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Endocrine consequences in children due to the COVID-19 pandemic social behavior changes

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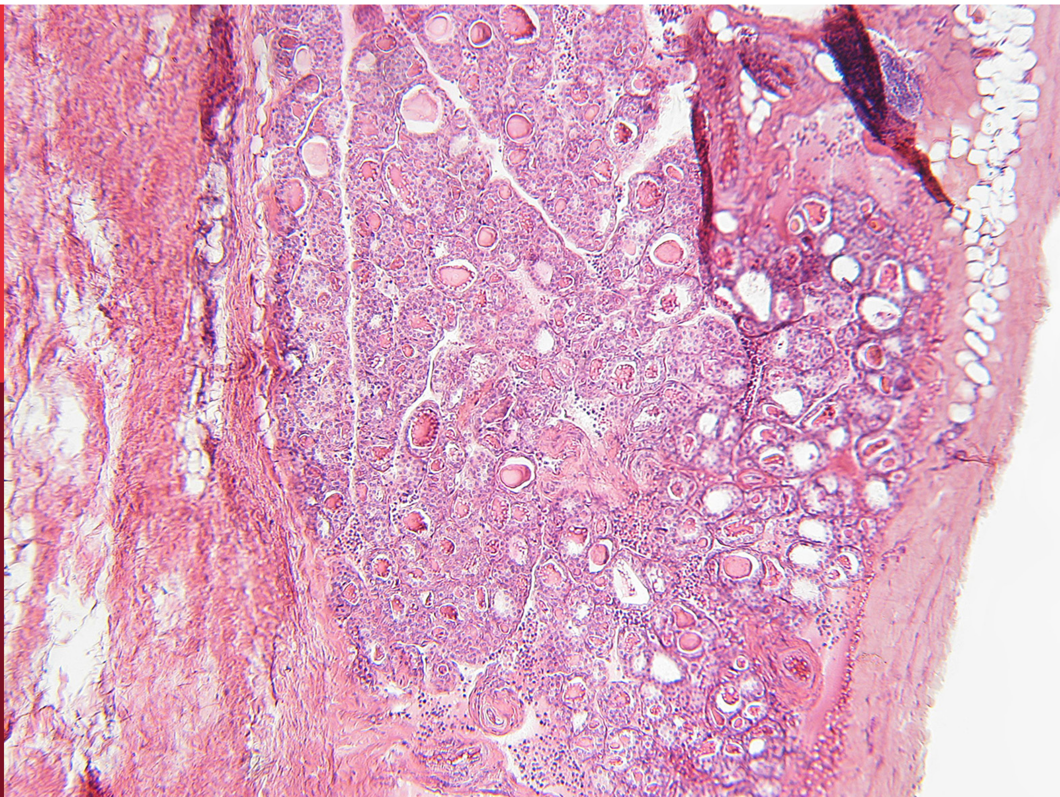

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Endocrine consequences in children due to the COVID-19 pandemic social behavior changes

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Editorial: Endocrine consequences in children due to the COVID-19 pandemic social behavior changes

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Editorial on the Research Topic
Endocrine consequences in children due to the COVID-19 pandemic social behavior changes

Over the last 3 years, the human race has faced the greatest healthcare challenge of the 21st century, a challenge made even greater, because the last time something of this magnitude occurred was over 100 years ago. To overcome the COVID 19 pandemic, the medical community was called on to use intellectual and industrial resources on a scale never seen before.

From the first cases, it was clear that the effects of COVID19 on the paediatric population would not be limited to acute respiratory conditions, but that young people's mental health would be severely effected due to lockdowns. Endocrinological consequences, whether directly caused by the virus, as shown in some studies on DM1 (1), or multifactorial, such as the increase in cases of precocious puberty (2) soon began to appear. Evidence of collateral damage to the endocrine system continues to emerge and research into its aetiology and pathophysiology is just beginning.

This special edition focuses on the endocrinological consequences of the COVID19 pandemic in children and adolescents. A good place to start is the work of Gnocchi et al., a review of the impact of the COVID-19 pandemic on paediatric endocrine disorders, which highlights well documented phenomena such as increases in obesity as well as less researched consequences, for example the impact on vitamin D and Calcium metabolism.

A widely noted phenomenon was the increase in cases of PP. Barberi et al. present interesting data on the role of electronic devices in triggering PP during the pandemic period in Italy. Choi and Park present important data on the increase in prevalence of PP from 2016 to 2021 in the Korean population, emphasizing the prevalence in boys which increased 2-fold during the pandemic period. Chen et al. suggest that ghrelin levels play a role in the regulation of puberty based on their analysis of the increase of PP cases in Shanghai during the first year of the COVID-19 pandemic compared with the five previous years.

Alfayez et al. conducted a systematic review and metanalysis showing that diabetic ketoacidosis (DKA) risk, especially for the severe form, increased significantly during the pandemic. Abdou et al. showed that during COVID waves 1 and 2, there was an increase in the incidence of newly diagnosed cases compared with the pre-COVID period, and that patients presented with more severe DKA with a significantly higher incidence of hypokalaemia. Zubkiewicz-Kucharska et al. analysed the influence of lockdown in T1D management, finding increases in weight gain and daily insulin doses during the period.

McCowan et al. showed that overall rates of thyroid dysfunction have not altered since the beginning of the COVID-19 pandemic, however the number of patients with transient thyroid dysfunction, not requiring ongoing treatment has increased. Finally, Corica et al. describe the difficulties that the pandemic brought for the management of obesity in children and adolescents.

More studies will be needed to explain these phenomena, focusing not only on clinical presentation but also on the role of epigenetics. The covid pandemics is over, however the challenge of interpreting its effects on the paediatric population has just started for paediatric endocrinologists and healthcare professionals.

Author contributions

GG: Writing – original draft. SS: Writing – review & editing.

Conflict of interest

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

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SYSTEMATIC REVIEW
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Incidence of Diabetic Ketoacidosis Among Pediatrics With Type 1 Diabetes Prior to and During COVID-19 Pandemic: A Meta-Analysis of Observational Studies

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Background: Previous reports suggest that the Coronavirus Disease-2019 (COVID-19) pandemic might have affected incidences of diabetic ketoacidosis (DKA) and new diagnoses of type 1 diabetes. This systematic review and meta-analysis aimed to estimate the risk of DKA, including severe DKA, during the COVID-19 pandemic versus the prior-to-COVID-19 period among pediatric patients with type 1 diabetes.

Methods: PubMed and EMBASE were searched for observational studies investigating the risk of DKA among pediatric patients with type 1 diabetes during the COVID-19 pandemic and the prior-to-COVID-19 period. A random meta-analysis model was performed to estimate the relative risk of DKA during the COVID-19 pandemic compared to before the pandemic. Subgroup analyses were conducted based on the type 1 diabetes status, established or newly diagnosed. In addition, sensitivity analysis was conducted for studies that reported results from adjusted analysis for potential confounders using fixed effect model.

Results: A total of 20 observational studies reported the risk of DKA, of which 18 reported the risk of severe DKA. The risks of DKA and severe DKA were 35% (RR 1.35, 95%CI 1.2-1.53, I^2 = 71%) and 76% (RR 1.76, 95%CI 1.33-2.33, I^2 = 44%) higher in the during-COVID-19 group compared to the prior-to-COVID-19 group, respectively. Among patients with newly diagnosed type 1 diabetes, the risk of DKA was 44% higher for the during-COVID-19 group compared to the prior-to-COVID-19 group (RR 1.44, 95%CI 1.26-1.65; I^2 = 64%). Only two studies reported the risk of DKA among patients with established type 1 diabetes and the cumulative risk was not statistically significant. In the sensitivity analysis, four studies reported an adjusted odds ratio (aOR) of the risk of DKA during COVID-19 compared to the prior-to-COVID-19 period. The fixed estimate from the meta-analysis found an increase in the risk of DKA in the during-COVID-19 group compared to the prior-to-COVID-19 group (aOR 2.04, 95%CI 1.66-2.50).

Conclusions: This study showed that DKA risk, especially the risk of severe DKA, has increased significantly during the pandemic. Healthcare systems must be aware and prepared for such an increase in DKA cases and take all necessary measures to prevent future spikes during the pandemic.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=272775, identifier PROSPERO [CRD42021272775].

Keywords: COVID-19, diabetic ketoacidosis, incidence, meta-analysis, pediatrics, systematic review, type 1 diabetes

INTRODUCTION

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes that can occur at type 1 diabetes onset (1, 2). The International Society of Pediatric and Adolescent Diabetes defined DKA patients as having a blood glucose level greater than 200 mg/dl, a pH level under 7.3, and a bicarbonate level under 15 mmol/L. Severe DKA, however, is recognized by a decline in pH level to under 7.1 or potentially a bicarbonate level under 5 mmol/L (3). The incidence rate of DKA at type 1 diabetes onset ranged from 13 to 80%, requiring hospitalization in most cases and leading to the consumption of more healthcare resources (3–5). The recently reported prevalence of DKA among children with newly diagnosed type 1 diabetes was around 30%, with much variation in the prevalence between 13 countries in the study (6).

Patients with diabetes are at greater risk of infection relative to the general population, and the risk is higher for patients with type 1 diabetes compared to patients with type 2 diabetes (7). The Coronavirus Disease-2019 (COVID-19) pandemic has dramatically affected the lifestyle of patients and their access to healthcare services worldwide, including delayed diagnosis or management of chronic diseases, such as type 1 diabetes (8, 9). Moreover, several studies reported an increase in DKA and severe DKA cases among the pediatric population (10–17). Also, some studies reported a possible increase in type 1 diabetes cases during the pandemic (11, 12, 18). Therefore, we conducted a comprehensive systematic review and meta-analysis to estimate the risk of DKA, including severe DKA, among patients with type 1 diabetes prior to and during the COVID-19 pandemic.

METHODS

Search Strategy and Databases

A systematic literature search was conducted by KSA, NHA, and NMB for observational studies using the PICO (population, intervention, comparison, outcome) framework (P: pediatric patients with type 1 diabetes, I: during the COVID-19 pandemic, C: prior to COVID-19, O: incidences of DKA). The electronic databases *PubMed* and *EMBASE* were searched from inception to December 28, 2021. The *Elsevier Coronavirus Research Repository Hub* was also searched for potentially eligible studies. The search strategy and keywords are available in **Supplemental Table 1**. This systematic review and meta-analysis was registered with PROSPERO (CRD42021272775), and the manuscript was prepared based on the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline (19).

Study Selection, Data Extraction, and Quality Assessment

All retrieved citations, after removing duplicates from the Rayyan software (20), were independently screened by the three investigators for eligibility; initially through titles and abstracts, then through a full-text review. Studies published as an abstract or in non-English language were excluded. Disagreements were resolved by consensus. Two investigators (KSA and NHA) extracted the following data into an Excel sheet: primary author's last name, year of publication, location of the study, study period, key inclusion/exclusion criteria, number of patients with type 1 diabetes, study period, and number of patients with DKA and severe DKA. Two other investigators (ARA and OMA) checked the extracted data and independently performed the quality assessment of included articles using the Newcastle-Ottawa Scale (NOS) (21, 22). Disagreements were resolved by consensus.

Data Synthesis and Analysis

The primary outcome of the analysis estimated the risk of DKA among pediatric patients with type 1 diabetes in the during-COVID-19 pandemic group relative to the prior-to-COVID-19 group using the risk ratio (RR) with a 95% confidence interval (95% CI). The secondary outcome is the relative risk of severe DKA in the during-COVID-19 group versus the prior-to-COVID-19 group. We performed the meta-analysis with a random effect model using R version 4.0.4 and presented the results on a forest plot, including the heterogeneity I^2 statistics. Egger's test was employed to assess the potential for publication bias. We performed subgroup analyses based on type 1 diabetes status (newly or established diagnoses) and sensitivity analyses for studies that reported adjusted point estimates (RR or OR) using the fixed effect model.

RESULTS

Characteristics of Included Studies

The systematic search yielded 372 citations, and 20 studies met the inclusion criteria (**Figure 1**) (10–18, 24–34). These studies included 37,174 patients with type 1 diabetes in the prior-to-COVID-19 pandemic group and 27,812 patients in the during-COVID-19 group. Most of the studies were conducted in European countries from hospitals or tertiary care centers (**Table 1**).

Risk of Bias Assessment

All the included studies had more than 7 points on the NOS scale, suggesting good (7–9) quality (**Supplemental Table 2**). However, only seven studies demonstrated a good quality on the comparability domain due to the adjustment for the baseline characteristics between the two groups (during-COVID-19 and prior-to-COVID-19).

Risk of DKA

A total of 20 studies investigated the risk of DKA during COVID-19 compared to the prior-to-COVID-19 period (**Figure 2**). Seven studies have shown an increase in the risk of DKA during the pandemic. The cumulative risk of DKA was 35% higher for the during-COVID-19 group compared to the prior-to-COVID-19 group (RR 1.35, 95%CI 1.20-1.53) but with significant heterogeneity (I^2 = 71%, p<0.01).

Risk of Sever DKA

Eighteen studies have investigated the risk of severe DKA during COVID-19 compared to the prior-to-COVID-19 period (**Figure 3**). Ten studies have shown an increase in the risk of severe DKA during the pandemic. The cumulative risk of severe DKA was 76% higher for the during-COVID-19 group compared to the prior-to-COVID-19 group (RR 1.76, 95%CI 1.33-2.33, I^2 = 44%, p=0.03).

Subgroup Analysis

Risk of DKA Among Patients With Newly Diagnosed Type 1 Diabetes

A total of 18 studies investigated the risk of DKA among patients with newly diagnosed type 1 diabetes during COVID-19 compared to the prior-to-COVID-19 period (**Figure 4**), with

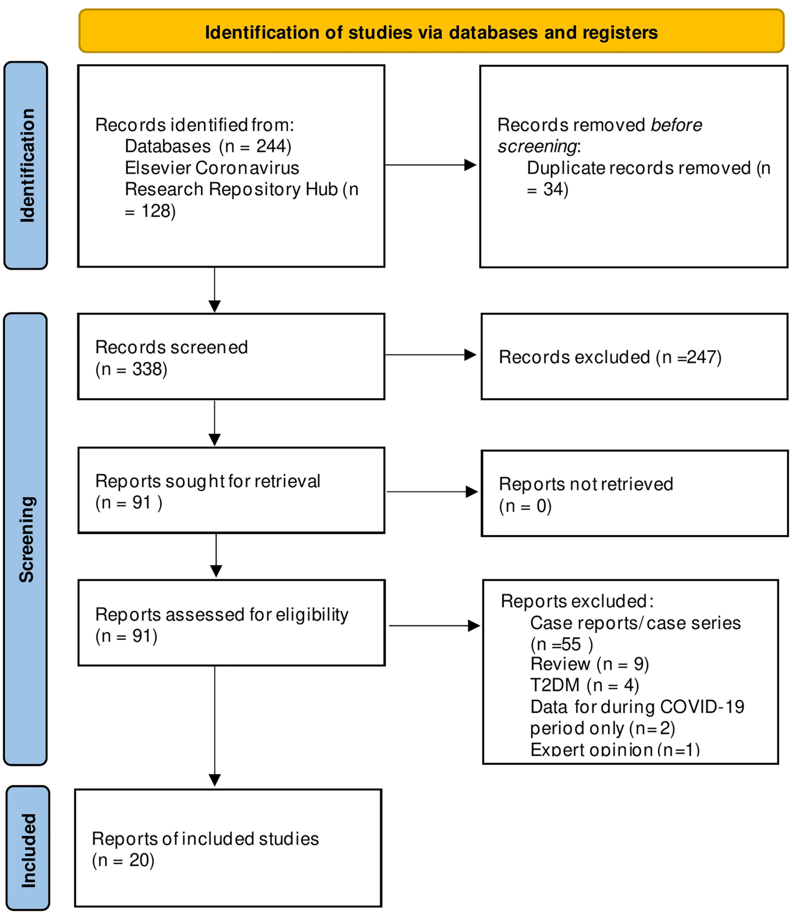

FIGURE 1 | PRISMA Flowchart of included and excluded studies. Copyright statement: this PRISMA diagram contains public sector information licensed under the Open Government Licence v3.0. Adapted From: Moher et al. (23).

TABLE 1 | Characteristics of the included studies.

Study	Location	COVID-19		Patient included	Setting
		During (N)	Prior (N)		
Dżygało, 2020 (17)	Poland	34	52	≤18 years	Single center
Kamrath, 2020 (10)	Germany	532	954	≤18 years	Multicenter
Rabbone, 2020 (18)	Italy	160	208	<15 years	Multicenter
Alaqeel, 2021 (32)	Saudi Arabia	106	154	1–14 years	Multicenter
Boboc, 2021 (11)	Romania	147	312	<18 years	Single center
Bogale, 2021 (24)	USA	42	370	≤18 years	Single center
Danne, 2021 (25)	Worldwide	25543	31258	≤21 years	Multicenter
Dilek, 2021 (12)	Turkey	74	46	<18 years	Single center
Hawkes, 2021 (26)	USA, Europe	73	92	<18 years	Single center
Ho, 2021 (13)	Canada	107	114	<18 years	Multicenter
Jacob, 2021 (14)	Israel	150	154	≤18 years	Multicenter
Lawrence, 2021 (15)	Australia	11	42	<18 years	Single center
McGlacken, 2021 (16)	UK	17	30	<18 years	Multicenter
Salmi, 2021 (27)	Finland	84	231	≤15 years	Multicenter
Zubkiewicz-Kucharska, 2021 (28)	Poland	30	1961	<18 years	Multicenter
Al-Abdulrazzaq, 2021 (29)	Kuwait	324	303	≤12 years	Multicenter
Goldman, 2021 (30)	Israel	146	364	<18 years	Multicenter
Kostopoulou, 2021 (31)	Greece	21	17	<18 years	Multicenter
Mameli, 2021 (32)	Italy	201	502	<18 years	Multicenter
Mi Seon Lee, 2021 (33)	Korea	10	10	<19 years	Single center

eleven reporting an increase in the risk of DKA during the pandemic. The cumulative risk showed a 44% increase in the risk of DKA for the during-COVID-19 compared to the prior-to-COVID-19 groups (RR 1.44, 95%CI 1.26-1.65), again with significant heterogeneity (I^2 = 64%, p<0.01).

Risk of DKA Among Patients With Established Type 1 Diabetes

Two studies have reported the risk of DKA among patients with established type 1 diabetes (**Figure 5**); one of them found an increase in the risk of DKA during the pandemic. However, the cumulative risk of DKA was insignificant (RR 1.14, 95%CI 0.83-1.56, I^2 = 76%, p=0.04).

Sensitivity Analysis

Four studies reported an adjusted odds ratio (aOR) of the risk of DKA during COVID-19 compared to the prior-to-COVID-19 period (**Supplemental Figure 1**). The fixed estimate from the meta-analysis showed an increase in the risk of DKA for the during-COVID-19 group compared to the prior-to-COVID-19 group (aOR 2.04, 95%CI 1.66-2.50). Conversely, three studies reported an adjusted relative risk (aRR) of DKA during COVID-19 compared to the prior-to-COVID-19 period (**Supplemental Figure 2**). The fixed estimate from the meta-analysis showed an increase in the risk of DKA for the during-COVID-19 group compared to the prior-to-COVID-19 group (aRR 1.27, 95%CI 1.18-1.36).

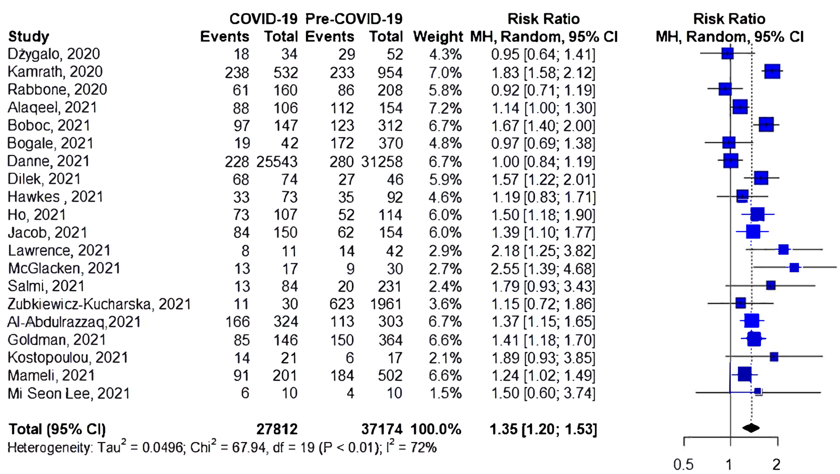

FIGURE 2 | Risk of DKA among patients with type 1 diabetes.

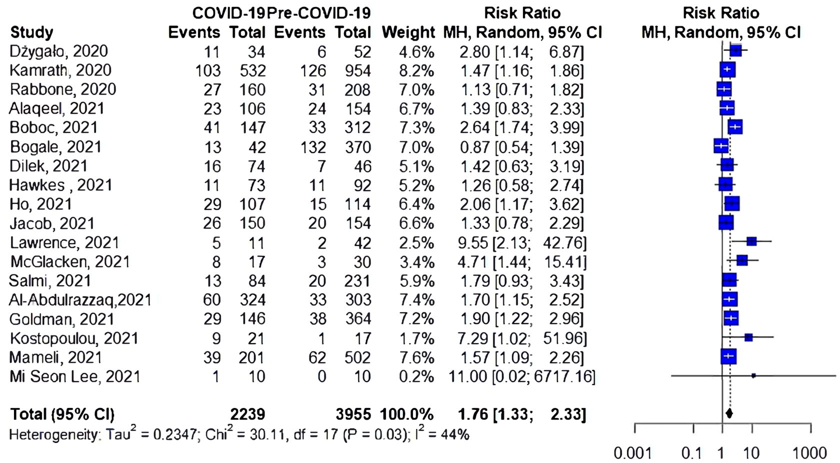

FIGURE 3 | Risk of severe DKA among patients with type 1 diabetes.

Publication Bias

The publication bias test was performed for all outcomes except for the subgroup analysis of the established type 1 diabetes cohort, which only included two studies. The results of Eager's test did not show potential for publication bias.

DISCUSSION

This meta-analysis aimed to estimate the risk of DKA, including severe DKA, among pediatric patients with type 1 diabetes during COVID-19 pandemic compared to prior-to-COVID-19. The cumulative risks of DKA and severe DKA were 35% and 76% higher, respectively, for the during-COVID-19 period compared to prior to COVID-19. The cumulative risk of DKA among patients with newly diagnosed type 1 diabetes showed a 44% increased risk of DKA for the during-COVID-19 compared to the prior-to-COVID-19 groups.

Several hypotheses were raised to explain the increase in incidences of DKA and severe DKA during the pandemic. A delay in seeking medical attention was suggested by several studies (10, 35, 36). Such a delay was attributed to fear of infection, cancellation of several medical services, or the closing of some centers due to an increase in infections among medical staff and admitted patients (10, 35, 37–39). For those newly diagnosed with type 1 diabetes presenting with DKA, it is hypothesized that delay in seeking medical help will be preceded by a longer duration of type 1 diabetes symptoms. However, several studies have reported that the duration of symptoms during the pandemic were comparable to duration prior to COVID-19 (11, 17, 28, 40). This finding suggests that the delay in diagnosing type 1 diabetes is not the only cause for an increased risk of DKA.

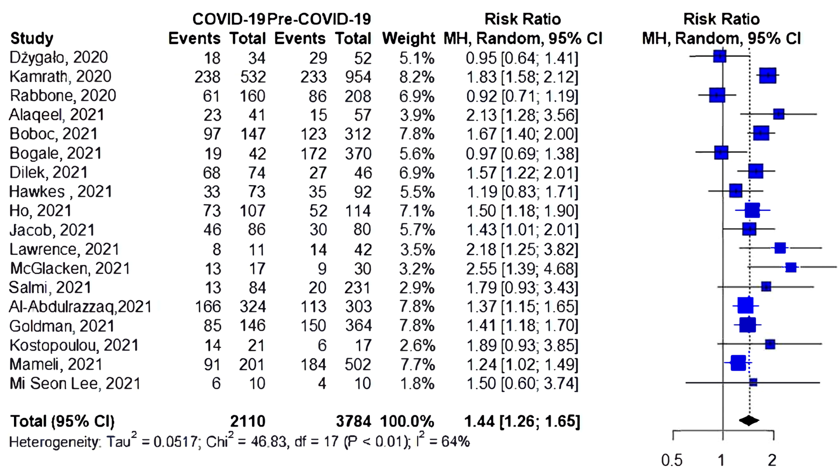

FIGURE 4 | Risk of DKA among patients with newly diagnosed type 1 diabetes.

Study	COVID−19 Events	COVID−19 Total	Pre−COVID−19 Events	Pre−COVID−19 Total	Weight	Risk Ratio MH, Random, 95% CI
Alaqeel, 2021	65	65	97	97	63.2%	1.00 [0.99; 1.01]
Jacob, 2021	38	64	31	74	36.8%	1.42 [1.01; 1.98]
Total (95% CI)		**129**		**171**	**100.0%**	**1.14 [0.83; 1.56]**

Heterogeneity: $Tau^2 = 0.0410$; $Chi^2 = 4.13$, df = 1 (P = 0.04); $I^2 = 76\%$

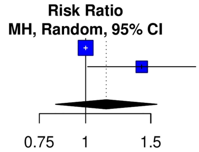

FIGURE 5 | Risk of DKA among patients with established type 1 diabetes.

This result might also be supported by the reported no-change or unexpected lower HbA1c levels during the pandemic (25, 28). That said, a limitation does exist regarding the duration of symptoms given that the information provided in the studies depends on parents' ability to recall those symptoms.

Most of the studies included in this meta-analysis investigated those who were newly diagnosed with type 1 diabetes, which makes it unlikely that worsening glycemic control during the pandemic led to the increase in DKA cases. Only two studies have reported DKA cases among patients with a history of type 1 diabetes. Jacob et al. reported a statistically significant increase in DKA during the pandemic (14), while Alaqeel et al. showed no difference in DKA cases in those with preexisting type 1 diabetes (34). Although some studies have reported a decrease in physical activities during the lockdown period (25, 41), many studies have observed good glycemic control during the lockdown period, which might be a result of close parental supervision during the lockdown or the increased use of diabetes-related technology in some countries (25, 42–45).

Another possible factor could be an increase in the incidence of type 1 diabetes among children during the pandemic. However, most of the studies investigating this idea did not report a significant increase in the incidence of type 1 diabetes during the pandemic. Boboc et al. reported a 30% overall increase in incidences of type 1 diabetes between March 2020 and February 2021 (11). Interestingly, incidences were found to be lower during the early weeks of the pandemic (March to April 2020). Rabbone et al. also reported a decrease in new cases of type 1 diabetes during the pandemic from February 2020 to April 2020 (18). Such an early decrease in incidences of type 1 diabetes during the pandemic might be attributed to lower overall exposure to viral infections during the lockdown period, as viral infections are known risk factor for developing type 1 diabetes (46–48). Moreover, it is also reported that new type 1 diabetes cases are usually higher in the winter season compared to summer (49–51). Thus, it is unlikely that the seasonality of type 1 diabetes is the reason for the decrease in type 1 diabetes incidences reported by those studies (11, 18). Overall, the results regarding the changes in the incidence of type 1 diabetes during the pandemic are inconclusive, making larger studies with a longer duration warranted.

COVID-19 infection has resulted in several complications. Some reports suggest that the virus might be able to affect the pancreas, resulting in a dysregulation of glucose metabolism (52, 53). A UK study suggested a possible link between COVID-19 infection and new-onset of type 1 diabetes or severe DKA (40). However, this study was limited by its small sample size. Conversely, a German study showed that COVID-19 infection did not increase type 1 diabetes cases when there was no evidence of autoimmunity. Importantly, this study only covered the first wave of the pandemic in Germany (approximately four months period) (54). Thus, possible links cannot be entirely ruled out, but larger studies are needed to confirm them. Unfortunately, among the studies included in this meta-analysis, only a small number of patients had COVID-19, and data regarding prior exposure to the virus are limited, making it difficult to attribute such an increase in DKA cases to current or prior COVID-19 infection.

Regardless of the actual cause of increased DKA during the pandemic, DKA remains to be a serious life-threatening complication that must be prevented. Early detection of type 1 diabetes symptoms and early diagnoses is key in preventing DKA. Overall, incidences of DKA at type 1 diabetes diagnosis is a challenge (2, 6, 55, 56), despite the pandemic. Missed diagnoses of type 1 diabetes by healthcare providers have been documented (56, 57). Children diagnosed with type 1 diabetes were more likely to have visited their primary care providers within the 30 days prior to diagnosis (57), which indicates missed opportunities for early detection of type 1 diabetes symptoms.

Efforts should be directed toward increasing awareness of healthcare providers, patients, and families regarding the symptoms of type 1 diabetes. Prevention campaigns have proven useful in reducing the prevalence rate of DKA in newly diagnosed children with type 1 diabetes (58–60). Cherubini et al. study suggested several actions that can optimize awareness campaigns such as targeting families of children under the age of 15 years, smaller geographic areas and family pediatricians in addition to utilizing innovative communication tools (61). Although public health campaigns might be challenging during pandemics given the public is receiving large amount of health information, they could be useful as a public health tool during such pandemic periods when DKA is on the rise.

In the past few years there have been significant improvements in identifying those with high risk for developing type 1 diabetes. Moreover, screening for type 1 diabetes through islet autoantibodies and genetic testing is currently reserved for research (62). However, one main advantage of such screening at the population level would be the reduction of DKA at type 1 diabetes onset (63). This was observed in two studies were significant reductions in DKA frequency was noted (64, 65). However, the cost-effectiveness of screening needs to be assessed. Given the significant increase in DKA and severe DKA cases observed during the COVID-19 pandemic, screening for type 1 diabetes during or right after such pandemics might be considered as a potential tool to aid preventing DKA cases in the future.

This study is not without limitations. All the included studies are observational and had some degree of heterogeneity.

Seven studies demonstrated a good quality in the comparability domain. Differences in inclusion criteria, analyzed periods, and number of subjects included might have played a role in the observed heterogeneity. Few studies presented an adjustment for potential confounders and included them in the sensitivity analysis. Only two studies reported DKA cases for those with a history of type 1 diabetes, which made it impossible to assess if poor glycemic control might have played a role in increased DKA cases. Besides that, the mean duration of type 1 diabetes was only reported in one study. Insufficient data were reported regarding COVID-19 infection status among the included studies which made it impractical to perform a subgroup analysis for those with positive COVID-19 infection at type 1 diabetes diagnosis.

In conclusion, the results of this meta-analysis showed a statistically significant increase in DKA and severe DKA risk among pediatrics during the pandemic in comparison to prior to the pandemic period. Such an increase might be attributed to several factors that might differ in magnitude from one country to another. Healthcare systems must be aware and prepared for such an increase in the risk of DKA or severe DKA during similar pandemic conditions. Timely access to healthcare, an increase in public and healthcare providers' awareness of type 1 diabetes symptoms through public health educational and screening campaigns, and proper diabetes management during pandemics or similar situations remain important and key to avoiding similar spikes in incidences of DKA or severe DKA in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

OMA and ARA contributed to the conception and design of this study. KSA, NHA, and NMB conducted the literature search. KSA and NaA performed the data extraction. ARA did the statistical analysis and wrote the methods section with inputs from MA, OAA, and OMA. All authors contributed to writing the manuscript. All authors revised and approved the final version of the manuscript. OMA is the guarantor of this work.

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Presentations, Complications, and Challenges Encountered During Management of Type 1 Diabetes in Egyptian Children During COVID-19 Pandemic: A Single-Center Experience

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Background: The coronavirus disease 2019 (COVID-19) pandemic has been associated with significant challenges pertaining to the management of children and adolescents with type 1 diabetes (T1D). Issues such as fear of infection and lockdown measures have resulted in delayed and more severe clinical presentations of this disease.

Objectives: This study aimed at reporting the frequency and severity of diabetic ketoacidosis (DKA) and the rate of DKA complications in children with diabetes who presented to the emergency unit during COVID-19 pandemic. Furthermore, the purpose of this study was to compare the data collected from the first and second COVID-19 waves with that of the pre-COVID-19 period and describe the challenges encountered during disease management.

Methods: This cross-sectional study included all children and adolescents with T1D who presented to the emergency department at Abo El Rish Children's Hospital, Cairo University, during the first and second COVID-19 waves. It also included data collected from the pre-COVID-19 period. Demographic and clinical data, investigations, and management details were collected from the patients' medical records.

Results: Three hundred twenty-four Egyptian children and adolescents diagnosed with T1D were recruited. One hundred forty patients (43.2%) presented with severe DKA, and approximately 66% were newly diagnosed with T1D. The participants presented with manifestations suggestive of COVID-19, such as fever (29.5%), respiratory manifestations (7.2%), and gastrointestinal symptoms (14.7%). Thirty-seven patients were tested for severe acute respiratory syndrome coronavirus 2 infection using nasopharyngeal swabs, and four patients tested positive. Around 18% of patients developed hypokalemia during disease management. A comparison between these data and the data from previous years revealed that there was a significant increase in the number of newly diagnosed cases with more severe DKA at presentation and a higher frequency of development of hypokalemia during both COVID-19 waves.

Conclusion: An increase in the frequency of newly diagnosed cases was identified during the first and the second COVID-19 waves compared with the pre-COVID-19 period. The patients presented with more severe DKA, probably due to a more delayed presentation. The frequency of hypokalemia development was also significantly higher, and the severity of DKA was associated with a longer ICU admission. Further studies are required to establish a definitive link between the COVID-19 pandemic and the severity of presentation.

Keywords: presentations, complications, challenges, type 1 diabetes, COVID-19, children and adolescents

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious respiratory syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Among the various modes of COVID-19 virus transmission, droplet infection is the most common, which is increased by close contact with positive cases (2, 3). Furthermore, it has been suggested that this virus can be transmitted through the fecal–oral route, as it was found to be shed in stools and urine. It is also found in the tears of infected individuals (2, 3). The clinical presentations of a COVID-19 infection can vary from asymptomatic to severely infected cases. It can sometimes lead to death (2). The symptoms in infected children are more likely to be mild. According to the findings of a Chinese study on children who tested positive, typical symptoms were found in 45% of cases, mild respiratory symptoms were found in 42%, 13% were asymptomatic, and no children had life-threatening symptoms (4). Children with immunocompromising conditions, such as diabetes, may be at a higher risk of a more severe disease (5).

The COVID-19 pandemic poses significant challenges to the management of children and adolescents with type 1 diabetes (T1D), especially in newly diagnosed cases. These challenges have affected both the institutional and self-management levels, particularly in limited-resource settings (6). More specifically, this pandemic has changed the way that patients access healthcare settings—from scheduled clinic and hospital visits to telemedicine (7).

