droplet and peripheral "squeezed" nucleus	Polygonal cells with several cytoplasmatic lipid droplets and a roundish nucleus	Paucilocular/Multilocular adipocytes with intermediate morphology
Ultrastructural morphology	Low mitochondrial content	Large, spherical and packed mitochondria which laminar cristae	High mitochondrial content
Innervation	Low noradrenergic fibers	Numerous noradrenergic fibers are found in fat lobules with blood vessels	-
Vascularization	5–7 times less vascularization than BAT	High vascularization	-
Markers	UCP-1 negative cells Leptin positive cells S100B positive cells	UCP-1 positive cells Leptin negative cells	UCP-1 positive cells S100 B positive cells Leptin positive
Localization	SAT and VAT depots and ectopic fat	Cervical-supraclavicular, perirenal and paravertebral regions and around the major vessels such as aorta	In various WAT human depots (inducible transition white to beige)
Embryological origin	WAT adipocyte precursors can derive from both *Myf5*+ and *Myf5*- lineages	The same of skeletal muscle deriving from specific cells of the dermomiotome (from Myf5+ cells)	White-to-brown adipocyte transdifferentiation and *de novo* differentiation of precursor cells
Function	Storage of energy	Thermogenic activity	Thermogenic or storage phenotype depending on environmental conditions
Changes with aging:			
-Chronic sterile inflammation	↑	↑	↑
-Progenitor cell decline	↑	↔	↔
-Senescence	↑	↑	↑
-Adipokines changes	↑	↔	↔

↑ = *increased;* ↔ = *unchanged.*

of human autopsy studies (31). It therefore seems that many, if not all forms of BAT, may undergo a gradual transition toward WAT with increasing age both in human as in rodent studies (30, 31).

In summary, aging is one of the most relevant determinants of BAT activity and it is associated with a ubiquitous decline of BAT activity throughout life (32, 33).

MECHANISMS OF BROWN ADIPOSE TISSUE DECLINE WITH AGING

Several mechanisms have been shown to be related to BAT decline with aging, including loss of mitochondrial function, impairment in the sympathetic nervous system and age-induced alterations in endocrine signals and inflammation (**Figure 2**).

Impairments in Mitochondrial Activity

During aging, there is a significant decline in UCP1 activity, a protein uniquely expressed in the inner mitochondrial membrane of brown adipocytes. Mitochondrial dysfunction has been recognized to have a relevant role in the pathogenesis of several age-related disorders, such as type 2 diabetes, obesity, heart failure, neurodegenerative diseases and tumorigenesis (34, 35).

In particular, mitochondrial dysfunction with aging is characterized by an increase in mitochondrial DNA mutations and a reduction in biogenesis and oxidative phosphorylation. For this reason, aging may be associated with an impairment in brown adipogenic stem/progenitor cell function and consequently with a reduction in the regenerative potential of BAT with storage of dysfunctional brown adipocytes (34, 36).

Decrease in the Sympathetic Nervous Stimulation and Sensitivity in BAT With Age

The sympathetic nervous system (SNS) plays a key role in regulation of BAT recruitment. Moreover, exposure to cold is a potent BAT stimulator through the SNS. Cathecolamines activate B3-adrenergic receptors located on the surface of brown adipocytes to promote UCP1 gene expression and activity related to thermogenesis and lipolysis (37, 38).

The sympathetic nervous system of BAT can be visualized by I-meta-iodobenzylguanidina SPECT (39). 123I-metaiodobenzylguanidine (123IMIBG), a radiolabeled norepinephrine analog, is commonly used for scintigraphic assessment of neuroendocrine tumors and cardiac sympathetic activity (39). 123I-MIBG scintigraphy, in particular, has already been used specifically to localize BAT in rats. Interestingly, a recent study in lean adult humans after cold exposure, measured BAT through the combination of the two imaging methods: the 123IMIBG SPECT/CT, as a measure of sympathetic stimulation and activation, and the 18F-FDG PET/CT, as an indicator of BAT metabolic activity (37–39). In older lean subjects, both sympathetic drive and BAT activity were lower compared to younger lean and obese men (37).

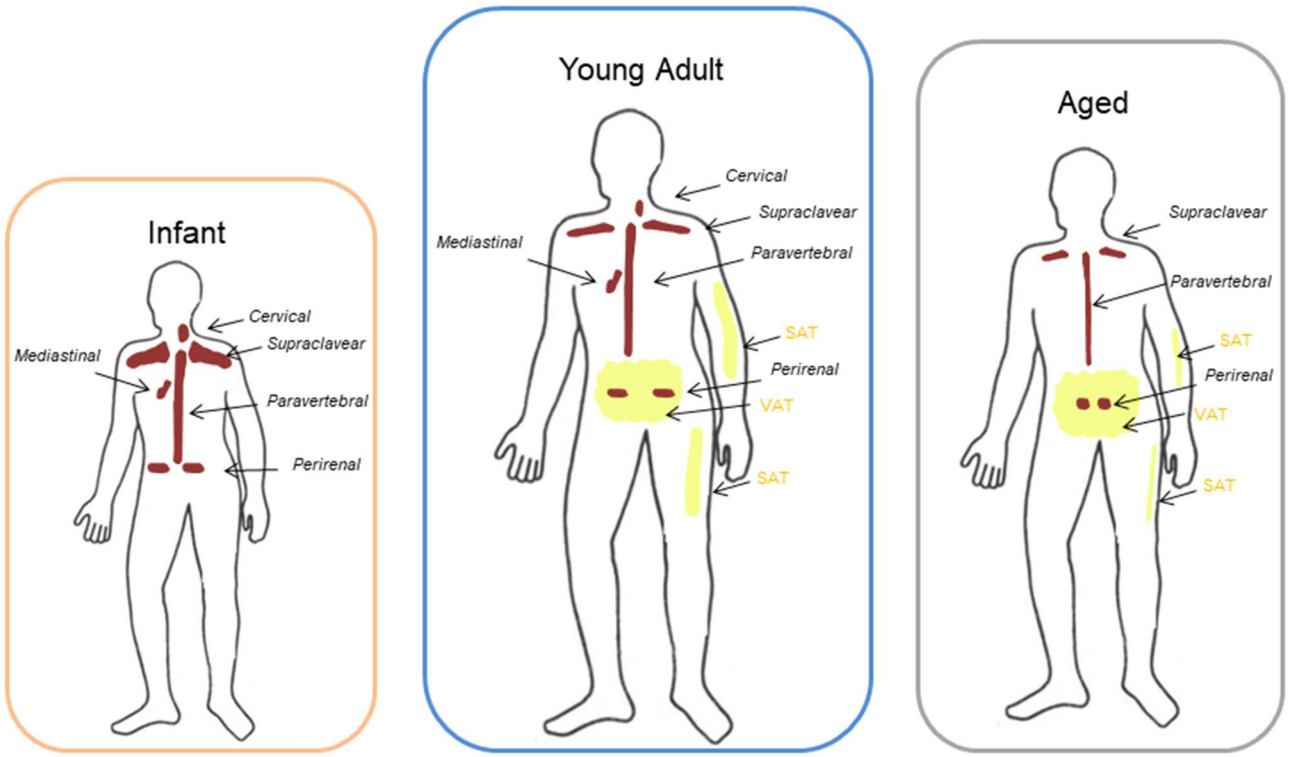

FIGURE 1 | Different location of BAT and WAT at different ages. Brown adipose tissue (BAT) in infants and young adults had been described to be localized mainly in the cervical-supraclavicular region as well as in periaortic areas inside the thorax and the abdomen, and in particular in the perirenal fat. With aging the amount of detectable BAT decreases progressively and it remains represented mainly in the supraclavicular and perirenal sites. Peripheral depots (interscapular) are the first to loose BAT with increasing age, whereas deeper BAT depots, such as the perivascular or perirenal depots, decline in later stages of life. Aging is also characterized by a redistribution of white adipose tissue (WAT) with a progressive loss of subcutaneous adipose tissue (SAT) from limbs and an accumulation in trunk and abdomen of visceral adipose tissue (VAT) compared to adults.

Therefore, it is possible that a lower absolute SNS signal and a possible decline in sensitivity of BAT for the SNS stimulation may result in a decreased ability to activate and recruit BAT in older men and may also explain why older humans have an inability to appropriately regulate their temperature when exposed to cold (37, 38).

Age-Related Hormonal Changes and BAT

BAT mass and/or function may decline during adulthood, as a consequence of changes particularly in the somatotropic and gonadotropic axes.

Human fetal BAT shows a high expression of estrogen receptors, suggesting that tissue-levels of estrogens may regulate BAT activity (40, 41). Recent evidence suggests that estrogens and androgens are positively related to BAT activity and function while glucocorticoids have negative effects. Glucocorticoids, such as dexamethasone, reduce the cathecholamine-induced expression of UCP1 (42). With aging, sex hormone levels decline, while glucocorticoid levels remain relatively stable; for this reason, this decrement in levels of gonadotropic hormones in late adulthood and relative increase in glucocorticoid activity may contribute to the loss of BAT activity with aging (41, 42).

Thyroid hormones are also known regulators of thermogenesis: UCP1 levels are related to triiodothyronine levels. Extensive evidence shows that T3 promotes UCP1 synthesis at transcriptional levels in BAT, as well as UCP1 activity by modulation of cAMP production. Aging is associated with a decrease in serum T3 and a reduced conversion of active T3 caused by an age-dependent loss of DIO2, as is demonstrated in murine WAT (43). Recent evidences demonstrated that UCP1 expression in WAT also correlates with circulating thyroxine serum levels (43, 44), suggesting that thyroid hormones may contribute to the browning of white adipose tissue and increasing thermogenesis (45).