Parents were reluctant in seeking prompt medical advice and therefore delayed the presentation of children with diabetes. Multiple factors contributed to this, including the fear of spread of infection especially among these vulnerable patients, the overwhelmed medical system by the care of SARS-CoV-2-infected patients in addition to the limited resources, and the lockdown measures. This might have affected the outcome especially in cases presenting with diabetic ketoacidosis (DKA) (8). Additionally, the need of managing children and adolescents with T1D in the emergency unit had affected the duration until the resolution of DKA and imposed an additional risk of infection. They were required to stay in the emergency unit along with other patients until all necessary investigations to exclude a COVID-19 infection were completed, in accordance with our center's policy. Provided that they test negative, these patients were transferred to the inpatient ward at the Diabetes, Endocrine, and Metabolism Pediatric Unit (DEMPU).

Even after DKA resolution, the length of hospital stay had to be minimized to reduce the risk of infection during admission. After discharge, children with diabetes were followed up *via* phone as an alternative way to regularly scheduled clinic visits in an attempt to minimize the risk of exposure to infection. This inadequate approach induced an additional load over both physicians and parents in limited-resource settings that lack the availability of continuous glucose monitoring (CGM). This was particularly noted in children who were recently diagnosed with diabetes and were still devastated by the diagnosis (9).

Data on the development, clinical presentation, and management of T1DM (both new onset and known) during the SARS-CoV-2 pandemic in Egyptian children are limited, with no available comparisons with patients during the pre-COVID-19 period. Therefore, the aims of this study were to identify the challenges during management and follow-up of children and adolescents with T1D and to report the severity and frequency of DKA together with the rate of DKA complications. Finally, we aimed at comparing the collected data with data from the pre-COVID-19 period.

MATERIALS AND METHODS

This cross-sectional study included Egyptian children and adolescents with T1D who presented to the emergency department at the Abo El Rish Children's Hospital, Cairo University, between June and July 2020 (first COVID-19 wave) and between December 2020 and February 2021 (second COVID-19 wave). All patients who presented with DKA or hyperglycemia either as a first presentation or with known diabetes were included. Their ages varied from 6 months up to 18 years. DKA was confirmed by the classic triad of hyperglycemia (blood glucose >200 using a glucometer), metabolic acidosis (pH <7.3, HCO_3 <15), and ketonuria using urinary dipsticks (10).

The patients were recruited at presentation to the ER during the first and the second COVID-19 waves after obtaining verbal consent from the patients and/or their parents and legal guardians. Data from the pre-COVID-19 period was collected retrospectively by reviewing the patients' medical records. The

DEMPU records were reviewed, and the following data were collected:

- Age, gender, onset of diabetes (newly diagnosed or known T1D), initial presentation (DKA or hyperglycemia), and the presence of signs of a neurological affliction.
- Duration of ICU admission (if applicable) and the full length of hospital stay.
- Symptoms suggestive of a COVID-19 infection.
- Management details especially pertaining to the antishock therapy received and the development of hypokalemia that necessitated correction.
- Investigations performed at presentation, including random blood glucose, ketone bodies in urine (using urinary dipsticks), and venous blood gases, upon which patients were classified into mild, moderate, and severe DKA (mild DKA: pH, <7.3; HCO_3, <15; moderate DKA: pH, < 7.2, HCO_3, <10; severe DKA: pH, < 7.1; HCO_3, <5) (10). Furthermore, electrolytes (Na and K), renal functions (urea and creatinine), and complete blood count (CBC) with differential (especially total lymphocyte counts) and C-reactive protein (CRP) were also included. Serum K levels <3.5 mEq/L were also used to diagnose hypokalemia. Hypokalemia was graded into mild (serum K, 3–3.4 mEq/L), moderate (serum K, 2.5–2.9 mEq/L), and severe (serum K, <2.5 mEq/L) (11).
- Radiological data, including computed tomography (CT) of the chest and brain in selected cases presenting with neurological symptoms and signs, were included.

The initial screening for a COVID-19 infection, according to hospital policy, included CBC and CT chest examinations. If CT was suspicious of COVID-19 and/or CBC revealed lymphopenia and/or leukopenia, the patients were kept in an isolation unit until a test swab was done to exclude or confirm a COVID-19 diagnosis. The normal lymphocyte count in adults is 1,000–4,800/µl ($1–4.8 \times 10^9$/L; in children <2 years, the normal count is 3,000–9,500/µl ($3–9.5 \times 10^9$/L). At the age of 6 years, the lower limit of normal count is 1,500/µl (1.5×10^9/L). Different laboratories may have slightly different normal values (12).

RESULTS

A total of 324 Egyptian children and adolescents with T1D were included in this study. One hundred fifteen patients were recruited during the first COVID-19 wave and 209 patients during the second COVID-19 wave. Male individuals constituted 51.2% of all patients, and the female individuals were at 48.8%. The participants' age ranged from 6 months to 18 years. Regarding the initial presentation during the first and the second COVID-19 waves, 70 patients (21.6%) presented with hyperglycemia, and 254 patients (78.4%) presented with DKA. One hundred forty patients (43.2%) had severe DKA, and 45% of them were admitted during the first COVID-19 wave and 55% during the second COVID-19 wave.

During both COVID-19 waves, 213 participants (65.7%) were newly diagnosed with T1D, and 111 (34.3%) were known to have diabetes. In total, 23% of the newly diagnosed patients presented with hyperglycemia, 9% with mild DKA, 17.3% with moderate DKA, and 50.7% with severe DKA. Whereas, 19% of patients known to have diabetes presented with hyperglycemia, 18% with mild DKA, which is approximately double the cases of newly diagnosed diabetes, 34.2% with moderate DKA, which is higher than the newly diagnosed group, and 28.8% with severe DKA. A comparison of the demographic and clinical data of the studied groups is presented in **Table 1**.

The mean age and SD of patients during the first and the second COVID-19 waves were 7.96 ± 3.55 and 8.1 ± 3.57 years, respectively ($p = 0.722$), revealing no statistically significant difference between both groups regarding age. The frequency of severe DKA was noted to be significantly higher during the first COVID-19 wave (54.8% of the cases) compared to the second wave (36.8% of the cases). Additionally, it was noted that the median bicarbonate level of patients admitted during the first wave was 4 mEq/L (range, 0.8–47 mEq/L), which was statistically significantly lower than the median bicarbonate level of patients admitted during the second wave (7.65 mEq/L, ranging from 0.8 to 27.9 mEq/L) ($p = 0.003$). There were statistically significant differences between the first and the second COVID-19 waves regarding the presence of features suggestive of a COVID-19 infection, such as fever, severity of initial presentation, presence of suspicious CT chest findings, and positive CRP ($p < 0.001$, $p < 0.001$, $p = 0.011$, $p < 0.001$, and $p < 0.037$ respectively). **Table 1** shows that these features were more prevalent during the first COVID-19 wave.

In the present study, 14 patients (7.4%) admitted during the second COVID-19 wave had hypokalemia at presentation—eight of them presented with mild hypokalemia, four had moderate hypokalemia, and two had severe hypokalemia—whereas the number of patients who developed hypokalemia as a complication during management in both COVID waves was 59, making up 18.3% of the study group (5 patients during the first COVID-19 wave and 54 patients during the second COVID-19 wave). Out of the 54 who developed hypokalemia as a complication during the second COVID-19 wave, 26 (12.5%) received oral correction and 28 patients (13.5%) received intravenous correction. A statistically significant association was observed between the rates of hypokalemia that developed during management and the amount of shock therapy received ($p < 0.001$), as shown in **Figure 1**. In contrast, there was no statistically significant association between hypokalemia development and intravenous bicarbonate treatment in some cases of severe DKA ($p = 0.092$) (**Figure 2**) or with the development of gastrointestinal symptoms ($p = 0.969$) in admitted patients with diabetes (**Figure 3**).

First COVID-19 Wave

The mean age of patients who presented with severe DKA was 7.6 ± 3.63 years (mean pH of 6.93 ± 0.105 and mean HCO_3 of 2.707 ± 1.018 mEq/L). In total, 58.7% of patients who presented with severe DKA were female individuals, and 41.3% were male individuals ($p < 0.021$, statistically significant). Approximately 77.8% of patients with severe DKA were newly diagnosed with

TABLE 1 | Comparison between the first and the second COVID-19 waves regarding the patients' demographic, clinical, laboratory, and radiological data.

Variables studied	First wave		Second wave		*P*-value
	Total (115)		Total (209)		
	N	%	*N*	%	
Gender					0.629
• Male	61	53.0%	105	50.2%	
• Female	54	47.0%	104	49.8%	
Diabetes status					0.118
• First presentation	82	71.3%	131	62.7%	
• Known to have T1D	33	28.7%	78	37.3%	
Positive clinical manifestations suggestive of COVID-19 infection	57	49.6%	33	15.9%	<0.001[a]
Fever	53	93.0%	25	12.1%	<0.001[a]
Respiratory symptoms suggestive of infection	6	10.5%	13	6.3%	0.272
Gastrointestinal symptoms suggestive of infection	8	13.8%	31	15.0%	0.822
Neurological manifestations (low GCS and/or seizures)	5	8.8%	28	13.5%	0.336
Metabolic status at presentation					0.011[a]
• Hyperglycemia	22	19.1%	48	23.0%	
• Mild DKA	8	7.0%	31	14.8%	
• Moderate DKA	22	19.1%	53	25.4%	
• Severe DKA	63	54.8%	77	36.8%	
Total leukocytic count at presentation					1.000
• Leukocytosis	53	46.5%	80	41.2%	
• Leukopenia	0	0.0%	7	3.6%	
• Normal	61	53.5%	107	55.2%	
Lymphocytic count at presentation					0.315
• Lymphocytosis	7	6.1%	7	3.6%	
• Lymphopenia	19	16.7%	24	12.4%	
• Normal	88	77.2%	162	83.9%	
CRP at presentation					<0.001[a]
• Positive	28	24.3%	17	8.2%	
• Negative	61	53.0%	42	20.3%	
• Not done	26	22.6%	148	71.5%	
CT chest suspicious of COVID-19 infection	14	12.5%	12	5.8%	0.037[a]
Nasopharyngeal swab for COVID-19					0.108
• Positive	3	2.6%	1	0.5%	
• Negative	15	13.0%	18	8.7%	
• Not done	97	84.4%	189	90.9%	
Complications during DKA management					<0.001[a]
• Hypokalemia	5	4.3%	54	26.0%	
• No hypokalemia	110	95.7%	154	74%	
• Hypernatremia	1	0.9%	4	1.9%	
• Other	10	8.7%	6	2.9%	

[a]*P-value less than 0.05 is considered statistically significant.*
N, number; CT, computed tomography; CRP, C-reactive protein; GCS, Glasgow Coma Scale; T1D, Type 1 diabetes.

T1D, whereas 22.2% were patients with known diabetes (p = 0.014, statistically significant), as shown in **Table 2**.

Only few patients (5%) who presented with severe DKA suffered from neurological symptoms (low Glasgow Coma Scale score and/or seizures) ($p = 0.041$, statistically significant). However, a high proportion of these patients showed leukocytosis with a longer duration of stay in the ICU ($p < 0.001$ for both). There were no other statistically significant associations with other variables, as shown in **Table 2**.

Second COVID-19 Wave

The mean age of patients admitted with severe DKA during this wave was 7.8 ± 3.48 years. There was no predilection to a certain gender among this group. The mean blood glucose of patients with severe DKA was 585 ± 175.27 mg/dl, with a mean pH value of 6.91 ± 0.103, mean HCO_3 value of 3.1 ± 1.23 mEq/L, and mean serum creatinine value of 0.976 ± 0.363 mg/dl. There were statistically significant differences in these parameters when compared with the values obtained from patients admitted with lesser grades of DKA or with hyperglycemia ($p < 0.001$). The mean total leukocytic count was statistically higher among subjects with severe DKA (25.39×10^3, $p < 0.001$). The mean time spent in the ICU (33 h) was also significantly longer ($p < 0.001$). Additionally, the mean number of times that patients with severe DKA received shock therapy was 3.92 times (each was 10 cc/kg), which was significantly more than those with milder presentations (mild DKA, moderate DKA, or hyperglycemia) ($p < 0.001$). Fifty-nine patients (76.6%) with severe DKA were newly diagnosed with T1D, whereas 18 patients (23.4%) were known to have T1D ($p = 0.001$).

Furthermore, we observed that the increased severity of DKA was associated with a significantly higher total leukocytic count and higher frequency of developing complications, especially

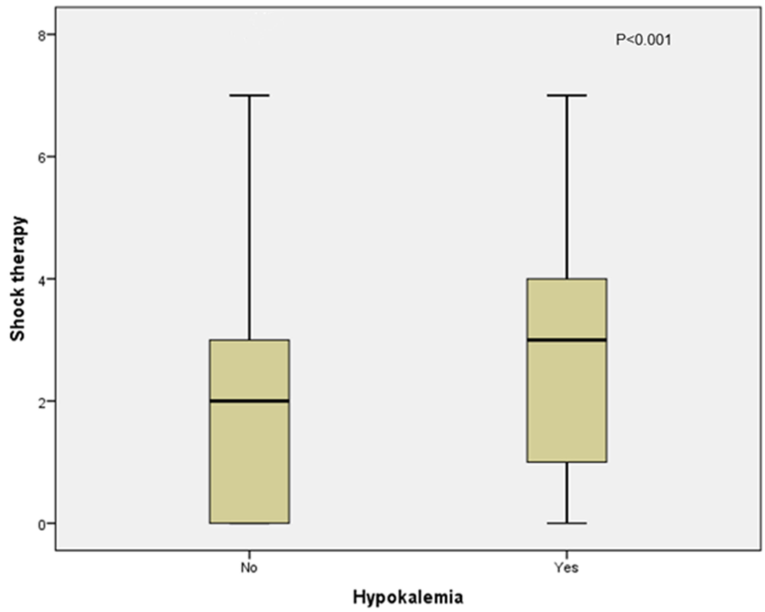

FIGURE 1 | Association between hypokalemia and the amount of shock therapy received in the second COVID-19 wave.

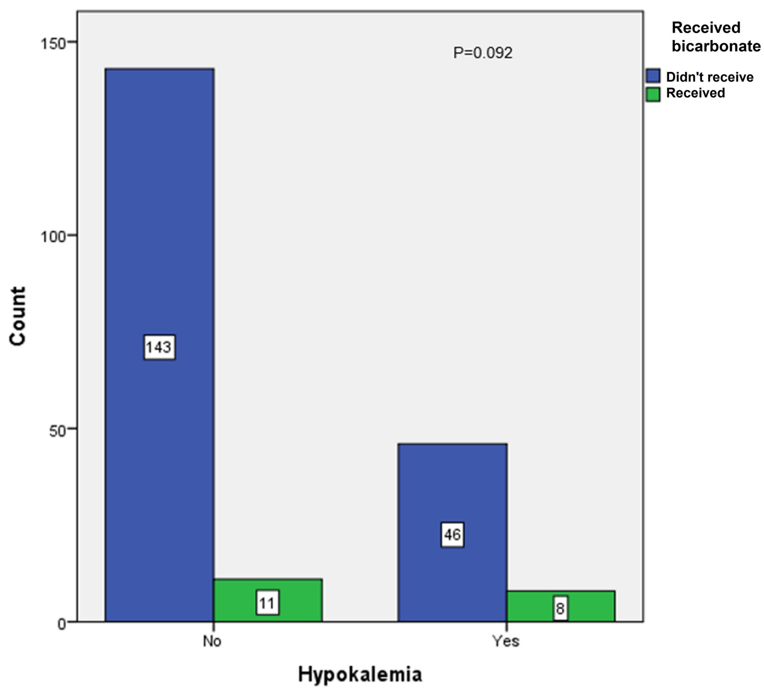

FIGURE 2 | Association between hypokalemia and intake of sodium bicarbonate in the second COVID-19 wave.

hypokalemia, during management ($p < 0.001$ for both). Despite the high number of cases presenting with severe DKA, only few suffered from neurological manifestations (in the form of low Glasgow Coma Scale score and seizures) ($p < 0.001$). During DKA management, only 19 out of 77 (24.7%) patients received IV bicarbonate therapy ($p < 0.001$). Finally, we did not identify any statistically significant association with other variables, as shown in **Table 3**.

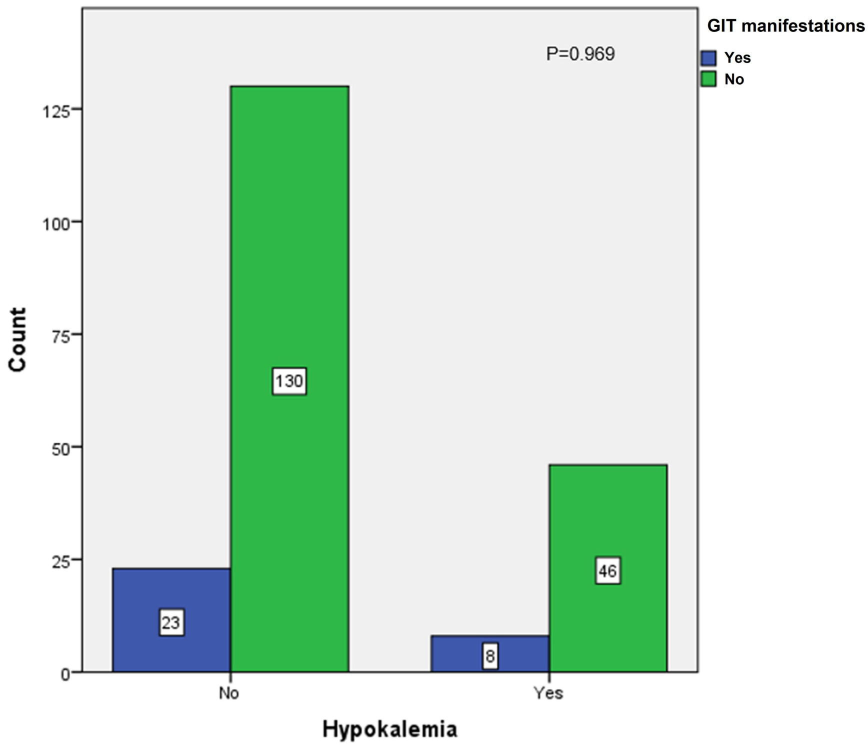

FIGURE 3 | Association between hypokalemia and development of gastrointestinal manifestations in the second COVID-19 wave.

A confirmation of diagnosis of SARS-CoV-2 infection in suspected cases was done by performing COVID-19 PCR using nasopharyngeal swabs. This procedure was performed in 37 children who fulfilled the local testing criteria (clinical, laboratory, and imaging). Only four of them tested positive (three in the first COVID-19 wave and one in the second COVID-19 wave). The patients had to stay for 48 h in the emergency department waiting for the result of the nasopharyngeal swab. This was associated with a significantly longer ICU stay (mean duration of ICU stay was 45.5 h for whom a swab was done *versus* 24.5 h for whom a swab was not done, p = 0.002), However, this long stay in the ER was not associated with more complications (p = 0.581).

Comparison Between the First and the Second COVID-19 Waves and the Pre-COVID-19 Period

This study also compared the data of patients with T1D admitted during the COVID-19 pandemic and of patients admitted during the pre-COVID-19 period. During the pre-COVID-19 period, 60 patients were admitted to the Abo El Rish Hospital between January and February 2018. Twenty-three of them (38.3%) were newly diagnosed diabetes cases, whereas 61.7% were known to have diabetes. Those numbers were significantly different from the number of patients admitted during the COVID-19 pandemic (where 65.7% of patients were newly diagnosed and 34.3% were known diabetic patients, $p < 0.001$) (**Table 4**).

During both the first and the second COVID-19 waves, we found that the mean HCO_3 level was 8.9 mEq/L, which was significantly lower than the mean HCO_3 level during the pre-COVID-19 period (11.8 mEq/L) (p = 0.012), as shown in **Table 4**. This indicates that the severity of DKA was significantly higher during the COVID-19 pandemic compared to the pre-COVID-19 period. We also noticed that hypokalemia, as a complication of DKA management, was more frequently observed during the COVID-19 pandemic compared to the pre-COVID-19 period. More specifically, 18.3% of patients admitted during the COVID-19 pandemic developed hypokalemia as a complication in comparison to 6.7% of patients in the pre-COVID-19, which was statistically significant (p = 0.001).

DISCUSSION

The current cross-sectional study was carried out to describe the characteristics of children and adolescents with T1D who presented to our center during the first and the second COVID-19 waves. Furthermore, the purpose of this study was to identify the challenges encountered during patient management and follow-up, with a focus on data pertaining to the clinical presentation and management of T1D (both new onset and known patients) during the SARS-CoV-2 pandemic, especially considering that data on children are still limited in Egypt.

TABLE 2 | Association of the grades of severity of DKA and the enlisted variables in the first COVID-19 wave.

	Initial presentation								*P*-value
	Hyperglycemia		Mild DKA		Moderate DKA		Severe DKA		
	N	%	*N*	%	*N*	%	*N*	%	
Gender									0.021[a]
• Male	17	77.3%	4	50.0%	14	63.6%	26	41.3%	
• Female	5	22.7%	4	50.0%	8	36.4%	37	58.7%	
Diabetes status									0.014[a]
• First presentation	17	77.3%	2	25.0%	14	63.6%	49	77.8%	
• Known to have T1D	5	22.7%	6	75.0%	8	36.4%	14	22.2%	
Fever	4	80.0%	4	80.0%	7	100.0%	38	95.0%	0.339
Gastrointestinal symptoms suggestive of infection	1	20.0%	1	20.0%	1	12.5%	5	12.5%	0.942
Respiratory symptoms suggestive of infection	0	0.0%	0	0.0%	0	0.0%	6	15.0%	0.415
Neurological manifestations (low GCS and/or seizures)	2	40.0%	1	20.0%	0	0.0%	2	5.0%	0.041[a]
CT chest suspicious of COVID-19 infection	5	23.8%	1	12.5%	0	0.0%	8	12.9%	0.141
Total leukocytic count at presentation									<0.001
• Leukocytosis	2	9.5%	3	37.5%	5	22.7%	43	68.3%	
• Leukopenia	0	0.0%	0	0.0%	0	0.0%	0	0.0%	
• Normal	19	90.5%	5	62.5%	17	77.3%	20	31.7%	
Lymphocytic count at presentation									0.232
• Lymphocytosis	2	9.5%	0	0.0%	0	0.0%	5	7.9%	
• Lymphopenia	2	9.5%	2	25.0%	1	4.5%	14	22.2%	
• Normal	17	81.0%	6	75.0%	21	95.5%	44	69.8%	
CRP at presentation									0.157
• Positive	5	22.7%	4	50.0%	3	13.6%	16	25.4%	
• Negative	9	40.9%	4	50.0%	12	54.5%	36	57.1%	
• Not done	8	36.4%	0	0.0%	7	31.8%	11	17.5%	
Nasopharyngeal swab for COVID-19									0.452
• Positive	1	4.5%	0	0.0%	0	0.0%	2	3.2%	
• Negative	4	18.2%	1	12.5%	0	0.0%	10	15.9%	
• Not done	17	77.3%	7	87.5%	22	100.0%	51	81.0%	
Complication during DKA management									0.093
• Hypokalemia	0	0.0%	0	0.0%	4	18.2%	1	1.6%	
• Hypernatremia	0	0.0%	0	0.0%	0	0.0%	1	1.6%	
• Other complications	3	13.6%	0	0.0%	0	0.0%	7	11.1%	

[a]*P-value less than 0.05 is considered statistically significant.*
N, number; TLC, total leukocytic count; CRP, C-reactive protein; CT, computed tomography; DKA, diabetic ketoacidosis; GCS, Glasgow Coma Scale; T1D, Type 1 diabetes.

During the first and the second waves of the COVID-19 pandemic, 254 (78.3%) patients presented with DKA to the emergency department at the Abo El Rish Children Hospital, 140 of whom (43.2%) had severe DKA (mean pH: 6.93 ± 0.1 SD and mean HCO_3: 2.7 ± 1 SD). Sixty-three (45%) patients with severe DKA presented during the first COVID-19 wave and 77 (55%) patients during the second COVID-19 wave. The newly diagnosed cases presenting with severe DKA during both waves were 108 (49 patients (77.8%) during the first wave and 59 patients (76.6%) during the second wave). This finding is consistent with the observations of a UK-based research study conducted during the first wave of the SARS-CoV-2 pandemic. Children and adolescents with diabetes, aged <17 years, were included in this study. They noticed that 70% of the patients with newly diagnosed T1D and who presented with DKA had severe DKA (13). The high proportion of children presenting with severe DKA could be explained by many factors, including lockdown measures, limited resources, and the overwhelmed medical system by the care of SARS-CoV-2-infected patients, which forced many parents to be worried and reluctant to seek prompt medical advice, therefore delaying the clinical presentation. Our observations agreed with those of the research conducted to study the specific considerations in the management of patients with diabetes during the coronavirus disease pandemic (8). Additionally, the period selected for conducting the current study and patient recruitment was between December 2020 and February 2021 (second COVID-19 wave), which coincided with the seasonal increase in the frequency of T1D and in cases presenting with DKA at first presentation. Regarding the severity of DKA in patients with known diabetes, 14 (22.2%) presented with severe DKA during the first COVID-19 wave and 18 (23.4%) during the second COVID-19 wave. This might reflect the fact that this pandemic had changed the way patients access healthcare. Telemedicine had greatly replaced scheduled clinic and hospital visits, especially during the first wave where we had expected higher rates of DKA. The transition period was associated with an increased burden for both patients and physicians, especially in Egypt where we experience limited resources and lack of CGM availability. This finding was consistent with the study conducted

TABLE 3 | Association of the grades of severity of DKA and the enlisted variables in the second COVID-19 wave.

	Initial presentation								P-value
	Hyperglycemia		Mild DKA		Moderate DKA		Severe DKA		
	N	%	N	%	N	%	N	%	
Gender									0.266
• Male	22	45.8%	17	54.8%	32	60.4%	34	44.2%	
• Female	26	54.2%	14	45.2%	21	39.6%	43	55.8%	
Diabetes status									0.001[a]
• First presentation	32	66.7%	17	54.8%	23	43.4%	59	76.6%	
• Known to have T1D	16	33.3%	14	45.2%	30	56.6%	18	23.4%	
Fever	3	6.5%	4	12.9%	4	7.5%	14	18.2%	0.166
Gastrointestinal symptoms suggestive of infection	3	6.5%	5	16.1%	7	13.2%	16	20.8%	0.189
Respiratory symptoms suggestive of infection	3	6.5%	2	6.5%	0	0.0%	8	10.4%	0.124
Neurological manifestations (low GCS and/or seizures)	1	2.2%	2	6.5%	2	3.8%	23	29.9%	<0.001[a]
CT chest suspicious of COVID-19 infection	3	6.5%	3	9.7%	1	1.9%	5	6.5%	0.484
Total leukocytic count at presentation									<0.001[a]
• Leukocytosis	1	2.3%	8	26.7%	17	33.3%	54	77.1%	
• Leukopenia	4	9.3%	1	3.3%	2	3.9%	0	0.0%	
• Normal	38	88.4%	21	70.0%	32	62.7%	16	22.9%	
Lymphocytic count at presentation									0.680
• Lymphocytosis	1	2.3%	0	0.0%	2	4.0%	4	5.7%	
• Lymphopenia	5	11.6%	2	6.7%	8	16.0%	9	12.9%	
• Normal	37	86.0%	28	93.3%	40	80.0%	57	81.4%	
CRP at presentation									0.026[a]
• Positive	2	4.3%	2	6.5%	0	0.0%	13	17.1%	
• Negative	10	21.3%	7	22.6%	10	18.9%	15	19.7%	
• Not done	35	74.5%	22	71.0%	43	81.1%	48	63.2%	
Nasopharyngeal swab for COVID-19									0.933
• Positive	0	0.0%	0	0.0%	0	0.0%	1	1.3%	
• Negative	4	8.5%	3	9.7%	5	9.4%	6	7.8%	
• Not done	43	91.5%	28	90.3%	48	90.6%	70	90.9%	
Received bicarbonate	0	0.0%	0	0.0%	0	0.0%	19	24.7%	<0.001[a]
Inotropic support	1	2.1%	0	0.0%	0	0.0%	5	6.5%	0.104
Cause of DKA									0.445
• Not known	5	50.0%	0	0.0%	7	31.8%	3	25.0%	
• Missed doses	4	40.0%	6	85.7%	14	63.6%	8	66.7%	
• Infection	1	10.0%	1	14.3%	1	4.5%	1	8.3%	
Hypokalemia	5	10.6%	6	19.4%	8	15.1%	35	45.5%	<0.001[a]
Hypernatremia	0	0.0%	1	3.2%	0	0.0%	5	6.5%	0.087
Admission in isolation	4	8.3%	3	9.7%	7	13.2%	7	9.1%	0.844

[a]*P-value less than 0.05 is considered statistically significant.*

N, number; TLC, total leukocytic count; CRP, C-reactive protein; CT, computed tomography; DKA, diabetic ketoacidosis; GCS, Glasgow Coma Scale; T1D, Type 1 diabetes.

by Ludvigsson et al. who explored the effect of the COVID-19 pandemic on the treatment of T1D in children. He found that this period represented an increased burden on both patients and physicians (9). The pandemic has had a great emotional impact and psychological stress that might have influenced the rates of new-onset disease by changing the risk of developing autoimmunity (14). Multiple factors have also affected patients living with diabetes during both waves of the pandemic, including psychological health issues, decreased physical activity, dietary changes that led to poor nutrition and weight gain, and, finally, sleep disruptions. All of those might have altered diabetes management behaviors (15–17). Moreover, individuals who were worried about COVID-19 and diabetes could have been more vulnerable for diabetes distress, acute and chronic hyperglycemia, and onset or exacerbation of depression and anxiety (2).

During both COVID-19 waves, some of the recruited patients presented with COVID-like manifestations, including fever (29.5%), respiratory manifestations in the form of rhinorrhea, pharyngitis, cough, and respiratory distress (7.2%), and gastrointestinal manifestations in the form of vomiting, abdominal pain, and diarrhea (14.7%). In accordance with our center's policy, these patients had to remain in the emergency department in full isolation until all necessary investigations were completed to exclude a COVID-19 infection. This was considered a challenge for us, as the patients spent a significant amount of time in the emergency department, a process that might have contributed to the delayed DKA resolution. Additionally, patients were then encountering other patients presenting with various conditions, which could have increased the risk of spreading infection and subsequent development of complications during patient management, such as electrolyte disturbance and neurological complications.

TABLE 4 | Comparison of data between the COVID-19 waves and pre-COVID.

Laboratory data at presentation	COVID waves *N* (319) Mean ± SD	Pre-COVID *N* (60) Mean ± SD	*P*-value
Initial pH	7.1127 ± 0.20522	7.0122 ± 0.68802	0.266
Initial bicarb (mEq/L)	8.9006 ± 7.39415	11.8067 ± 8.13244	0.012[a]
Na (mEq/L)	134.5397 ± 6.59422	135.7117 ± 6.92245	0.237
K (mEq/L)	4.3555 ± 0.70945	4.5770 ± 0.92326	0.092
Serum creatinine (mg/dl)	0.8809 ± 0.31444	0.8983 ± 1.24839	0.915
Blood glucose (mg/dl)	506.1053 ± 166.17674	498.6167 ± 132.84400	0.749
Presence of ketones in urine	2.409 ± 0.9228	2.867 ± 0.3428	<0.001[a]

[a]*P-value less than 0.05 is considered statistically significant.*

A confirmation of diagnosis in patients with suspected SARS-CoV-2 infection was done by performing COVID-19 PCR using nasopharyngeal swabs. This procedure was performed in 37 children who fulfilled the local testing criteria (clinical, laboratory, and imaging). Only four of them tested positive (three in the first COVID-19 wave and one in the second COVID-19 wave). This finding was similar to the results of a study performed in the UK where the authors performed nasopharyngeal swabs in 21 children who fulfilled the local testing criteria, of whom only two tested positive (13). Children who tested positive completed their treatment in the isolation unit until DKA was resolved, received COVID-19 treatment according to the Egyptian Ministry of Health protocol, and were then discharged following improvement, while patients who tested negative for COVID-19 were transferred to the DEMPU inpatient unit to complete their therapeutic management planning while attending diabetes education sessions. Physicians and dieticians played a particularly important role in diabetes education by attempting to simplify and explain each item and process, especially to newly diagnosed cases with T1D. Phone calls were used as an alternative way to regularly schedule clinic visits to minimize the risk of exposure to infection.

In the current study, 59 patients (18.3%) developed hypokalemia as a complication during DKA management. Fifty-four (26%) of them were admitted during the second COVID-19 wave (12.5% received oral correction and 13.5% received intravenous correction). Hypokalemia was not associated with any cardiac complications, and its association with gastrointestinal manifestations was not statistically significant. This was different from what was observed in the previously mentioned UK-based study where the authors identified three patients with severe DKA who developed refractory hypokalemia. One child with SARS-CoV-2 PCR suffered from hypokalemia related to cardiac arrest but subsequently recovered following 1 day of ventilation (13).

Different factors associated with the severity of DKA were investigated during the current study. It was noted that only 5% of the severe cases during the first COVID-19 wave and 29.9% of the severe cases during the second COVID-19 wave developed neurological manifestations in the form of low Glasgow Coma Scale score and/or development of seizures (p = 0.041 and <0.001, respectively). This was despite the fact that lower bicarbonate levels induce a greater risk of developing neurological complications. This was similar to the study conducted by Bialo et al. who investigated the rare complications of pediatric diabetic ketoacidosis, including neurological complications (18). Additionally, we found that there was a statistically significant association between DKA severity and the presence of leukocytosis ($p < 0.001$ for both waves) and also with a longer duration of ICU stay ($p < 0.001$ for both waves).

Leukocytosis is a sign of infection, which is by far the commonest precipitating factor for DKA. Several researchers have identified a number of factors that might contribute to the occurrence of leukocytosis during DKA, especially in its most severe presentation. These include insulin deficiency, inflammatory processes, increased levels of stress hormones, such as adrenaline and cortisol, and infection. Furthermore, a significant association was detected between the total leukocytic count and the blood pH at the onset of presentation with DKA. The lower the pH value, the higher the leukocytic count (leukemoid response) (19).

A comparison between the data collected during the COVID-19 period and the pre-COVID-19 period underlines that the number of newly diagnosed cases admitted during the first and the second COVID-19 waves was significantly higher compared to that of the pre-COVID-19 period (65.7 *vs.* 38.3%, $p < 0.001$). This comes in agreement with the findings of a multicenter study conducted in the UK that observed an increase of 80% in newly diagnosed cases over a typical year before COVID-19 (13). Furthermore, another study performed in Finland showed a significant increase in the admissions of new-onset T1D cases during the COVID-19 pandemic (20). This might be explained by the high expression of angiotensin-converting enzyme 2 (ACE2) receptors on the B cells of the islets of Langerhans, which has also been proposed to be the binding site for SARS-CoV-2 (13). However, our results showed that only four patients had a positive nasopharyngeal swab for the COVID-19 virus, which makes this link doubtful, and thus further studies are required to verify this point. It was also observed that the severity of DKA was significantly higher during the COVID-19 era, a finding that might be due to the significant delay in seeking medical advice from professionals due to lockdown, overwhelmed medical system, and fear of infection (p = 0.012). This was also stated in the summary of the recommendations of International Society of Pediatric and Adolescent Diabetes (ISPAD) regarding children with diabetes and COVID-19 (21). The frequency of developing hypokalemia was also observed to be higher during the COVID-19 period compared to the pre-COVID period.

Intravenous infusion of insulin remains the treatment of choice for DKA management, and it should be provided in an ICU setting according to the 2018 ISPAD guidelines. However, these guidelines have been updated during the COVID-19 pandemic to help reduce the burden on the ICU services and teams who are overwhelmed by the number of critically ill COVID-19-infected patients. The new recommendations state that, in case of uncomplicated, mild, and moderate DKA, management could be carried out outside the ICU using subcutaneous insulin (22).

It has been thought that the severe acute respiratory syndrome coronavirus 2, which is the causative organism of the COVID-19 pandemic, exerts its effects on various systems, such as the respiratory system, the vascular system, and the gastrointestinal tract, including the intestines and pancreas, by binding to ACE2, a surface receptor found on various body organs. This, in turn, results to an increase in the inflammatory processes and vascular permeability of various organs, including the pancreas, which might be a direct cause for developing T1D. The rapidly spreading virus and the emergence of various mutations and strains are considered to be a red flag that warns scientists globally regarding future long- and short-term health consequences. Given the limited information on the mode of action of SARS-CoV-2 and its different effects on organs, it is hypothesized that the increasing incidence of T1D during the COVID-19 pandemic might be triggered by infections, which raise concerns about a future increase in the number of T1D cases (23).

Further studies are required to detect and describe the association between a SARS-CoV-2 infection and the incidence of new-onset diabetes, the severity of presentation, and the development of complications during management, especially hypokalemia. Furthermore, it is essential to evaluate the impact of using telemedicine as an alternative to regularly scheduled clinic visits on the long-term glycemic control of patients and on the development of both short- and long-term complications (2).

CONCLUSION

A significant increase in the frequency of newly diagnosed T1D cases was evident during the first and the second COVID-19 waves compared to the pre-COVID-19 period. The patients also presented with more severe DKA, probably due to a more delayed presentation, and the frequency of hypokalemia was significantly higher. The severity of DKA was associated with a longer ICU admission. Furthermore, few patients who presented with DKA developed neurological complications. The development of hypokalemia was not associated with any cardiac consequences. The severity of DKA was associated with a longer ICU admission. Further studies are required to establish a definitive link between the COVID-19 pandemic and the severity of presentation.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the bioethical research committee, Faculty of Medicine, Kasr Alainy University Hospitals, Cairo, Egypt. Written informed consent from the participants' legal guardian/next of kin was not required for them to participate in this study in accordance with the national legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

MA shared in study design, data collection and interpretation, critical revision of the article, drafting the manuscript, and final approval for publishing. MH shared in study design, critical revision of the article, data interpretation, and final approval for publishing. SH shared in study design, analysis and interpretation of data, critical revision of the article, and final approval for publishing. EE shared in statistical analysis and interpretation of data, article revision, and final approval for publishing. RS shared in design of study, critical revision of the article, data interpretation, drafting the manuscript, and final approval for publishing. All authors analyzed the data, discussed the results, commented on the manuscript, and finally approved it for publishing.

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Difference of Precocious Puberty Between Before and During the COVID-19 Pandemic: A Cross-Sectional Study Among Shanghai School-Aged Girls

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Objective: To compared the incidence rates and clinical features of precocious girls before and during the COVID-19 pandemic among Shanghai school-aged girls, and explored the potential mechanisms.

Methods: This cross-sectional study collected medical data about precocious girls between 2016 and 2020 from Shanghai Children's Medical Center. Data of inpatient precocious girls from March to August in 2016-2019 (n=246) and 2020 (n=237) were collected. Subjects with abnormal brain and pituitary gland MRI reports, other endocrine diseases or chronic diseases were excluded. Finally, 209 precocious girls were included in the 2016-2019 group and 191 precocious girls were include in the 2020 group. Monthly incidence rates and clinical features were compared between before and during the COVID-19 pandemic. Linear regression models were used to examine the associations between biomarkers to explore the potential mechanisms.

Results: Monthly incidence rates of precocious puberty in outpatient girls from March to December 2020 (0.44-1.36%) and in inpatient girls from March to August 2020 (27.04-47.83%) were higher than those in 2016-2019 (0.30-0.52% and 10.53-18.42%, respectively). Serum concentrations of GnRH were higher in the 2020 group than in the 2016-2019 group (2.81 vs 1.99 mg/L). Serum concentrations of MKRN3 (1.02 vs 1.93 ng/ml) and ghrelin (0.38 vs 0.88 ng/ml) were lower in the 2020 group than in the 2016-2019 group. Moreover, the serum concentration of ghrelin was positively associated with the serum concentration of MKRN3 [β=0.891 (*95% CI*, 0.612, 1.171); p<0.001].

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Conclusions: These findings suggest an increased incidence of precocious puberty during the COVID-19 pandemic among Shanghai school-aged girls, which may be associated with decreased serum concentrations of MKRN3 and ghrelin, and indicated ghrelin as a potential regulatory mechanism of puberty.

Keywords: precocious puberty, girl, COVID-19, ghrelin, MKRN3

INTRODUCTION

Since early December 2019, coronavirus 2019 (COVID-19) has spread rapidly and widely worldwide (1, 2). It was suggested that children are less susceptible to COVID-19 than adults (3), and pediatric patients have less severe clinical manifestations than adult patients (2). However, increasing evidence has demonstrated that control policies for COVID-19, such as enforced social distancing, school closures, online courses and lifestyle changes that reduce physical activities, may lead to other serious problems in children (4).

Among these problems, the increased incidence of precocious puberty in girls attracted our attention (3, 5). Li et al. found that the spectrum of disease for children changed dramatically before and after the breakout of COVID-19 in Hangzhou (3). It showed that the greatest increases in visits were for problems related to precocious and accelerated puberty (3). Stagi et al. also suggested that there was an increased incidence of precocious and accelerated puberty in girls during and after the Italian lockdown for the COVID-19 pandemic (5). Compared with previous years, precocious girls during and after lockdown showed a faster rate of pubertal progression (5). Shanghai is an international city with a large domestic and overseas population. The task of epidemic prevention is still grim, and policies for pandemic control remain strict in Shanghai. However, very few studies have investigated the changes in precocious incidence and clinical features before and during COVID-19 in school-aged girls in Shanghai.

In this study, we analyzed data on outpatients and inpatients in 2016-2020 from Shanghai Children's Medical Center (SCMC) to compare the incidence rates and clinical features of precocious girls before and during the COVID-19 pandemic among Shanghai school-aged girls. Furthermore, serum concentrations of biomarkers were detected for inpatient precocious girls to explore the potential mechanisms.

METHODS

Study Design and Participants

This study was conducted in SCMC, Shanghai Jiao Tong University School of Medicine, Shanghai, China. SCMC is one of the National Children's Medical Centers in China, accounting for 15-20% of the total number of pediatric patients in Shanghai, with more than 1,700,000 visits in the outpatient department and more than 35,000 visits in the inpatient ward per year.

Participants were diagnosed with precocious puberty according to the onset of breast development (Tanner stages≥B2) before the chronological age (CA) of 8 years (6). Precocious girls who showed slow progress of puberty were followed in the outpatient department. Other girls who showed accelerated puberty were admitted in the endocrinology ward for further examinations. Data of these precocious girls in 2016-2020 from SCMC were recorded.

Girls younger than 6 years were more susceptible to intracranial pathology (7). We collected data on precocious girls equal or older than 6 years from the endocrinology ward from March to August in 2016-2020. Detailed data of physical and laboratory examinations were recorded for these inpatient precocious girls, including anthropometric measurements, pubertal staging, direct radiography of the left hand and wrist, pelvic ultrasonography, magnetic resonance imaging (MRI) of the brain and pituitary gland and gonadotropin-releasing hormone (GnRH) stimulation tests.

Subjects with any one of the following conditions were excluded: 1) abnormal brain and pituitary gland MRI reports, including Rathke's cleft cysts, pineal cysts, arachnoid cysts, hamartoma and germinoma; 2) other endocrine diseases, including hypothyroidism, hyperthyroidism, short stature, diabetes and adrenal disease; and 3) chronic diseases, including chronic nephrosis, asthma, epilepsy and hematological disease. After that, inpatient precocious girls were included in the 2016-2019 group and 2020 group (**Figure 1**), and their clinical features were compared.

Physical examination

The body weight (kg) and height (cm) of all subjects were measured and recorded using the same type of apparatus and following the standard procedures recommended by Cameron (8). Body mass index (BMI) was calculated by the equation of weight in kilograms (kg) divided by height in meters squared (m2). Secondary sexual characteristics of these subjects were evaluated and recorded by endocrinologists from the Department of Endocrinology using Tanner stages (9).

Laboratory examination

Bone age (BA) (10), pelvic ultrasonography (11), magnetic resonance imaging (MRI) of the brain and pituitary gland, gonadotropin-releasing hormone (GnRH)-stimulation test, serum concentrations of sex hormone-binding globulin (SHBG) and hormones [estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), GnRH, kisspeptin, makorin ring finger protein 3 (MKRN3), leptin and ghrelin)] were detected for inpatient precocious girls in the 2016-2019 group and 2020 group (**Figure 1**).

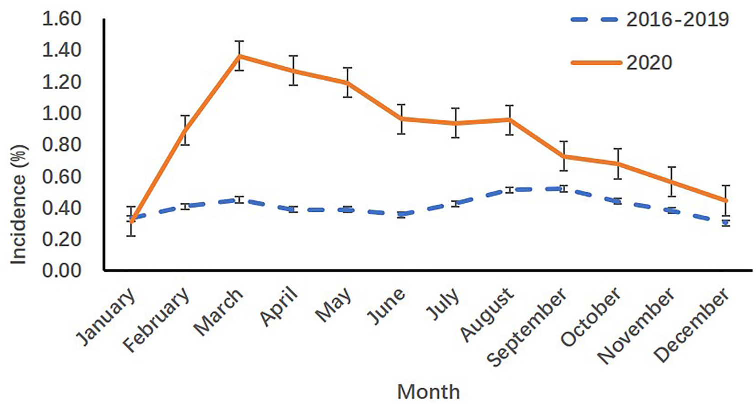

FIGURE 1 | Monthly incidence rates of precocious girls before (2016-2019) and during (2020) the COVID-19 pandemic in the outpatient department.

Gonadorelin acetate (Gonadorelin, BBCA, Anhui, China) was used for the GnRH stimulation test, which was conducted between 8 am and 10 am in a fasting state for all of the cases in the 2016-2019 group and 2020 group, by intravenous injection of gonadorelin acetate at a dose of 2.5 μg/kg body weight (the maximum total dose was 100 μg) (12). Venous blood samples were collected before the injection of gonadorelin acetate to detect the serum concentrations of SHBG, E2, LH, FSH, GnRH, kisspeptin, MKRN3, leptin and ghrelin at 0, 30, and 60 min after the injection of gonadorelin acetate to detect the serum concentrations of LH and FSH at 30 and 60 min.

Serum was separated from the blood samples less than 1 hour after collection. For the concentrations of SHBG, E2, LH and FSH, serum samples were detected just after being collected. For the concentrations of GnRH, kisspeptin, MKRN3, leptin and ghrelin, serum samples were stored in the biobank at -80°C until the detection. We lost some of our samples because of updates to the biobank electronic system (**Figure 1**). Serum samples were detected by the clinical laboratory of SCMC. Serum concentrations of SHBG, E2, LH and FSH were detected by chemiluminescence immunoassay (CMIA; Abbott Diagnostics, IL, USA) on an Architect i2000SR (Abbott Diagnostics), with detection limits of 0.02 nmol/L, 10 pg/ml, 0.09 IU/L and 0.05 IU/L, respectively; intra-assay and inter-assay coefficients of variation (CV) were less than 6.4% and 8.4%, respectively. Serum concentrations of GnRH, kisspeptin, MKRN3, leptin and ghrelin were measured using enzyme-linked immunosorbent assay (ELISA) by commercial human ELISA kits (BFS, Beijing, China), with detection limits of 20 ng/L, 5 ng/L, 10 ng/L, 0.05 ng/ml and 5 ng/L, respectively; intra-assay and inter-assay CV were less than 10% and 12%, respectively.

Questionnaire Survey

According to questionnaires used in our previous investigations (13), a structured questionnaire was designed to investigate lifestyles of precocious girls during the COVID-19 pandemic. Face-to-face interviews were conducted for inpatient precocious girls in the 2020 group through the questionnaire, including detailed information about dietary pattern, rate of weight gain, sleep duration, amount of exercise and screen exposure duration during the COVID-19 pandemic. Totally, 23.56% (45/191) of precocious girls and their parents completed the questionnaire due to the inconvenient return visit during the COVID-19 pandemic.

Statistical Analysis

The monthly incidence of precocious puberty in outpatient girls was calculated by monthly visits of precocious girls divided by monthly visits of all patients in the outpatient department. Monthly incidence of precocious puberty in inpatient girls was calculated by monthly visits of precocious girls divided by monthly visits of all patients in the endocrinology ward. Comparisons among groups were analyzed using chi-square (χ^2) tests for categorical variables and Wilcoxon rank sum tests for continuous variables due to their skewed distributions. The relationships of serum ghrelin with serum GnRH and MKRN3 concentrations in precocious girls were analyzed using linear regression models, adjusting for girls' age, BMI and the menarche age of their mothers (14). Serum concentrations of GnRH, MKRN3 and ghrelin were transformed to log10 scale due to their skewed distributions. Statistical analyses were performed with SPSS 25.0 (SPSS Inc., Chicago, IL, USA) based on two-tailed tests, and statistical significance was set at $p< 0.05$.

Ethics

All participating parents provided written informed consent, and all research activities were approved by the institutional review board of SCMC, Shanghai Jiao Tong University School of Medicine (approval number: SCMCIRB-K2021014-1).

RESULTS

When compared with the incidence in 2016-2019 years, both the monthly visits and monthly incidence rates of precocious girls increased from March to December 2020 in the outpatient department of SCMC (p<.001) [(**Table 1**) and (**Figure 1**)].

When compared with the incidence in 2016-2019 years, the monthly incidence rates of precocious girls in 2020 increased from March to August and in December in the endocrinology ward of SCMC (p<0.05) [(**Table 2**) and (**Figure 2**)].

According to the criteria mentioned above, 209 precocious girls (age 7.92 ± 0.71 years) were included in the 2016-2019 group and 191 precocious girls (age 7.95 ± 0.77 years) were included in the 2020 group (**Figure 3**). All subjects were Han Chinese girls. The ratio of peak LH/peak FSH and the mean concentration of GnRH in the 2020 group were higher than those in the 2016-2019 group (1.23 vs 0.83, p<0.001 and 2.81 vs 1.99 mg/L, p=0.012, respectively) (**Table 3**). The mean age of mother's menarche, the mean concentration of SHBG, basal FSH, peak FSH after the GnRH stimulation test, MKRN3 and ghrelin in the 2020 group were lower than those in 2016-2019 group (12.74 vs 13.19 years, p=0.024; 70.30 vs 81.64 nmol/L, p=0.001; 2.77 vs 3.60 IU/L, p<0.001; 10.66 vs 16.49 IU/L, p<0.001; 1.02 vs 1.93 ng/ml, p<0.001; 0.38 vs 0.88 ng/ml, p<0.001, respectively) (**Table 3**).

With the peak value of LH ≥5 IU/L after the GnRH stimulation test, activation of hypothalamus-pituitary-gonadal (HPG) axis were presented in 299 precocious girls (153 in the 2016-2019 group and 146 in the 2020 group), diagnosed as central precocious puberty (15). 64.88% (194/299) of these girls showed complete records of serum concentrations of GnRH, MKRN3 and ghrelin. For these girls, no correlation was identified between serum ghrelin and serum GnRH concentrations. While, a positive correlation was found between serum ghrelin and serum MKRN3 concentrations [β=0.891 (*95% CI*, 0.612, 1.171); p<0.001] (**Table 4**).

46.67% (21/45) of precocious girls consumed much more meat than vegetables (data not shown). The ranges and percentiles of weight gain within 3 and 6 months, BMI gain within 3 and 6 months, sleep duration at night, amount of exercise, amount of outdoor activities and amount of electronic screen exposure per day of these subjects were shown in **Table 5**. The median value of weight gain in 6 months was 2 kg in these girls, the total amount of exercise per day was less than 1 hour, and the amount of electronic screen exposure per day was up to 3 hours.

TABLE 1 | Monthly visits and monthly incidence rates of precocious girls before (2016-2019) and during (2020) the COVID-19 pandemic in the outpatient department.

Month	Average visits of patients before the COVID-19 pandemic (2016-2019)			Visits of patients during the COVID-19 pandemic (2020)			χ2	p
	Precocious girls	All patients	Incidence (%)	Precocious girls	All patients	Incidence (%)		
January	454	136950	0.33	398	127277	0.31	0.73	0.394
February	395	97130	0.41	244	27386	0.89	98.14	**<0.001**
March	573	127022	0.45	636	46740	1.36	409.16	**<0.001**
April	496	127545	0.39	863	68025	1.27	497.60	**<0.001**
May	540	139369	0.39	1021	85561	1.19	499.53	**<0.001**
June	479	135167	0.35	917	95455	0.96	341.80	**<0.001**
July	606	143060	0.42	1056	112767	0.94	256.97	**<0.001**
August	725	141594	0.51	1135	118776	0.96	179.17	**<0.001**
September	664	127436	0.52	856	118034	0.73	41.51	**<0.001**
October	582	132369	0.44	786	115948	0.68	64.02	**<0.001**
November	559	146758	0.38	695	123445	0.56	48.13	**<0.001**
December	474	157299	0.30	663	149415	0.44	42.07	**<0.001**

Bold indicates p < 0.05.

TABLE 2 | Monthly incidence rates of precocious girls before (2016-2019) and during (2020) the COVID-19 pandemic in the endocrinology ward.

Month	Average visits of patients before (2016-2019) COVID-19 pandemic			Visits of patients during (2020) COVID-19 pandemic			χ2	p
	Precocious girls	All patients	Incidence (%)	Precocious girls	All patients	Incidence (%)		
January	3	40	8.13	8	65	12.31	0.205	0.650
February	4	45	9.44	4	20	20.00	0.722	0.396
March	6	52	10.53	19	61	31.15	6.512	**0.011**
April	9	48	18.42	49	123	39.84	6.850	**0.009**
May	8	49	15.38	66	138	47.83	15.004	**<0.001**
June	9	47	18.18	42	94	44.68	8.847	**0.003**
July	9	82	11.04	43	159	27.04	8.255	**0.004**
August	13	99	12.69	61	190	32.11	12.301	**<0.001**
September	16	68	23.81	29	93	31.18	1.142	0.285
October	16	59	27.00	20	97	20.62	0.873	0.350
November	8	56	13.78	6	50	12.00	0.097	0.755
December	5	53	9.91	25	71	35.21	10.995	**0.001**

Bold indicates p < 0.05.

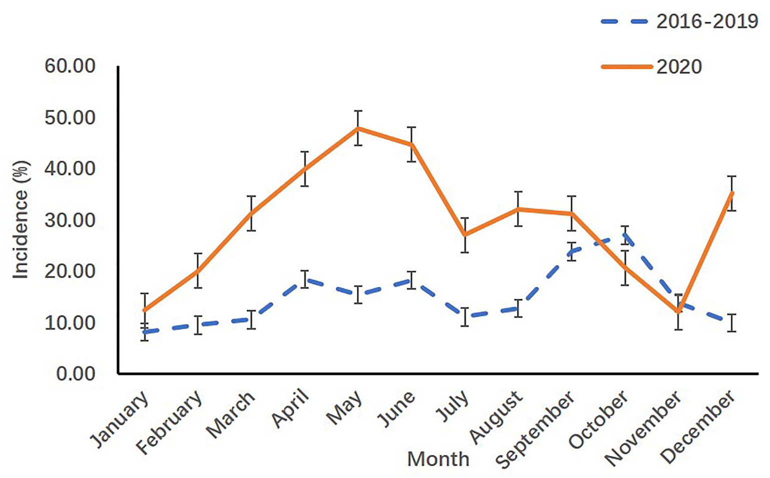

FIGURE 2 | Monthly incidence rates of precocious girls before (2016-2019) and during (2020) the COVID-19 pandemic in the endocrinology ward.

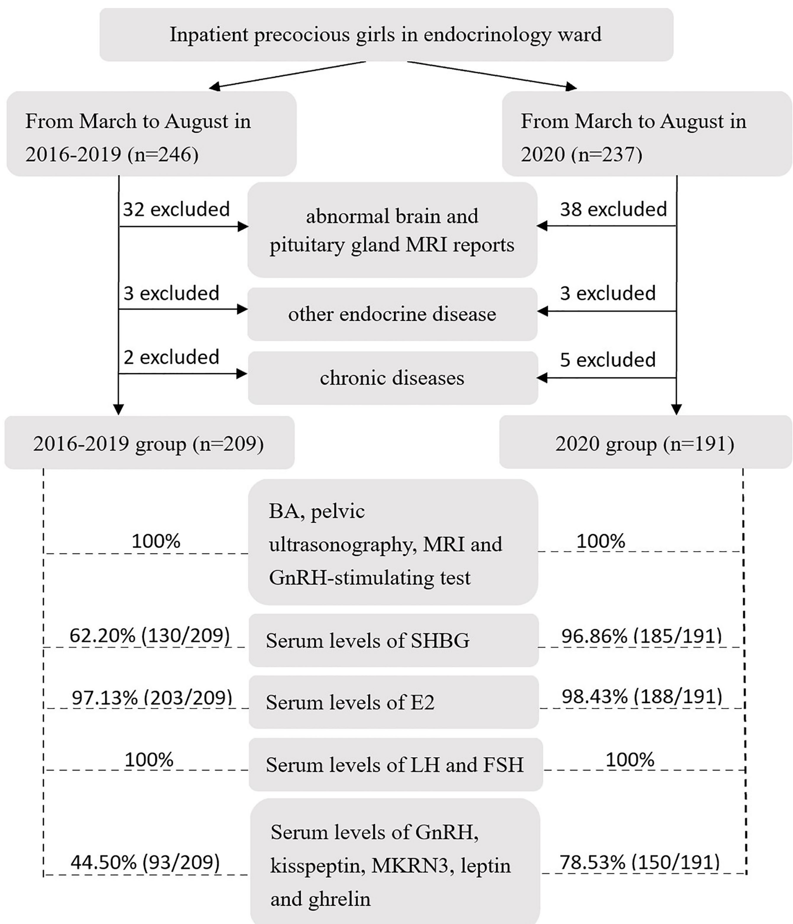

FIGURE 3 | Flow diagram of criteria and examination for inpatient precocious girls in the endocrinology ward in the 2016-2019 group and 2020 group (MRI, magnetic resonance imaging; BA, bone age; GnRH, gonadotropin-releasing hormone; SHBG, sex hormone-binding globulin; E2, estradiol; LH, luteinizing hormone; FSH, follicle-stimulating hormone; MKRN3, makorin ring finger protein 3).

TABLE 3 | Characteristics of inpatient precocious girls in the endocrinology ward.

Characteristics	2016-2019 group (n = 209)	2020 group (n = 191)	Statistics Z/χ^2	p
Age (years)	7.92 ± 0.71 7.98 (6.12-8.99)	7.95 ± 0.57 7.99 (6.13-8.98)	-0.073	0.942
6<age ≤ 8	105 (50.24%)	98 (51.31%)	0.046	0.831
8<age ≤ 9	104 (49.76%)	93 (48.69%)		
BMI (kg/m^2)	17.12 ± 2.41	17.48 ± 2.20	-1.960	0.050
Mother's menarche age (years)	13.19 ± 1.49	12.74 ± 1.16	-2.258	**0.024**
BA-CA	1.28 ± 1.13	1.48 ± 1.13	-1.683	0.092
SHBG (nmol/L)	81.64 ± 33.28	70.30 ± 30.06	-3.254	**0.001**
Basal E2 (pg/mL)	22.31 ± 16.25	21.35 ± 13.35	-0.345	0.730
Basal LH (IU/L)	0.67 ± 0.77	0.72 ± 0.85	-0.604	0.546
Basal FSH (IU/L)	3.60 ± 1.96	2.77 ± 1.50	-4.455	**<0.001**
Peak LH (IU/L)	13.23 ± 13.79	13.30 ± 11.75	-0.576	0.564
≥5	153 (73.21%)	146 (76.44%)	0.553	0.457
<5	56 (26.79%)	45 (23.56%)		
Peak FSH (IU/L)	16.49 ± 5.69	10.66 ± 3.79	-10.842	**<0.001**
Peak LH/FSH ratio	0.83 ± 0.71	1.23 ± 0.86	-5.246	**<0.001**
GnRH (mg/L)	1.99 ± 2.03	2.81 ± 2.89	-2.514	**0.012**
Kisspeptin (ng/ml)	1.90 ± 1.38	2.13 ± 1.71	-0.345	0.730
MKRN3 (ng/ml)	1.93 ± 1.09	1.02 ± 0.84	-6.908	**<0.001**
Leptin (ng/ml)	7.14 ± 5.25	5.75 ± 2.46	-1.454	0.146
Ghrelin (ng/ml)	0.88 ± 0.43	0.38 ± 0.18	-10.719	**<0.001**

Wilcoxon rank sum tests were used for continuous variables.
χ2 tests were used for categorical variables.
Bold indicates p < 0.05.

TABLE 4 | Relationships of serum ghrelin with GnRH and MKRN3 concentrations (n=194) determined by linear regression models.

Biomarkers	β^a	95% *CI*	p
Ghrelin	*Reference*		
GnRH (mg/L)	-0.012	-0.184-0.159	0.888
MKRN3 (ng/ml)	0.891	0.612-1.171	**<0.001**

[a]Models adjusted for the girls' age, BMI and menarche age of their mothers.
Bold indicates p < 0.05.

TABLE 5 | Lifestyle features of precocious girls during the COVID-19 pandemic.

Items	n	Range	Percentiles		
			25th	50th	75th
Weight (kg) or BMI (kg/m2) gain					
Weight gain within 3 months	24	0-4.00	0.50	1.00	2.00
BMI gain within 3 months	23	-0.68-1.96	-0.07	0.18	0.57
Weight gain within 6 months	27	0-5.00	1.50	2.00	3.63
BMI gain within 6 months	24	-1.43-2.08	-0.27	0.30	0.97
Sleep duration at night per day (h)	45	8.00-11.00	9.00	9.50	10.00
Amount of exercise per day (h)					
High intensity	44	0-1.14	0	0.07	0.29
Moderate intensity	45	0-2.14	0.14	0.29	0.43
Low intensity	42	0-2.50	0.14	0.36	1.00
Total	41	0.11-3.50	0.49	0.86	1.27
Amount of outdoor activities per day (h)	45	0-4.50	0.50	1.00	1.75
Amount of screen exposure per day (h)	45	0.50-8.00	1.59	3.00	4.75

DISCUSSION

In the present study, we found that the incidence rates of precocious puberty were increased and concentrations of serum MKRN3 and ghrelin were decreased during the COVID-19 pandemic among Shanghai school-aged girls. Furthermore, a positive association between the serum concentration of MKRN3 and indicated ghrelin as a potential regulatory mechanism of puberty.

The COVID-19 pandemic has spread rapidly and widely worldwide since early December (1, 2). Compared with adults, children are less susceptible to COVID-19 (3), and pediatric patients have less severe clinical manifestations (2). Studies have demonstrated that after the outbreak of COVID-19, the spectrum of disease for children changed dramatically, with an increased incidence of pubertal development problems and a decreased incidence of other infectious diseases (3). Li et al. analyzed data from Hangzhou before (from January 1, 2019 to March 31, 2019) and after (from January 1, 2020 to March 31, 2020) the breakout of COVID-19. Compared with 2019, the visit rate for problems related to precocious and accelerated puberty increased more than 3-fold during the period in 2020 (3). Stagi et al. compared medical records of precocious girls in Italy from March to July 2020 with the same period of the previous 5 years (March to July 2015-2019). An increased incidence of newly diagnosed precocious puberty in girls in 2020 and an accelerated rate of pubertal progression in precocious girls in 2020 were reported (5). In the present study, we evaluated historical data from the outpatient department and inpatient endocrinology ward in SCMC, which is one of the largest comprehensive pediatric medical centers in China, and obtained similar results. Compared with historical data in 2016-2019, the monthly incidence rates of precocious puberty in outpatient girls from February to December in 2020 ($p<.001$) and in inpatient girls from March to August in 2020 ($p<.05$) increased continually. The monthly incidence rates of precocious puberty in inpatient girls from September to November 2020 was not different from that in 2016-2019 ($p>.05$), but it increased again in

December 2020 (p=.001), followed by a partial and transient relief of COVID-19 cases in late November in Shanghai. The decreased physical activities, increased food consumption and rapid weight gain may be associated with the increased visits of pubertal development problems during the pandemic.

SHBG is a circulating glycoprotein that transports steroid hormones in the blood (16). Most steroid hormones in the plasma are bound to proteins in the inactive bound state (17). Serum concentrations of SHBG rise significantly from birth to early childhood (18), are stable during childhood, and then decline during puberty (19). It has been hypothesized that during childhood, SHBG may restrict the actions of sex steroids in the inactive bound state and then decrease during puberty, resulting in increased levels of free sex steroids in the active unbound state (20). Increasing evidence has shown that lower concentrations of serum SHBG are associated with early puberty (19, 21). In the present study, we found that the serum concentrations of SHBG in the 2020 group were lower than those in 2016-2019 group (70.30 vs 81.64 nmol/L) (p<.001). The mechanism by which concentrations of serum SHBG are reduced during puberty is still unknown.

Functioning as a bridge between the hypothalamus and the gonads, FSH and LH, which are synthesized and secreted in the pituitary, play important roles in the normal function of the HPG axis (22). The secretion of FSH is regulated by a complex interplay of different factors, including negative steroid hormone feedback from the gonads, endocrine disruptor factors and stress (15). Pescovitz et al. reported that compared with girls with isolated thelarche, girls with complete sexual development showed lower serum concentrations of peak FSH after the GnRH stimulation test (23). In the present study, we found that the serum concentrations of basal FSH (2.77 vs 3.60 IU/L, p<.001) and peak FSH after the GnRH stimulation test (10.66 vs 16.49 IU/L, p<.001) were lower in the 2020 group than those in the 2016-2019 group. Although there was no difference in serum concentrations of peak LH between the two groups, the peak LH/FSH ratio, which could represent progressive puberty (23), was higher in the 2020 group than in the 2016-2019 group (1.23 VS 0.83, p<.001). As a cross-sectional study, we were unable to collect information about the progression of the precocious girls in our study. Data from Italy have shown an accelerated rate of pubertal progression in precocious girls in 2020 (5). This highlights the need to monitor pubertal progression for precocious girls in the 2020 group in the follow-up.

Early activation of the HPG axis inducing pulsatile secretion of GnRH could give rise to early onset of puberty (24). Pulsatile secretion of GnRH is positively regulated by kisspeptin and negatively regulated by MKRN3 (**Figure 4**) (6). Compared with normal healthy girls, precocious girls showed higher concentrations of serum kisspeptin (12) and lower concentrations of serum MKRN3 (25, 26). In the present study, we found that the

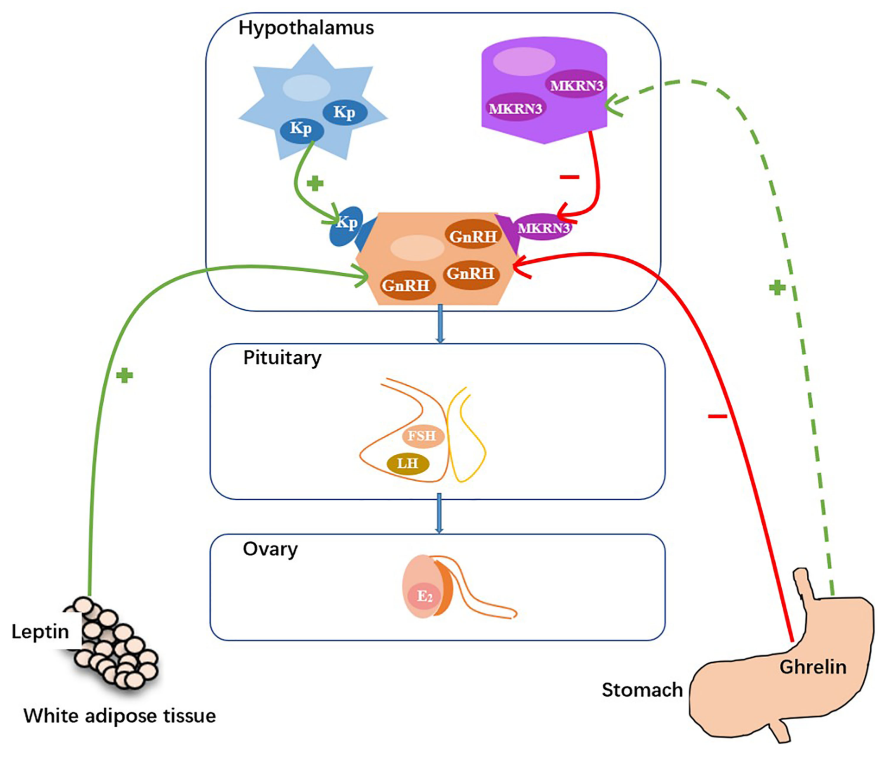

FIGURE 4 | Hypothetical model for the control of GnRH secretion (Kp, kisspeptin; MKRN3, makorin ring finger protein; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol. +, stimulatory effect; –, inhibitory effect.).

serum concentrations of GnRH in 2020 group were higher than those in the 2016-2019 group (2.81 vs 1.99 mg/L, p=.012) and the serum concentrations of MKRN3 in 2020 group were lower than those in 2016-2019 group (1.02 vs 1.93 ng/ml, p<.000). However, the serum concentrations of kisspeptin between the two groups were not different (2.13 vs 1.90 ng/ml, p=.730).