A few recent papers suggest ghrelin signaling as an important thermogenic regulator in aging. The ablation of the ghrelin receptor, the growth hormone secretagogue receptor (GHS-R), decreases the risk of age-associated obesity and insulin resistance. Ghrelin and obestatin are derived from the same preproghrelin gene; however, in brown adipose tissue, ghrelin reduces the expression of UCP-1 but obestatin increases it. During aging, plasma ghrelin and GHS-R expression in BAT are increased, but plasma obestatin is stable; this may lead to an imbalance in thermogenic regulation, which may in turn exacerbate age-related thermogenic impairment. Moreover, GHS-R ablation

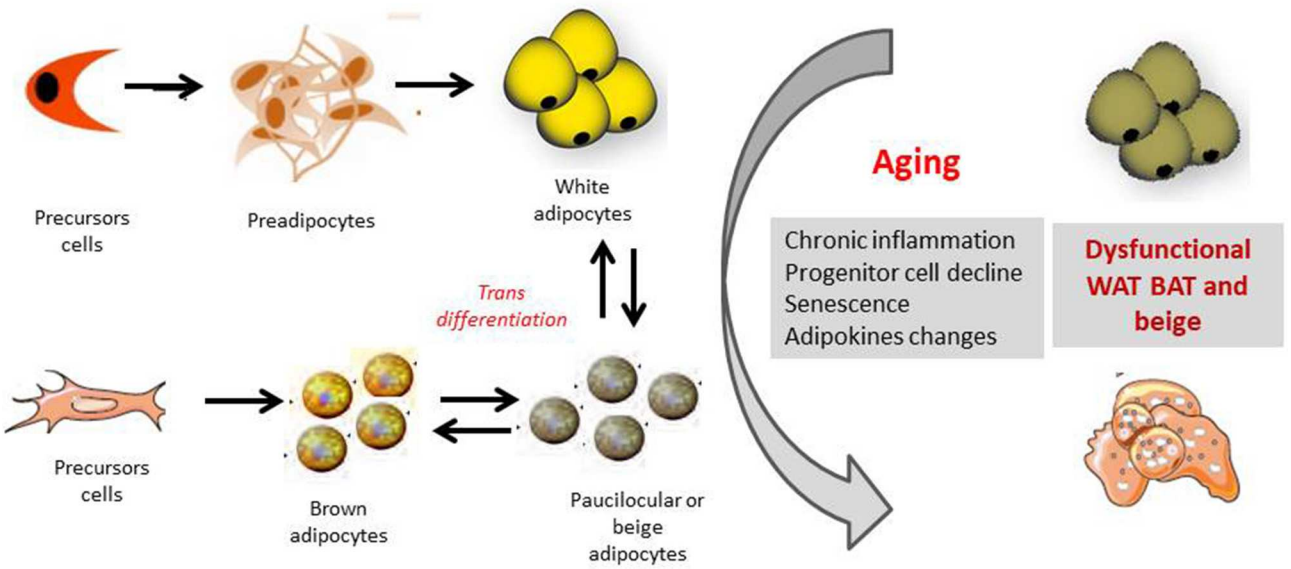

FIGURE 2 | Orgin of white, brown and beige adipocytes and effect of aging. The appearance of beige cells among white adipose tissue (WAT) depots is referred to as "browning." It has been hypothesized that these cells origin from the *de novo* differentiation of a distinct sub-population of WAT resident progenitors, which express the markers CD 137 and TMEM26 on their surface. Moreover beige-type cells may generate also from white-to-brown adipocyte transdifferentiation, from MYF5 positive cells. Several mechanisms as chronic inflammation, progenitor cell decline, senescence of the different adipose cell compartments as well as changes in adipokines productions, may together contribute to a dysfunctional adipose organ with aging.

activates thermogenic signaling, enhances insulin activation, mitochondrial biogenesis, and improves BAT mitochondrial function (46, 47).

In recent papers, it has been suggested that fibroblast growth factor 21 (FGF21), secreted by the liver and adipose tissue, may also play a role in the browning process of WAT depots. In fact, mice with a FGF21 deficiency display an impaired ability to adapt to chronic cold exposure, with reduced browning of WAT. In particular, it has been demonstrated that adipose-derived FGF21 increases the expression of UCP1 and other thermogenic genes in fat tissues in an autocrine/paracrine manner (48, 49). However, aging is characterized by a progressive increase in FGF21 levels from 5 to 80 years, independently of body composition (49). This discrepancy between the increase in FGF21 levels and decrease browning of WAT with aging could be at least in part reconciled, hypothesizing an FGF21-resistant state with age itself. In fact, evidences from studies conducted on rodents supported the existence of an age-related FGF21-resistant state (50). Similarly, in some metabolic states such as obesity and diabetes, FGF21 levels are elevated and an FGF21-resistant condition has been suggested to also accompany these diseases (51).

Inflammaging

The production of pro-inflammatory mediators and the infiltration of immune cells in AT, a process of chronic inflammation typical of obesity and metabolic conditions, also increases with age, so that has been referred to as "inflammaging" (52–54).

Several evidences have suggested that compared to WAT, brown and beige adipose tissue are less likely to undergo local inflammation due to immune cells infiltration, but present an increased production of inflammatory cytokines as TNF-alpha and MCP-1, in presence of dysregulated metabolism linked to obesity (53).

It has been hypothesized that inflammation with the production of these cytokines may indirectly impair the thermogenic activity in BAT because of altered insulin sensitivity and reduced glucose uptake (53).

Several pro-inflammatory cytokines are suggested to be involved in these mechanisms that globally reduce UCP-1 gene expression and browning phenomena (52, 54). In particular, TNF-a, one of the principal cytokines that increases during these inflammatory processes, via Toll-like receptor (TLR) activation induces apoptosis of brown adipocytes and inhibits the expression of UCP1 and b3-adrenergic receptor on adipocytes, ultimately decreasing thermogenesis in BAT (52). Other inflammatory mediators, such as pattern recognition receptors (PPR) and nucleotide-oligomerization domain containing proteins (NODs), have been suggested to have a critical role in modulating BAT activity during inflammation via activation of NF-kB and MAPK signaling pathways (53, 54).

BEIGE ADIPOCYTES AND AGING

Beige/brite adipocytes are likely to originate from both a white-to-brown transdifferentiation mechanism and *de novo* differentiation from specific precursor cells (**Figure 2**).

The phenomenon by which the appearance of beige cells among WAT depots is observed is referred to as "browning"

(55); this mechanism is mainly based on adrenergic signals and cold exposure. The beige-type cells in white fat depots are genetically different from those in classic interscapular and perirenal BAT, which are derived from myogenic factor 5 (MYF-5) positive precursors (56). Moreover, recent evidence suggests that both BAT and WAT adipocytes derive from the vascular endothelial cells of adipose tissue, supporting a role for transdifferentiation (57). This induction of beige adipocytes depends on several mechanisms, including, in addition to the aforementioned environmental temperature, genetics factors, diet, developmental periods and anatomic location of the adipose tissues (58).

With regard to the *de novo* differentiation, adipose stem and/or progenitor cells reside within WAT, which can proliferate and differentiate into either white or beige/brite adipocytes. In particular, a distinct sub-population of WAT resident progenitors, which express the markers CD 137 and TMEM26 on their surface, show a greater ability to differentiate into beige cells (59).

As a consequence of this, the age-related dysfunctional regeneration and reduction of classical brown and beige tissues could be due to a defective ability to proliferate and differentiate from inducible WAT or due to a loss of CD137/TMEM 26+ progenitors.

Moreover, different molecular mechanisms have been described that underlie the loss of beige adipose tissue during aging. Interestingly, SIRT1, an important target in AT biology (60), drives the browning of adipose tissue by promoting the interaction between PPARgamma and PRDM16, a potent inducer of beige adipose-specific genes (61). A recent study demonstrated another role of SIRT1, via the regulation of the senescence pathway p53/p21 (62). By reducing the expression of p53, a transcription factor of p21, SIRT1, enhances beige adipocyte differentiation capability of elderly adipose tissue-derived mesenchymal stem cells (AT-MSCs). During aging there is a reduction in SIRT1 levels, but how its expression is regulated into these stem cells is still unclear. Recently, it has been demonstrated the microRNA 34a (miRNA 34a) is a direct regulator of SIRT1 (63). Interestingly, miRNA-34a suppresses the process of browning under conditions of obesity, in part via its regulation of SIRT1 and FGF-21. This evidence supports its role of being a candidate molecule for improving the differentiation ability of elderly AT-MSCs as a treatment of aging obesity (63).

BROWN AND BEIGE AGING: POTENTIAL INTERVENTION TARGETS

White and brown AT has been suggested as a target for the prevention of type 2 diabetes, lipid disorders, as well as for delaying aging. Counteracting the age-associated loss of brown and beige adipose tissue could be an interesting and innovative therapeutic approach. Different types of strategies and molecular targets have been suggested for implementing possible interventions to slow age-related changes in brown and beige adipose tissue.

Physical Exercise

Well known and widely studied are the effects of physical exercise on adipose tissue physiology, since it is well known that regular physical activity improves glucose tolerance and reduces white adipose tissue mass. Several studies have shown that physical exercise is associated with changes in both subcutaneous and visceral fat, a reduction of adipocyte size and lipid content, enhanced expression of metabolic pathway genes, modified secretion of adipokines and increased mitochondrial activity (64). However, less well-known and studied are the effects of physical exercise in AT of elderly humans, and in particular on BAT.

Studies evaluating the effect of exercise on BAT in old rodents and humans have been published with conflicting results. In a recent study conducted in old rats, both strength and aerobic training determined an increase in BAT, in mitochondrial activity, thus reducing total body fat (65). These results were also confirmed in other rodent models, where the physical exercise-associated browning of subcutaneous WAT has been demonstrated (66).

However, these findings were not confirmed in elderly subjects as a decrease in mitochondrial activity and in glucose uptake in BAT after training has been shown (67).

More examination is mandatory to completely understand the impact of the complex relationships between different types of exercise and exercise-induced adaptations in WAT and BAT, as it is a field of study of considerable interest.

Nutritional Strategies

Since intermittent fasting was proved to optimize energy metabolism (68), in a recent study rodents were kept on an every-other-day fasting regimen: this approach favored the activation of beige fat thermogenesis and improved obesity-related metabolic diseases, probably via a microbiota-beige fat axis (69). Interestingly, in a human model, Orava and colleagues observed that insulin stimulated a 5-fold increase in FDG uptake in BAT, suggesting that BAT may contribute to postprandial energy metabolism in humans (70).