Under the policies of city lockdown, enforced social distancing, and school closures, the lifestyles of children changed, with less physical activities, more electronic screen exposure and increased food consumption, may lead to rapid weight gain during the pandemic (27, 28).According to questionnaires completed by 45 precocious girls and their parents in the 2020 group, the median value of weight gain in 6 months was 2 kg, and the maximum value was as high as 5 kg, which demonstrates the rapid weight gain for precocious girls in 2020 during the COVID-19 pandemic.

Rapid weight gain leads to increased concentrations of leptin and decreased concentrations of ghrelin (29). Increasing evidence has demonstrated that leptin promotes pulsatile GnRH secretion and that ghrelin suppresses pulsatile GnRH secretion, therefore they can play important roles in pubertal onset (**Figure 4**) (6, 30, 31). Kang et al. reported that serum leptin concentrations were higher in precocious girls than in normal healthy girls (30). Eshmawy et al. reported that compared with normal healthy controls, boys with constitutional delay of growth and puberty had lower serum leptin concentrations and higher serum ghrelin concentrations (31). However, few data exist on the relationship between serum ghrelin concentrations and pubertal onset in girls. We found that the serum concentrations of leptin between the two groups were not different (5.75 vs 7.14 ng/ml, p=.146). While, the serum concentrations of ghrelin in the 2020 group were significantly lower than those in the 2016-2020 group (0.38 vs 0.88 ng/ml, p<.001).

How does ghrelin contribute to the regulation of pulsatile secretion of GnRH, directly or indirectly? As far as we know, reports about that were limited. In the present study, no correlation was found between serum ghrelin and serum GnRH concentrations [β=-0.012 (95% *CI*, -0.184, 0.159); p=0.888]. While, a positive correlation was found between serum ghrelin and serum MKRN3 concentrations [β=0.891 (*95% CI*, 0.612, 1.171); p<0.001]. According to the results, we assume that the lower concentrations of ghrelin may downregulated the concentrations of MKRN3, and then upregulated the pulsatile secretion of GnRH to promote the onset of puberty (**Figure 4**). To the best of our knowledge, this is the first report of a positive correlation between serum ghrelin and serum MKRN3 concentrations in precocious girls.

LIMITATIONS

It should be kept in mind that prolonged frozen storage of samples for the detection of GnRH, kisspeptin, MKRN3, leptin and ghrelin may lead to some extent of degradation of hormones. Although we found that precocious girls during the COVID-19 pandemic had insufficient exercise time, excessive weight gain and excessive amount of electronic screen exposure, the small number of questionnaires (23.56%) and the lack of questionnaires from precocious girls in the 2016-2019 group prevented us from analyzing the relationship between lifestyle changes and precocious puberty in girls. Moreover, as a cross-sectional study, we could not assess whether there was a causal relationship between serum ghrelin and MKRN3 concentrations. We suggest that longitudinal studies on this topic should be carried out urgently.

CONCLUSIONS

In summary, compared with data from 2016-2019 years, the monthly incidence of precocious puberty among Shanghai school-aged girls was increased in 2020. Furthermore, a positive correlation between serum concentrations of ghrelin and MKRN3 was found, which indicated ghrelin as a potential regulatory mechanism of puberty. Longitudinal studies are needed to determine the causal relationship between ghrelin and MKRN3.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YC, JC, SL and XW contributed to conception and design of the study. YT, QZ, YW, QL, XL and ZW organized the database. YC and SL performed the statistical analysis. YC and JC wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Impact of Covid-19 Pandemic on the Effectiveness of Outpatient Counseling in Childhood Obesity Management

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The Covid-19 pandemic drastically modified social life and lifestyle, in particular, among children and adolescents, promoting sedentary behaviors and unhealthy eating habits. The aims of this study were to assess the rate and the factors associated with outpatient drop-out in childhood obesity management, and to evaluate how the Covid-19 pandemic influenced weight status and lifestyle of children and adolescents with obesity. One hundred and forty-five children and adolescents with obesity were identified, including 80 subjects evaluated before the Covid-19 pandemic (group A) and 65 subjects in the period straddling the Covid-19 pandemic (group B). Anamnestic (family history of obesity, dietary habits, physical activity, screen time), socio-cultural (economic status, employment and schooling of parents, household composition, place of living) and clinical (weight, height, BMI, waist circumference) data were retrospectively analyzed for each subject in both groups at baseline (V0) and 12-months (V1) at in-person assessment. Glycemic and lipid profiles were assessed at V0. Drop-out rate did not differ significantly between the two groups. BMI SDS at V0 (OR=2.52; p=0.004), female sex (OR=0.41; p=0.035), and the presence of a single parent in the household (OR=5.74; p=0.033) significantly influenced drop-out in both groups. Weight loss between V0 and V1 was significantly greater among group A patients compared to group B (p=0.031). In group B, hours spent in physical activity significantly decreased from V0 to V1, being significantly lower than group A at V1; on the contrary, screen time significantly increased in the same period. The consumption of sugary drinks and snacks was significantly greater in group B than group A at V1. Our study documented that the Covid-19 pandemic, although not affecting the drop-out rate of obese children in a follow-up program, negatively influenced lifestyle and reduced the effectiveness of outpatient counseling in childhood obesity treatment.

Keywords: childhood obesity, Covid-19, physical activity, lifestyle, nutrition

INTRODUCTION

The coronavirus disease (Covid-19), caused by Sars-CoV-2, firstly reported in late December 2019 in Wuhan, China, quickly became an emerging, rapidly evolving situation, spreading inevitably outside China and the Asian continent, and was declared a pandemic in March 2020. Governments of several countries worldwide enforced emergency measures and a lockdown policy, including closure of schools and many other activities, to slow infection spread down. In Italy, the Government imposed a lockdown from March 9, 2020 to May 4, 2020, which was followed by a gradual restart of activities, although school activities continued with distance learning through to the end of the school year, and most extracurricular activities previously attended by children did not restart after closing. These safety measures radically modified social life and drastically changed people's lifestyle, in particular for children and adolescents (1). Youth lifestyle behaviors were significantly affected due to extended school closures and home confinement, leading to a reduction in physical activity in favor of a sedentary lifestyle, particularly impacting children and adolescents with obesity. A sedentary lifestyle, characterized by increased time spent watching TV or playing video games, promotes unhealthy behaviors which favor the onset or worsening of obesity, such as high consumption of fast food and sugar-sweetened beverages, as well as sleep disorders (2, 3). These issues can be further exacerbated by stress due to isolation, which can result in increased food intake, with a particular focus on highly palatable foods (sugary, salty and high-calorie foods), an increase in emotional instability and in overall worsening of the quality of life (2). On the other hand, it has been suggested that lockdown and social distancing policies may have resulted in a reduction in the risk of developing or worsening obesity as a result of reduced out-of-home meal occasions (restaurants and fast food) (4, 5). Therefore, the effects of the Covid-19 pandemic on pediatric weight status are not completely clear. Moreover, many studies have based their results on questionnaires or telephone interviews rather than in-person assessments. In this scenario, the effectiveness of the outpatient approach for pediatric obesity, already burdened by a high drop-out rate, may decrease due to restrictions imposed by the Covid-19 pandemic.

The aims of this study were to assess the rate and the factors associated with outpatient drop-out by comparing two groups of children and adolescents with obesity evaluated before and during the Covid-19 pandemic, and to evaluate how the Covid-19 pandemic influenced the weight status and lifestyle of these subjects.

MATERIALS AND METHODS

Study Population

This is a single-center, observational, retrospective study. Patient inclusion criteria were age ranged between 5 and 16 years, and BMI ≥ +2 standard deviation score (SDS) at baseline, in accordance with the definition of obesity by the World Health Organization (WHO) for children from the age of 5 years. Exclusion criteria were genetic and/or endocrine causes of obesity, chronic diseases, and chronic pharmacological therapies.

Children and adolescents, referred to our pediatric endocrinology outpatient clinic for obesity, who completed annual follow-ups, were divided into two groups: group A included subjects evaluated before the Covid-19 pandemic and group B included subjects followed in the period straddling the Covid-19 pandemic. Specifically, each subject belonging to the two groups was evaluated retrospectively at a first in-person evaluation (V0) and at a 12-month follow-up in-person visit (V1). Group A patients underwent V0 assessment between October and November 2018 and V1 evaluation between October and November 2019, while patients of group B underwent V0 between January and February 2020 and V1 evaluation between January and February 2021.

Anamnestic Assessment

Anamnestic information was obtained by evaluating both face-to-face interview with parents, conducted during appointments, and medical records. In particular, information regarding the following was collected: family history for obesity in parents, socio-cultural aspects including household composition (complete or incomplete with separated parents), employment of both parents (yes or no), family economic status (low/moderate or high status) estimated indirectly in relation to the employment of one or both parents, level of education of both parents (years of school attendance including university), place of living (town or village). In addition, for each patient assessed, at both V0 and V1, information regarding the following was collected: hours spent daily on video games, TV, tablets, smartphone (screen time), the practice of physical activity (yes or no) and the number of hours per week spent on physical activity, hours of sleep during the school period and during the weekend, number of daily meals, sugar-sweetened beverage intake frequency (every day, once a week, many times a week, very rarely, never), snack intake frequency (every day, once a week, many times a week, very rarely, never), improvement in eating habits (yes or no) between V0 and V1 defined in relation to change in consumption of snacks and sugary drinks reported by parents during the face-to-face interview at V1.

Clinical and Biochemical Evaluation

Clinical information was obtained from medical records. At V0 and V1, a physical evaluation was performed according to standardized procedures, including assessment of height, weight, BMI, BMI SDS, waist circumference (WC), WC-to-height ratio (WHtR), systolic and diastolic blood pressure (6). Weight loss was defined as a reduction in BMI SDS > 0.25 (7).

At V0, children of both groups underwent fasting biochemical assessments (oral glucose tolerance test (OGTT), lipid profile, thyroid, kidney and liver function tests, c-reactive protein), according to methodology previously described (8). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (mIU/L) × fasting glucose (mg/dL)/405 (9).

Statistical Analysis

Numerical data were expressed as mean and standard deviations score (SDS) and the categorical variables as absolute frequencies and percentages. The parametric approach was used since most numerical variables were not normally distributed, as verified by the Kolmogorov Smirnov test.

To compare group A and group B features, the Mann Whitney test was applied with reference to numerical parameters, and the Chi Square test with reference to categorical variables both at V0 and V1.

To perform intra-group comparison analysis between two time-points (V0 and V1), both in group A and group B separately, we applied the Wilcoxon test for numerical parameters and Mc Nemar's test for dichotomous variables. Multivariate logistic stepwise regression models were estimated to identify significant predictors of drop-out (model covariates: belonging to group A or B, obesity of mother and father, economic status, education level of parents, family structure, parents' employment, place of living, sex, and age, pubertal stage, BMI SDS at V0) and predictors of weight loss (model covariates: belonging to group A or B, obesity of mother and father, economic status, education level of parents, family structure, parents' employment, place of living, sex, age and pubertal stage at V0, and hours of sleep, sugar-sweetened beverage and snack intake frequency, screen time and practice and weekly hours of physical activity at V1). The results were expressed as Odds Ratio (OR), 95% confidence interval and p-value. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22 (Armonk, NY, IBM Corp.). A p-value < 0.05 was considered statistically significant.

RESULTS

One hundred and forty-five children and adolescents with obesity were evaluated, including 80 subjects in group A and 65 subjects in group B. Subjects of the two groups were matched for age, sex, pubertal stage, BMI and BMI SDS (**Table 1**). Thyroid, liver and kidney function tests were normal in the entire population. At V0, there were no significant differences between the two groups with regard to clinical and biochemical parameters (**Table 1**). Socio-cultural and lifestyle characteristics of the two groups at V0 and V1 are shown in **Table 2**. Subjects who continued outpatient follow-up, reevaluated at V1, were 43.8% for group A and 35.4% for group B. The drop-out rate did not differ significantly between the two groups (56.2% vs 64.6%; p=0.410). BMI SDS at V0, female sex, and the presence of a single parent in the household (incomplete) significantly influenced drop-out in both groups (**Table 3**).

Intra-group comparison analysis between the V0 and V1 evaluations documented a significant decrease in BMI SDS in group A (3.0 ± 0.57 vs 2.59 ± 0.7; p=0.008), while among group B patients BMI SDS did not change significantly (3.12 ± 1.07 vs

TABLE 1 | Comparison analysis between group A and group B on baseline clinical and biochemical parameters.

	Group A (n=80)	Group B (n=65)	p
Age (year)	11.6 ± 2.3	11.8 ± 2.7	0.738
Sex (male/female)	36/44	29/36	0.963
Pubertal/pre-pubertal	55/25	43/22	0.740
Height SDS	0.36 +/- 1.066	0.38 +/- 1.14	0.913
BMI (kg/m^2)	29.75 +/- 4.37	29.79 +/- 4.76	0.962
BMI SDS	3.00 +/- 0.57	3.12 +/- 1.07	0.455
WC (cm)	87.56 +/- 9.41	89.78 +/- 12.01	0.271
WHtR	0.89 +/- 0.07	0.89 +/- 0.08	0.924
SBP (mmHg)	114.80 +/- 11.84	116.26 +/- 12.43	0.510
DBP (mmHg)	71.31 +/- 10.66	71.16 +/- 10.94	0.940
Fasting glucose (mg/dl)	94.29 +/- 7.31	94.69 +/- 10.87	0.798
Fasting insulin (mIU/L)	23.49 +/- 16.78	20.85 +/- 10.60	0.250
HbA1c	5.44 +/- 0.38	5.41 +/- 0.41	0.061
2h-glucose (mg/dl)	123.76 +/- 20.64	122.32 +/- 29.46	0.742
2h-insulin (mIU/L)	127.07 +/- 100.22	104.68 +/- 60.95	0.100
HOMA-IR	5.52 +/- 4.02	4.91 +/- 2.63	0.407
Total cholesterol (mg/dl)	168.11 +/- 26.54	174.51 +/- 29.52	0.177
HDL cholesterol (mg/dl)	47.77 +/- 10.17	51.14 +/- 12.49	0.083
LDL cholesterol (mg/dl)	96.36 +/- 22.71	100.12 +/- 29.77	0.347
Triglycerides (mg/dl)	97.09 +/- 48.81	90.52 +/- 37.73	0.363
TSH (µUI/ml)	3.08 +/- 1.35	2.68 +/- 1.42	0.087
FT4 (ng/dl)	1.26 +/- 0.15	1.22 +/- 0.14	0.144
ALT (U/L)	24.59 +/- 28.58	23.34 +/- 15.70	0.739
AST (U/L)	26.56 +/- 31.15	21.00 +/- 6.89	0.124
GGT (U/L)	15.16 +/- 7.02	14.75 +/- 8.23	0.795
Uric acid (mg/dl)	4.92 +/- 1.25	5.05 +/- 1.16	0.516
CRP (mg/dl)	3.25 +/- 7.54	2.89 +/- 3.16	0.701

Subjects evaluated before the Covid-19 pandemic (Group A); subjects evaluated in the period straddling the Covid-19 pandemic (Group B), Body mass index (BMI), standard deviation score (SDS), waist circumference (WC), WC-to-height ratio (WHtR), systolic blood pressure (SBP), diastolic blood pressure (DBP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Gamma-Glutamyl Transferase (GGT), glycated haemoglobin (HbA1c), 120-minutes OGTT glucose levels (2h- glucose), 120-minutes OGTT insulin levels (2h-insulin), model assessment of insulin resistance (HOMA-IR), free thyroxine (FT4), thyroid stimulating hormone (TSH), c-reactive protein (CRP).

TABLE 2 | Comparison analysis between groups on baseline (2A) and 12-month (2B) anamnestic assessment.

2A

	Group A (n=80)	Group B (n=65)	p-value
Physical activity (yes/no)	50/30	40/25	0.608
Physical activity (hours)	2.22 +/- 2.35	1.69 +/- 1.36	0.091
Screen time (hours)	3.81 +/- 2.23	3.25 +/- 1.58	0.098
Number of meals	5.05 +/- 0.70	4.68 +/- 0.86	0.007
Sleep school (hours)	8.33 +/- 1.41	7.74 +/- 0.94	0.005
Sleep weekend (hours)	9.35 +/- 1.42	8.60 +/- 1.09	0.001
Age of obesity onset (years)	5.67 +/- 2.65	6.27 +/- 2.88	0.214
Obesity of mother (yes/no)	42/38	35/30	0.774
Obesity of father (yes/no)	39/41	27/38	0.096
Family economic status (Low/moderate-high)	32/48	26/39	0.738
Household composition (complete/incomplete)	63/17	62/3	0.004
Employment of mother (yes/no)	35/45	25/40	0.410
Employment of father (yes/no)	63/17	50/15	0.291
Place of living (town/village)	39/41	29/36	0.620
Mother's education (school years)	11.22 +/- 3.37	9.90 +/-2.96	0.019
Father's education (school years)	11.22 +/- 3.64	10.21+/- 3.10	0.091

2B

	Group A (n=35)	Group B (n=24)	p-value
Physical activity (yes/no)	20/15	2/22	0.001
Physical activity (hours)	1.82 +/- 1.54	0.46 +/- 1.06	0.011
Screen time (hours)	2.76 +/- 1.53	5.45 +/- 2.11	0.000
Number of meals	4.97 +/- 0.17	4.81 +/- 1.12	0.519
Sleep school (hours)	8.45 +/- 0.95	7.50 +/- 1.05	0.002
Sleep weekend (hours)	9.40 +/- 1.31	8.35 +/- 1.18	0.004

Subjects evaluated before the Covid-19 pandemic (Group A); subjects followed in the period straddling the Covid-19 pandemic (Group B).

2.97 ± 1.19; p=0.454) and BMI in absolute value increased significantly (29.79 ± 4.76 vs 30.98 ± 4.82; p=0.003). Moreover, comparison analysis between the groups documented a significantly higher BMI SDS among group B patients compared with those belonging to group A at V1 (30.98 ± 4.82 vs 28.51 ± 4.13; p=0.041). Consistently, weight loss was significantly greater among group A patients compared to group B at V1 (67.6% vs 32.4%; p=0.031).

Hours spent in physical activity decreased significantly in group B from V0 to V1 (1.69 ± 1.36 vs 0.46 ± 1.06; p= 0.001), whereas it did not change significantly between the two assessments in group A (2.22 ± 2.35 vs 1.82 ± 1.54; p= 0.068). Moreover, hours spent in physical activity, which were not significantly different between the two groups at V0 (**Table 2A**), were significantly greater among group A subjects compared to subjects of group B at V1 (**Table 2B**). In addition, the number of subjects who had engaged in regular physical activity between V0 and V1 was significantly higher in group A than group B (**Table 2B**).

Screen time decreased significantly in group A from V0 to V1 (3.81 ± 2.23 hours vs 2.76 ± 1.53; p=0.000), whereas it increased significantly in group B between the two assessments (3.25 ± 1.58 vs 5.45 ± 2.11 hours; p=0.002). Moreover, screen time, which was not significantly different between the two groups at V0 (**Table 2A**), was significantly greater among patients in group B at V1 evaluation (**Table 2B**).

Improvement in eating habits between V0 and V1 was greater in group A than in group B (86% vs 35%, p=0.000). Consistently, the intragroup comparison analysis showed a significant reduction in snack and sugary drink intake between V0 and V1 in group A, whereas no significant difference was documented in group B

TABLE 3 | Stepwise logistic regression analysis for drop-out and weight loss outcomes.

Predictors	OR	95%CI	*p*
DROP-OUT			
Sex (Female)	0.41	0.18 - 0.94	0.035
Household composition (incomplete)	5.74	1.15 - 28.58	0.033
BMI SDS (V0)	2.52	1.35 - 4.70	0.004
WEIGHT LOSS			
Group (A)	0.16	0.32 - 0.82	0.028
Weekly hours of physical activity (V1)	2.27	1.05 – 4.96	0.038

Odds ratio (OR), 95% confidence interval (95%CI), baseline assessment (V0), 12-month assessment (V1) subjects evaluated before the Covid-19 pandemic (Group A).

TABLE 4 | Intragroup comparison analysis concerning snack (4A) and sugar-sweetened beverage intake (4B) between baseline (V0) and 12-month evaluation (V1).

4A

	Group A			Group B		
INTAKE FREQUENCY	V0 (N=80)	V1 (N=35)	p	V0 (N=65)	V1 (N=23)	p
Never	3.8%	25.7%	0.000	9.3%	21.7%	0.125
Every day	27.5%	8.6%	0.024	44.6%	26.1%	0.121
Once a week	28.8%	2.9%	0.002	13.8%	17.4%	0.677
Many times a week	21.2%	11.4%	0.212	18.5%	30.4%	0.236
Very rarely	18.8%	51.4%	0.000	13.8%	4.4%	0.224

4B

	Group A			Group B		
INTAKE FREQUENCY	V0 (N=80)	V1 (N=35)	p	V0 (N=65)	V1 (N=23)	p
Never	7.5%	34.3%	0.000	15.4%	17.4%	0.822
Every day	25%	5.7%	0.016	27.7%	26.8%	0.934
Once a week	22.5%	2.9%	0.009	18.4%	4.3%	0.102
Many times a week	11.2%	8.6%	0.675	18.4%	34.3%	0.119
Very rarely	33.8%	48.6%	0.135	20%	17.4%	0.787

Chi-square test was applied.
Subjects evaluated before the Covid-19 pandemic (Group A); subjects followed in the period straddling the Covid-19 pandemic (Group B).

(**Table 4**). Moreover, comparison analysis between the groups documented a significantly more frequent consumption of sugary drinks and snacks in group B compared to group A at V1 (**Table 5**).

Hours spent in physical activity (OR=2.27, p=0.038) and belonging to group A (OR=0.16, p=0.028) were the only factors influencing weight loss (**Table 3**).

DISCUSSION

The Covid-19 pandemic is causing significant health, social, and economic implications that have drastically modified social life. These include the interruption of regular school attendance and extracurricular activities for children and adolescents, which has led to an increase in sedentary behaviors and unhealthy eating habits, especially during the lockdown period. The pandemic has promoted a sedentary lifestyle and high consumption of fast food and sugar-sweetened beverages (10). Moreover, Xiang et al. documented a drastic decrease in median time spent in physical activity, showing a 435 min/week reduction on average, and a significant increase in screen time during the Covid-19 pandemic (11). Unhealthy diet, excessive screen time, insufficient time spent on physical activity and nightly rest are known behavioral risk factors for the onset or worsening of obesity (12).

TABLE 5 | Between-group comparison analysis regarding sugar-sweetened beverage (5A) and snack (5B) intake between baseline (V0) and 12-month evaluation (V1).

5A

	V0			V1		
INTAKE FREQUENCY	Group A (N=80)	Group B (N=65)	p	Group A (N=35)	Group B (n=23)	p
Never	7.5%	15.4%	0.132	34.3%	17.3%	0.160
Every day	25%	27.7%	0.714	5.7%	26.8%	0.025
Once a week	22.5%	18.4%	0.545	2.9%	4.3%	0.771
Many times a week	11.2%	18.4%	0.221	8.6%	34.3%	0.015
Very rarely	33.8%	20.0%	0.065	48.6%	17.4%	0.017

5B

	V0			V1		
INTAKE FREQUENCY	Group A (N=80)	Group B (N=65)	p	Group A (N=35)	Group B (n=23)	p
Never	3.8%	9.3%	0.176	25.7%	21.7%	0.729
Every day	27.5%	44.6%	0.033	8.6%	26.1%	0.074
Once a week	28.8%	13.8%	0.031	2.9%	17.4%	0.057
Many times a week	21.2%	18.5%	0.687	11.4%	30.4%	0.073
Very rarely	18.8%	13.8%	0.422	51.4%	4.3%	0.000

Chi-square test was applied.
Subjects evaluated before the Covid-19 pandemic (Group A); subjects followed in the period straddling the Covid-19 pandemic (Group B).

Our study documented that the Covid-19 pandemic negatively influenced the lifestyle of children and adolescents with obesity in outpatient follow-up, promoting a worsening severity of overweight. In our study, although there was no increased drop-out rate during the pandemic period, a significant reduction in time spent on physical activity and a significant increase in screen time and junk food consumption was documented after one year of follow-up among patients followed during the pandemic period compared to those in follow-up before the Covid-19 pandemic.

With a telephone interview conducted three weeks after the beginning of lockdown in Italy, Pietrobelli et al. assessed the implications of "staying home" on food intake and daily habits in children followed at their clinics, to document whether indeed young people with obesity show unfavorable trends in lifestyle behaviors when away from structured school activities and confined to their homes. Specifically, the authors documented a significant increase in the number of meals consumed per day and an increased intake of crisps, red meat, and sugary drinks as reported by parents during the telephone interview. In addition, sleep and screen time had increased significantly, while sports time had decreased significantly (1).

Similarly, in another study based on data from a questionnaire completed online by parents, Pujia et al. reported a significant increase in consumption of "comfort food", including packaged sweet snacks, chocolate, ice cream, dessert, but also processed meat, bread, pizza, and bakery products, in 439 Italian children and adolescents. Among these subjects, approximately 60% reported an increase in body weight, which was significantly greater in adolescents than in children (13). Consistently, Appelhans et al. demonstrated a significant weight gain among low-income, racial minority, obese children followed during the Covid-19 period compared to those followed in the pre-pandemic period at 12-month assessment (14).

These findings support the thesis that the Covid-19 pandemic exacerbated the risk factors for the so-called "summer break-associated weight gain" due to school closures, which, in this case, was imposed during the lockdown (15). Previous studies highlighted that weight control programs are less effective among youth while they are at home than when they are engaged at school. A study by von Hippel et al. analyzed the effects of school versus non-school environments on overweight in childhood, demonstrating that BMI gain was faster during summer vacations compared to the in-session school year (16). This finding may be due to the opportunity provided by school environments for structure and routines for mealtimes, physical activity, and sleep schedule, the three predominant factors that, if altered, may increase the risk of obesity (17).

Worldwide, a significant reduction in daily physical activity has been demonstrated since the pandemic onset (18). Moreover, besides contributing to weight gain, the drastic reduction in physical activity during the pandemic and the concomitant overuse of electronic devices contributed to a significant increase in diagnoses of sleep disorders and psychiatric disorders, such as anxiety and depression, among children and adolescents (19, 20).

We documented that physical activity was the main factor influencing weight status and that the Covid-19 pandemic resulted in a significant reduction in time spent on physical activity among children with obesity. Performing physical activity, even at home, plays a crucial role in containing the increase of childhood obesity. Children and adolescents should perform 1 hour of daily physical activity of moderate to vigorous intensity to promote and maintain good health and weight in the normal range; in addition, activities to strengthen the musculoskeletal system should be included at least 3 times per week. In our study, patients followed at the outpatient clinic in the pandemic period had performed significantly fewer hours of physical activity than patients followed in the pre-pandemic period at the annual follow-up. In this pandemic period, physical activity at home has to be promoted, using the same electronic devices that are often the cause of sedentariness, with online physical activity classes, exercise apps on mobile devices, or video games that have a physical activity component.

With regard to the effects of the Covid-19 pandemic on the social life of children and adolescents, it should be considered that, besides the period of strict lockdown, the resumption of school and extracurricular activities has been gradual, and to date in many cases have not returned to pre-pandemic levels. Due to the persistence of the Covid-19 pandemic and related restrictions, school closures and even restrictions on social activities for children and adolescents have frequently reoccurred over the last two years, promoting an unhealthy lifestyle. Moreover, a regular outpatient follow-up of children and adolescents with obesity, which often requires closely-timed visits to be effective, has been made difficult by the above-mentioned restrictions. Elbarbary et al., in an International Cross-Sectional Electronic Survey distributed to the global network of endocrine societies, estimated a 41.5% delay in obesity diagnosis and a perceived worsening in obesity management in 83% of cases due to the COVID-19 pandemic (21). Our study showed that, although outpatient follow-up would not appear to have been compromised, its efficacy was lower in obese patients followed during the pandemic period compared with those followed in the pre-pandemic period, due to the increase of an unhealthy lifestyle characterized by a significant reduction in physical activity and increased time spent watching TV, playing video games and using electronic devices, and by an increased consumption of junk food. Continuity of care is a key aspect in the treatment of obesity, so discontinuation or limitation of outpatient follow-up and of activities that promote movement due to pandemic restrictions has negatively affected care in childhood obesity. In this context, telemedicine, if properly regulated, could be an effective solution to continue the follow-up of obese patients, relying on a chronic model of care. This option will need to be considered if restrictions are to continue, having the potential to play a key role in long-term multidisciplinary management of childhood obesity (22, 23). The results of our study may not fully reflect the weight status of individuals who are not similarly followed by professional medical care providers, since only patients who attended our pediatric endocrinology clinic before and during the pandemic were included in the study. Therefore, the study results should be considered in light of this possible limitation. The major strengths of this study consist in the study design, carried out by comparing two homogeneous groups assessed before and during the pandemic, and in the sourcing of data from in-person evaluation.

CONCLUSIONS

Our study documented that the Covid-19 pandemic, although not affecting the drop-out rate of obese children, negatively influenced lifestyle, causing a decrease of time spent in physical activity and a significant worsening of eating habits, ultimately reducing the effectiveness of outpatient counseling. The persistent restriction of school and extracurricular activities due to the Covid-19 pandemic is likely to worsen obesity and to further reduce the effectiveness of the outpatient approach to treating childhood obesity. Continuity of care is crucial for successful treatment of childhood obesity. Strategies to manage unhealthy weight gain are urgently needed in the context of Covid-19. With this in mind, institutions and parents should recognize this growing problem by promoting physical activity and healthy eating at school and in extracurricular settings, by supporting telemedicine when necessary, and by encouraging anti-Sars-Cov-2 vaccination in children and adolescents.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study with human participants in accordance with local legislation and institutional requirements for retrospective studies, but notification was sent to the Local Ethics Committee regarding the retrospective evaluation of the data. Written informed consent from the participants' legal guardian was not required for retrospective study in accordance with national legislation and institutional requirements. The study was conducted according to the guidelines of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

DC and MW contributed to conception and design of the study. AL, AT, AG, SC performed literature research. DC, TA, GP, SC, AL organized the database and prepared the tables. AA performed statistical analysis. DC, AL and MW wrote the first draft of the manuscript. DC and MW wrote the final version of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Current evidence on the impact of the COVID-19 pandemic on paediatric endocrine conditions

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Severe acute respiratory coronavirus 2 (SARS-CoV-2) interacts with the host cells through its spike protein by binding to the membrane enzyme angiotensin-converting enzyme 2 (ACE2) and it can have a direct effect on endocrine function as ACE2 is expressed in many glands and organs with endocrine function. Furthermore, several endocrine conditions have features that might increase the risk of SARS-CoV-2 infection and the severity and course of the infection, as obesity for the underlying chronic increased inflammatory status and metabolic derangement, and for the possible changes in thyroid function. Vitamin D has immunomodulatory effects, and its deficiency has negative effects. Adrenal insufficiency and excess glucocorticoids affect immune conditions also besides metabolism. This review aims to analyze the rationale for the fear of direct effects of SARS-Cov-2 on endocrinological disorders, to study the influence of pre-existing endocrine disorders on the course of the infection, and the actual data in childhood. Currently, data concerning endocrine function during the pandemic are scarce in childhood and for many aspects definite conclusions cannot be drawn, however, data on properly managed patients with adrenal insufficiency at present are re-assuring. Too little attention has been paid to thyroid function and further studies may be helpful. The available data support a need for adequate vitamin D supplementation, caution in obese patients, monitoring of thyroid function in hospitalized patients, and confirm the need for an awareness campaign for the increased frequency of precocious puberty, rapidly progressive puberty and precocious menarche. The changes in lifestyle, the increased incidence of overweight and the change in the timing of puberty lead also to hypothesize that there might be an increase in ovarian dysfunction, as for example polycystic ovarian disease, and metabolic derangements in the next years, and in the future we might be facing fertility problems. This prompts to be cautious and maintain further surveillance.

KEYWORDS

lockdown, thyroid, vitamin D, obesity, precocious puberty, hyponatraemia, COVID-19, endocrinology

Introduction

Since December 2019 the world has been facing one of the most challenging health issues of the last centuries. Starting from Wuhan, in the Hubei province in China, a new unknown pathogen later identified as the severe acute respiratory coronavirus 2 (SARS-CoV-2) began to spread, causing an outbreak of severe atypical pneumonia (1).

In early January 2020 the causative virus of this new emerging illness was isolated and identified by the Chinese Center for Disease Control: the 2019 novel coronavirus was a positive-sense, single-stranded, enveloped RNA virus that belongs to β-coronavirus group, subfamily *Orthocoronavirinae* (family Coronaviridae) (2). Two other human β-coronaviruses have been responsible in recent years for severe lung infections: the severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV) coronavirus. Nevertheless, most coronaviruses known to date, such as Human coronaviruses 229E, NL63, OC43, and HKU1 are common agents of mild upper respiratory tract infections that mainly affect young children (3).

Despite COVID-19 infection tends to have a milder clinical course in the pediatric population with much less pulmonary disease and fewer deaths compared to adults, in some cases systemic involvement due to an abnormal hyperinflammatory response can be observed (4).

According to the WHO by October 2021 the incidence of COVID-19 infection in children under five years of age accounted for 2% of reported global cases, 7% between 5 to 14 years and 15% in adolescents and young adults (15 to 24 years) with a much lower mortality rate than in adults being the percentage of total deaths less than 0,5% of reported global deaths for subjects below the age of 25 years (5).

These data, however, have changed in recent months. In Italy, a significant increase of COVID-19 infection rate in the population 5-11 years with respect to other school-age children has been reported since October 2021, then followed by an overall increased incidence of the disease in older children and adolescents reported in the last weeks. Moreover, it is worth noting that the hospitalization rate in children under five years of age has strongly risen (> 10 hospitalizations per 1,000,000 inhabitants) with a less significant increase in the 16-19 age group in the last period (6). This must be kept in mind when considering the actual evidence in childhood as one must be aware that we still lack a complete figure of the effects of COVID-19 in the pediatric population, despite the recent increase of infection rates in this group. Moreover, given the higher mortality rate and overall worst outcome in adults suffering from chronic diseases, the question regarding a possible greater vulnerability in high-risk pediatric groups, such as children with underlying medical conditions, has arisen over time.

However, currently, strong evidence between specific chronic conditions and severe COVID-19 illness in children is limited, although it is well known that several medical conditions are known to be able to increase SARS-CoV-2 infection severity, such as inherited or acquired immunodeficiencies, immunosuppression, cancer, neurologic, endocrine and metabolic conditions. More generally, patients with multimorbidity affected by genetic diseases (i.e. Down syndrome), cardio-vascular diseases or other chronic conditions (i.e. asthma or chronic pulmonary disease) show an increased vulnerability to COVID-19 infection (7).

SARS-CoV-2 interacts with the host cells through its spike protein by binding to the membrane enzyme angiotensin-converting enzyme 2 (ACE2), an homolog of ACE, which represents the main viral receptor. The entry of SARS-CoV-2 in the host cell through ACE2 activates the STAT3/NF-kB pathway leading to the production of proinflammatory cytokines and chemokines that can cause a severe systemic hyperinflammation known as “cytokine storm”, responsible for acute respiratory distress syndrome (ARDS) and multi-organ failure (8).

Although SARS-CoV-2 mainly affects the upper and lower respiratory tract with symptoms ranging from flu-like symptoms to atypical pneumonia, ACE2 expression is not exclusive to the lungs and it may also involve the gastrointestinal tract, the kidneys, the cardio-vascular system and the brain, thus justifying the multi-organ involvement that is commonly observed in COVID-19 disease (9).

Several endocrine tissues also exhibit ACE2, such as thyroid, the ovaries and the testis (the latter in particular with high levels of expression), for which the function of several glands may be affected by SARS-CoV-2 infection (Figure 1) (10, 11).

In addition, the treatment of endocrine diseases could be indirectly affected by difficulties arisen because of the pandemic. The scientific societies across the globe having endocrinology as a focus have provided recommendations since the beginning of the pandemic. The European Society for Pediatric Endocrinology (ESPE) highlighted that there was no evidence at that time that children affected by hypopituitarism (GHD, central hypothyroidism, diabetes insipidus, hypogonadotrophic hypogonadism or any combination of the aforementioned diseases) presented a higher risk of contracting the infection or experiencing a severe disease course (12). However, patients affected by hypopituitarism and secondary adrenal insufficiency potentially had a higher risk of undergoing an adrenal crisis during the SARS-COV2 infection as for any other infection (13).

Recommendations to continue current replacement therapy and to modify hydrocortisone replacement doses as indicated for all cases of intercurrent illness, doubling or tripling the dosage according to the severity of the clinical picture and conditions, also considering admission and parental hydrocortisone administration when necessary have been published by many

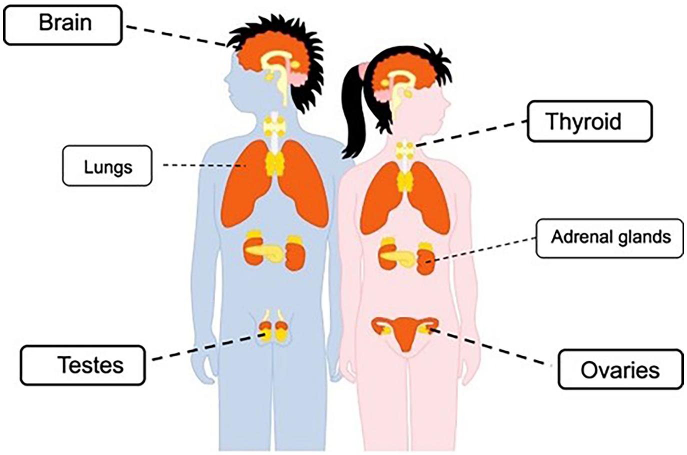

FIGURE 1
Representation of ACE2 expression in endocrine tissues.

scientific societies (14–16). Moreover, it was underlined to keep closely in touch with the reference centers (17).

This review aims to analyze the rationale for the fear of direct effects of SARS-Cov-2 on endocrinological disorders, to study the influence of pre-existing endocrine disorders on the course of the infection, and the actual data in childhood.

Dysnatraemia, diabetes insipidus and pituitary function

SARS-COV 2 virus can access the central nervous system rapidly through the olfactory nerve (18), causing potential damage to hypothalamus and pituitary regions.

Previous studies that examined prevalence and outcomes of dysnatraemia in patients hospitalized with COVID-19 described a higher prevalence of hyponatremia than hypernatremia, but both these conditions were associated with an increased hospital length of stay, while the risk of in-hospital mortality was increased in patients with moderate or severe hypernatremia (19, 20).

Adequate treatment of hyponatremia requires immediate recognition of its etiology: blood tests are required to evaluate serum and urinary osmolality, serum concentrations of sodium, glucose, urea, creatinine, urate, cortisol, thyroxine and TSH (20).

One of the causes of hyponatremia highlighted by observational studies on adults with SARS-COV2 infection was posterior pituitary dysfunction, presenting mainly as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (21). In two adult patients described in the Literature, having severe COVID-19 and SIADH, the MRI scans showed T2/FLAIR hyperintensity of mammillary bodies, hypothalamus- pituitary swelling and upper globular hypophysis pedunculus (22). To the best of our knowledge, to date there still are no reports in children, however, considering the high incidence of gastroenterologic symptoms during SARS-COV2 infection in children (23) a concern for an increased risk of hypernatremia in patients affected by diabetes insipidus yet remains.

Diabetes insipidus (DI) is a rare disease characterized by polyuria (urine volume greater than 100–110 mL/kg/24 h until the age of 2 and 2000 mL/mq/24 h after the age of 2) caused by vasopressin secretion deficiency (central DI) or AVP resistance (nephrogenic DI) (24). Hyponatraemia (plasma sodium < 135 mmoL/L) is the major complication of chronic therapy with desmopressin; to prevent this condition electrolyte checks are recommended, but during the pandemic, considering the possibility of limited access to blood testing, expert recommendation was to avoid excessive water intake and delaying a dose of desmopressin until aquaresis occurs. While in patients known to have recurrent hyponatremia, one dose each week can be avoided, although greater polyuria may occur (25).

Patients with DI who develop respiratory complications of COVID-19 are at significantly increased risk of hypernatremic dehydration. However, experts agree to accept mild hypernatremia (<155 mmoL/L) rather than increase the risk of pulmonary oedema if it is corrected (25).. Hypernatremia and the related hyperosmolar state can cause physiologic alterations that are responsible for increased mortality. DI is associated also with a hypercoagulable state and low molecular weight heparin therapy is recommended in these cases, until eunatraemia is restored, as well as in patients with a hypercoagulable state during COVID 19 (26).

At present data in childhood in relationship with the pandemic are lacking but the same recommendations described in the guidelines published by the Society of Endocrinology in 2018 are valid for patients with DI with COVID-19 (27).

Tumors of the hypothalamus and pituitary region

There are no data in the literature indicating that patients with pituitary and hypothalamic tumors

are more susceptible to infection with SARS-COV2. The only exception seems to concern corticotropic adenomas in patients with uncontrolled Cushing's disease. These patients indeed show an increased risk of developing infections with subsequent increased risk of mortality (28, 29).

There are no reports of an increased severity of COVID-19 in patients with pituitary secreting adenomas or non-functioning adenomas that do not require steroid replacement therapy. However, it should be noted that risk factors may coexist in patients with pituitary tumors, which could adversely affect the course and the management of SARS-COV2 infections (30).

Another important factor to take into account is the possible diagnostic delay of tumors that may occur in the pandemic era because of the difficulty accessing primary care, necessary instrumentation and laboratory tests (31). This may stem both from the internal arrangements of hospitals which are committed to fighting the pandemic and providing attention and resources to critically infected patients, and from the patients own fear of exposing themselves to the risk of infection, with potentially serious consequences (32).

Fleseriu et al. summarized some diagnostic and management issues encountered during the pandemic, inherent to the diagnostic and therapeutic process of patients with pituitary tumors (33). These authors provided practical guidance to make the management of these patients as effective as possible in the era of COVID-19. In the case of patients in follow-up, routine care has generally been routinely provided worldwide through telemedicine avoiding face-to-face contact. Telemedicine has in fact greatly developed during the pandemic, it has enabled doctors to provide care to their patients, improving the management of chronic diseases (34). Outpatient visits could be postponed in most cases by 3-6 months, providing patients and caregivers with essential information to detect warning signs deserving immediate medical attention and clinical evaluation. It was suggested that laboratory investigations, if deemed relevant to clinical decisions, should be performed in laboratories close to home (or exceptionally performed at home in case of high-risk patients) and transferred to the specialist center (33). In Italy, to our knowledge this has happened in most parts of the country.

It was highlighted that patients with Cushing disease deriving from an adenoma or having comorbidities such as diabetes, hypertension and obesity should be reminded of their increased risk of severe infection (35–37).

In the case of newly diagnosed patients, it is necessary to collect a detailed history and perform an evaluation through a virtual or in-person visit, to identify any comorbidities and assess the timing within which to submit the patient to laboratory tests. In the case of pituitary tumors causing severe visual impairment, surgery should be the first therapeutic choice (38). As happened, testing the patients for SARS-Cov-2 infection before surgery is essential, especially in case of trans-sphenoidal surgery (considered a procedure with high risk of infection for which surgical antimicrobial prophylaxis is recommended) (39). If the test is positive, it would be recommended to postpone the surgery until the infectious picture is resolved. If this is not possible the operating team must carefully wear safety equipment (40).

These recommendations, including the use of telemedicine, have currently become routine practice.

Thyroid gland

The possible involvement of the thyroid gland in patients with COVID-19 infection has been widely investigated since the beginning of the pandemic, given the demonstrated ability of SARS-CoV-2 to attack thyroid follicular cells *via* ACE2 that is highly expressed in this tissue (10). Along with the direct mechanism of invasion of the thyroid tissue, indirect mechanisms represent another hypothesis of damage. In fact, acute hypothalamus/pituitary/thyroid axis dysfunction and abnormal activation of inflammatory factors and cytokines due to severe ongoing COVID-19 infection may be responsible for both acute dysthyroidism and the immune-mediated damage (Figure 2) (41).

A recent systematic review analyzed 27 documented and reported cases of subacute thyroiditis (17 case reports and 2 case series) likely related to SARS-CoV-2 infection. All reported patients were adults, the majority being women, with a median time of onset of the thyroid dysfunction 30 days after SARS-CoV-2 detection on swabs. Clinically, they showed typical symptoms of subacute thyroiditis (i.e. fever, fatigue, neck pain, palpitations) in association with thyrotoxicosis and elevated inflammatory markers in serum and ultrasonographic signs of thyroiditis. Interestingly, most patients were affected by mild to moderate COVID-19 disease with only three patients requiring hospitalization during the course of the infection. According to international guidelines for the treatment of subacute thyroiditis most patients were given corticosteroids with a progressive normalization of thyroid function and subsequent return to a euthyroid state. However, considering the large spread of the virus worldwide and the relatively lack of published data, at the

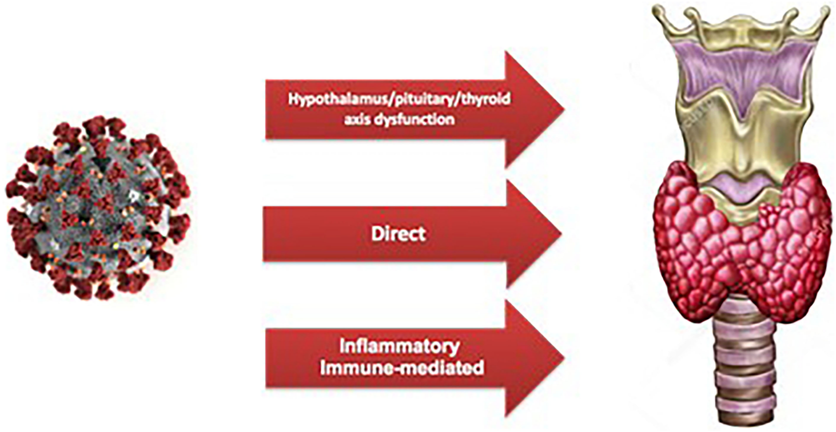

FIGURE 2
Representation of mechanisms of damage of SARS-CoV-2 to the thyroid gland.

moment it is only possible to consider that subacute thyroiditis represents a rare complication of SARS-CoV-2 infection with a clinical course that is similar to the one that is commonly observed when subacute thyroiditis is supposed to be triggered by other infections (42).

Conversely, other forms of thyroid dysfunction have been frequently reported in patients with severe COVID-19 disease, such as euthyroid sick syndrome or non-thyroidal illness syndrome (decreased fT3 but normal TSH levels) but also hypo- and hyperthyroidism as exacerbations of pre-existing disorders or *de-novo* diagnosis (43). Laboratory findings of low fT3 levels have been frequently observed in critical patients as a consequence of the abnormal hyperinflammatory state, representing an independent risk factor for COVID-19 severity. Therefore, considering the possible involvement of the thyroid during the course of COVID-19 infection and the heterogeneity of manifestations, routine assessment of thyroid function in those patients may be useful to detect thyroid abnormalities and start adequate treatment, thus improving the overall outcome (44, 45). It is important to point out, however, that all studies mentioned above concern adult patients and to date no reports regarding the association between COVID-19 and thyroid abnormalities in children are available.

On the other hand, well-managed thyroid disease does not appear to increase the risk of getting infected or develop severe COVID-19 illness both in children and adults, whereby international societies do not suggest a different management of children with pre-existing thyroid disease compared to healthy peers (46). Neither a pre-existing severe thyroid hormone deficiency (congenital hypothyroidism) if properly treated nor autoimmune diseases (Hashimoto's thyroiditis or Graves' disease) are associated with a weakened immune response or greater susceptibility to bacterial or viral infections. Anyhow, at the moment there is no evidence of an increased risk even in the case of poorly controlled thyroid dysfunction and no extra investigations are required, except for patients with thyrotoxicosis that may be at greater risk of complications because of the possible worsening of the thyroid storm in case of infection (47).

Parents of children who are being treated with antithyroid drugs such as methimazole should be advised about the possible bone marrow toxicity of these molecules: the onset of nonspecific symptoms such as fever, sore throat and cough may be the indicator of severe infection due to agranulocytosis that may present with a strong clinical overlap with COVID-19 infection, thus the necessity of prompt medical evaluation. Neither antithyroid drugs nor L-thyroxine are immunosuppressive agents and children who are administered with these medications do not present an increased risk of getting infected with SARS-CoV-2 (46).

However, the relative lower spread of SARS-CoV-2 infection among children may partially explain the current lack of significant correlation between COVID-19 disease and thyroid dysfunction in the pediatric population, with the need of further studies that may confirm the available recommendations.

Adrenal insufficiency and hypercortisolism

Patients having primary adrenal insufficiency (i.e. CAH and Addison's disease) are known to have a greater risk of life-threatening complications in case of infection because of the acute increased demand of glucocorticoids that may lead to adrenal crisis (48). Moreover, it has been demonstrated that adrenal failure makes these patients even more susceptible to common infections in general due to an impaired neutrophil and natural killer cell immune activity: this phenomenon could be explained by the altered circadian gene pattern expression of peripheral immune cells due the non-physiological delivery of glucocorticoids with the conventional replacement therapy (49). Different studies have indeed demonstrated that the use of daily modified-release preparations that mimic the physiological secretion of glucocorticoids helps restore an effective immune cell activity, thus improving hypoadrenal patients' response to infections (50, 51). On the other hand, the replacement therapy itself, in consideration of the possible supraphysiologic doses of glucocorticoids chronically administered, may contribute to explain the increased risk of infections in patients affected by adrenal insufficiency.

Therefore, although at the moment there is no clear evidence of increased risks for COVID-19 infection in patients with primary adrenal insufficiency, all the reported data suggest the need for a careful management with close monitoring of these patients in case they get infected with SARS-CoV-2 because of their intrinsic condition of greater vulnerability to infections (52).

Therefore, as specified above, it has been repeatedly reminded that children presenting primary or secondary adrenal insufficiency should be treated following the general "sick day rule": in case of mild to moderate infection (fever >38° C, bad cold or flu symptoms, diarrhea) their usual daily hydrocortisone dose should be immediately doubled or tripled if the fever is >39°C along with substantial oral hydration. In the case of a severe course of the infection or vomiting and subsequent inability of taking medications by mouth, urgent medical evaluation is mandatory in order to initiate parenteral administration of glucocorticoids and avoid a potentially life-threatening adrenal crisis. Conversely, asymptomatic patients should continue their daily replacement therapy without increasing the dosage (53). Moreover, the children who are being treated chronically with corticosteroids may develop tertiary adrenal insufficiency with a higher risk of getting infected by SARS-CoV-2 because of the subsequent iatrogenic immune impairment. Even though the level of suppression of the hypothalamus-pituitary-adrenal axis depends on the patient's innate sensitivity and cannot be predicted, these patients must be considered to be at increased risk of a severe course of COVID-19 disease (16).

In line with these considerations, hypercortisolism due to an endogenous abnormal secretion (Cushing syndrome) may also increase the subject's susceptibility to SARS-CoV-2 infection as a consequence of the immunosuppressive effect (54).

A few studies have analyzed both in Cushing syndrome and in different conditions characterized by adrenal insufficiency, the rate of infection and the course of COVID-19. In adults, during the first months in 2020 in Lombardy region in Italy, it has been shown that patients with active hypercortisolism were more prone to develop COVID-19 disease with a more severe clinical course with respect to the general population, thus identifying those affected by Cushing disease as a fragile population (55). In fact, it is worth considering that chronic cortisol excess leads to multiple comorbidities such as hypertension, hyperglycemia and obesity with an increase in visceral fat that have been widely associated with a greater risk of developing severe COVID-19.

Conversely, another observational case-control study also conducted during the early stages of the pandemic in Lombardy involving adult patients affected by adrenal insufficiency showed no significant differences in the incidence of SARS-CoV-2 infection, mortality rate, disease course and severity between patients having adrenal insufficiency and controls. However, all patients were on active follow-up and had been previously instructed on the possible risks and correct management of the infection (56).

At present few evidence is available because of the rarity of glucocorticoid-related diseases and pediatric scientific societies are currently collecting data, and at variance with the initial hypothesis with what had been initially hypothesized in relationship with adrenal insufficiency, possibly due to proper management, there does not seem to be an increased incidence of COVID-19 in these patients nor severe courses have been reported (14, 57).

One must also keep in mind that the initial phases of the pandemic have concerned few children and adolescents and currently the rate of vaccination is also increasing.

Vitamin D deficiency, disorders of calcium homeostasis and parathyroid glands

Vitamin D has an undoubted role in the regulation of the immune system and deficient states have already been associated with an increased risk of developing upper respiratory tract infections and higher mortality rates in critically ill children (58, 59).

Indeed, most cells of the innate and adaptive immune system exhibit vitamin D receptors with the subsequent on-site production of 1,25$(OH)_2$ vitamin D (the most active metabolite) that acts in an autocrine and paracrine way having immunomodulatory effects. Moreover, vitamin D receptors are also involved in the regulation of inflammatory cellular pathways, and their stimulation inhibits pro-inflammatory and pro-fibrotic response to tissue injury (60).

Based on this evidence, the potential role of vitamin D deficiency in COVID-19 patients' outcome has been investigated since the beginning of the pandemic. Several randomized controlled trials in adults have actually confirmed the positive association between adequate vitamin D serum concentrations and a lower risk of getting infected by SARS-CoV-2 and developing severe complications (61). Moreover, important research studies that have collected and analyzed data coming from several countries have actually confirmed the positive correlation between vitamin D deficiency and COVID-19 infection and mortality rates in Asian countries, while in the European continent this correlation turned out to be significant only for COVID-19 related deaths with no impact on the total number of SARS-CoV-2 infections (62).

With regard to the pediatric population, only few studies are currently available concerning the effects of vitamin D deficiency on COVID-19 disease. A retrospective cohort study performed on hospitalized patients aged 0-18 years showed a significant relationship between low serum vitamin D concentrations, severe disease and elevated inflammatory markers: in particular, vitamin D levels were positively correlated with white cell blood count and negatively with C-reactive protein and fibrinogen levels (63, 64). However, the actual impact of vitamin D deficiency on COVID-19 infection is still under debate and further investigations are yet needed to clarify this matter. Meanwhile, considering vitamin D multiple skeletal and extraskeletal beneficial actions in association with its immunomodulatory effects, prophylactic vitamin D supplementation is highly recommended in the pediatric population as an easily modifiable risk factor that may protect from SARS-CoV-2 major complications (65).

Since several studies conducted in the pre-COVID era have demonstrated that vitamin D supplementation of deficient populations may help prevent infections, the prompt correction of hypovitaminosis with therapeutic dosages has become now mandatory and seems useful also in hospitalized patients with severe COVID-19 (66, 67).

Calcium is recognized to play an important role in viral infections, and hypocalcemia has been reported in many cases of adult patients with covid-19 and requiring admission to hospital (68, 69), and has been related also with a higher mortality risk (70). Although vitamin D deficiency is one of the main causes of hypocalcaemia, inappropriate levels of parathyroid hormone (PTH) are a contributing factor (71). Although there are no reports in childhood, recently two case reports evidence that SARS-CoV-2 infection can cause primary hypoparathyroidism and decompensate previous primary hypoparathyroidism independent of vitamin D levels (72, 73).

Obesity

Obese people experience functional impairment and a major tendency to comorbidities, resulting in a greater susceptibility to infection from SARS-CoV-2 and a more severe course of COVID 19, with higher risk of developing a critical situation (74). A higher body mass index (BMI > 40 kg/m^2) correlates with an increased risk for hospitalization, in particular in intensive care units, and for mortality, as previously highlighted for other respiratory viruses also by Fezeu et al. in their meta-analysis based on a systematic review of the Medline and Cochrane databases (75–77).

Gao et al. designed a prospective, community-based, cohort study and found that the risk of critical disease and death increased linearly with BMI for values above 23 kg/m^2, mostly in people younger than 40 years and black. In detail, for a BMI above 23 kg/m^2, every unit rise increases the risk for hospitalization (Hazard Ratio 1.09, 95% CI 1.08-1.10), intensive care need (Hazard Ratio 1.13, 95% CI 1.11-1.16) and death (Hazard Ratio 1.17, 95% CI 1.11-1.23) by COVID-19 disease (78).

The reason for the increased susceptibility is related to many factors. COVID-19 stimulates a cytokine storm, which worsens the subclinical basal inflammation associated with obesity. Inflammation then determines mechanisms leading to insulin resistance, hyperglycemic status and major thrombotic risk, establishing a vicious circle of harmful events (79).

Liu et al. have stated that the levels of circulating IL-6 and C-reactive protein may efficiently predict the severe course of the disease and the adverse outcome of patients affected by SARS-CoV-2 (80).

Actually, Gao et al. found that patients affected by SARS-CoV-2 infection and metabolic dysfunction associated with fatty liver disease (MAFLD) present an increased level of the inflammatory cytokine IL-6 compared to patients without MAFLD. Moreover, elevated IL-6 levels correlated with a greater risk of developing severe COVID-19, thus high IL-6 levels were associated with a major hazard for severe COVID-19 in patients with MAFLD than in those without (Figure 3) (81).

Within the frame of inflammation, the role of HMGB1 should also be recalled. Patients with increased serum concentrations of this NFkb activator and damage-associated molecular pattern protein and alarmin. It is well known to be associated with obesity, insulin resistance, and diabetes, and is involved with thrombosis-related diseases, sepsis, triggered beta amyloid accumulation in central nervous system, gene polymorphisms associated with hypertension, all associated with a severe course of COVID-19 or related risk factors (82).

The pathogenesis of the major severity of the disease could be explained by the virus-induced cytokine storm intensified by MAFLD that causes the secretion of inflammatory cytokines by the liver. Furthermore, COVID-19 could activate macrophages, resulting in the release of IL-6 with further worsening of the cytokine storm (83).

Obesity leads to a wide range of clinical complications (Figure 4). Respiratory system compliance and the functional residual capacity are reduced, whilst abdominal pressure, oxygen expense and respiratory fatigue are augmented up to muscle exhaustion. Moreover, obstructive apnoea syndrome is most frequently experienced by obese people, making the airways management harder (84).

Obesity is a contributing cause of cardiovascular impairment, deriving from a higher blood volume leading to

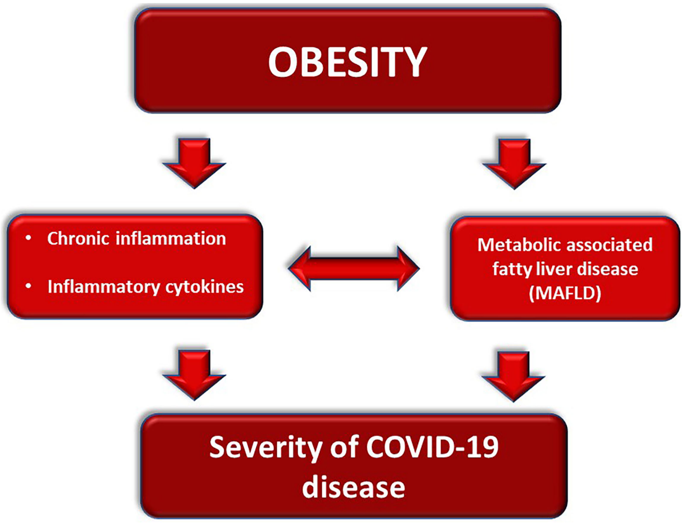

FIGURE 3
Obesity-related mechanisms worsening the course of COVID-19.

heart failure. It is inextricably linked to metabolic syndrome, as it indirectly influences dyslipidemia and blood pressure increasing the hazard for ischemic cardiopathy (85).

Kidney function is also impaired by obesity, which is directly linked to acute kidney injury; moreover, blood overload due to overweight leads to glomerular sclerosis and comorbidities as type 2 diabetes and hypertension are well-known risk factors for chronic kidney disease (86).

Nonetheless, hospitalized obese people experience mechanical and practical issues too: the management of these patients in intensive care unit is more difficult, as they develop ARDS more frequently, but intubation is challenging as well as proning; in addition, it is more difficult to cannulate peripheral vessels and central accesses are at higher risk of infection (87).

Thus, institutions should continue addressing prevention measures to obese people aiming to reduce the individual and population burden of the disease which has become increasingly more difficult during the pandemic (88).

Evidence confirms that we are facing a double pandemic, meaning both the spread of COVID-19 and obesity. These considerations are of considerable importance in light of the fact that the pandemic has deeply affected the population

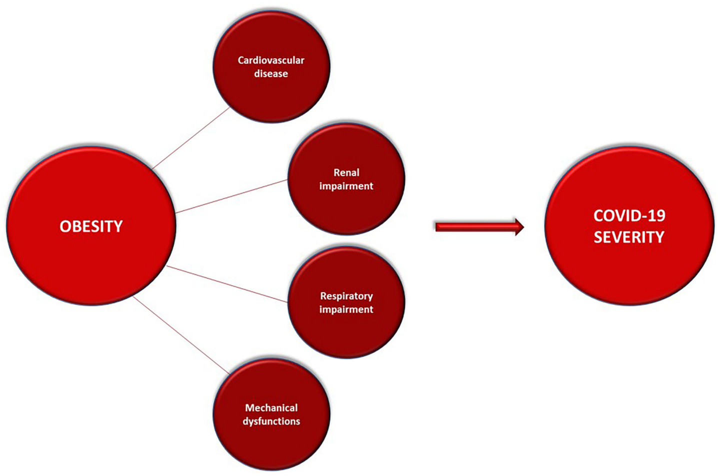

FIGURE 4
Obesity-related clinical complications that can underly and worsen the course of COVID-19.

lifestyle. This is particularly evident for certain categories such as adolescents, among whom the prevalence of overweight has increased during the lockdown. On one hand, this may be due to physical inactivity, and on the other hand to the worsening of eating habits. These problems also result in psychological discomfort which is experienced by children and young people during this pandemic (89).

A high rate of changes in eating habits was recently shown in a study in 1,519 people to whom a specific questionnaire was administered. Specifically, a higher use of frozen food and an increased consumption of coffee and sweets, leading to weight gain was observed in the majority of participants. At the same time, a decrease in physical activity was also reported (90).

These feedbacks confirm an overall worsening of lifestyle that leads to psychological distress: children and adolescents experience a high risk of developing obesity during the pandemic, because they are facing new stressing situations. New routines have replaced the protective environments of school and family and social interactions, increasing stress and subsequently aggravating disparities, health problems, economical concerns and social issues (91).

The daily grind of both patients and healthcare professionals has suddenly changed, making it urge to find new tools and practices responding to current needs. Under this scenario, telemedicine has often answered to requirements of this new situation (92). Pecoraro et al. have evaluated the utility of telemedicine in the follow-up of obese patients by offering exercises, tutorials and games to play during the lockdown. At the end of this period, they measured anthropometric parameters (body mass index, waist circumference, fat mass and fat free mass) and found an improvement in body composition, with reduced fat mass (93). While considering the limitations of the short period and the small sample analyzed, this study paves the way for further research to improve patient status using technology.

Central precocious puberty

The incidence of central precocious puberty (CPP) has been steadily increasing over the last century, with average age at menarche dropping from 17 years in the early-1800s to 13 years by the mid-1900s, with a further minor decline through the last three decades (94).

Such trend in age at pubertal onset – known as "secular trend of puberty" – recognizes both genetic and environmental factors which contribute to determine the timing and the *tempo* of puberty.

Following the COVID-19 outbreak in February 2020, a significant increase in the diagnoses of CPP, rapidly progressing puberty and precocious menarche has been reported by some paediatric Endocrinologists in Italy (95–97). Stagi *et al.* were the first to evaluate retrospectively the incidence of newly diagnosed CPP and the rate of pubertal progression in girls previously diagnosed with CPP between March and July 2020, and compared these data with medical records from the same period of time of the previous five years (2015-2019) (95). They found that the number of newly diagnosed CPP in 2020 was significantly higher than that in each year from 2015 to 2019 (37 vs 17.8 ± 1.3 patients, range from 16 to 19 cases/same period/year), along with a significantly younger chronological age at stage B2 onset/CPP diagnosis and a more advanced Tanner stage at CPP diagnosis. Moreover, they described a greater number of patients with previously diagnosed CPP moving from a slowly progressing puberty to a rapidly progressing puberty following the Italian lockdown, in comparison with the previous five years (12 vs 2.2 ± 0.4 patients, range from two to three cases/same period/year). Similar findings were reported by Verzani et al. who retrospectively analyzed medical records of their outpatient clinic from March to September 2020, comparing them with the same interval of time in 2019, and reported a significant increment of CPP in girls, observing no differences for boys (96).

A more recent Italian retrospective study has likewise reported a significantly increased incidence of both suspected and confirmed CPP in girls from March to September 2020, in comparison with the same period in 2019 (98). No difference was found in the anthropometric and hormonal parameters between 2019 and 2020, whilst girls diagnosed with CPP in 2020 showed an increased use of electronic devices paired with an overall more sedentary lifestyle.

The literature currently lacks studies enlisting larger samples of CPP patients. Moreover, data from the experience of Pediatric Endocrinology centers abroad are very scarce. A single-center retrospective study carried out in Turkey confirmed the Italian findings, reporting an increased incidence of idiopathic CPP in girls from April 2020 to March 2021, following their national lockdown, when compared with the same period of time in the previous three years (2017-2019) (99). Conversely, they did not observe significant differences in the frequency of rapidly progressing puberty and obesity before and after the COVID-19 pandemic.

When it comes to the possible underlying causes of this phenomenon, both direct and indirect mechanisms – secondary to the lockdown and the deep changes in our society and everyday life – must be taken into account. Possible factors contributing to CPP and rapidly progressing puberty are reported in Table 1.

As for the direct effects of the SARS-CoV-2 infection, Nagu et al. very well described the different routes for invasion of the CNS, which include the binding to the ACE-2 receptors – diffusely expressed on the endothelial cells of capillaries –, a cytokine storm syndrome, a hematogenous route and a olfactory route (100). Intriguingly, the olfactory tract shares its embryonic origin with the Gonadotropin Releasing Hormone (GnRH) neurons in the hypothalamus, which pulsatile activation determines the onset of puberty (97). Moreover, a recent work

TABLE 1 Possible factors contributing/causing precocious puberty and rapidly progressive puberty.

Direct mechanisms	Indirect mechanisms
•Effects of SARS-CoV-2 on the CNS through: - ACE-2 receptor - cytokine storm syndrome - hematogenous route - olfactory route	• Increased food consumption • Decreased physical activity • Increased BMI • Increased use of electronic devices • Changes in sleep habits and changes in melatonin secretion • Increased mental stress and emotivity • Possible increased exposure to some endocrine disruptors due to increased indoor life

CNS, central nervous system.

found a positive correlation between the volume of the olfactory bulb and the incidence of CPP, suggesting that the olfactory tract plays a major role in determining the timing of puberty (101). In addition, the olfactory route is very abundant of GABAergic neurons, which contribute to determine the timing of puberty (102).

As for the indirect effect of the COVID-19 pandemic, the deep changes in our society and everyday life must be carefully addressed given the profound impact that they could have on the timing and *tempo* of puberty. The adjustment in food habits, the reduced access to physical activities, the overall increase in BMI, the increased use of digital devices, the worsened quality of sleep and the global emotional stress that children of all ages have undergone in the last two years could all be contributing factors to the increased risk of CPP.

At present, we lack studies which aim to analyze the role of each one of these mechanisms in the increasing trend which has been observed. Further investigations should be pursued in order to better investigate this phenomenon and understand the triggering role of each single environmental factor on the timing and the *tempo* of pubertal onset.

Conclusions

Current findings related to COVID-19 and pediatric endocrine conditions are reassuring in terms of rate of infection and severity of the disease in almost all properly managed conditions. The data support a need for adequate vitamin D supplementation, caution in obese patients, monitoring of thyroid function in hospitalized patients, and confirm the need for an awareness campaign for the increased frequency of precocious puberty, rapidly progressive puberty and precocious menarche. The changes in lifestyle, the increased incidence of overweight and the change in the timing of puberty lead also to hypothesize that there might be an increase in the following years of ovarian dysfunction as polycystic ovarian disease, and metabolic derangements, therefore requiring a continuous surveillance.

Author contributions

MES conceived, designed and supervised this study. MG, TD, CL and GM performed the literature review and wrote the first draft of the manuscript. MES, MP and VP contributed to the interpretation of the results and in writing the manuscript. MES and SE provided scientific contributions and critically revised the paper. All the authors read, revised, and approved the final manuscript.

Conflict of interest

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

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An increasing tendency of precocious puberty among Korean children from the perspective of COVID-19 pandemic effect

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Introduction: This study was conducted to investigate changes and new trends over the past 6 years by analyzing the current status of precocious puberty (PP) treatment and treatment costs in Korea between 2016 and 2021.

Materials and methods: Annual and monthly number of patients diagnosed with PP from 2016 to 2021 were reviewed using the data from Healthcare Bigdata Hub. Annual medical insurance expenses for the treatment of PP were also reviewed. The data were compared by the gender of the patients.

Results: The number of patients diagnosed with PP rose from 86,352 in 2016 to 166,645 in 2021, while medical expenses rose from KRW 64,111,689,000 in 2016 to KRW 134,642,100,000 in 2021. The percentage of male PP patients increased from 9.21% in 2016 to 19.55% in 2021.