Recent researches have demonstrated that some food ingredients may be involved in promoting energy expenditure and fat oxidation in BAT. In fact, it has been shown that capsaicin and its analogs in hot peppers, as well as caffeine and catechins in green tea, could be related to an increased energy expenditure (71, 72). In particular, capsaicin may induce a browning program in WAT, stimulating UCP-1 and promoting SIRT1 expression and activation through TRPV1 (transient receptor potential channels) channels (73). Josse et al. have reported that an ingestion of meals supplemented with capsinoids may increase energy expenditure and lipid oxidation through an activity on Beta3-adrenergic receptors (74, 75).

It has also been shown that PUFAs (Long-chain omega-3 polyunsaturated fatty acid) and, in particular, eicosapentaenoic acid (EPA), known for their anti-inflammatory and cardio protective effects, reduce high-caloric diet related obesity and insulin resistance in mice. The mechanism underlying BAT activation seems to depend on FGF21 expression, also without

cold exposure, suggesting that EPA supplementation alone may mimic the cold induced BAT activation (76).

All of this evidence may demonstrate future area of research for a non-pharmacological strategy to treat obesity and age-related metabolic disease, also in elderly individuals.

Cold Exposure

It is now widely known from studies on mice and humans that exposure to cold increases the activity of brown adipose tissue (27). Saito et al. found an unexpected high presence of cold-activated BAT by performing FDG-PET/CT scans in healthy adults under warm and cold conditions, which suggests an important role of temperature in the regulation of BAT activity and body fat content. More recently, gene expression profiles and metabolic pathways activated in BAT exposed to cold have been investigated; in an interesting study conducted in mice, it was shown that cold exposure highly influenced BAT metabolic activity. Exposure to cold is characterized by lower levels of glycolysis and gluconeogenesis intermediates, higher levels of tricarboxylic acid cycle metabolites, free fatty acids and acyl-carnitine metabolites, suggesting that glycolysis and β-oxidation of fatty acids in BAT are biological pathways that contribute to increased thermogenesis by cold exposure (77, 78).

Recent studies have evidenced that mitochondrial reactive oxygen species (ROS) play an important role in modulating thermogenesis and UCP1 activity. In fact, cold exposure is characterized by an increased mitochondrial superoxide and oxidation of lipids and proteins in BAT. Furthermore, acute cold exposure leads to enhanced oxidation and a decrease of reduced glutathione in BAT; this process is associated by increased protein thiol oxidation, which has been suggested as a vital signaling mechanism required for UCP1-induced thermogenic metabolism (79, 80).

Pharmacological Strategies

The PPARgamma agonist rosiglitazone exerts its thermogenic effects on adipocytes by increasing PRDM16 (regulator PR domain containing 16) protein half-life, a zinc-finger transcriptional factor that plays a key role in the differentiation of adipocytes (61). In fact, PRDM16 controls the bidirectional switch between brown adipocytes and myoblasts. PRDM16 determines the brown fat-like gene expression and thermogenesis in both BAT and WAT. Moreover, the expression of this transcriptional regulator is strongly correlated with beige cell-selective genes, in the so-called browning process (61). From a therapeutical point of view, some reports have supported extensive inhibition of adipokines production, including resistin, 1-acidglycoprotein, and haptoglobin, by treatment of white adipocytes with thiazolidinedione (TZD) and non-TZD synthetic PPARgamma ligands (81).

Moreover, Finlin et al. have suggested that mirabegron, a beta 3-agonist, induces the expression of UCP1 and beige adipocyte markers to a higher degree than 10 days of repeated cold exposure. This phenomenon may be exploited to increase beige adipose tissue in older, insulin-resistant, obese individuals (82).

Vitamin A metabolites or retinoids are other hormones required for BAT activation. Retinoic acid strongly induces UCP1 expression in adipocytes, indicating that body thermogenic capacity may also be related to the vitamin A status. Retinoic acid may also determine adipocyte differentiation and survival, with high doses inhibiting and low doses promoting adipogenesis of adipose cells precursors *in vitro* (83). The administration of retinoids in high-fat diet mice is associated with an increase in adipose UCP1 expression and a reduction in body weight. However, its role in humans is still controversial: UCP1 expression is differently affected by all-trans retinoic acid (ATRA) in mouse and human adipocytes (84).

Bone morphogenetic proteins (BMPs) are a family of secreted molecules that contribute to the differentiation of mesenchymal stem cells and drive the formation and thermogenic activation of BAT (85). BMP9 treatment has been shown to determine the browning of subcutaneous WAT, to improve glucose tolerance and reduce weight gain in *in vivo* experiments (86). A role for BMP8B in the regulation of thermogenesis has also been described; this protein regulates nutritional and thermogenic factors in mature BAT, improving the response to noradrenaline through enhanced p38MAPK/CREB signaling and increased lipase activity. *Bmp8b*$^{-/-}$ mice show impaired thermogenesis and decreased metabolic rate, determining weight gain despite hypophagia. BMP8B is also expressed in the hypothalamus, and *Bmp8b*$^{-/-}$ mice display altered neuropeptide levels and reduced phosphorylation of AMP-activated protein kinase (AMPK), indicating an anorexigenic state (87).

Fibrates exert their lipid-lowering activity via PPARalpha. The new compound, GW9578, was demonstrated to enhance insulin sensitivity and to decrease adiposity *in vivo* (88). Moreover, the PPARalpha agonist GW9578 stimulates expression of the thermogenic gene program in beige adipocytes and rescues the beige-to-white fat transition phenotype induced by loss of Lsd1 (89).

However, most of the research about transcriptional factors involved in the regulation of BAT development has been carried out in mice and the expression of these marker genes seems less consistent in the humans, with a lack of specific data for elderly subjects in particular.

CONCLUSIONS

Further human studies are needed to investigate the effectiveness of nutritional and pharmacological stimulation to maintain BAT and beige mass and sensitivity during aging.

However, any therapeutical targeting of BAT activity and/or mass will first require a clear understanding of the mechanisms involved in potentiating BAT activity.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Aging and Imaging Assessment of Body Composition: From Fat to Facts

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The aging process is characterized by the chronic inflammatory status called "inflammaging", which shares major molecular and cellular features with the metabolism-induced inflammation called "metaflammation." Metaflammation is mainly driven by overnutrition and nutrient excess, but other contributing factors are metabolic modifications related to the specific body composition (BC) changes occurring with age. The aging process is indeed characterized by an increase in body total fat mass and a concomitant decrease in lean mass and bone density, that are independent from general and physiological fluctuations in weight and body mass index (BMI). Body adiposity is also re-distributed with age, resulting in a general increase in trunk fat (mainly abdominal fat) and a reduction in appendicular fat (mainly subcutaneous fat). Moreover, the accumulation of fat infiltration in organs such as liver and muscles also increases in elderly, while subcutaneous fat mass tends to decrease. These specific variations in BC are considered risk factors for the major age-related diseases, such as cardiovascular diseases, type 2 diabetes, sarcopenia and osteoporosis, and can predispose to disabilities. Thus, the maintenance of a balance rate of fat, muscle and bone is crucial to preserve metabolic homeostasis and a health status, positively contributing to a successful aging. For this reason, a detailed assessment of BC in elderly is critical and could be an additional preventive personalized strategy for age-related diseases. Despite BMI and other clinical measures, such as waist circumference measurement, waist-hip ratio, underwater weighing and bioelectrical impedance, are widely used as a surrogate measure for body adiposity, they barely reflect the distribution of body fat. Because of the great advantages offered by imaging tools in research and clinics, the attention of clinicians is now moving to powerful imaging techniques such as computed tomography, magnetic resonance imaging, dual-energy X-ray absorptiometry and ultrasound to obtain a more accurate estimation of BC. The aim of this review is to present the state of the art of the imaging techniques that are currently available to measure BC and that can be applied to the study of BC changes in the elderly, outlining advantages and disadvantages of each technique.

Keywords: aging, body composition, fat and lean mass, age-related diseases, imaging techniques

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INTRODUCTION

The rapid increase of elderly population represents a global health problem (1) together with the concurred increased incidence of age-related diseases, including type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome and cardiovascular diseases (CVD). The new field known as "geroscience" recognized that these chronic pathologies and aging itself share seven interconnected common mechanistic pillars such as epigenetics, adaptation to stress, stem cells and regeneration, proteostasis, macromolecular damage, metabolism and inflammation (2). To date, gerontologists propose to focus on these basic aging mechanisms to successfully counteract all the major age-related diseases, and to slow down the aging process (3). In particular, the chronic low grade inflammatory status occurring during aging, called "inflammaging," (4, 5) is tightly linked to metabolism, because any impairment of metabolic pathways can fuel inflammation. This metabolism-induced inflammation has been recently named "metaflammation" (6). Modern research aimed at finding potential sources of low-grade inflammation is now focusing on the major molecular and cellular mechanisms such as cellular senescence, mitochondrial dysfunction, activation of the inflammasome (7) and changes in gut microbiota composition, which mostly overlap with metaflammation and inflammaging (8). Several studies showed that metaflammation may trigger obesity-induced insulin resistance, suggesting a causative role in T2DM itself (9) and in diabetes-induced complications (10). Murine models of diabetes and obesity showed that an overexpression of pro-inflammatory molecules in fat tissue occur, which in turn increases insulin sensitivity (11). Several studies also revealed that the adipose tissue is a main source of inflammatory molecules, such as IL-6 and MCP1 (12, 13). Metaflammation is mainly driven by overnutrition and nutrient excess (3, 14), which are present in metabolic diseases, but body composition changes occurring with age can also contribute. Indeed, the aging process is characterized by an increase in body total fat mass and a concomitant decrease in lean mass and bone density, that are independent from general and physiological fluctuations in weight and body mass index (BMI) (15). Moreover, the accumulation of muscle fat, visceral fat and liver fat, in form of lipid droplets (LD), also shows an age-dependent increase, while an opposite tendency is observed for subcutaneous fat mass (16). However, it should be taken into account that when the decrease of subcutaneous peripheral fat becomes excessive, it is associated with a pro-inflammatory status, and a reduction of LDs is associated with lipotoxicity (17) leading to CVD, an increased risk of insulin resistance and T2DM. Thus, in order to preserve a metabolic homeostasis and a health status positively contributing to longevity, it is desirable to maintain a balanced rate of fat content and distribution (18). For this reason, a detailed assessment of body composition (BC) in elderly is critical and could be an additional preventive personalized strategy for age-related diseases. The most commonly used method to investigate BC employs a five-level model, which make it possible to classify the human body according to five levels of increasing complexity: I, atomic; II, molecular; III, cellular; IV, tissue-organ; V, whole body. To date, whole-body, organ-tissue, and molecular levels are the most studied in human BC assessment. BMI measurement is widely used as a surrogate measure for body fatness, due to the simplicity of anthropometric methods and the widespread availability of techniques to assess it, however it does not reflect the precise distribution of body fat. A hierarchical cluster analysis based on BMI together with BC parameters revealed that clusters with very similar BMI have a different amount of fat, lean and bone masses (19). Numerous clinical methods and techniques such as waist circumference measurement, waist-hip ratio, underwater weighing and bioelectrical impedance analyses are also available. However, the attention of clinicians has recently focused to several imaging techniques to study BC, because of the great advantages offered by imaging tools in the research and clinical aspects of this field (20, 21). The imaging methods used to analyze BC aim to divide body mass into its components based on their different physical properties. Depending on the information sought, several methods can be used to measure BC, such as computed tomography, magnetic resonance imaging, dual-energy X-ray absorptiometry and ultrasound, each showing specific advantages and limitations. In selecting the diagnostic imaging method, one should consider the accuracy and type of the information obtained, the safety of assessment (*e.g.* in terms of radiation exposure), the time required and costs (equipment and personnel) (**Tables 1**, **2**). Nowadays, Dual-energy X-ray Absorptiometry (DXA) represents a reference method for the assessment of human BC in the research field (22, 23), due to its fast acquisition time, low radiation exposure and relatively low cost when compared to other available techniques (24–27). Within the framework of the European NU-AGE project (conducted from 2011 to 2016) a DXA scan has been carried out in a large number ($N = 1{,}121$) of sex-balanced, free-living, apparently healthy older adults aged 65–79 years enrolled in 5 European countries (Italy, France, United Kingdom, Netherlands and Poland) (28) for the first time. The results showed that BC characteristics are different in elderly women and men across Europe (19) and that a better adipose-related inflammatory profile is associated to a more favorable BC in terms of fat and lean mass markers (29). In this review, we summarize the present knowledge of available imaging methods to measure BC, with a focus on the measurement of BC changes occurring with age and we discuss *pros* and *cons* of each technique.