Conclusion: Increasing numbers of Korean patients diagnosed with PP. Consistent with the situation in other countries, the rapid increase in the number of cases since April 2020 appears to be a result of the COVID-19 pandemic. In Korea, this is considered a nationwide phenomenon. Also on the rise is the incidence of PP in males, which appears to be due to an increased awareness of the phenomenon. Further investigations are required to determine the possible causes in increasing prevalence of PP.

KEYWORDS

precocious puberty (PP), early puberty, COVID-19, pandemic, social distancing

Introduction

When secondary sex characteristics appear before the age of 8 in females and 9 in males, this is referred to as precocious puberty (1). Since the 1970s, the onset of secondary sex characteristics has sped up by 0.24 years every decade on a global scale (2). This early onset of puberty is a sign of socioeconomic and environmental change.

Although the number of children and adolescents in Korea is declining, the number of patients diagnosed with precocious puberty and the associated costs continue to rise (3). Kim et al. demonstrated that the incidence of precocious puberty rose from 2004 to 2010 (4), and Kim et al. demonstrated that the prevalence of precocious puberty rose steadily and dramatically from 2008 to 2014 (5). Since then, 8 years have passed, and the world is undergoing rapid social change as a result of the COVID-19 pandemic. Among these changes, since the COVID-19 pandemic in Italy, Turkey, India, China, etc., the number of patients with precocious puberty increased significantly, according to the results released (6–12). This study was conducted to observe the trends of annual and monthly number of patients with precocious puberty and their medical expenses in Korea from 2016 to 2021.

Materials and methods

Based on the census (13) of the national statistical portal (Korean Statistical Information Service, KSIS), the number of youth (0–19 years old) by year and the ratio of the youth population to the total population were investigated. The data for 2021 was derived from population projections for the future (14).

Every patient who visits hospital in Korea are registered with diagnoses according to the Korean Classification of Disease 10th revision (KCD-10). We investigated the data of the Healthcare Big Data Hub (15) registered as E301 (Early puberty, according to KCD-10). The number of patients diagnosed with precocious puberty by year, month, gender, and age in increments of 5 years, and region, as well as the status of insurance treatment costs, were analyzed.

Results

Domestic changes in youth population by year

The youth population in Korea decreased from 9,906,000 in 2016 to 8,490,000 in 2021. The ratio of the youth population to the total population also decreased from 19.32% in 2016 to 16.41% in 2021 (**Table 1**).

Status of patients with precocious puberty by year

The number of patients treated in medical facilities for E301 increased 1.93-fold between 2016 and 2021, from 86,352 to 166,521 (**Figure 1**). From 7,957 to 27,254, the number of male patients increased 3.43-fold, and the number of female patients increased 1.78-fold from 78,395 to 139,391. The proportion of male patients increased from 9.21% in 2016 to 19.55% in 2021 (**Figure 2**). The highest portion of female patients was in the 5-9-year age group, while the highest proportion of male patients was in the 10-14-year age group (**Figures 3**, **4**).

Status of patients with precocious puberty by region

The ratio of patients with precocious puberty to the total number of youths has increased nationally between 2016 (**Figure 5**) and 2021 (**Figure 6**). Daegu had the highest proportion of patients with precocious puberty.

Monthly status of patients with precocious puberty

29,916 patients were treated at medical institutions for E301 during the month of January 2016. The number stayed in the 30,000's for 4 years and 2 months until March 2020, a 1.2-fold increase. In April 2020, the number increased 1.5-fold compared to the previous month, reaching 41,255. A year later, in March 2021, the number reached 58,195, a 1.68-fold increase compared to January 2016 (**Figure 7**).

Cost of treatment for precocious puberty

The total cost of medical care for E301 patients treated at medical institutions increased 1.99-fold from KRW 43,579,409,000 in 2016 to KRW 86,846,620,000 in 2021. Likewise, the costs of accession deductible payment increased 2.33-fold, from KRW 20,532,280,000 to KRW 47,795,480,000 (**Table 2**).

Discussion

Secondary sex characteristics, rapid skeletal maturation, and rapid growth appear during puberty (16). Hormones of the hypothalamus-pituitary-gonadal axis (HPG axis) exist at the center of this change. The pituitary gland secretes follicle stimulating hormone (FSH) and luteinizing hormone (LH) in response to hypothalamic gonadotropin-releasing hormone (GnRH) stimulation. This leads to gonadal secretion of testosterone in males, and estradiol (E2) in female, resulting in the fertility of both sexes (17). Since hormones are sensitive to changes in both the external environment and the genetic unit, puberty has been a significant socioeconomic milestone.

Using statistical data from the national statistical portal and the Healthcare Big Data Hub, this study analyzed

TABLE 1 Korea adolescent population aged 0–19 (in thousands).

	2016	2017	2018	2019	2020	2021*
Total population	51,270	51,423	51,630	51,779	51,829	51,744
Population under 19	9,906	9,605	9,316	9,030	8,704	8,490
Percentage of population under 19 (%)	19.32	18.68	18.04	17.44	16.79	16.41

*Projected population figures.

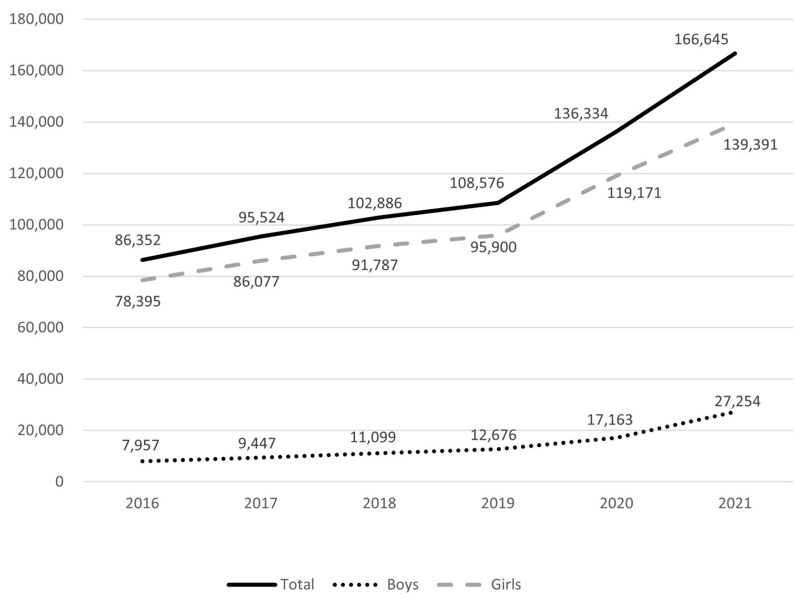

FIGURE 1
Annual number of patients diagnosed with precocious puberty.

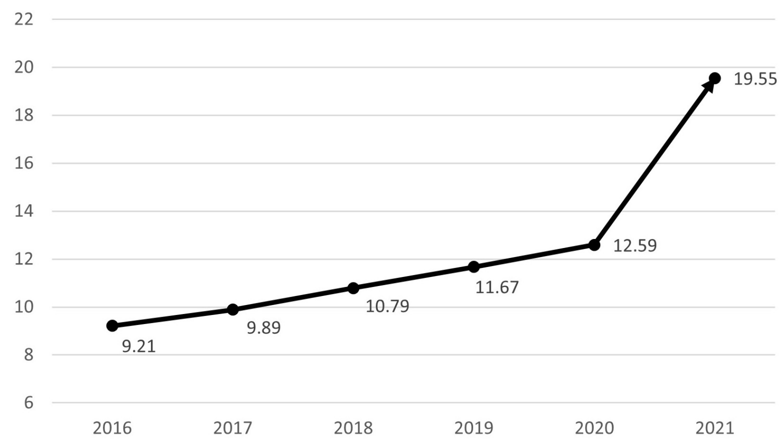

FIGURE 2
Increasing tendency for boys diagnosed with precocious puberty compared to girls (%).

the medical status of patients with precocious puberty in Korea from 2016 to June 2021. Compared to 2016, the number of patients diagnosed with precocious puberty increased 1.93-fold in 2021. During the same time period, the population of youth aged 0–19 decreased, and the proportion of adolescents diagnosed with precocious puberty increased 2.25-fold, from 0.87% in 2016 to 1.96% in 2021, a greater increase than the increase in the number of patients (**Figure 8**). In addition, the ratio of patients with precocious puberty to the population is rising in nearly all

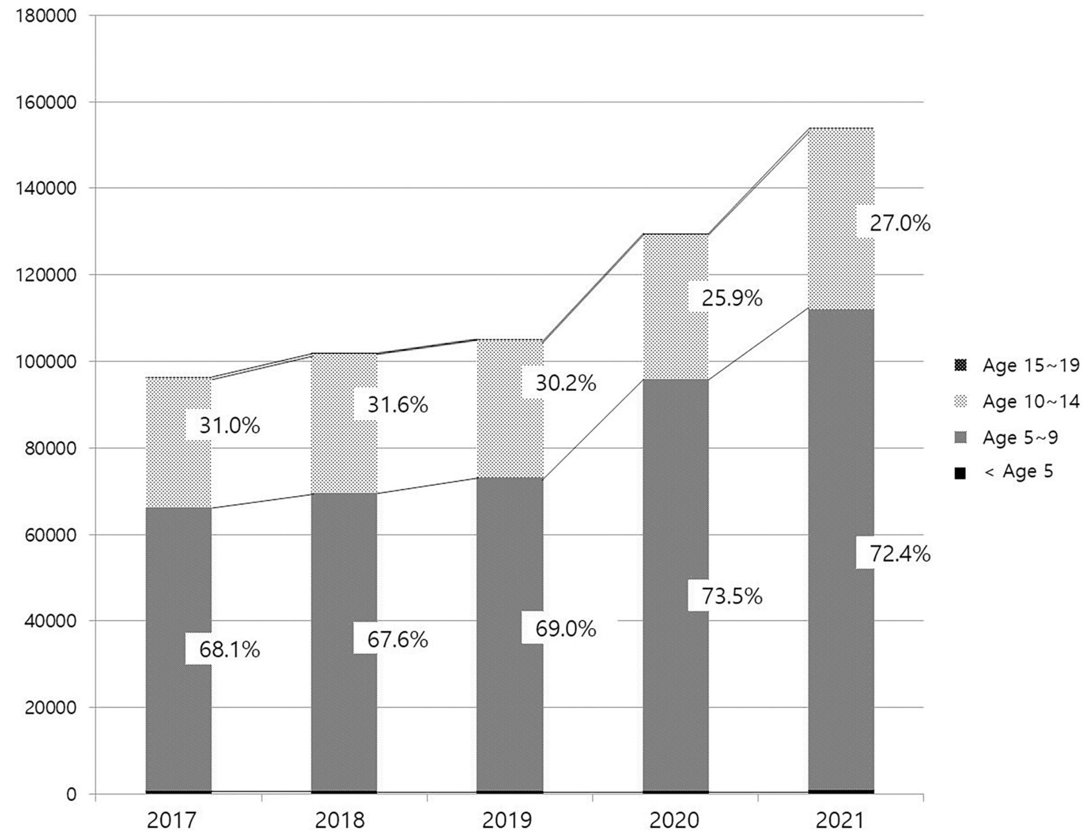

FIGURE 3
Age distribution of female patients with precocious puberty.

regions, indicating that the rise in the number of patients with precocious puberty is a nationwide phenomenon. As the number of patients increases, so do the costs associated with precocious puberty. The total cost of medical care and the amount of accession deductible payment increased 2.1-fold between 2016 and 2021, from KRW 64,111,689,000 to KRW 134,642,100,000. Considering previous research (3), it is believed that the number of patients with precocious puberty in Korea continues to rise.

In this study, the authors discovered two new trends. One is the significant increase in patients seen after April 2020. The growth rate between 2019 and 2021 is steeper than the change between 2016 and 2019, and a monthly analysis reveals a meteoric rise beginning in April 2020. This trend continued until June 2021. After the first COVID-19 outbreak in China at the end of 2019, the world entered a crisis, and each country implemented lockdowns or equivalent measures in 2020, making telecommuting and remote learning the norm, and outdoor activities restricted. Changes in lifestyle have caused an increase in endocrine diseases (18). In Italy, outpatient treatment for suspected symptoms of early puberty and precocious puberty increased dramatically compared to the same time period in 2019 (7). In addition, the phenomenon of accelerated puberty onset was identified, and the rate of precocious puberty diagnosis increased (6). Compared to the 3 years preceding the pandemic, the diagnosis rate of idiopathic central precocious puberty (ICPP) in Turkey has more than doubled (8). Both central precocious puberty (CPP) and rapidly progressive early puberty (RPEP) increased by greater than threefold in other studies (10). After lockdown, the referrals for precocity and the number of children diagnosed with ICPP quadrupled in India (11). The prevalence of precocious puberty in Shanghai, China also has more than doubled (12). It is suggested that excessive use of digital devices is the primary cause of this phenomenon. In a study conducted between October 2020 and March 2021, the salivary melatonin levels of 39 females diagnosed with precocious puberty were significantly lower than those of the control group. This was attributed to the effects of light stimulation and electromagnetic fields (EMF) generated by electronic devices (19). Low melatonin levels affect the HPG axis, thereby accelerating the onset of puberty (20). In addition, restriction of physical activity and increased BMI due to high-calorie food consumption, fear of the pandemic, mental factors such as anxiety, changes in sleep patterns, exposure to environmental hormones, and direct stimulation of the central nervous system due to COVID-19 infection are

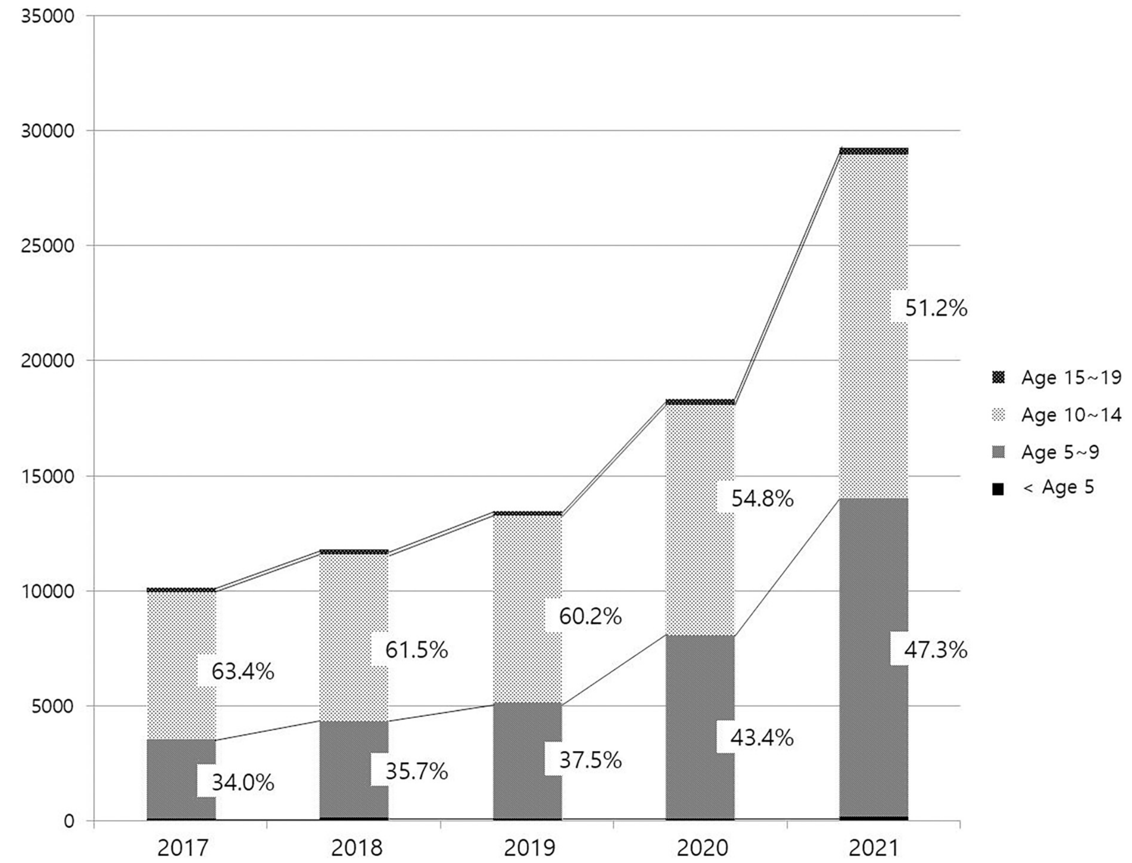

FIGURE 4
Age distribution of male patients with precocious puberty.

cited as potential causes (21, 22). The situation in Korea is similar. After the first COVID-19 patient was reported (23) in January 2020, strict social isolation measures were implemented, school was suspended until May 2020, and some classes are still conducted remotely. According to a study (24) conducted by the Department of Pediatrics at Eulji University Hospital, the proportion of overweight and obese children who presented with precocious puberty in 2020 was significantly higher than in 2019. This was more prevalent in males. Moreover, while the overall number of pediatric outpatients has been decreasing, the number of outpatients due to short stature, precocious puberty, and obesity is increasing, and this is thought to be due to the decrease in physical activity as a result of the COVID-19 pandemic. In this study we confirmed that the number of patients diagnosed with precocious puberty increased from April 2020 to April 2021 in Korea. We could speculate several possible factors for this trend based on the previous studies. First, increasing obesity due to the lack of physical activities could be the main factor. It has been suggested that obesity, fast food consumption, and the consumption of growth-related health functional foods are factors accelerating the onset of puberty in Korean adolescents (25). The BMI of elementary school students has risen significantly over the past year, as the physical activity of adolescents has decreased, and their consumption of fast foods has increased as a result of COVID-19 (26). Meanwhile, the immune-related health functional food industry is experiencing a boom that is unprecedented (27). Under these conditions, it appears inevitable that the number of patients receiving treatment for precocious puberty will increase rapidly. Second, overuse of digital devices during the social distancing and remote learning period could affects this phenomenon, too. According to the Korea Information Society Development Institute's "Comparison of Media Usage Behaviors of Adolescents Before and After COVID-19" report (28), the use of paper media decreased as a result of online classes, while time spent on laptops, tablets, desktops, and smartphones increased. Third, endocrine-disrupting chemicals are possible factor of this tendency. Since social distancing caused non-contact delivery culture, it is also necessary to observe a correlation between the rapid increase in the use of disposable items such as plastic and vinyl and precocious puberty (29). These chemicals are known to the factors that lead to precocious puberty. All of these factors working together, precocious puberty patients are steeply increasing during the pandemic in Korea.

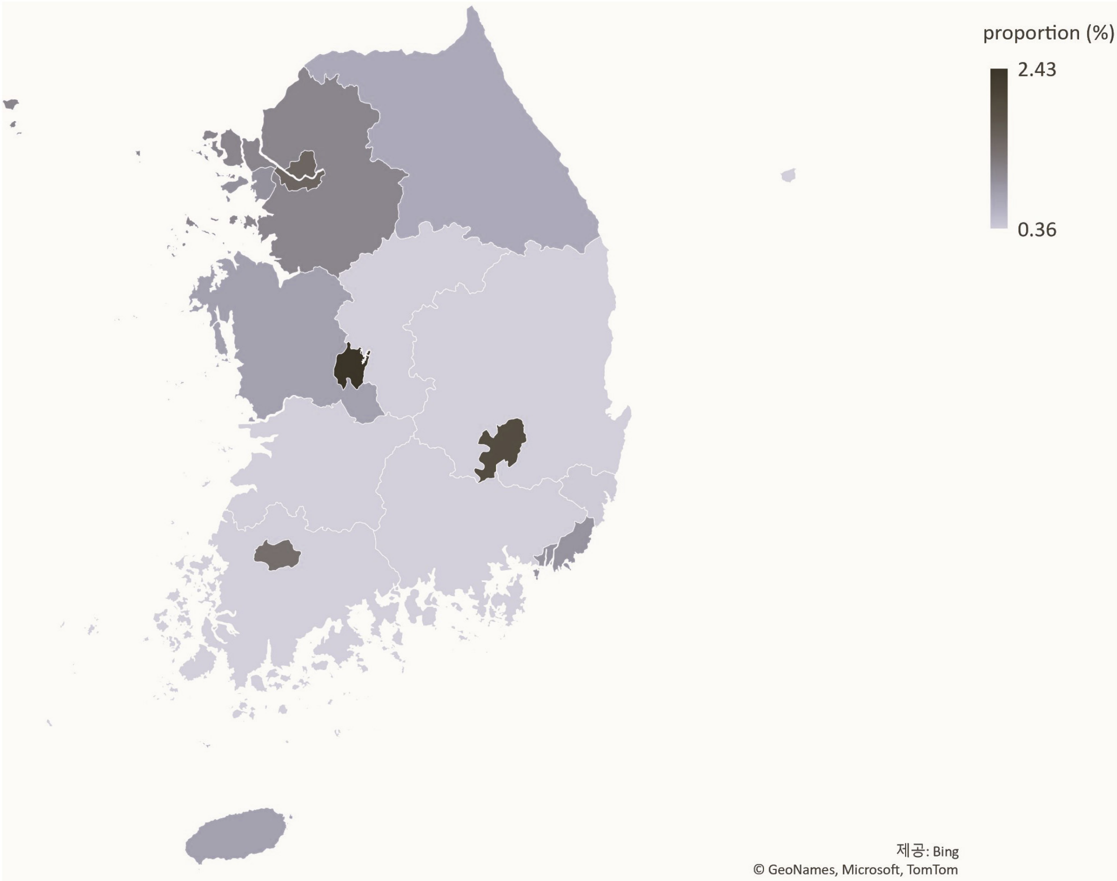

FIGURE 5
Population distribution of precocious puberty by region in 2016 (%).

An increasing proportion of males are diagnosed with precocious puberty, which is another trend. Since 2016, the proportion of males, who accounted for less than 10% in the previous study, has steadily risen, reaching 12.59% in 2020 and 19.55% in 2021. Particularly, the rate of medical treatment among 5 to 9-year-olds increased from 34 to 47.3%, which appears to have contributed to the rise in male patients. Existing studies show that the precocious puberty is 10 times more prevalent in females than in males; however, severe cases accompanied by abnormalities of the central nervous system, such as malformations, tumors, or inflammation, are more prevalent in males; therefore, referral to a tertiary medical institution has been deemed necessary (13, 30). However, according to an analysis of male patients with precocious puberty in Korea from 2001 to 2016 by Lee et al. (31) in 2018, the rate of idiopathic precocious puberty, for which it is difficult to identify a specific cause, has increased with the annual increase in the number of patients, accounting for more than 60%. After the age of eight, the proportion increases even further. These results are attributed to an increase in parental awareness through the Internet and broadcast media, in addition to environmental factors such as nutritional improvement and endocrine disrupting substances. Males, unlike females, have an unclear onset of secondary sex characteristics, making it easy to miss the opportunity to diagnose precocious puberty. In this study, the increase in the proportion of male patients before 9 years of age and the total number of male patients occurred simultaneously, which means, the treatment rate has increased as a result of the growing awareness of precocious puberty in males. In addition, the sudden increase in male patients coincided with the period of COVID-19 social distancing. As mentioned previously, this is likely due to the fact that the restrictions on physical activity and tendency toward obesity caused by the pandemic are more pronounced in previously active males. This supports the possibility that the increase in the number of patients with precocious puberty during this time period is due to changes in lifestyle brought about by the COVID-19 pandemic.

The trend of precocious puberty in Korea over past 6 years was analyzed by year, gender, age, and region in this study. Through this process, it was possible to confirm the need for a large-scale correlation study on various factors that can

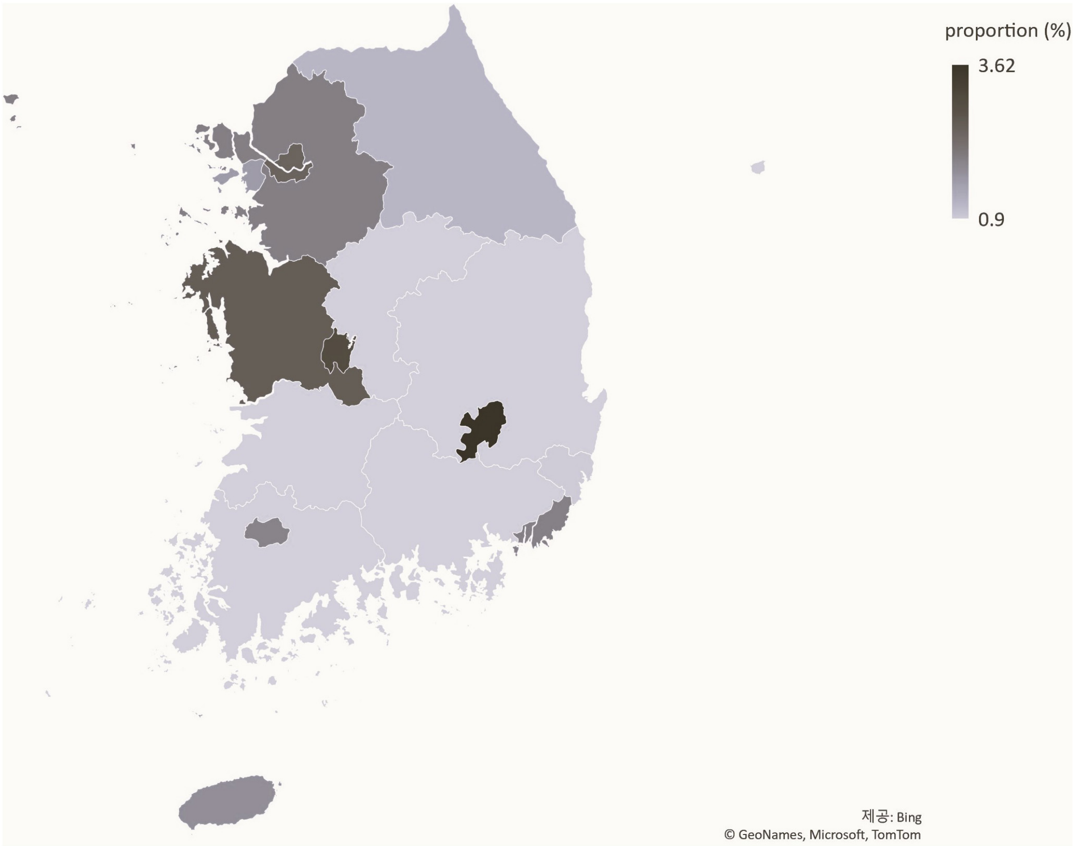

FIGURE 6
Population distribution of precocious puberty by region in 2021 (%).

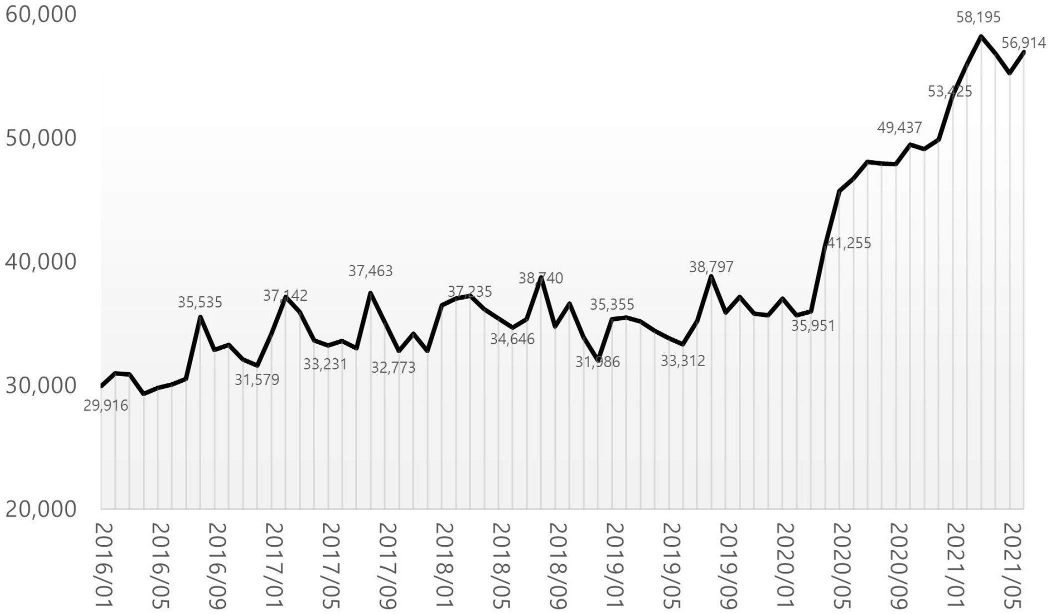

FIGURE 7
Monthly number of patients diagnosed with precocious puberty.

TABLE 2 Annual medical insurance expenses for precocious puberty (KRW 1000 won).

	2016	2017	2018	2019	2020	2021
Medical care benefits	43,579,409	49,264,944	52,220,670	50,846,925	65,078,828	86,846,620
Accession deductible payment	20,532,280	23,650,423	25,948,170	26,181,533	35,033,886	47,795,480
Total expenses	64,111,689	72,915,367	78,168,840	77,028,458	100,112,714	134,642,100

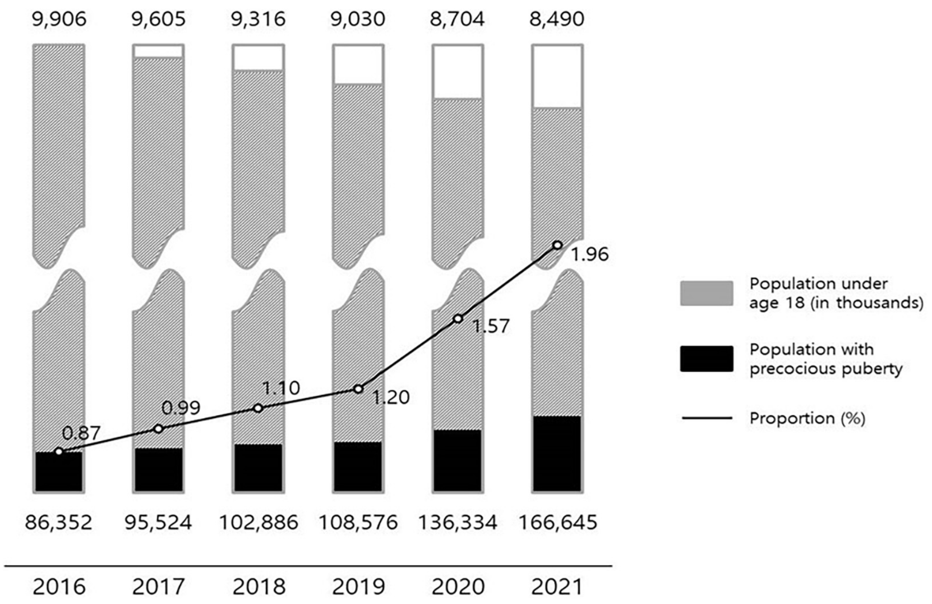

FIGURE 8
Annual number of patients diagnosed with precocious puberty compared with population.

influence precocious puberty. In addition, Korea is a country where Western medical treatment for precocious puberty utilizing GnRH agonist and oriental medical treatment (32) utilizing herbal medicine to regulate hormones coexist. The majority of non-insured patients receiving oriental medical treatment are omitted from this study's statistics. In the future, research should be conducted on the current status of treatment for precocious puberty by various medical institutions and the effects thereof.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethics review and approval/written informed consent was not required as per local legislation and institutional requirements.

Author contributions

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

Conflict of interest

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

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Weight gain in type 1 diabetes during the SARS-CoV-2 pandemic. Does lockdown affect the metabolic control of pediatric patients?

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Background and aims: Due to the severe acute respiratory syndrome coronavirus 2 pandemic, governments of many countries decided to implement lockdowns, which included school closures. This major lifestyle change also applied to people with diabetes. The aim of this paper was to analyze how the COVID-19 pandemic and related restrictions influenced the metabolic compensation of diabetes in the pediatric population.

Methods: Patients with type 1 diabetes (T1D), treated by one therapeutic team, who in 2020 and 2021 paid at least two in-person visits in the outpatient clinic, were included in the study. The time in range (TIR) and HbA1c, as well as the total daily dose (TDD) of insulin and BMI from the visit before the announcement of the pandemic restrictions (March 2020) and during the lockdown (second visit after 6 months) and within the period of loosened restrictions (two visits in 2021) were analyzed.

Results: A total of 185 patients with T1D were included in the study (96 boys), aged 2–18 years (11.5 ± 3.5); 135 of them (72.9%) use CSII and 142 (76.8%) use CGM or FGM. During the first months of the studied period, despite comparable ($p>0.05$) TIR (57.5 ± 21.4% *vs*. 59.9 ± 20.5%), improvement of HbA1c was noticed (7.9 ± 1.6% *vs*. 7.5 ± 1.4%, $p=0.0336$), whereas in the following months, both HbA1c and TIR were comparable. Also, the TDD increased significantly (from 37.3 ± 18.9 units/day on the first visit up to 46.8 ± 22.7 units/day on the last visit, $p=0.0003$); however, TDD/kg remained constant ($p>0.05$) (0.8 ± 0.2 units/kg/day *vs*. 0.8 ± 0.3 units/kg/day) possibly due to an increased BMI (19.1 ± 3.7 kg/m^2 *vs*. 20.9 ± 4.1 kg/m^2, $p=0.0001$). The percentage of basal insulin in the TDD remained stable ($p>0.05$) (39.7 ± 11.3% *vs*. 39.3 ± 13.6%). Furthermore, a significant ($p=0.0001$) change in the BMI percentile was noticed [from 58.9 ± 26.2 percentiles (%iles) before lockdown *vs*. 64.6 ± 26.0%iles on the second visit]. However, the BMI percentile returned to baseline (58.1 ± 28.4%iles) at the visit at the end of the observation period.

Conclusions: The parameters of metabolic control in pediatric patients with T1D during the pandemic period remained stable; however, weight gain and an increase in daily insulin dose have been observed, possibly due to reduced physical activity.

KEYWORDS

BMI, metabolic control, type 1 diabetes, COVID-19 lockdown, children

A novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)], which had caused a cluster of pneumonia in the Chinese province of Hubei in late 2019, spread throughout the world rapidly. On 11 March 2020, the World Health Organization (WHO) declared a pandemic of the disease induced by this virus—coronavirus disease 2019 (COVID-19).

SARS-CoV-2 is spread by droplet transmission. As it is a new pathogen for humanity, in early 2020, vaccination against this virus was not available. Therefore, it can be concluded that only the minority of the human population who suffered from COVID-19 had developed adaptive immunity against SARS-CoV-2, whereas the majority were susceptible to infection. The reproduction ratio, R0, of SARS-CoV-2 was estimated to be between 2 and 3.5. This means that every patient with COVID-19 infects, on average, two to three people, and, as so, the number of affected people doubles every week (1).