DUAL-ENERGY X-RAY ABSORPTIOMETRY (DXA)

DXA was originally developed to evaluate bone mineral density, but it has gained popularity as a method to assess whole-body and regional soft-tissue composition. DXA divides the body into three components; bone mineral content (BMC), lean mass (LM) and fat mass (FM). Since the method assesses three body-composition components at a molecular level, it is widely considered as the gold standard for BC assessment in clinical practice.

This technique is based on the physical principle that X-rays of different energies are differentially attenuated when passing

TABLE 1 | Overview of body composition methods for assessing adiposity and regional fat depots in older adults.

Method	Frequently used measures	Body fat compartment			Low cost	Availability	Radiation exposure	Precision	Accuracy
		Visceral fat	Inter-/ intramuscolar fat	Whole body fat					
Anthropometry	Body Mass Index	+	+	++	+++	+++	+++	+	++
	Skinfold thickness	+	+	++	+++	+++	+++	+	+
	Waist circumference	++	+	++	+++	+++	+++	+	+
	Arm circumference	+	+	+	+++	+++	+++	+	++
	Predicted fat mass	+	+	++	+++	+++	+++	+	+
Bioelectrical impedance	Predicted fat mass	+	+	++	+++	+++	+++	+	+++
Ultrasound	Mid-tight image	(+)++	++	+	+++	+++	+++	++	+++
Dual energy X-ray absorptiometry	Whole body scan	++	+	+++	++	++	++	+++	+++
Computed tomography	Abdominal image	+++	++	+	+	+	+	+++	++
	Mid-tight image	+	+++	+	+	+	+	+++	+++
Magnetic resonance imaging	Abdominal image	+++	++	+	+	+	+++	+++	++
	Mid-tight image	+	+++	+	+	+	+++	+++	+++
	Total body multi image	+++	+++	+++	+	+	+++	+++	++

+++ indicates a very positive feature of the method, while + indicates a less positive feature.

TABLE 2 | Overview of body composition methods for assessing whole body and regional skeletal muscle in older adults.

Method	Frequently used measures	Skeletal muscle compartment		Low cost	Availability	Radiation exposure	Precision	Accuracy
		Regional muscle	Whole body muscle					
Anthropometry	Arm circumference	++	+	+++	+++	+++	+	+
	Calf circumference	++	+	+++	+++	+++	+	+
	Predicted ASMM	+	++	+++	+++	+++	+	+
Bioelectrical impedance	Predicted FFM mass	+	+	+++	+++	+++	+	+++
	Predicted ASMM	++	++	+++	+++	+++	+	+++
Ultrasound	Mid-tight image	++	+	+++	+++	+++	++	+++
Dual energy X-ray absorptiometry	Whole body scan	+++	++	++	++	++	(+)++	+++
Computed tomography	Mid-tight image	+++	+	+	+	+	+++	+++
Magnetic resonance imaging	Mid-tight image	+++	+	+	+	+++	+++	+++
	Total body multi image	+++	+++	+	+	+++	+++	++

ASMM, Appendicular Skeletal Muscle Mass; FFM, Fat-Free Mass.
+++ indicates a very positive feature of the method, while + indicates a less positive feature.

through the various tissues of human body. By radiating the body in anterior-posterior direction using two different energies, and assuming a two-compartment model in each measurement point (pixel), the image can be reconstructed; the two-compartment model assumes that pixels not containing bone depend on LM and FM ratio, and that pixels containing bone depend on BMC and soft tissue ratio with a subsequent interpolation of LM and FM ratio based on neighboring pixels not containing bone.

DXA allows total-body and standard regional body composition measures, including trunk, arms, legs, android and gynoid regions, and ideally, can estimate every human body part of interest (**Figure 1**).

In addition, it is now possible to estimate with DXA the amount of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in the android region that represent, a harmful factor and a presumable protective factor, respectively, in cardio-metabolic status of patient.

The DXA approach represents a good candidate to be a gold standard technique to measure longitudinal changes in BC in multiple pathologic or paraphysiologic conditions because of its high accuracy and precision, large availability, and low-cost.

DXA is a non-invasive, quick and safe method for BC assessment, and the radiation exposure is considered small and safe for repeated measures (a whole-body scan takes only 6–10 min and the radiation exposure is equivalent to a day spent sunbathing).

Currently available DXA systems for scanning whole-body tissue composition are capable to analyze a wide range of weights and sizes, including severe obese subjects (>200 kg with relatively wide scanning space >65 cm).

A marked impaired hydration status may affect DXA accuracy because of the programmed assumption of a constant and uniform LM hydration (25).

Reference values of BC assessed by DXA on adults over 60 years old are available from the National Health and Nutrition Examination Survey 1999–2004 and from other studies on local population (30).

ULTRASOUND (US)

Ultrasound is another technique that has been used for a long time to assess FM. US, based on echo reflections, offers a two-dimensional gray-scale image, between black (no echoes) and white (strong reflections), and shows skin-subcutaneous fat borders, fat-muscle, and muscle-bone interfaces (31). Although US procedures are considered accurate, reproducible, and fast for the analysis of abdominal adiposity by allowing a local, easy and close-at-hand evaluation of subcutaneous and visceral fat compartments (32), there are different opinions about its validity. Borkan et al. suggested that with respect of ultrasound, skinfolds were a better measure of subcutaneous fat (33), while Fanelli and Kuczmarski proposed that US was identical to skinfolds when determining body fat (34). US intra-abdominal thickness measurement was introduced by Armellini and colleagues to demonstrate that US was the most powerful identifier of visceral adipose tissue area into intra-abdominal thickness (35, 36).

It is easy to understand how the absence of a straight standardized protocol leads to a decrease in accuracy and reliability of US measurements of BC, mainly for visceral adiposity. In a recent study was demonstrated that reproducibility and repeatability, especially for visceral fat, were proved more stable in fasting state and expiration (37).

COMPUTED TOMOGRAPHY (CT) AND MAGNETIC RESONANCE IMAGING (MRI)

CT and MRI are cross-sectional imaging modalities providing 2D or 3D maps of pixels allowing for the *in vivo* measurement of lean mass and total adipose tissue and its subdepots (subcutaneous, intermuscular, and visceral).

CT presents great practical significance due to its routinely use for diagnosis and follow-up in various diseases and allows an accurate quantification of whole-body composition (**Figure 2**).

Being a volumetric technique, CT allows to measure body components at tissue-level using pre-established Hounsfield Units (HU) to recognize different tissue density (soft tissue: 30–50 HU; fluid-sovrafluid: 0–30 HU; adipose tissue: −100 HU; bone and calcification: 100–1000 HU).

CT imaging at L3 level provides total, visceral or subcutaneous adipose fat area, visceral adipose volume, total psoas area, and skeletal muscle index (SMI) (38). Moreover, according to ethnicity- and sex-specific data, CT has been used to derive a predictive cardio-metabolic risk (CMR) equation (39). This type of evidence endorsed other specific research, analyzing pericardial fat, intrathoracic fat and epicardial fat, showing the potential contribution in CMR stratification (40). Also, because CT images targeted on the III lumbar vertebra are similar to those on chest, they could be tentatively performed solely. As CT usage has now increased in clinical practice, the radiation exposure should be taken in mind, since it represents a risk factor for oncologic disease development.

Differently from CT that is calibrated against the Hounsfield scale, signal intensities in MRI are often non-quantitative because image intensity values do not reflect physical properties of the imaged body. MRI allows to measure body fat-free mass such as skeletal muscle mass at arms, legs and trunk level, specific organ masses, and provides also an estimate of bone marrow adipose tissue (41). From a technical point of view body composition measurement with MRI is based on the different magnetic properties of hydrogen nuclei contained in water and fat. Several MRI sequences have been developed to measure body fat, using variations in radiofrequency pulse to differentiate between adipose tissue and fat-free mass (27). A variety of pulse sequences are thus available to generate contrast between fat and non-adipose tissue (42). Adipose tissue is characterized by a short T1 and a long T2 relaxation time; in T1-weighted spin-echo sequence, fat appears as a high signal (white) because of a high concentration of relative immobile protons, thus differentiating it from muscles, fluids, bone and internal organs, which appear as gray signals (43). The time of acquisition for such sequences is relatively long and implies some issues, such as respiratory/motion artifacts. Variations of this sequence have been developed in order to reduce the acquisition time. Nowadays, a whole-body MRI scan of an individual can be obtained in about 5 min, allowing for the detailed evaluation of total and regional fat depots. Whole-body scanning is the most accurate and reproducible protocol to obtain an accurate quantitative map of body fat distribution and content, but it has been mainly limited to research studies due to the high scan costs and the need of time-consuming image analysis (44). In fact, the amount of data generated by whole-body MRI requires a complex analysis, generally not manually feasible, except for very small studies. In the last years, this has led to the development of semiautomated or automated methods for MRI-based body

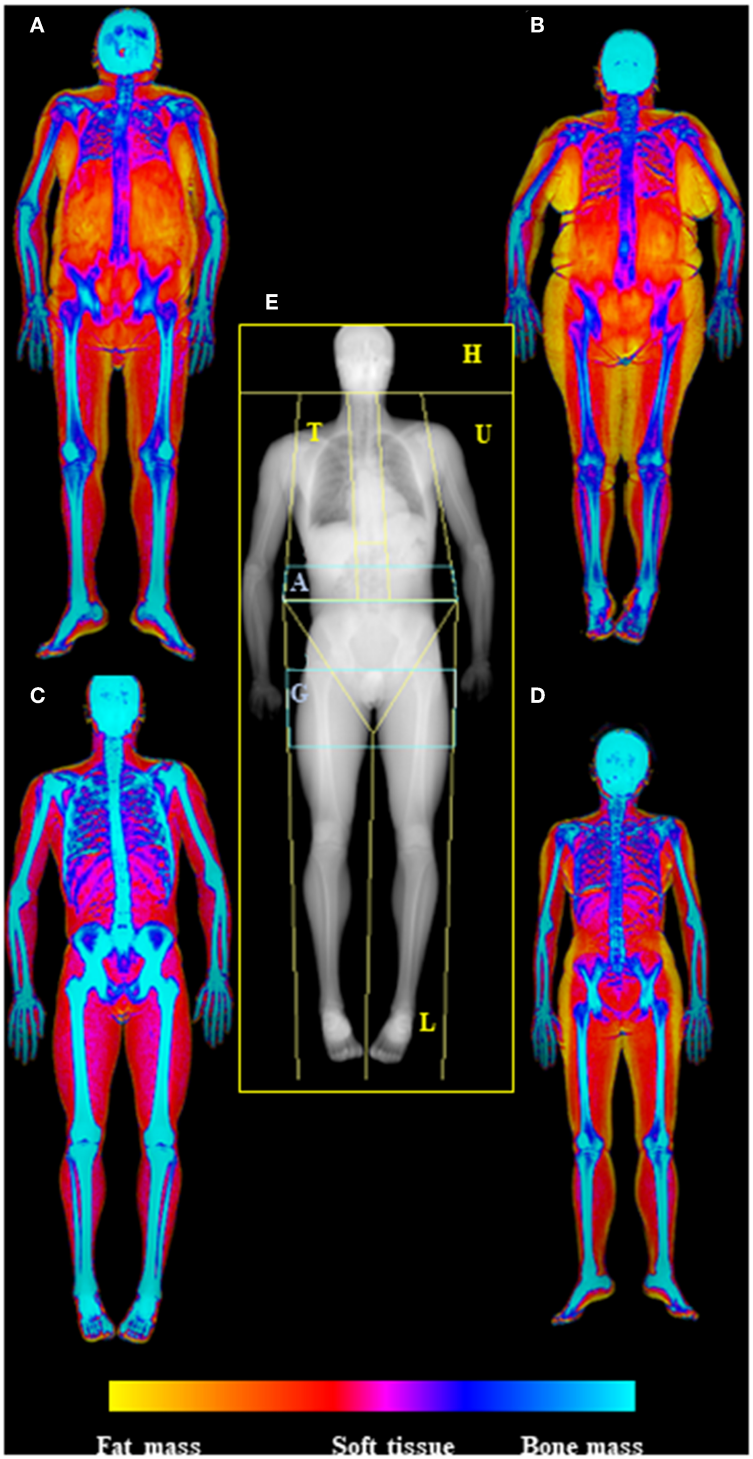

FIGURE 1 | Dual-energy X-Ray absorptiometry (DXA) examination of body composition. In the center of the picture **(E)** is represented the skeletal map of whole body scan by DXA highlighting the standard ROIs specifics for body composition assessment (head—H, trunk—T, upper limbs—U, lower limbs—L), with the two regions at "high metabolic significance" representing by gynoid (G) and android (A) regions. On the side are depicted the soft tissue maps of whole body DXA scan (from fat mass—yellow—to bone mass—blue); in particular on the left are visualized old **(A)** and young **(C)** males (respectively upper and lower), while in the right old **(B)** and young **(D)** females (respectively upper and lower), highlighting the increase of fat mass in aging. Images are kindly provided by IRCCS Rizzoli Orthopedic Institute, Unit of Diagnostic and Interventional Radiology (2019).

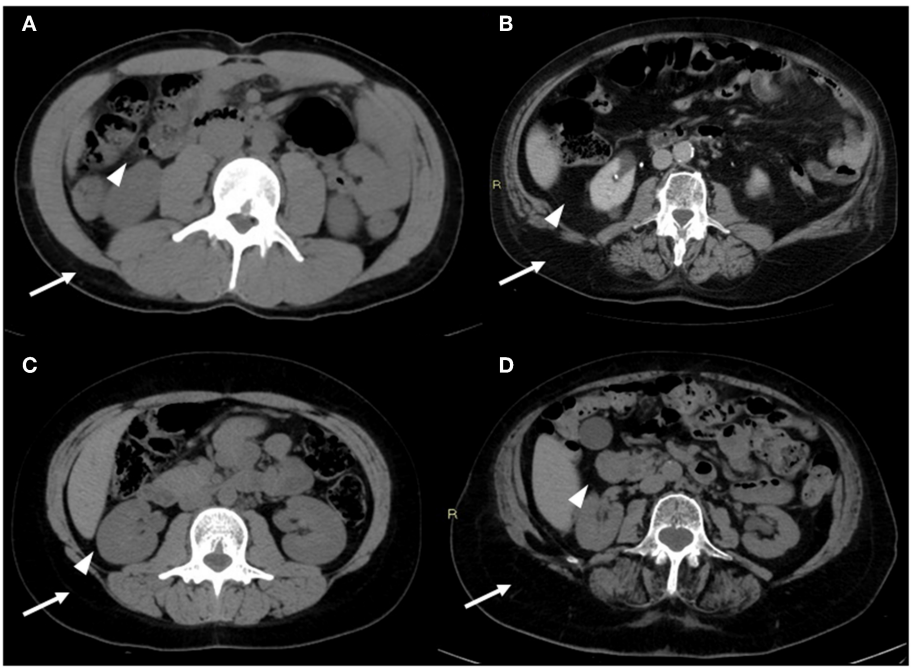

FIGURE 2 | CT images of the android region. CT image slices of the android region showing changes in adiposity distribution (visceral fat—arrowheads; subcutaneous fat—arrows) depending on age and sex: **(A)** young male, **(B)** old male, **(C)** young female, **(D)** old female. With advancing age, there is a redistribution of fat mass compartment with increase of visceral compartment for both sexes (in particular for males); it is also noteworthy that the subcutaneous compartment is prevalent in females, both in young and old age. Images are kindly provided by IRCCS Rizzoli Orthopedic Institute, Unit of Diagnostic and Interventional Radiology (2019).

composition analysis. Furthermore, single-slice and region-specific multi-slice protocols were developed to make data analysis easier and faster (**Figure 3**) (43, 45). An alternative to whole-body imaging is the acquisition of the solely abdominal region, which allows to measure fat depots frequently associated with CMR factors, like visceral adiposity (46). Multi-slice protocols have become the preferred method for large population studies, while single-slice protocols have been mainly used in small cohort studies, even if a number of protocols differ in the landmarks to be used for acquisition; the level of L4–L5 has been the most commonly reported anatomical landmark for single-slice imaging, while a level close to L2–L3 has been considered by several authors as the preferable site to evaluate visceral adipose tissue depot (41, 43). A poor prediction of visceral and subcutaneous tissue changes was reported in a longitudinal study with single-slice MRI evaluation at L4–L5 level (47).

There is an increasing interest in using MRI to evaluate age-related muscle changes to understand the contribution of poor muscle quality and fat infiltration in sarcopenia. Recently, Yang et al. demonstrated that a single slice cross-sectional area at mid-femur can be used in clinical practice for a fast and non-invasive diagnosis of sarcopenia in old adults (48). Compared to other imaging techniques, a key advantage of MRI is the ability to detect changes in the muscle structure occurring during the aging process or during disease progression, making this technique a powerful tool in longitudinal studies. Quantitative magnetic resonance imaging (QMRI) can be achieved by proton nuclear magnetic spectroscopy or magnetic resonance spectroscopy (MRS), which allows the accurate measurement of intramyocellular lipid and extramyocellular lipid in muscle fibers. MRS can precisely discriminate adipose and lean tissue by enhancing contrast, offering the possibility to estimate the accumulation of tryglicerides in non-adipose tissue (ectopic lipid). Diffuse fat infiltration in organs and lean tissue can be also estimated using "quantitative fat-water imaging," which is based on Dixon imaging, a gradient recalled echo imaging method which uses the chemical shift between proton resonance frequencies in water and in fat (44). MRI shows the best contrast between fat and muscle tissue, allowing for an accurate evaluation of muscle quality. It has been shown to possess a higher sensitivity compared to CT in detecting early fatty replacement in muscles (49). Differently from DXA, QMRI has the great advantage to be independent of fat-free mass hydration level, showing great accuracy and low-minimal changes detectable in longitudinal studies. However, underestimation of fat mass and overestimation of fat-free mass by QMRI compared with a 4-compartments model has been reported (50). In old adults infiltration of adipose tissue is recognized as a predictor of poor muscle and mobility functions. MRI was used to study intramuscular adipose tissue in frail and non-frail individuals, showing that more muscle fat infiltration was detectable in older frail subjects (18.0 vs. 11.7%) (51). In women over 50 years old, MRI-measured muscle fat infiltration was reported to be positively associated with increased fracture risk (52),