For obvious reasons, before the development of vaccination against this virus, the only effective method to reduce the spread of COVID-19 was social distancing. In order to reduce viral exposure and possible contamination, social isolation, "stay at home" orders, followed by lockdowns or semi-lockdowns were imposed in many countries, including Poland. To reduce public gatherings, many public spaces were closed, including gyms and swimming pools. Moreover, distance learning in schools and universities was introduced, which globally affected more than 90% of students (2). As a consequence of schools' closure, limitation of participation in sports activities and reduction of children's physical activity, as well as an increase in sedentary behavior, occurred. Furthermore, homeschooling alters eating habits, including snacking between meals and comfort eating (3, 4). All those changes might have affected the physical health of children with diabetes, including possible weight gain and worsening of metabolic control.

Obesity in children and adolescents is a growing health problem. According to Majcher et al., in the group of 656 Polish children with excess body weight, 21.8% had 2nd-degree obesity; furthermore, 84% of those patients were already obese at the age of 6 (5). The increasing prevalence of overweight and obesity is also observed in people with type 1 diabetes (T1D), affecting up to 35% of patients, as well as augmenting the risk of chronic complications of diabetes. In T1D, like in the general population, a high supply of simple carbohydrates and fats in the diet along with sedentary lifestyle and physical inactivity are factors contributing to the increase in the BMI (6). Furthermore, both overweight and physical inactivity in patients with T1D influence beta-cell residual function; therefore, it may negatively impact diabetes remission occurrence and duration (7).

In this regard, the aim of the paper was to analyze whether the restrictions introduced due to the COVID-19 pandemic have influenced the metabolic control of children with T1D, as well as the change in the body mass of those patients.

Patients and methods

In this retrospective study, we evaluated pediatric patients with T1D from at least 12 months before the first visit, treated by one therapeutic team, who had at least two in-person visits in the outpatient clinic in 2020 (before and 6 months after the lockdown announcement in Poland), as well as at least two in-person visits in 2021 (6 and 12 months following the last visit in 2020). The following data were analyzed: the time in range (TIR) (70–180 mg/dl, %), HbA1c, as well as the total daily dose (TDD) of insulin (IU/day and IU/kg of body mass), height (measured to the nearest 0.1 cm), and weight (measured to the nearest 0.01 kg) from the visit before the announcement of the pandemic restrictions (15 March 2020), during the lockdown (second visit after 6 months in 2020), and within the period of loosened restrictions (two visits in 2021 in 6 months interval). The body mass index (BMI, kg/m^2) together with BMI percentile (BMI%ile) were calculated. BMI%ile was calculated according to WHO BMI growth charts (8). BMI%ile is a measure of the relative BMI, adjusted for a child's age and sex. If a child has maintained the BMI over time, BMI%ile would not change despite the difference in the absolute value of the BMI, whereas an increase or decrease in BMI%ile indicates that the BMI gain is greater or less in comparison with the reference sample of peers of the same age and sex. Nutrition status terminology was based on Ref (9). Underweight was defined as

BMI < 5th %ile, a normal BMI was recognized when the BMI was within 5th to 85th %ile, overweight was diagnosed if BMI ≥ 85th %ile and < 95th %ile, and obesity if BMI ≥ 95th %ile. Newly diagnosed T1D, complete remission of T1D, and other types of diabetes were the exclusion criteria.

Descriptive statistics were calculated for all four time points. The data were presented as the arithmetic mean (x) and standard deviation (SD) for continuous variables and as percentages for categorical variables. As only patients with complete data from all four visits were included in the study, no data imputation was required. The W Shapiro–Wilk test was used to verify the compliance of the distribution of quantitative variables of the analyzed sample with the normal distribution. To determine if there was a change from one measurement to the other, the paired Student's t test was used if the distribution of the samples did not differ significantly from the normal distribution with statistically equal variance. If those assumptions were not met, the Wilcoxon signed-rank test was used. To detect differences among multiple dependent samples, repeated-measures ANOVA or Friedman tests were used appropriately, followed by *post hoc* analysis with the Tukey test or Dunn test with Bonferroni correction. In order to evaluate the difference between the BMI category of studied children on each visit, the McNemar test for paired proportions was used, as patients served here as their own control. In all statistical tests, a significance level of $\alpha = 0.05$ was assumed.

The study was approved by the Bioethical Committee of Wrocław Medical University, Wrocław, Poland (No. KB-487/2022).

Results

A total of 185 patients with T1D were included in the study (96 boys, 51.9%), aged 2–18 years (11.5 ± 3.5), with disease duration from 1 to 15 years (4.4 ± 3.1). Furthermore, 135 of them (72.9%) use continuous subcutaneous insulin infusion (CSII), and 142 (76.8%) use continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) systems. Boys and girls did not differ according to age or duration of the disease (p=0.8025 and p=0.6411, respectively).

During the first months of the studied period, despite comparable TIR (57.5 ± 21.4% vs. 59.9 ± 20.5%, p=0.3604), a significant improvement in HbA1c was noticed: 7.9 ± 1.6% vs. 7.5 ± 1.4%, (p=0.0336). It was followed by the stabilization of metabolic control, with comparable results regarding both TIR and HbA1c on second, third, and fourth visits: 59.9 ± 20.5% vs. 63.8 ± 17.6% vs. 63.1 ± 16.4%, p=0.4796, and 7.5 ± 1.4% vs. 7.6 ± 1.3% vs. 7.7 ± 1.3%, p=0.6065, respectively. Those observations were comparable for both sexes, although the HbA1c concentration on the last visit in girls was significantly lower compared with the HbA1c concentration in boys (Table 1, Figure 1). Furthermore, the TIR on the second and third visits was significantly lower in girls than in boys.

During the whole study period, the TDD increased significantly (p=0.0003) from 37.3 ± 18.9 units/day on the first visit to 41.7 ± 21.1 units/day on the second visit (p=0.0353) up to 46.8 ± 22.7 units/day on the fourth visit (p=0.0258); however, insulin demand related to body mass remained constant (0.8 ± 0.2 units/kg on the first visit vs. 0.8 ± 0.3 units/kg on the last visit, p=0.4857). Likewise, the proportion of basal insulin in the TDD was comparable throughout the observation (39.7 ± 11.3% on the first visit vs. 39.3 ± 13.6% on the last visit, p=0.7428). Those findings were similar for both sexes (p>0.05).

The BMI, as well as BMI%ile, of the examined patients increased significantly during the study period (p=0.0027 and p=0.0001, respectively), especially in the first months of restrictive lockdown (from 19.1 ± 3.7 kg/m^2 before lockdown vs. 20.1 ± 3.6 kg/m^2 on the second visit, p<0.0001, and from 58.9 ± 26.2 before lockdown vs. 64.6 ± 26.0 on the second visit, p<0.0001), stabilizing when the pandemic limitations were loosened (20.4 ± 3.9 kg/m^2 on the third visit vs. 20.9 ± 4.1 kg/m^2 on the last visit, p=0.2302, and 60.7 ± 26.6 kg/m^2 on the third visit vs. 58.1 ± 28.4 kg/m^2 on the last visit p=0.4098). It is noteworthy that a significant increase in BMI

TABLE 1 Metabolic control in children with type 1 diabetes before and during SARS-CoV-2 pandemic according to sex.

		Total	Boys	Girls	*P* value
Visit 1	HbA1c [%]	7.9 ± 1.6	7.8 ± 1.8	8.0 ± 1.4	0.7458
	TIR [%]	57.5 ± 21.4	61.4 ± 21.3	51.4 ± 20.0	0.1007
Visit 2	HbA1c [%]	7.5 ± 1.4	8.0 ± 1.9	7.6 ± 1.4	0.1070
	TIR [%]	59.9 ± 20.5	60.5 ± 20.4	52.8 ± 21.2	0.0127
Visit 3	HbA1c [%]	7.6 ± 1.3	7.8 ± 1.7	7.4 ± 1.0	0.0550
	TIR [%]	63.8 ± 17.6	68.5 ± 16.7	58.4 ± 17.6	0.0001
Visit 4	HbA1c [%]	7.7 ± 1.3	7.9 ± 1.4	7.5 ± 1.0	0.0276
	TIR [%]	63.1 ± 16.4	63.9 ± 16.2	62.1 ± 17.0	0.4618
P value *(ANOVA)*	HbA1c	0.0678	0.7654	0.2979	
	TIR	0.8363	0.3324	0.0952	

TIR, time in range, 70–180 mg/dl.

was observed in girls but not in boys, with a clear difference on the last visit. BMI%ile, however, changed during the study period regardless of sex (Table 2, Figure 2), overall indicating significant weight gain in girls and reduction of body mass in boys.

The prevalence of overweight and obesity in the studied population is presented in Table 3 and Figure 3. The overall proportion of different categories of BMI was stable (p>0.05) throughout the study period; however, there was a significant change in the percentage of patients with overweight and obesity, with an increase during the lockdown period from 18% on visit 1 to 28% on visit 2 (p<0.0001), and the reduction to 23% on visit 3 (p<0.0001), stabilizing afterward to 23% on visits 3 and 4 (p>0.05). Finally, the percentage of patients with excess body mass increased during the observation by 5.4% (Table 4).

Lastly, we evaluated whether overweight and obesity at the beginning of the observation influenced the change in body mass during the study period. The difference between the BMI on the first and last visits was significantly (p=0.0078) greater in patients who had excess body mass before the pandemic (-1.8 ± 4.8 kg/m^2) than in children with normal body weight (0.3 ± 2.2 kg/m^2). On the other hand, those patients reduced their BMI%ile by 0.1 ± 7.0 (p=0.0046), whereas children without excess body mass gained weight and their BMI%ile increased by 1.9 ± 8.7 (p=0.0002). The difference was not significant between those groups (p=0.2554).

Discussion

Rundle et al. hypothesized that restrictive mitigation measures due to the COVID-19 pandemic will exacerbate the risk factors of weight gain in children mainly by increasing food insecurity along with higher consumption of ultraprocessed and calorie-dense food. Consequently, children will experience higher calorie diets. Furthermore, social distancing and "stay at home" recommendations reduce opportunities for physical activities and enhance sedentary behaviors and screen time (10). Observations done during the early months of the COVID-19 pandemic by Pietrobelli et al. support Rundle's hypothesis. In this small study on lifestyle changes during lockdown in 41 obese children, the authors found an increased number in meals eaten per day followed by an increased intake in potato chips, sugary drinks, and red meat. Sleep time and screen time increased significantly, whereas sports time decreased significantly. Although post-confinement measurements of body mass were not performed in this study due to pandemic limitations, it may be assumed that the above-mentioned negative lifestyle changes will result in an excess weight gain during the lockdown (4).

Obviously, a negative association of mitigation measures related to the pandemic with reduced activity level, increased sedentary behavior, and weight gain is observed not only in the general population but also in people with diabetes. In a cohort of children with T1D, we have observed a significant increase in BMI, as well as BMI%ile, during the study period. Weight gain was especially distinct in the first months of restrictive lockdown; nevertheless, when pandemic mitigations were loosened, both the BMI and BMI %ile stabilized. Moreover, we have found that the prevalence of overweight and obesity increased during the study period by 5.4%; however, the greatest augmentation, reaching 10.3%, happened during lockdown. Our results are in line with Weaver et al.'s observation that COVID-19 led to an accelerated increase in the BMI z-score gain. This interesting investigation was designed as an interrupted time-series study with anthropometric data collected in August/September from 2017 to 2020, followed by an estimation of mixed-effects linear regression of the yearly BMI z-score change before and during the COVID-19 pandemic (i.e., 2017–2019 and 2019–2020, respectively). It was found that the non-pandemic yearly BMI z-score change was stable, reaching +0.03 every year (95% CI=-0.10, 0.15; difference 0.0, 95% CI=-0.09, 0.08), whereas during the pandemic year, it was +0.34 (95% CI=0.21, 0.47), with an acceleration in the BMI z-score change of +0.31 (95% CI=1.19, 0.44). The increase in the BMI z-score during the COVID-19 pandemic corresponded with an increased risk of excess adiposity in those children (odds ratio 1.80, 95% CI=1.40, 2.33) (11). Similarly, Jarnig et al.'s study showed that in a cohort of 764

TABLE 2 Body mass index in type 1 diabetic children before and during SARS-CoV-2 pandemic according to sex.

		Total	Boys	Girls	*P* value
Visit 1	BMI [kg/m^2]	19.1 ± 3.7	18.9± 3.4	19.3 ± 4.0	0.6043
	BMI%ile	58.9 ± 26.2	64.8 ± 23.6	52.5 ± 27.7	0.0417
Visit 2	BMI [kg/m^2]	20.1 ± 3.6	18.8 ± 2.7	19.4 ± 3.9	0.2225
	BMI%ile	64.6 ± 26.0	64.3 ± 26.1	64.9 ± 26.3	0.9295
Visit 3	BMI [kg/m^2]	20.4 ± 3.9	20.1 ± 4.2	20.8 ± 3.4	0.2165
	BMI%ile	60.7 ± 26.6	60.2 ± 27.1	61.3 ± 26.4	0.8532
Visit 4	BMI [kg/m^2]	20.9 ± 4.1	20.3 ± 4.5	21.6 ± 3.5	0.0304
	BMI%ile	58.1 ± 28.4	57.8 ± 31.1	58.5 ± 25.5	0.8858
P value *(ANOVA)*	BMI [kg/m^2]	p=0.0027	0.0956	0.0220	
	BMI%ile	0.0001	0.0009	0.0019	

BMI, body mass index; BMI%ile, body mass index percentile.

TABLE 3 The prevalence of underweight, overweight, and obesity in children with type 1 diabetes before and during SARS-CoV-2 pandemic.

	BMI criterion*	Total	Boys	Girls	*P* value
Visit 1	Underweight	3%	0%	6%	0.1280
	Normal BMI	80%	82%	78%	0.6690
	Overweight	14%	10%	17%	0.3803
	Obese	4%	8%	0%	0.0852
Visit 2	Underweight	3%	0%	7%	0.1257
	Normal BMI	68%	73%	63%	0.4107
	Overweight	23%	21%	26%	0.6510
	Obese	5%	6%	4%	0.7283
Visit 3	Underweight	3%	0%	6%	0.1446
	Normal BMI	74%	77%	71%	0.5812
	Overweight	15%	12%	20%	0.3770
	Obese	8%	11%	3%	0.2143
Visit 4	Underweight	2%	4%	0%	0.0992
	Normal BMI	74%	70%	79%	0.2238
	Overweight	17%	17%	20%	0.6475
	Obese	6%	9%	1%	0.0332
P value		0.9905	0.7687	0.8425	

* Underweight (BMI < 5th %ile); normal BMI (BMI 5th - 85th %ile); overweight (BMI ≥ 85th %ile – 95th %ile); obese (BMI ≥ 95th %ile) (9). BMI, body mass index.

Austrian children, the implementation of strict pandemic limitations was associated with an increase in the BMI z-score by 0.16 ± 1.10 during 1 year of observation. In this study, the percentage of children with excess adiposity increased by 3.8%, from 20.3% to 24.1% (12).

One explanation of the observed weight gain, as mentioned by Pietrobelli et al. and Rundle et al., is the unhealthy change in eating behavior, including the increased consumption of ultraprocessed, calorie-dense comfort foods (4, 10). As the TDD increased during the observation, we may suspect in the studied cohort of an increased caloric intake during the pandemic; however, regrettably, it was not evaluated in a direct manner. Still, downloads of personal insulin pump data revealed a higher number of meal boluses during lockdown (data not shown). Moreover, in some children, an increased basal rate during the day might have covered snacking. Increased calorie intake is apparently not the whole story. The other part is the decrease in physical activity, as school closures and social distancing orders issued across the world reduced the opportunities to exercise (4, 10). Restrictions imposed in many countries, including Poland, resulted in limited occasions to be physically active. The negative association of pandemic mitigation measures with the level of physical activity and sedentary behavior, and subsequent decreased physical fitness, was described in numerous studies and is considered to be the indirect consequence of the COVID-19 pandemic (4, 12–16). Unfortunately, in our study, we did not measure the level of physical activity, which is undoubtedly a limitation of the study. It has to be underlined, however, that the initial COVID-19 mitigation measures implemented in Poland were rigorous and included the closure of not only gyms and swimming pools, but also playgrounds and parks, as well as prohibiting children under the age of 16 to stay outside their home without adult supervision. Together with physical education classes, all other organized sport activities were suspended. Therefore, we may assume that weight gain found in our study, at least in part, was the result of reduced activity. Pandemic mitigation measures implemented in Poland were comparable to those imposed in Austria. Hence, Jarnig et al.'s study, which examined the association of COVID-19 restrictions with changes in

TABLE 4 The difference between paired proportions of patients with overweight and obesity on each visit.

Visit interval	Difference	95% Confidence Interval	*P* value (McNemar test)
Visit 1–Visit 2	10.3%	5.9% to 14.6%	<0.0001
Visit 2–Visit 3	-4.6%	-7.6% to -1.7%	<0.0001
Visit 3–Visit 4	0%	0%	
Visit 1–Visit 4	5.4%	2.1% to 8.7%	<0.0001

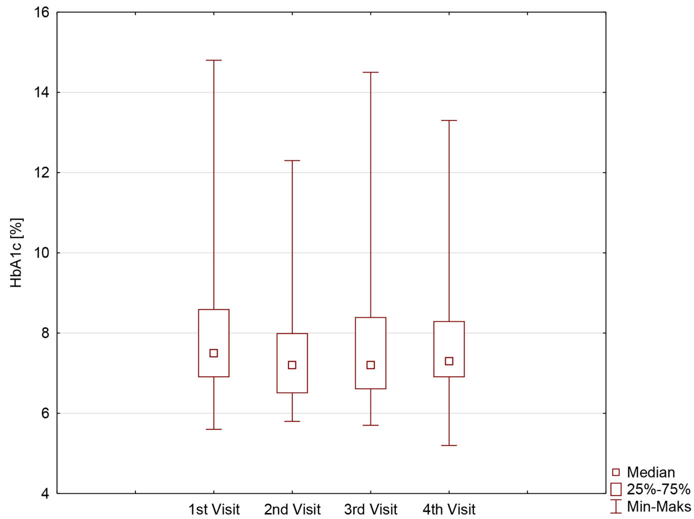

FIGURE 1
HbA1c [%] in children with type 1 diabetes before and during the SARS-CoV-2 pandemic.

cardiorespiratory fitness (CRF) in primary schoolchildren, could be referred to the situation in our country and in our cohort (12). They found that, along with weight gain, the CRF SD scores decreased (-1.06, 95% CI=-1.13, -1.0) apparently due to lower physical activity, especially those of higher intensity (12, 17, 18). The increased TDD of insulin, noticed in our study during the lockdown period, may also be the indirect evidence of reduced physical activity, since in children who exercise, a significant reduction in insulin dose is observed and recommended (19–21).

It was assumed that overweight and obese patients tend to gain more weight than subjects with normal body mass. The explanation for this observation seems to be simple: people with excessive adiposity more often present unhealthy dietary habits, including increased consumption of sweets, meat, and fried food, while their physical activity is lower (3, 22). Indeed, the increased quantity and decreased quality of meals were confirmed in multicenter studies to be associated with a higher BMI (23). The survey from Poland revealed that obese subjects had the lowest frequency of vegetables, fruits, and legumes consumption

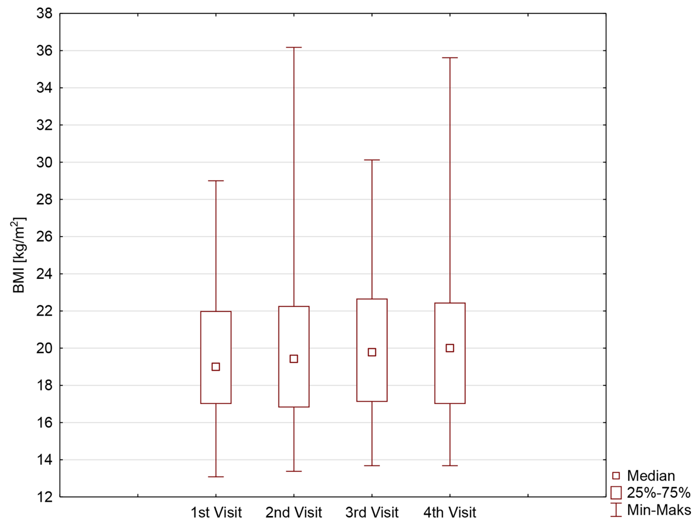

FIGURE 2
The body mass index (BMI) [kg/m^2] in patients with type 1 diabetes before and during SARS-CoV-2 pandemic.

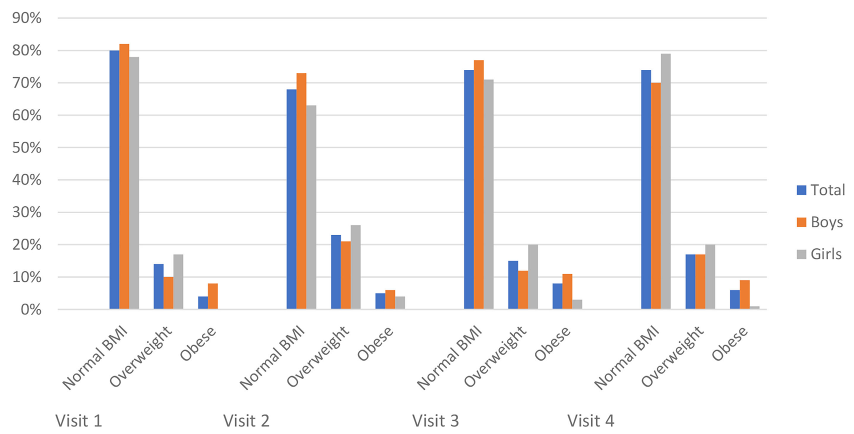

FIGURE 3
The prevalence of overweight and obesity in children with type 1 diabetes before and during SARS-CoV-2 pandemic.

on a daily basis (58.5% and 13.8%, respectively), whereas everyday consumption of fast foods and meat was the highest (3.2% and 40.4%, respectively). The weight gain in overweight and obese people was the greatest. The authors conclude that mitigation measures may amplify preexisting excess adiposity and, therefore, magnify health issues related to body mass (24). The meta-analysis by Bakaloudi et al. confirmed that there was a tendency toward an increase in body weight during lockdown in the majority of studies and populations (25).

The meta-analysis by Tu-Hsuan Chang et al. showed that there was an increase in the BMI of children in the general population (MD 0.77, 95% CI 0.33–1.20;p= 0.0006), associated with the period with strict restrictions, followed by the increased rates of obesity (OR 1.23, 95% CI 1.10-1.37; p = 0.0002) and overweight (OR 1.17, 95% CI 1.06-1.29; p = 0.001). The authors performed the subgroup analysis according to the study population, which showed that the BMI did not change significantly during the lockdown both in children with T1D mellitus and obesity. It has to be underlined though that the substantial heterogeneity among studies, also in the subgroup analysis, was reported (26). On the contrary, in our study, the BMI as well as BMI%ile of pediatric patients with T1D increased significantly during the study period, especially in the period of restrictive lockdown, stabilizing subsequently with the withdrawal of the pandemic limitations. On the other hand, in overweight and obese patients with T1D, in absolute values, the change of the BMI was significantly higher in comparison with normal-weight children; however, overweight and obese subjects reduced their BMI%ile during lockdown. Thus, it can be concluded that children who had excess adiposity before the COVID-19 pandemic did not experience accelerated weight gain during the pandemic. Comparable results were reported by Weaver et al., who revealed that the BMI z-score gain increase was enhanced during the pandemic lockdown, but this observation did not apply to pre-pandemic overweight and obese children (11). We may only speculate that improved parental control while being together during the lockdown, and less possibility to buy unhealthy snacks, resulted in less weight gain.

The question is whether the observed changes in body weight could be transitory once the imposed restrictions are withdrawn. Matsumoto et al. found that in obese patients, a decrease in body fat was significantly higher during lockdown in comparison with the group unaffected by mobility restrictions. On the other hand, their exercise tolerance (VO2 at anaerobic threshold and peak VO2) was significantly lower (27). This corresponds with Jarnig et al.'s study in children, who observed reduced CRF due to reduced physical activity during lockdown (12). The time after COVID-19 mitigations were withdrawn worldwide is too short to be sure whether children will recover from the consequences of the previous restrictions. Our study brings some data on this. As in many other studies, we have observed an increase in the BMI and BMI%ile during the period of restrictive lockdown. It resulted in an increase in the prevalence of overweight and obesity in the studied cohort by approximately 10%, from the initial 18% on the pre-pandemic visit to 28% on the second visit (the lockdown visit). Fortunately, a further increase in both the BMI and BMI%ile was not observed, indicating the stabilization of patients' body mass when pandemic mitigations were loosened and the intensification of physical activity was possible. Furthermore, the prevalence of excess adiposity was reduced by 4.6% between the second and third visits, giving the overall increase in overweight and obesity rate by 5.4% throughout the study period. It clearly indicates the importance of physical activity in maintaining body mass (17, 18).

The deterioration of metabolic control may be expected in patients with T1D as a result of lower intensity of physical activity, negative change in nutritional habits, and an increased level of stress accompanying the sudden change of lifestyle due to lockdown and separation anxiety. Indeed, people with diabetes who reported deterioration in metabolic control experienced higher stress, followed by increased insulin demand during lockdown, as reported by Ruissen et al., but, surprisingly, an elevated level of anxiety was not associated with HbA1c itself. Furthermore, in this study, 40.9% of patients reported weight gain and 45.7% decreased physical activity without any difference between people with type 1 and type 2 diabetes, and, again, without any influence on HbA1c. Ruissen et al. showed in people with T1D that HbA1c was lower during lockdown than before this period (7.52 ± 1.1% *vs.* 7.68 ± 1.2%, p<0.0001), even though the mean difference is not clinically relevant. Additionally, glucose monitoring data showed higher time in range (63.4% *vs.* 60.5%, p=0.0009) together with lower time above range (32.1% *vs.* 34.6%, p<0.003), but glucose variability did not change. The authors concluded that the improvement in metabolic control was a consequence of more focus on diabetes self-management, indicated by more frequent glucose monitoring, as the number of FGM scans per day increased from 9.6 ± 6.5 before lockdown to 11.8 *vs.* 8.1 during lockdown (p<0.01). Interestingly, the biggest improvement in HbA1c was reported in patients in the highest pre-lockdown tertile of HbA1c (28). Continuous glucose monitoring systems significantly improved the metabolic control of diabetes (29). Similar results were observed in our cohort, where HbA1c lowered by 0.4% during the lockdown, despite comparable time in range. The following visits showed the stabilization of improvement in the metabolic control achieved during the first months of the studied period. Our results are in agreement with an Italian report on 62 patients, showing the time in range increased by 3% (p=0.008), resulting in the improvement from 7.4% to 7.25% of the glucose management indicator during the first 3 months of lockdown. Furthermore, glucose variability lowered as glucose standard deviation and coefficient of variation improved across the study (p<0.0001 and p=0.001, respectively) (30). Another Italian study revealed the dependence of metabolic results on the patient's age because CGM metrics improved during the lockdown in children (glucose standard deviation, p=0.029 and time below range, p=0.029) and adults (time in range, p<0.001), whereas, in teenagers, CGM metrics remained unchanged during lockdown. Furthermore, it was reported that adult patients who improved metabolic control were more physically active and younger, whereas those who worsened glucose control showed higher perceived stress compared with others (31). Eberle and Stichling in their systematic review, which included 33 studies with 2,881 T1D participants and 1,823 type 2 diabetes participants, concluded that the glycemic control of patients with T1D improved significantly during lockdown (32). The authors of the above studies suggest that continuous parental management associated with positive changes in self-management of the disease could have beneficial effects on metabolic control in T1D. The role of telemedicine was also underlined (30–32). The results from the Diabetes Prospective follow-up registry regarding metabolic control during the COVID-19 pandemic lockdown in a large cohort of German children with T1D showed comparable metabolic control before, during, and after lockdown in the spring months of 2020. The authors aggregated HbA1c values from laboratory measurements and, from continuous glucose monitoring, derived estimates into a combined glucose indicator (CGI), which is analogous to HbA1c itself. The CGI values of 19,729 patients for 2020 were insignificantly higher compared with those for 2019, whereas the time in range increased and the mean sensor glucose decreased in 2020. It is noteworthy that there were fewer hospitalizations in 2020 in comparison with 2019 (33). This is in line with the observation of our center (data not shown). Stable metabolic control during the period of COVID-19 related mitigation measures was also found in pediatric patients with T1D from Greece and Israel (34, 35). To our knowledge, no study has indicated a deterioration of metabolic control in patients with T1D. Again, the "stay at home" rule may have had a positive effect on metabolic control in diabetic patients by increasing the time spent under parental supervision and parental diabetes management. Furthermore, slowdown in daily activities might have resulted in focusing on one's diabetes management, whereas spending more time in a private environment reduced the embarrassment in performing diabetes care with others present and the diabetes-related stigma, especially in adolescents (36, 37).

Undoubtedly, the COVID-19 pandemic and necessary restrictions resulting from it have worsened the burden of childhood obesity. Furthermore, the reduction of physical activity along with the increase in sedentary behavior not only negatively influenced changes in the BMI but also impaired relevant health-related parameters including cardiorespiratory fitness (CRF). The CRF level is negatively correlated with markers of adiposity: BMI, waist circumference, and quantity of body fat. The higher the level of CRF during childhood, the lower the risk factors of metabolic syndrome and cardiovascular disease (CVD) later in life (38). The role of diabetes as a cardiovascular risk factor is well known. Fortunately, restrictions related to COVID-19 generally did not impair metabolic control in people with T1D (39–41). Treatment of CVD risk factors, including excess adiposity, as well as regular physical activity plays an important role in the primary and secondary prevention of CVD (42). This observation is true not only in the general population but also in people with diabetes (43). Therefore, it could be assumed that increasing obesity and worsening of CRF due to prolonged periods of forced inactivity will likely have additional implications for the health of children and adolescents with diabetes. Hence, interventions to ensure the recovery to an age-adequate BMI and CRF level are needed and should be undertaken (44).

Conclusions

The parameters of metabolic control in pediatric patients with T1D during the pandemic period remained stable; however, weight gain and an increase in daily insulin dose have been observed, possibly due to reduced physical activity.

Data availability statement

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

Ethics statement

This study was reviewed and approved by The study was approved by the Bioethical Committee of Wrocław Medical University, Wrocław, Poland (No. KB-487/2022). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and institutional requirements.

Author contributions

AZ-K: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Validation; Writing - original draft, review & editing. BW: Investigation; Methodology; Validation; Writing - review & editing. AN: Conceptualization; Methodology; Supervision; Writing - review & editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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The effect of COVID-19 on the presentation of thyroid disease in children

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Introduction: Although studies suggest a potential link between COVID-19 and thyroid dysfunction in adults, there are insufficient data to confirm that association in children, and whether there is any effect on presentation to healthcare services.

Aims: To identify whether presentations of thyroid dysfunction in children to a tertiary paediatric hospital changed as a result of the COVID-19 pandemic.

Methods: A retrospective case note review was conducted of all children with abnormal thyroid function tests between 1st January 2016 and 31st December 2021 at a tertiary paediatric endocrine centre in the United Kingdom.

Results: Overall, 244 children whose first presentation was within the timeframe of interest were included in this study, with a median age (range) of 11.5 (6.1, 16.8) years. Of these, 43 (18%) were hyperthyroid and 201 (82%) were hypothyroid. The greatest number of thyroid presentations occurred in 2021 (n=60, 25% of total over time period) and the fewest in 2020 (n=10, 4% of total over time period). Prior to this, the median (range) number of presentations per year was 34 (28, 39). There were no statistically significant differences in biochemistry, antibody status or other clinical characteristics between those who presented with hyperthyroidism prior to the pandemic or after. In those with hypothyroidism, baseline biochemistry was similar between the 2 groups, but the presence of other autoimmune conditions was greater pre-pandemic (17.2% vs 15.0%, p=0.03). In addition, patients were more likely to have transient thyroid dysfunction, which did not require treatment post-pandemic (70.0% vs 49.6%, p=0.0086).

Conclusions: Although overall rates of presentation with thyroid dysfunction have not altered since the first wave of the COVID-19 pandemic, presentations with transient thyroid dysfunction, not requiring ongoing treatment have increased. Further research regarding the relationship between COVID-19 and thyroid function in children and young people, is needed.

KEYWORDS

coronavirus, virus, thyrotoxicosis, hypothyroidism, antibodies

Introduction

Approximately 1-2% of children will have a thyroid disease before the age of 16 years (1). During the COVID-19 pandemic, there have been concerns regarding potential for increased rates of thyroid dysfunction, potentially due to the mechanism of entry of the virus *via* angiotensin-converting enzyme 2 (ACE2), which is highly concentrated on thyroid cells (2, 3). In addition, thyroiditis as a result of viral infection triggers pre-formed colloid release which enables raised thyroid hormone concentration, i.e. thyrotoxicosis. Both autoimmune and viral thyroiditis can destroy follicular cells, further escalating thyrotoxicosis (4). In particular, COVID-19 can cause a cytokine storm, characterised by hyperactivity of the Th1/Th17 immune response with increased production of proinflammatory cytokines, for example IL-6, which has been strongly associated with thyroiditis (5).

Studies regarding thyroid function and COVID-19 in adults suggest that the virus can contribute to increased rates and severity of thyroid dysfunction. One systematic review incorporating 1,237 adult patients, identified a positive correlation between thyroid dysfunction and clinical severity of COVID-19, with prevalence of thyroid dysfunction in patients positive for COVID-19 varying between 13-64% (6). Most commonly studies report lower Thyroid Stimulating Hormone (TSH) and free triidothyronine (fT_3) levels (7–9) in association with the virus.

There are very limited data available to date describing the effects of the pandemic on presentation with thyroid disease in children and young people. One study from an outpatient paediatric practice in New York reported increased numbers of thyroid screening tests but with no differences in TSH in children between the ages of 6-18 years pre- and post-pandemic (10). There have also been case reports in children showing an association between COVID-19 and significant thyroid dysfunction including thyroid storm (11), as well as increased risk of admission to Paediatric Intensive Care units (12).

Of note, the COVID-19 pandemic also caused significant changes to the provision of healthcare throughout the world. For example, in one centre in the United Kingdom, nearly 1/3 of children with trisomy 21 did not receive the recommended annual TSH screening in 2020 compared to 3% in 2015 (13). A study in 25, 361 adults with thyroid disease in Japan found that thyroid control deteriorated with delayed follow up during the pandemic (14). It is possible therefore, that rates and clinical characteristics of presentation with thyroid dysfunction in all children may also differ pre- and post-pandemic.