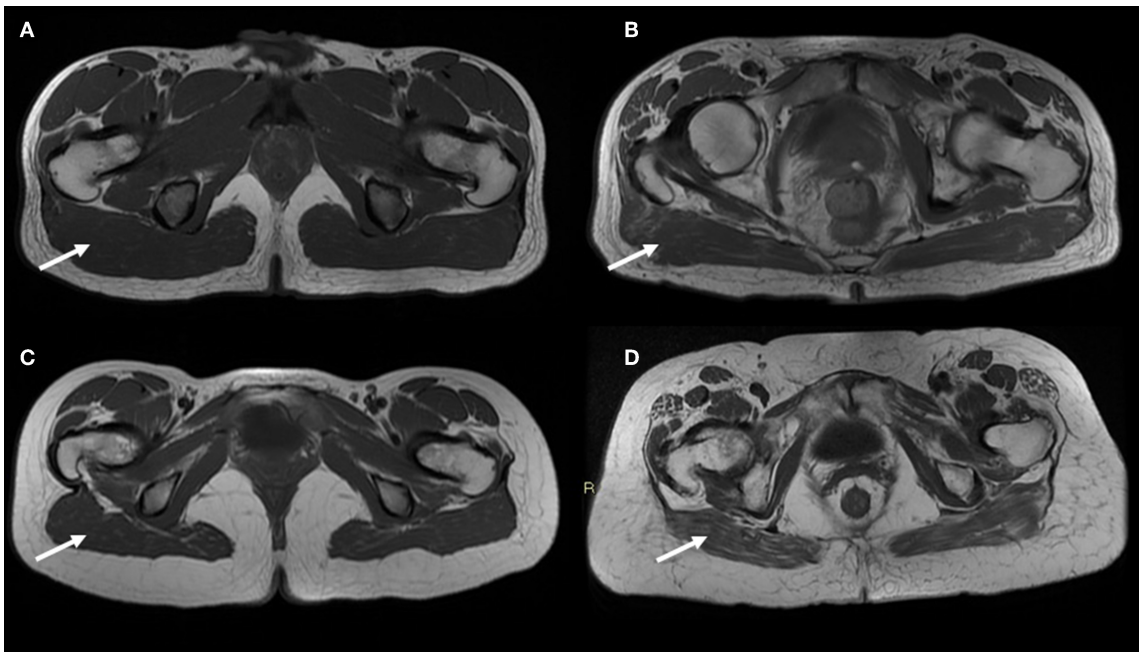

FIGURE 3 | MR T1-weighted image slices of the gynoid region showing age-related muscle changes in both sexes (poor muscle quality and fat infiltration—arrows). In addition larger subcutaneous adipose tissue are observed in the gynoid region of an old female **(D)** compared to a young female **(C)**; on the contrary the representation of subcutaneous compartment in the same region is the same both for a young male **(A)** and an old male **(B)**. Images are kindly provided by IRCCS Rizzoli Orthopedic Institute, Unit of Diagnostic and Interventional Radiology (2019).

while lower extremity muscle fat infiltration was shown to be negatively associated with performance based measures of physical function (53).

Currently, MRI represents the most advanced and accurate technique for the study of body composition, by allowing the measurement and quality assessment of muscle volume and cross-sectional analysis. Its ability to detect changes in the muscle structure occurring with aging makes this technique extremely fascinating to understand age-related progressive loss of muscle strength and quality. MRI, together with CT, represents the gold-standard technique in exploring muscle mass and quality for research purpose, however the limited access to the equipment, the complexity of data analysis and high cost, limit the use of MRI routinely in clinical practice (54). A strong methodological weakness is represented by the lack of a standardized evaluation protocol in image analysis, limiting comparison between studies (55).

CHANGES IN BODY COMPOSITION WITH AGE

Overall Adiposity

From young age to about 75 years old, body weight and consequently BMI usually increases. This trend is followed by a decline with an intermediate period of stability (56). Due to physiologic height loss with aging, the BMI in elderly may be overestimated in weight-stable persons and this condition is particularly true in women >85 years old (57). In elderly, recurrent weight changes events are usual and the individual evolutions of body weight and BMI are very miscellaneous (58, 59).

In a healthy Italian population, an increase of FM and a decrease of LM were detected up to 70 years old, although women were less affected by this phenomenon. As the matter of fact FM in women increased up to the first four decades of life and remained steady afterwards, differently from the development of FM in men (remarkable increase, especially after 60 years old) (22).

Consequently, the percentage of body fat in both sexes increases up to ∼70 years old, but these percentage modifications appear less evident later, because of a trend to a reduction in fat mass after 80 years old (60). In weight stable old adults, the loss of skeletal muscle mass contributes to an increase in body fat percentage (61, 62).

The complex and partially unknown endocrine role of adipose tissue on muscle metabolism emphasizes the existence of an adipo-muscular axis that can influence metabolic changes between physiologic and pathologic states, including obesity and inflammation, but also in para-physiologic conditions such as aging. As examples, an accelerated loss of LM has been associated with greater body fatness in old age and a significantly greater quantity of LM is lost during weight loss than is gained during weight increase, specifically in old men (63, 64).

Body Fat Distribution

A general increase in trunk fat (largely visceral fat) and a decrease in appendicular fat (largely subcutaneous fat) have been observed with age. The reduction in subcutaneous adipose tissues has

also been confirmed using whole-body MRI as well as CT data of the mid-thigh or US measurements at abdominal level. The increase in abdominal adiposity has been estimated through anthropometric methods such as waist circumference, but a direct measurement can be obtained only by imaging techniques such as CT and MRI (expensive but accurate) as well as US and DXA (available but less accurate).

In a recent study evaluating adiposity markers of visceral fat by US, no differences were found between males and females in their 30 to 50 s, while a significant difference emerged for those in their 60 to 70 s; the visceral fat content increases noticeably during aging in males, while in females major changes were significantly observed in the preperitoneal circumference (65).

Considering DXA imaging analysis, a significant redistribution of both central and visceral FM was shown to happen for men during their lifetime, but not for women. In a healthy sample, android and visceral fat progressively increased in elderly males, while females, in old decades, seem to go toward a less pronounced android or visceral redistribution of fat. While in healthy females the central FM distribution maintains a stable android/gynoid ratio, Bazzocchi et al. showed that in males a linear progression to an abdominal redistribution of FM could be observed over time. In particular, SAT depots were significantly higher in females, becoming nearly overlapping in males and females from 50 to 70 years old (22).

Apart from the redistribution of body fat, another feature of old age-related BC changes are the accumulation of fat infiltration into non-fat tissues. The alterations in ectopic fat have been mostly studied in aging muscles, especially with the support of whole-body MRI scans. Several evidences in literature suggests that the amount of inter-muscular adipose tissue increases rapidly with aging: about +10% and +6% per year in old men and women, respectively. In particular, the increase in inter-muscular adipose tissue is most visible in those who underwent an increase in total body weight, but it also accumulates in people who experience weight loss (66–68).

Skeletal Muscle Mass

In 1997, the age-related loss of muscle mass was termed sarcopenia, from the Greek words *sarx* (meaning flesh) and *penia* (meaning loss). Forbes and Reina were among the first to report prospective data that showed an age-related decrease in lean body mass (about −0.41 kg per year in adults).

However, it is globally accepted today that the concepts of low lean mass and decreased muscle function should necessarily be both incorporated into a current definition of sarcopenia.

According to this tendency, several working groups worldwide have new consensus definitions of sarcopenia published in recent years, even if a unique consensus with regard to the specific cut-off point or the most appropriate technique for assessment of low skeletal muscle mass in old adults has not been identified yet (23, 69–71).

In some studies, the deterioration in skeletal muscle mass in elderly have been measured by using 24-h urinary creatinine excretion and CT cross-sectional area, providing an accurate assessment of the skeletal muscle mass loss because other lean tissues, in particular bone and visceral organs, are excluded from muscle evaluation. From these findings, the relative yearly decline in the skeletal muscle mass was evaluated to be between −0.64 and −1.29% per year for old men, and between −0.53 and −0.84% per year for old women (63, 66, 67, 72–74). Both the increase in body fat and the loss of muscle mass with age make old adults at a higher risk of developing sarcopenic obesity, a condition characterized by excess of body adiposity associated with a reduced muscle mass and/or strength (75, 76).

More recent studies using DXA showed a general decrease of LM at upper and lower limbs with age in both sexes. Considering FM/LM distribution at the appendicular body, the decrease of LM was associated to an increase of FM. In particular, LM impoverishment was reported after 40 years in men (remarkably after 50 years old), and later, in the 50 years old, in women. Moreover, women seemed to maintain a more favorable arm masses ratio during aging. In this study, anthropometry was reported to be scarcely representative of LM of arms in both genders, independently of age, therefore the authors suggested that a correct assessment of BC at limbs should be achieved by imaging such as DXA (22, 77).

ASSOCIATIONS OF FAT MASS WITH MOBILITY, DISABILITY, AND MORTALITY

In the elderly, obesity determined by a high BMI has been shown to be tightly associated with a decline in functional performances, possibly leading to disability. For example, a prospective study from Koster et al. involving almost 3,000 participants between 70 and 79 years old showed that a BMI above or equal 30 kg/m^2 was associated with a 60% increased risk of mobility limitations, which was reported to be independent of the participants lifestyle habits. This finding is consistent with the idea that obesity could be an important factor affecting the functional status of individuals rather than a mere indicator of physical inactivity (78).

It is not clear if an increased risk of functional limitations in the elderly is also associated with overweight, i.e., a BMI comprised between 25.0 and 29.9 kg/m^2. A study involving 406 participants aged 70–89 years showed that the risk of developing major mobility limitations was reduced in overweight individuals compared to normal weight or obese subjects. However, several studies indicated that a high abundance of body adiposity in the elderly may lead to an increased risk of mobility limitations and disability (79–85).