The aim of this study was to identify whether presentations of thyroid dysfunction in children to a tertiary paediatric hospital changed as a result of the COVID-19 pandemic.

Methods

Patients and methods

A retrospective case note review was conducted of all children with abnormal thyroid function tests between 1st January 2016 and 31st December 2021 at the Royal Hospital for Children in Glasgow, Scotland. This is a tertiary paediatric hospital, which takes new patient referrals from birth to the age of 16.9 years from throughout the West of Scotland, but primarily from the Greater Glasgow and Clyde area.

Children were identified *via* a primary search of laboratory results. Inclusion criteria were: age 5.0 to 16.9 years old, TSH>5mU/L or a fT_4>21pmol/L and recorded between 01/01/2016 to 31/12/2021. Exclusion criteria were: diagnosis of secondary thyroid disease, abnormal thyroid function result prior to 01/03/2016, or where clinical information were not available. Where a child had more than one abnormal test result recorded within the timeframe and identified in the primary search, the first abnormal result was used for analysis if it was in the study period. It was not known if the children had exposure to COVID-19, prior or current COVID-19 infection, or COVID-19 vaccination. However, COVID-19 vaccination was not available to children in the United Kingdom during this time period. Routinely collected hospital data were collected from the child's electronic medical records to determine whether treatment was started for the thyroid dysfunction, as well as sex and age at the time of the blood test and the presence/absence of some key symptoms of thyroid disease. The children were seen by different members of the Paediatric Endocrinology team so absolute standards for starting treatment, for example, may differ although in all cases, this was in response to clinical condition as well as biochemistry. For the purposes of analysis, 'pre-pandemic' refers to results prior to 01/03/2020.

Biochemical analyses

All biochemical analyses were performed on the Abbott Architect platform using chemiluminescent microparticle immunoassays (CMIA). The functional sensitivity for TSH was 0.01 U/L. The inter-and intra-assay coefficients of variation (CVs) were for TSH were; (inter) 3.1%, 2.0% and 2.2% and (intra) 4.1%, 2.9% and 4.7% at levels of 0.7 U/L, 5.2 U/L and 23.9 U/L. The functional sensitivity for fT_4 was 5 pmol/L. The inter- and intra-assay CVs for FT4 were; (inter) 2.6%, 2.9% and 7.1% and (intra) 1.5%, 0.8% and 4.9% at levels of 8.9 pmol/L, 18.9 pmol/L and 33.4 pmol/L. The functional sensitivity for Total T_3 (T_3) was 0.4 U/L. The inter-and intra-assay CVs were for (T_3) were; (inter) 2.6%, 1.2% and 1.3% and (intra) 4.6%, 2.2% and 1.6% at levels of 1.2 nmol/L, 2.6 nmol/L and 3.9 nmol/L. The functional sensitivities for Thyroid peroxidase (TPO) antibodies and thyroid receptor antibodies (TRAb) these assays were 1.0 U/ml and 1.3 U/l respectively The inter- and intra-assay CVs for thyroid peroxidase (TPO) antibodies were (inter) 3.2%, 3.5% and 1.8% and (intra) 5.5%, 4.6% and 4.3% at levels of 25.2 U/ml, 72.5 U/ml and 197 U/ml. The inter- and intra-assay CVs for thyroid receptor antibodies (TRABs) were; (inter) 4.8%, 1.8% and 1.1% and (intra) 5.2, 2.0 and 1.2 at levels of 2.9, 9.8 and 29.9 U/l.

Ethics

Caldicott Guardian approval was obtained for this study.

Statistical analyses

Data processing and statistical analysis was conducted using GraphPad Prism v 8.01. To compare differences before and after the pandemic, non-continous variables were analysed using Fisher Exact Test. Continuous variables were analysed using Mann–Whitney U test. A p-value <0.05 was regarded as statistically significant.

Results

The primary search identified 1,239 abnormal TSH or fT_4 results (TSH>5mU/L or a fT4>21pmol/L) between the dates of 01/01/2016 to 31/12/2021 at the Royal Hospital for Children, Glasgow. A total of 995 (80%) of these were excluded, as they were repeat blood tests in known patients, already receiving treatment for thyroid dysfunction. Overall, 244 children whose first presentation was within the timeframe of interest were therefore included in this study, with a median age (range) of 11.5 (6.1, 16.8) years. Of these, 43 (18%) were hyperthyroid and 201 (82%) were hypothyroid (Figure 1). None of the children in the post-pandemic group had a history of trisomy 21, whereas 5 (3%) of the pre-pandemic group did.

With regards to the distribution of thyroid presentation by year within the timeframe of the study, this increased over the study period (Figure 2). The median (range) number of presentations with thyroid dysfunction prior to the pandemic was 34 (28, 39) per year. The greatest number of thyroid presentations occurred in 2021 (n=60, 25% of total over time period) and the fewest in 2020 (n=10, 4% of total over time period) (Figure 2).

Presentation of hyperthyroidism

In those who were hyperthyroid, 33 patients presented prior to the pandemic (median (range) 8 (5-13) per year, 0.2 per week) and 10 patients presented during/after the pandemic (n=2 in 2020 and n=8 in 2021, 0.1 per week overall) (Table 1). There was a female preponderance in both groups. Median (range) age pre-pandemic was 12 years (7, 15) compared to 14 (7, 16) during the pandemic. There were no statistically significant differences in biochemistry or other clinical characteristics between the 2 groups. In all cases where treatment was not started, this was because repeat blood tests had normalised. There were no differences in the proportions of children presenting with unrecordably low TSH pre- and during/after the pandemic (75% vs 65%, p=0.4) or with unrecordably high fT_4 (0% vs 0%, p>0.999).

Presentation of hypothyroidism

In the hypothyroid group 141 patients presented before the pandemic and 60 patients presented during the pandemic (0.3 per week overall) (Table 2). In 2021 there were 52 presentations of hypothyroidism, compared to a median (range) of 28 (13, 44) and a total of only 8 presentations during 2020. Overall, the weekly presentations of hypothyroidism increased from 0.3 new referrals per week to 0.6 post pandemic. The median (range) age in those who presented pre-pandemic was 11 years (6, 16), with the median (range) age in those presenting during/after the pandemic also being 11 (7, 16).

Presenting pre- or during the COVID-19 pandemic did not affect TSH, free T_4 or TPO antibodies in hypothyroid patients. The presence of other autoimmune conditions was greater pre-

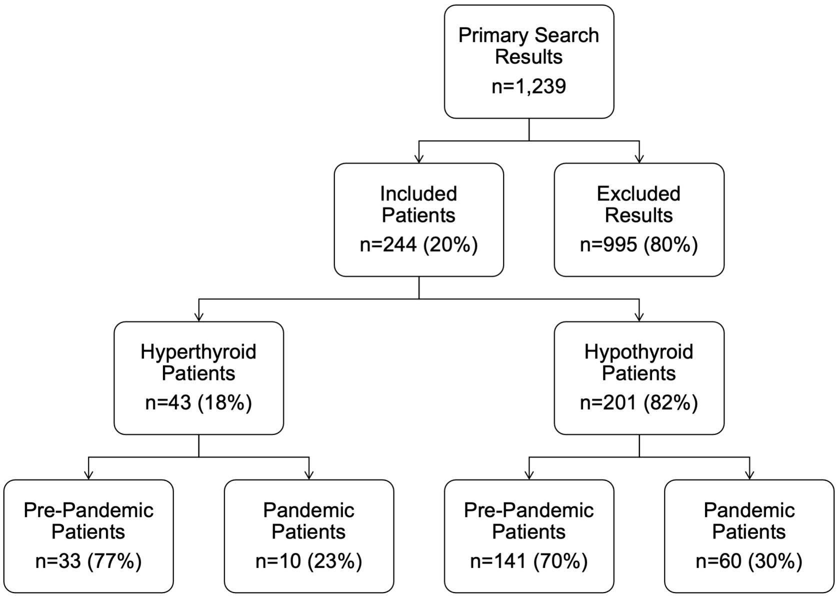

FIGURE 1
Flow diagram detailing the inclusion and exclusion of patients. 'Pre-pandemic' refers to the period 1st January 2016 to 1st March 2020. 'Post-pandemic' refers to the period between 2nd March 2020 and 31st January 2021.

pandemic with a prevalence of 17.2% compared to during the pandemic where there was a prevalence of 15.0%, (p=0.03). Fewer patients received treatment for thyroid dysfunction during the pandemic, with 50.4% of the patients who presented before the pandemic being treated compared to 30.0% who were commenced on treatment during/after the pandemic (p=0.0086). Again, in all cases where treatment was not started, this was because repeat blood tests had normalised. There were no differences in the proportions of children presenting with unrecordably high TSH pre- and during the pandemic (10.0% vs 11.8%, p=0.8) or with unrecordably low fT_4 (8.5% vs 10.3%, p=0.7).

Discussion

This retrospective observational study found that the presentation of thyroid dysfunction in children within a

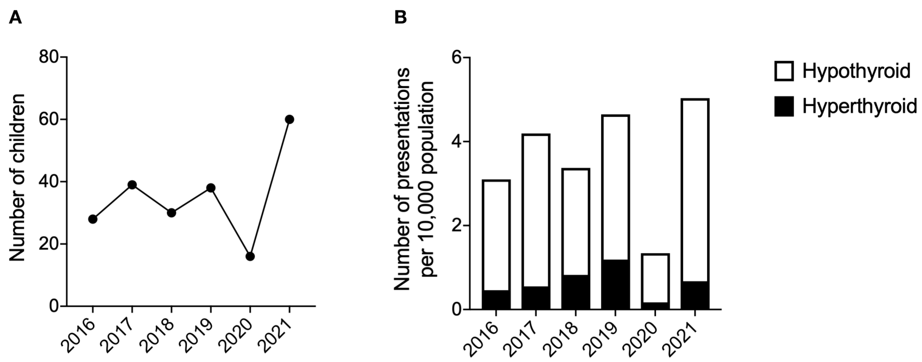

FIGURE 2
Number of presentations with thyroid dysfunction. **(A)** Number of children presenting with thyroid dysfunction per year. **(B)** Number of presentations of hyperthyroidism and hypothyroidism per 10,000 population. Years 2016-2019 used the mid-2016 population estimate for 5-15year olds in Greater Glasgow. Years 2020-2021 used the mid-2020 population estimate for 5-15year olds in Greater Glasgow. Population data from the National Records of Scotland (15).

TABLE 1 Characteristics of hyperthyroid patients.

	Pre-Pandemic n=33 (76.7%)	Pandemic n=10 (23/3%)	p-value
Female sex (%)	21 (63.6)	6 (60.0)	>0.9999
Median age (years) (range)	12 (7, 15)	14 (7, 16)	0.6729
Median TSH (mU/l) (range)	<0.01 (<0.01, 4.5)	<0.01 (<0.01, 2.38)	0.9021
Median fT4 (pmol/l) (range)	26.7 (15.7, 49.4)	34.8 (21.4, 64.4)	0.2017
Median fT3 (pmol/l) (range)	6.2 (1.4, >12.3)	7.1 (4.3, >9.2)	0.3729
Median TPO antibodies (U/ml)(range)	349.0 (1.1, >2000.0)	535.4 (<1.0, 1497.8)	0.9402
No +ve TPO antibodies (%)	21 (63.6)	7 (70.0)	>0.9999
Median TRABs (U/ml) (range)	18.0 (1.1, 77.0)	7.3 (<1.0, 33.0)	0.0800
No +ve TRABs (%)	21 (63.6)	8 (80.0)	0.4557
Goitre (%)	13 (39.4)	7 (70.0)	>0.9999
Tremor (%)	8 (24.2)	6 (60.0)	>0.9999
Menarche (% of females)	5 (23.8)	2 (20.0)	>0.9999
Autoimmune history (%)	6 (18.2)	0 (0.0)	0.1405
Family history (%)	11 (33.3)	2 (33.3)	0.1357
Treated (%)	21 (63.6)	8 (80.0)	0.457

TSH, Thyroid Stimulating Hormone; fT4, thyroxine; T3, triiodothyronine; TPO, thyroid peroxidase; TRAB, thyroid receptor antibody.

TABLE 2 Characteristics of hypothyroid patients (n=201) prior to the pandemic and during the pandemic.

	Pre-Pandemic n=141 (70.2%)	Pandemic n=60 (29.8%)	p-value
Female sex (%)	93 (65.9)	43 (71.7)	0.5106
Median age (years) (range)	11 (6, 16)	11 (7, 16)	0.1498
Median TSH (mU/l) (range)	8.2 (5.01, >500)	6.71 (5.01, >500)	0.8371
Median fT4 (pmol/l) (range)	11.1 (<0.01, 20.7)	11.7 (<0.01, 17.0)	0.1614
Median fT3 (pmol/l) (range)	2.0 (0.9, 4.1)	2.4 (1.6, 3.1)	0.8831
Median TPO antibodies (U/ml)(range)	373.5 (<1.0, >2000)	366.2 (<1.0, >2000)	0.7163
No +ve TPO antibodies (%)	72 (51.1)	31 (51.7)	>0.9999
Median TRABs (U/ml) (range)	1.4 (<1.0, >40.0)	<1.0 (<1.0, 7.3)	0.779
No +ve TRABs (%)	12 (8.5)	5 (8.3)	>0.9999
Goitre (%)	23 (17.2)	6 (10.0)	0.4222
Tremor (%)	0 (0)	1 (1.7)	0.3269
Menarche (% of females)	16 (23.8)	2 (20.0)	>0.9999
Autoimmune history (%)	30 (21.3)	9 (15.0)	**0.0343***
Family history (%)	29 (20.6)	17 (28.3)	0.6238
Treated (%)	71 (50.4)	18 (30.0)	**0.0086****

TSH, Thyroid Stimulating Hormone; fT4, thyroxine; T3, triiodothyronine; TPO, thyroid peroxidase; TRAB, thyroid receptor antibody. *p<0.05. **p<0.01.
Bold mean they are statistically significant.

tertiary paediatric endocrine centre did not significantly change pre- and post-pandemic. This study adds to a small, but rapidly growing pool of evidence around the effect of the COVID-19 pandemic on thyroid function. Shidid et al. (10) recently reported no significant differences observed in percentage of abnormal TSH tests reported pre- and post- pandemic in children. The findings of our study support this statement and expand on it as we included fT_4, fT_3, TPO antibodies and TRABs as well as characteristics of presentation.

Within the hypothyroid cohort, more children presented with other autoimmune conditions or trisomy 21 in the pre-pandemic time frame compared to during/after the pandemic. This is contrast to studies in adults which have reported an increase in autoimmune mediated dysfunction after the pandemic (16). These data have not yet been reported in children. This may be because there was a reduction in total number of presentations of any children to healthcare services due to the constraints of the pandemic, and as such, additional autoimmune conditions, such as coeliac disease, may not have been identified during this time. The first lockdown in the UK was commenced in March 2020; therefore COVID-19 might have been circulating in the community or the population may have changed its behaviour in response to the virus in the months before this. Indeed, overall presentations in 2020 are likely to have been lower due to limited access to healthcare during the peak of the pandemic.

In the hypothyroid cohort, there was also a reduction in the number of children requiring treatment post-pandemic. This suggests that these children may have had minor transient thyroid dysfunction, perhaps secondary to COVID-19 related thyroiditis, which then resolved prior to the need for treatment. A systematic review into thyroid dysfunction related to COVID-19 has reported thyroiditis, which spontaneously improves within 3 months of infection (17). As such, it would be interesting to determine the COVID-19 antibody status of children within this group, but this was not possible within this study. Future prospective studies should consider antibody status and its effects on health status.

This study reports data from a single health board region, which may limit its generalisability and data from paediatric endocrine centres elsewhere in the world may therefore differ accordingly. That said, the Greater Glasgow and Clyde health board reflects a geographical area with the highest density population of Scotland along with huge health discrepancies (15). Differences in the number of presentations with thyroid dysfunction may reflect challenges associated with access to health services during the pandemic.

Although overall rates of presentation with thyroid dysfunction have not altered since the first wave of the COVID-19 pandemic, presentations with transient thyroid dysfunction, not requiring ongoing treatment have increased. Further research regarding the relationship between COVID-19 and thyroid function in children and young people, is needed. Where possible, further prospective longitudinal studies should therefore be conducted.

Data availability statement

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

Author contributions

RM and EW undertook data collection and drafting of the manuscript. They contributed equally to the manuscript and should be considered as joint 1st authors. AL-H undertook data analysis and redrafting of the manuscript. JM, AM, SCW, SFA, and MGS provided data for analysis and revised the manuscript. All authors have read and approved the manuscript for submission.

Conflict of interest

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

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Implicating factors in the increase in cases of central precocious puberty (CPP) during the COVID-19 pandemic: Experience of a tertiary centre of pediatric endocrinology and review of the literature

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Sexual development is a complex mechanism activated by the hypothalamic-pituitary-gonadal axis. Over the last one hundred years there has been a decline in the age at puberty onset in industrialised countries. Some Italian studies showed an increase in diagnoses of Central Precocious Puberty (CPP) during the COVID-19 pandemic. It is thus supposed that in this period there was an increased impact of factors that can influence pubertal development. Our retrospective monocentric study aimed to confirm the existence of this phenomenon and analysed possible related factors. We retrospectively evaluated clinical, laboratory, radiological and ultrasound (US) data of 154 girls referred to our Tertiary Centre of Paediatric Endocrinology from January 2019 to April 2021 for different forms of Precocious Puberty. We subdivided the cases into subgroups according to the final diagnosis: CPP, Early Puberty (EP), isolated thelarche and isolated pubarche. The observation period was subdivided into: Period 1, before lockdown (1 January 2019 – 8 March 2020) and Period 2, lockdown and the following months (9 March 2020 – 30 April 2021). Period 2 was further divided into "restrictive lockdown period" (Period 2.1) (March 2020 – 14 June 2020, in which the schools were closed) and "less restrictive lockdown period" (Period 2.2) (15 June 2020 – 30 April 2021). We analysed data regarding the use of electronic devices before and during lockdown in a group of girls with CPP diagnosed in Period 2 and we compared the data with that of a control group. Our data show an increase in the number of new diagnoses of CPP during lockdown and in the following months, compared with the previous period. We also detected a higher use of PCs and smartphones in girls with CPP diagnosed in Period 2, compared with the control group. The percentage of the presence of endometrial rhyme detected during the pelvic ultrasound was higher in girls with CPP in Period 2, compared with the previous period. Based on our data we assume there was an environmental effect on pubertal timing that calls our attention to factors such as food, use of electronic devices and stress. We will need further studies to better understand this data.

KEYWORDS

central precious puberty, COVID - 19, early puberty, thelarche premature, electromagnetic field, BMI - body mass index, endometrial rhyme, isolated pubarche

Introduction

The complex mechanism that leads to sexual development starts from the activation of the hypothalamic-pituitary-gonadal axis by an unknown primary input. Over the last one hundred years there has been a decrease in age at puberty onset in industrialised countries; menarche appears on average in girls about 12 and a half years old, and thelarche in girls between 9 and a half and ten years old (1, 2). The basis of this decline involves not only genetic factors (2, 3) but also environmental factors such as BMI (4), dietary habits, physical activity, stressors (5) and exposure to ECDs and electromagnetic fields (6, 7).

In Italy, the restrictions due to the coronavirus pandemic led to deep changes in people's habits. Italians had to stay at home for several months. The schools closure and the beginning of distance learning led to an increase in the use of electronic devices. These devices were also used more frequently for extracurricular reasons (video games, TV, PC games) that resulted in an accumulation of hours spent in front of screens.

Forced home - staying at home also led a reduction in physical activities and an increase in consumption of junk food resulting in body weight gain.

In addition, the pandemic situation led to a growth in stressors for many families (fear of illness, fear for the health of loved ones, economic problems…).

Some previous Italian studies reported an increase in the number of new cases of Central Precocious Puberty (CPP) in girls during the COVID-19 pandemic (8–11) It has been assumed that during this period, the impact of factors interfering with pubertal development increased.

This retrospective monocentric study aimed to confirm the existence of this phenomenon and analysed possible related factors.

Materials and methods

We retrospectively evaluated clinical, laboratory, radiological and ultrasound (US) data on 154 girls referred to our Tertiary Centre of Paediatric Endocrinology from January 2019 to April 2021 for different forms of Precocious Puberty. We subdivided the cases into subgroups according to the final diagnosis: CPP, Early Puberty (EP), isolated thelarche and isolated pubarche. CPP was defined according to Consensus Guidelines (12). Early puberty was defined as the onset of pubertal signs between 8 and 9 years old (13).

The observation period was subdivided into: Period 1, before lockdown (1 January 2019 – 8 March 2020), and Period 2, lockdown and the following months (9 March 2020 – 30 April 2021). Period 2 was further divided into "restrictive lockdown period" (Period 2.1) (9 March 2020 – 14 June 2020, in which the schools were closed) and "less restrictive lockdown period" (Period 2.2) (15 June 2020 – 30 April 2021).

We analysed data regarding the use of electronic devices obtained through a questionnaire (Figure 1) administered to 17 girls diagnosed with CPP in Period 2 and to 26 "short normal" controls matched for sex and age referred to our Centre in the same period.

We excluded girls with CPP associated with hypothalamic–pituitary congenital malformations, neurological, neurosurgical and/or genetic diseases, psychomotor delay, oncological diseases. We also excluded adopted girls with CPP.

Age, sex, ethnicity, family history of precocious and EP, mid-parental height, age at the onset of pubertal signs, and age at first observation were recovered from clinical records. Height, weight, birth weight and BMI were expressed as a standard deviation score (SDS) according to Italian standards (14). Pubertal stage was recorded according to Marshall and

1. How much time (minute or hours /day) did you spend using electronic devices before the lockdown period:

	Never	<30'	30'-60'	1-2 hours	2-3 hours	3-4 hours	4-5 hours	>5 hours
PC								
TV								
Tablet								
PC/TV games								
Smartphone								

2. During lockdown (march 2020 – June 2020) how much time (minute or hours/day) on average did you spend using electronic devices (including the hours of remote learning)

	Never	<30'	30'-60'	1-2 hours	2-3 hours	3-4 hours	4-5 hours	>5 hours
PC								
TV								
Tablet								
PC/TV games								
Smartphone								

3. At what time did you use electronic devices on average before lockdown period?

☐ 8-13
☐ 13-20
☐ 20-24

4. At what time did you used electronic devices during lockdown period (march 2020 – June 2020)

☐ 8-13
☐ 13-20
☐ 20-24

5. Do you usually use electronic devices in your bedroom before falling asleep?

☐ YES ☐ NO

FIGURE 1
Questionnaire regarding the use of electronic devices.

Tanner's genital stage (15); we analysed the rate of progression of pubertal signs. We defined "rapid progression" as a transition from B2 to B3 in less than six months.

When available, we recorded levels at baseline of follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol [E2]. A Gonadotropin-releasing hormone (GnRH) test was performed by i.v. administration of GnRH to 94 girls (37 in Period 1 and 57 in Period 2) with LH and FSH measurement at 0, + 30 and + 60 min.

A basal level of LH > 0,3 IU/L and/or a peak response of LH after GnRH infusion > 5 IU/L, with or without serum estradiol levels > pg/ml, were considered suggestive of CPP (16–18).

We estimated bone age (BA) from an X-ray of the left hand and wrist using the Greulich & Pyle atlas (19). Bone age advancement was defined as the difference between BA and chronological age expressed in years.

Pelvic ultrasound was trans-abdominally performed by a group of paediatric evaluation expert radiologists. It was used a Convex ecotomograph with B-mode ultrasound signal and a variable wavelength between 3.5 and 5.0 MHz (Philips). The subject was examined in a supine position with distended bladder and we're detected uterine measurements [longitudinal diameters (LD), tranverse diameter (DT) and antero-posterior diameter (APD)] and ovarian measurements. It was also evaluated the visibility of the endometrial rhyme. The uterine volumes were obtained through the ellipsoid formula [(DL x DT x ADP x 0.52)/1000]. A uterine longitudinal diameters (ULD) > 34 mm and/or a uterine volume (UV) > 4 ml and/or the presence of endometrial rhyme were considered suggestive of estrogenic stimulation and advanced pubertal development (20).

Statistical analysis

We performed a descriptive analysis of central trend measures (mean and median), with range maximum and minimum value and standard deviation of continuous variables (age at diagnosis, SDS height, SDS BMI, Tanner stage, neonatal weight, rate of progression of pubertal development, basal and peak value of LH and FSH, estradiol, bone age, uterine volume and longitudinal diameter of uterus).

We analysed Tanner stage with frequency tables. We analysed data with Chi squared tests.

We realised frequency tables for distribution analysis of descriptive variables (presence of endometrial rhyme, Tanner stage and medical therapy).

We used Student's t-distribution tests to evaluate differences between means of the following variables, in the different groups defined on the basis of diagnosis: SDS weight, SDS height, SDS BMI, birth weight, rate of progression of pubertal development, age at diagnosis, basal and peak value of LH and FSH, bone age, uterine volume, longitudinal diameter uterus.

We used non-parametric tests (Mann–Whitney) for data with non-normal distribution and two proportion zeta tests and chi squared tests for frequency analysis.

All statistical tests were two-tailed and $P < 0.05$ was considered statistically significant.

Statistical analyses were performed with the use of NCSS 2021 (NCSS 2021 Statistical Software. NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss, 2020) for statistical analyses.

Results

Table 1 shows the frequency of the different diagnoses in the two periods of observation. Compared to Period 1, the Group CPP only increased significantly the frequency of diagnosis in Period 2.

Table 2 shows auxological data at diagnosis and rate of pubertal progression in girls with CPP diagnosed in period 2, compared with girls with CPP diagnosed in period 1. We did not find any significant difference in the rate of pubertal progression. As regards isolated pubarche, our data show a lower onset age in the pre-Covid group with statistical significance (6.75 ± 0.04 years vs 7.33 ± 0.2 years, $p < 0.005$), probably due to the diagnostic delay during the pandemic.

Table 3 shows hormonal data at diagnosis in girls with CPP subdivided by observation period. We did not find any difference in the two groups.

Table 4 shows US data in girls with CPP subdivided by observation period. The percentage of girls with endometrial rhyme at diagnosis was higher in period 2, compared to period 1, but this difference was not significant, probably due to the small sample of patients.

We found 3 girls with CPP and 14 girls with EP in sub-Period 2.1 and 14 girls with CPP and 34 girls with EP in sub-Period 2.2. The comparative analysis of sub-Period 2.1 and 2.2 did not show any differences in auxological, laboratory and radiologic data except for BMI SDS that showed a significant increase in the period after the restrictive lockdown in the EP group (sub-Period 2.1: -0.73 ± 1.39, sub-Period 2.2 0.26 ± 0.72). We did not find any significance in the group with CPP, probably due to the sample's reduced size (sub-Period 1 0.07 ± 0.79 vs sub-Period 2 0.79 ± 0.53).

In regard to the results of the questionnaire on the use of electronic devices in girls with CPP, the percentage of girls with CPP that used PCs and tablets more than 2 hours a day was significantly higher during the lockdown period, compared with the preceding period (PC 85.5% vs 0%, Tablet 15% vs 0, $p < 0.005$). In addition, the percentage of girls that used PCs and smartphones more than 2 hours a day during lockdown was significantly higher in girls with CPP compared with the control group (PC 85.5% vs 73%, $p < 0.005$, Smartphone 29% vs 10% $p < 0.005$).

Discussion

CPP is a rare disease that involves mainly females and in most cases it is idiopathic.

The results of our study, in line with other Italian studies recently published (8–11), show an increase in the number of new diagnoses of CPP during lockdown and in the following months, compared with previous period.

Moreover, in accordance with the results of Chioma et al (10), this increase is observed only in patients with the classical form of CPP, with onset before 8 years of age, while it was not observed in girls with isolated forms of pubarche and thelarche. These results therefore prompt the hypothesis that the factors potentially responsible for this increase specifically induce the precocious activation of hypothalamic-pituitary axis.

During the SARS-CoV-2 pandemic, people's habits changed radically; we think that an environmental change in lifestyle may influence pubertal timing.

We assumed that obesity and the increase of BMI in the paediatric population are possible contributing factors of the pubertal onset advance seen in the last few decades in industrialized countries. The increase in fat mass may lead to an augmented production of adipocyte hormones like leptin, which has a permissive role in HPG axis activation (21) (22), and insulin, which promotes GnRH activity, mostly mediated by leptin (23) (24). The increased weight leads to augmented hypothalamic ceramide levels, a lipid signalling molecule with a permissive

TABLE 1 Frequency of different diagnoses of precocious puberty in Period 1 and Period 2.

	N° of patients	Period 1 (N%)	Period 2 (N%)	p value
CPP	26	9 (35%)	17 (75%)	**<0.05**
EP	67	28 (42%)	39 (48%)	NS
Pubarche	38	20 (52%)	18 (48%)	NS
Telarche	23	10 (43%)	13 (47%)	NS

NS, not statistically significant.

TABLE 2 Auxological data at diagnosis and rate of pubertal progression in girls with CPP subdivided by observation period.

	Period 1 (9 cases)	Period 2 (17 cases)
Age at onset (yrs, M ± SD)	6.96 ± 0.55	6.43 ± 1.5
Age at diagnosis (yrs, M ± SD)	7.27 ± 0.6	6.99 ± 1.38
Weight SDS (M ± SD)	0.93 ± 0.95	0.83 ± 0.85
Height SDS (M ± SD)	1.25 ± 1.15	1.10 ± 1.30
BMI SDS (M ± SD)	0.57 ± 0.92	0.66 ± 0.6
SDS target height (M ± SD)	-0.5 ± 0.51	0.57 ± 1.3
Rate of pubertal progression (months)	6.5 ± 2.12	4 ± 2.83
EO-EC (years, months)	1.89 ± 1.20	1.64 ± 1.16

TABLE 3 Hormonal data at diagnosis in girls with CPP subdivided by observation period.

	Period 1 (9 cases)	Period 2 (17 cases)
Basal LH (pg/mL) (M ± SD)	2.5 ± 3.92	1.15 ± 0.64
Peak LH (M ± SD)	7.37 ± 5.03	11.42 ± 13.76
E2 > 15 pg/mL (% cases)	50%	69%

TABLE 4 Ultrasound (US) data at diagnosis in girls with CPP subdivided by observation period.

	Period 1 (9 cases)	Period 2 (17 cases)
Uterus D.L. (M ± SD)	40.38 ± 10.78	39.53 ± 7.32
Uterine volume (M ± SD)	5.21 ± 3.63	3.88 ± 2.10
Endometrial rhyme % cases	12.5%	40%

role on the HPG axis (25) and lead to a reduction of Sirtuin 1, a deacetylase that negatively influences pubertal activation.

In our experience, we found no significant increase in SDS BMI in girls with CPP diagnosed in Period 2, but only a trend of increasing BMI in months after lockdown in girls with EP. Indeed only in Stagi's study (8) was an increase observed in BMI in girls with CPP diagnosed during lockdown, while no other Italian studies detected this change. On the other hand, we have to consider the reduction of physical activity that characterized the lockdown and the following months, with the persistence of distance learning in the paediatric population. This lack of physical activity may have had a negative influence on body composition resulting in an increase in fat mass without an increase in BMI (10).

In regard to a greater pubertal thrust that characterized the diagnosis of forms of CPP detected during lockdown, as compared with forms identified in the previous period, there is contrasting literature data.

The studies of Stagi (8) and Umano (11) report levels of gonadotropins significantly higher in girls with CPP diagnosed during lockdown compared with the previous period. Our data, according to the multicentre study of Chioma et al (10), show no differences in hormone levels at diagnosis.

In Stagi's (8) study the number of girls with CPP who experienced a transition from slowly progressive pubertal development to accelerated pubertal development during lockdown was significantly higher compared with the previous

5 years. We did not observe this increase in pubertal progression, although our evaluation was based on referred data and not on clinical evaluation.

On the other hand, as concerns US data, our study is the only one in literature that shows a higher percentage of girls with the presence of endometrial rhyme during lockdown, compared with previous period.

It is well known that the presence of endometrial rhyme is a really specific parameter of estrogenic secretion and significant pubertal activation (24). It could be assumed that the estrogenic boost was more intensive in patients with onset during lockdown and that this favoured the onset of endometrial rhyme, despite the similarity of laboratory data.

We must however considerer that controversial results in the literature could depend on the difficulty of comparing studies having different numbers of patients, inclusion criteria and observation period.

The lifestyle change due to lockdown led to an increase in the use of electronic devices. The use of PCs increased more than other devices, due to distance learning. We detected that patients with CPP used more PCs and smartphones during lockdown, compared to the control group. Some studies assume that the electromagnetic radiation produced by electronic devices causes a down regulation in melatonin secretion (6, 7, 26). Normally, melatonin levels decrease during puberty and this down regulation leads to an activation of GnRH *via* genetic transcription (27). The increased use of electronic devices could have determined a melatonin level reduction that may have favoured the development of precocious puberty in susceptible individuals. This data may justify the stability of other forms of non-central precocious puberty like EP, isolated pubarche and thelarche.

Psychological factors linked to the pandemic are other environmental factors that we may consider. Some studies showed an increase of stress factors (fear of disease, drastic change of habits, break up of social contacts) (8, 9). Stress factors lead to an increase and then a decrease of cortisol levels. Cortisol has a negative feedback on the HPG axis; we can assume that a decrease in cortisol could have favoured the development of puberty. The examination of psychological effects is outside our analysis but we can assume there was indeed an increase in stress factors in our patients.

Strengths

We performed all the evaluations in the same Centre with homogeneous criteria of diagnosis and evaluation.

We also analysed the frequency of other forms of precocious puberty without central involvement, in contrast to other published studies.

We used a control group for the examination of the questionnaires regarding the use of electronic devices.

Limits

The limitations of our study are largely related to the emergency situation due to the pandemic, which did not allow prospective, controlled studies.

The sample small size and restrospective nature are also in the limitations of our study.

The data are preliminary and other evaluations need to be carried out through multicentre analyses with wider case studies.

Conclusion

The SARS-CoV-2 pandemic led to radical habit changes and we assume that these changes influenced the increase in frequency of CPP. Based on our data we assume there was an environmental effect on pubertal timing that calls our attention to factors such as food, use of electronic devices and stress. We will need other studies to better understand this data. By improving our knowledge of these factors, we could better understand some of the physiopathological aspects of puberty and implement preventive and corrective actions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by UOC Ricerca e Innovazione - Scudeller Startup/ Istruttoria (CE Locale) IRCCS Azienda Ospedaliero-Universitaria di Bologna Policlinico S.Orsola-Malpighi. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

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

Conflict of interest

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

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