Adiposity is not the only determinant of functional status in old age; individual lifetime histories of being overweight or obese is also to be considered when considering the risk of disability. It has been reported that in older men and women who have been overweight or obese since age 25, the risk of developing mobility limitations was almost 3 times higher compared to individuals which maintained a normal weight throughout their lifetime. Conversely, individuals who became overweight or obese only in old age showed a risk 1.7 times higher. Thus, a longer history of high body fatness appears to augment the risk of functional failure in old age. Weight gain is another significant determinant of functional performances in advancing age, as suggested by

several prospective studies. For example, in a cohort of almost 3,000 Italian individuals over 65 years old, a weight gain of more than 5% after their 50s was correlated with an augmented risk of limitations in activities of daily living (ADLs) (86–89).

However, it was also observed that a 7-years weight gain pattern among men and women over 65 years old did not increase the risk of limitation in ADL or mobility compared to individual who maintained a stable weight (59).

Weight instability and oscillations have been associated with a higher risk of limitation of ADL and mobility infirmity in the elderly (59, 79, 90).

Most of the weight changes reported in these studies were unintentional. In other intervention studies, improvements of physical performances in obese old adults after intentional weight loss following dietary restriction were reported. Thus, the American Society for Nutrition has recognized the functional benefits of intentional weight loss in obese elderly (91–93); nevertheless, additional studies are required to set up optimal weight loss strategies for obese older adults and to assess their long-term benefits.

Generally, the correlations between BMI and mortality in the elderly have been described showing U-shaped or J-shaped relationships. An increased risk of death is associated with a low BMI (underweight), although a possible causal relationship linking an underlying illness (for example cancer) causing a low BMI and the consequent increased mortality rate cannot be excluded. An increased mortality risk has been sometimes reported only for obese elderly, while others indicate an increased mortality risk in overweight old adults. Therefore, a clear relationship is still a matter of debate (94–96).

Surprisingly, in some observational studies a protective effect of high levels of body fatness on mortality have been reported in the elderly (97). However, these studies are potentially inconsistent due to methodological biases in sampling and statistical analysis that may increase the reported protective effects on mortality. In fact, other studies not suffering from sampling or grouping biases conclude that being either overweight or obese decrease the chance of a healthy aging. A J-shaped association between BMI and 10-years mortality was detected among non-smokers older adults (98). A systematic review and meta-analysis examining the impact of a high BMI on mortality risk in older adults concluded that BMI in the overweight range is not associated with an increased risk of mortality, whereas obesity showed a significant association with a higher mortality risk. More recent studies have supported the finding that a high BMI negatively affects healthy life expectancy, and it is also associated with an increased risk for cancer mortality, in particular for colorectal cancer. A difference between men and women exists in the degree that excess body weight increases mortality risk (99–106).

Limiting the analysis to very old adults only, obesity appears to be unrelated to mortality risk and no protective effect of adiposity was observed (107, 108). It is possible that the relationship between adiposity and mortality can assume different meanings depending on the age, and that in some circumstances a higher BMI may be protective, even though more studies are required to gain more insights into this relationship. However, most of the studies conducted so far consider only the BMI as a measure of adiposity. Since the complexity of body fatness cannot be completely explained using the sole BMI, some studies investigated the relationship between mortality risk and adiposity by assessing the impact of different fat compartments. Even these studies resulted in conflicting evidences (102, 109–112).

Another important predictor of mortality risk in old adults is represented by body weight change. In particular, a recent study considering a multiethnic cohort of 63,040 individuals showed that weight loss rather than gain was associated with an increased mortality risk (59, 113–118).

As discussed above, these results suggest that unintentional weight loss may increase mortality risk in older adults, but not intentional weight loss. Unintentional weight loss may be the consequence of an underlying disease. Unfortunately, in most of the studies conducted so far intentional rather than unintentional weight loss distinction is not very clear. Body weight increase has not been found to be associated with a higher mortality risk in older adults (59, 114).

However, using a reliable BC measurement approach, researchers showed that elderly men who gained >5% fat mass over a 4.6-years follow-up had a higher mortality risk compared to men who did not change their fat mass (116). Since weight gain may be the result of an increase in fat as well as muscle mass, which can have a different impact on the associated risks, it is necessary for upcoming studies to evaluate the actual changes in different body compartments to consider their effects on mortality risk. A large waist circumference has been associated with mobility limitations and disabilities in several studies (119–123). In prospective studies, a high-risk waist circumference at baseline (of $\sim$ >102 cm in men and >88 cm in women) was correlated with a higher incidence of mobility and functional limitations, with a greater association in inactive older adults (78, 124–130). A longitudinal study assessing a 5.5-years modification in waist circumference showed that this was not associated with a change in the self-reported disability, reporting that the main predictor associated with physical decline was indeed the reduction in appendicular fat-free mass (74).

Muscle quality and muscle fat infiltration assessed by CT was associated with a higher risk of incident mobility limitations in men and women over 70 years old (84, 131–133).

High waist circumference in old adults is also a predictor of mortality. Increased mortality risk was observed also in normal BMI individuals who showed a large waist circumference, even if this association was reported to be dependent on cardiorespiratory fitness. It is possible that especially in older men, waist circumference could be a stronger predictor for mortality risk than BMI itself. In fact, in a study evaluating the associations between BMI, waist circumference and specific causes of mortality (such as deaths from lung cancer and chronic respiratory disease), waist circumference but not BMI showed statistically significant positive associations with deaths from major specific causes (102, 110, 134–138). In contrast, it has been shown a protective effect of a larger waist circumference in adults of 65 years old (100, 108).

Some studies suggest a negative impact of abdominal fat in life expectancy of old adults. A J-shaped relationship between DXA-assessed central adiposity and mortality was described (112). Similarly, visceral adiposity determined by CT was shown to be

correlated with an increased risk in men over 50 years old (111, 139). A recent analysis investigating the relationship between BC and inflammation in a large European cohort of elderly has shown that BC and regional lean/fat distribution can define BC clusters that differently associate with inflammatory markers and inflammatory profiles (29).

ASSOCIATIONS OF LEAN MASS WITH MOBILITY, DISABILITY, AND MORTALITY

It has been suggested that skeletal muscle mass reduction, or sarcopenia, that occurs in aging is associated with a decline in functional status in the elderly (70). Indeed, several studies have shown that sarcopenia is related to a poorer functional status or to a 5-years functional decline in old age. Surprisingly, two studies have shown that muscle mass gain rather than loss may lead to a worse functional status or greater functional decay. However, this may be due to the interfering role of excess adiposity, which is associated with a higher skeletal muscle mass but a poor functional status, thus the importance of considering the role of body fatness when investigating the correlations between skeletal muscle mass and functional status changes in the elderly (139–144). Several studies have shown that sarcopenia is not associated with or only weakly associated with: (A) a compromised functional capacity (145–149) and (B) a future functional decline (84, 85). According to these studies, which performed careful adjustments for both body fat and body height, the high body fat mass strongly affects functioning in old men and women, regardless of the physical activity level of the participants. This suggests that the impact of an excess body fat on the functional status in old age is far more important than a low skeletal muscle mass. In 2004, the concept of sarcopenic obesity (defined as having a body fat percentage >40% and a skeletal muscle index <5.45 kg/m^2) was launched, following the results of a study that showed a twofold higher risk of developing instrumental ADL disability in old sarcopenic adults (based on a threshold amount for the appendicular skeletal muscle mass divided by the body height squared) who had a high proportion of body fat compared to elderly with normal fat levels and without sarcopenia. However, more recent cross-sectional studies have not supported the finding that a mixture of low muscle mass and high body fat mass is more disadvantageous to the functional status than a high body fat mass alone. Considering sarcopenia alone, no association with an increased risk of a poor functional status was observed. One other recent study conducted on French women showed that compared to obese women, the sarcopenic obese women tended to have a higher risk of difficulty descending stairs but no differences were found for the other six physical function elements investigated in the study (148, 150–153). According to the present literature, is not possible to convey that the combination of obesity and sarcopenia is more damaging for physical performance than obesity alone. Additionally, it remains unclear whether the risks associated with sarcopenic obesity are higher than the sum of the

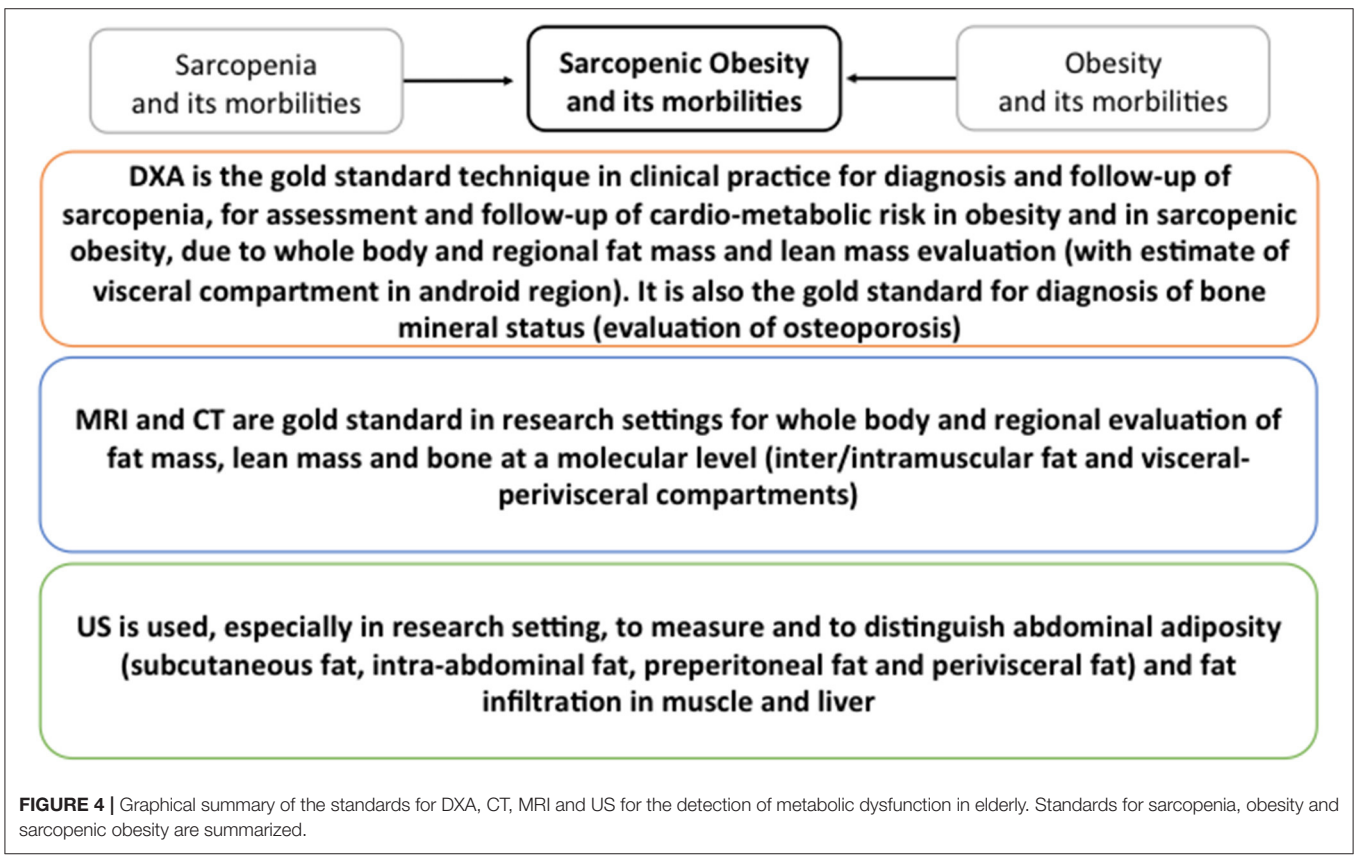

FIGURE 4 | Graphical summary of the standards for DXA, CT, MRI and US for the detection of metabolic dysfunction in elderly. Standards for sarcopenia, obesity and sarcopenic obesity are summarized.

single risks of obesity and sarcopenia together. The evaluation of body masses by the imaging methods described in this review could support clinical practice for the diagnosis of metabolic dysfunctions in elderly. In particular, because DXA scan can evaluate total and regional fat, lean and bone masses with accuracy for the visceral adiposity in the android compartment, it represents the gold standard for the diagnosis of sarcopenia, osteoporosis as well as of the CMR in both obesity and sarcopenic obesity. MRI, CT, and US are mainly used in research settings. MRI and CT are gold standards for the evaluation of inter/intramuscular fat and visceral-perivisceral compartments particularly important in sarcopenic obesity diagnosis. US is mainly used to measure subcutaneous, peritoneal and visceral fat thus being of particular use for the diagnosis of CMR risk in obesity. The graphical summary reported in **Figure 4** shows the standards for each technique.

A clear association between low muscle mass and functional decline in elderly has not been assessed due to the lack of evidences, although it has been suggested that a marked skeletal muscle mass waste in old age might intensify the chance of functional limitations and disability. As an example, a study involving 159 elderly (both males and females) who were monitored up for 5.5 years, showed that the loss of the appendicular muscle mass and leg muscle mass (as measured by DXA) was correlated with a decline of the disability score (74). Changes in the appendicular skeletal muscle mass over 5 years had a faint and positive association with changes in physical functioning measures (144). Unfortunately, it remains not clear whether the actual shrinkage in skeletal muscle mass or the involuntary decrease of body weight, which in turn leads to a decrease in skeletal muscle mass, could be the crucial factor inducing the functional status decline occurring with age. A recent trial showed that after voluntary weight loss, the loss of fat mass in the abdomen and thighs compared to the changes in skeletal muscle mass was the main determinant of improved functional performance (154, 155).

Only three prospective studies conducted so far evaluated skeletal muscle mass in an accurate and precise way and investigated the association between sarcopenia and mortality in older adults. The Health, Aging and Body Composition Study showed that the low muscle mass in the inferior limbs (as assessed by CT or DXA) was not strongly associated with a 4.9-years mortality risk in males and females aged 70–79 years (156). While in men, the low midthigh muscle cross-sectional region (as measured by CT) was associated with mortality (HR, 1.26; 95% CI, 1.02–1.55), in women this relationship was not observed (HR, 0.94; 95% CI, 0.61–1.35). In a cohort of 934 old adults over 65 years old from the In Chianti study it was discovered that the calf muscle area (as measured by peripheral quantitative CT) was not associated with a 6-years mortality (111).

In addition, also sarcopenic obesity was not associated with an increased mortality risk. Lastly, data from 3,153 65+

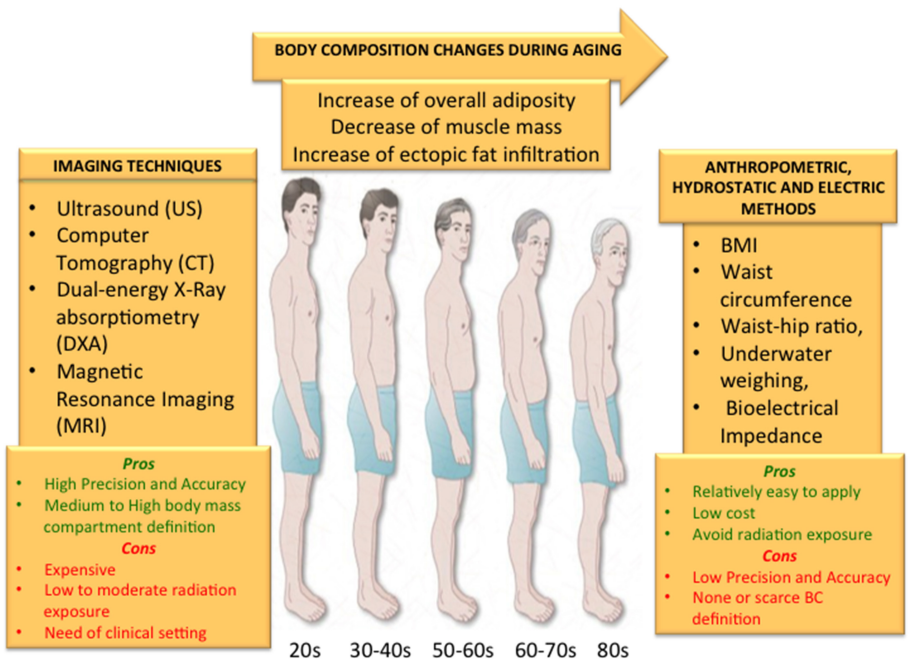

FIGURE 5 | The changes that usually occur with age such as overall increase of body fat and ectopic fat infiltration and the decrease of skeletal muscle should be accurately measured in order to add this information to a personalized preventive strategy to counteract age-related disease and disabilities. Although anthropometric measures, underwater weighting and electric bioimpedance represent cheap, easy and completely safe methods, they do not guarantee a high precision and accuracy to define BC compartments with none or a scarce definition. On the other hand, imaging techniques can guarantee a very high definition of body compartments either in fat or lean mass with a high accuracy and precision. However, all the imaging methods expose the subjects to low or medium levels of radiation, are not easily available and are quite expensive. Depending on the information sought, all these aspects should be taken into account when selecting the method to measure BC.

Chinese adults, showed similarities between sarcopenic and non-sarcopenic subjects in terms of 5-years mortality risk (144). On the whole, these studies systematically show that a higher mortality risk is not associated with a low muscle mass. Conversely, a recent study conducted during a 4.6-years follow-up found that the loss of appendicular muscle mass (as measured by DXA) was associated with an increased mortality risk in 4,331 males aged 65–93 years (116).

According to the available literature evidence, it is not possible to rule out the possibility that the increased mortality is actually caused by the weight loss experienced and the underlying cause of this loss, considering that in old adults the loss of skeletal muscle mass is strictly correlated with weight loss (154).

CONCLUSIONS

The changes in BC occurring during lifetime are strictly related to health status. The increase of fat mass and the decrease of lean mass typical of elderly have indeed been associated with the increase of age-related pathologies and functional decline. A reduced mobility, the onset of disabilities and falls are among the major cause of reduced quality of life among elderly. Moreover, the specific increase of visceral fat in abdomen and of the ectopic fat storage in other organs and tissues and the decrease of skeletal muscle mass have been associated with an increased pro-inflammatory status and insulin resistance that can further increase the risk of pathologies including CVD and T2D. For these reasons, the study of composition and distribution of body masses it is becoming urgent because the inclusion of information regarding quantity and quality of fat, lean, and bone tissues could personalize preventive strategies for age-related pathologies.

Anthropometric measures such as BMI, waist circumference, waist to hip ratio, underwater weighing and more recently bioelectrical impedance are widely used to measure BC because of easy application, low costs and avoid radiation exposure.

However, the precision and accuracy of these methods is rather low and the level of distinction among different components of body mass and compartments is poor.

To date, the use of imaging techniques such as US, CT, MRI and DXA in clinical, but also in research is increasing due to an elevated precision and accuracy associated with a satisfactory level of discrimination among body masses.

However, depending on the information requested, specific advantages and limitations could be envisaged (**Figure 5**):

i) MRI and CT are imaging modalities that provide very precise and accurate information for whole body, inter/intramuscular and visceral fat and for whole body and regional muscle but they both require a clinical setting, thus their availability is low, they are quite expensive and the exposure to radiation is high, in particular for CT;
ii) DXA provides images of whole-body fat and regional muscle with high precision and accuracy as well as MRI and CT. It is the most widely used technique for the study of bone composition and even if it requires a clinical setting it is relatively available and cheap, while involving a very low exposure to radiation;
iii) US is mainly used to measure abdominal adiposity. It is a low cost technique and avoids exposure to radiation, however its accuracy and reliability is still debated.

Collectively, imaging techniques are very promising in the study of BC and age-related changes. However, further efforts are needed to decrease the costs and thus increase the availability to population.

Lastly, the creation of standardized reference normative databases should be encouraged among researchers and to this aim a valid method for the cross-calibration among different scanners should be established to compare results among different research centers.

AUTHOR CONTRIBUTIONS

FP, AB, and AS contributed to the concept, analysis of literature, and writing of the manuscript. DM, CG, MC, and MM contributed to the analysis of literature. CF and LS contributed to the analysis of literature and critical discussion. All authors reviewed and/or edited the manuscript before submission.

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