Endocrinología, Diabetes y Nutrición 69 (2022) 566–575

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

ORIGINAL ARTICLE

Prevalence and risk factors associated with different comorbidities in obese children and adolescents

Juan Pablo López-Galisteo[a], Teresa Gavela-Pérez[b], Francisco Javier Mejorado-Molano[b], Pilar Pérez-Segura[b], Isabel Aragón-Gómez[b], Carmen Garcés[c], Leandro Soriano-Guillén[b,*]

[a] *Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Spain*
[b] *Unidad de Endocrinología Infantil, Servicio de Pediatría, Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain*
[c] *Laboratorio de Lípidos, Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, Spain*

Received 7 June 2021; accepted 18 October 2021
Available online 5 November 2022

KEYWORDS
Childhood obesity;
Comorbidities;
Vitamin D deficiency;
Insulin resistance;
Dyslipidaemia;
Hyperuricaemia;
Arterial hypertension

Abstract
Introduction: Different obesity-related comorbidities already present in childhood, such as: vitamin D deficiency, impaired carbohydrate metabolism, dyslipidaemia, arterial hypertension and non-alcoholic steatohepatitis. In this study, we aim to analyse the prevalence of comorbidities and to determine the predictive factors that affect these comorbidities.
Material and methods: Anthropometric, demographic and biochemical variables were collected from obese patients between six and 18 years of age. Subsequently, a statistical analysis was performed to describe the characteristics of the patients and the prevalence of comorbidities, as well as their predictive factors.
Results: A total of 158 obese children (76 boys and 82 girls) with a mean age at diagnosis of 12.48 years and a BMI Z-score of +3.24 SDS were included. The most prevalent comorbidities were vitamin D deficiency (64.2%), insulin resistance (45.1%), dyslipidaemia (32.2%), hyperuricaemia (18.5%) and arterial hypertension (15%). Age, BMI Z-score, percentage of fat mass and male sex have been found to be predictors of these comorbidities.
Conclusion: Obese children and adolescents have a high prevalence of comorbidities. Once the diagnosis of obesity has been established, it would be very useful to identify early those patients with a higher risk of comorbidities, knowing their relationship with sex, age, BMI Z-score, percentage of fat mass and pubertal stage.

* Corresponding author.
E-mail address: leandro.soriano@uam.es (L. Soriano-Guillén).

2530-0180/

PALABRAS CLAVE
Obesidad infantil;
Comorbilidades;
Déficit de vitamina D;
Insulinorresistencia;
Dislipemia;
Hiperuricemia;
Hipertensión arterial

Prevalencia y factores de riesgo asociados a distintas comorbilidades en niños y adolescentes obesos

Resumen

Introducción: Diferentes comorbilidades relacionadas con la obesidad se presentan ya en la etapa infantil como, por ejemplo: déficit de vitamina D, alteración del metabolismo hidrocarbonado, dislipemia, hipertensión arterial y esteatohepatitis no alcohólica. En el presente estudio queremos analizar la prevalencia de estas comorbilidades en niños y adolescentes obesos y estudiar los factores predictores relacionados con la aparición de las mismas.

Material y métodos: Se recogieron variables antropométricas, datos demográficos y bioquímicos de pacientes obesos entre seis y dieciocho años. Posteriormente, se realizó un análisis estadístico para describir las características de los pacientes, la prevalencia de comorbilidades, así como los factores predictores de las mismas.

Resultados: Se incluyeron un total de 158 niños obesos (76 niños y 82 niñas) con una edad media al diagnóstico de 12,48 años y un IMC Z-Score de +3,24 SDS. Las comorbilidades más prevalentes fueron déficit de vitamina D (64,2%), insulinorresistencia (45,1%), dislipemia (32,2%), hiperuricemia (18,5%) e hipertensión arterial (15%). Como factores predictores de estas comorbilidades se han encontrado la edad, el IMC Z-Score, el porcentaje de masa grasa y el sexo masculino.

Conclusión: Los niños y adolescentes de nuestro entorno presentan una elevada prevalencia de comorbilidades. Establecido el diagnóstico de obesidad, sería de gran utilidad reconocer precozmente aquellos pacientes con mayor riesgo de comorbilidades, conocida su relación con el sexo, la edad, IMC Z-Score, porcentaje de masa grasa y estadio puberal.

Introduction

In recent decades, increasing economic development and the growth of the food industry have led to an increase in adoption of diets richer in calories and saturated fats. At the same time, there has been a trend towards more sedentary lifestyles[1]. These things have contributed to the alarming increase in obesity rates in childhood and adolescence. In this vein, a recent global study found the prevalence of obesity to exceed 0.7%–5.6% in girls and 0.9%–7.8% in boys between 1975 and 2016 in individuals 5–19 years of age[2]. Unfortunately, Spain is no stranger to this first-order social and health problem. Spain has one of the highest prevalences of obesity in children six to nine years of age among European countries, at 17.7%[3]. Even more alarmingly, the prevalence of severe obesity in this age group is 4%[4].

Studies in recent years have found that obese preschool and school children are very likely to remain obese in adolescence and adulthood[5,6]. For a decade now, perpetuation of excess weight in childhood has been linked to a state of low-grade inflammation[7]. More recently, research has revealed that changes in adipose tissue deposits and function contribute to modifying the synthesis and release of different adipokines, creating a state of chronic inflammation, which fosters the development of various comorbidities[8].

The onset of comorbidities in obese patients is, unfortunately, not exclusive to adulthood. In fact, an increase in cases of childhood obesity at younger ages, together with an increase in detection of children with severe obesity, has led to a paradigm shift in the care of obese children and adolescents. The most recent guidelines recommend screening for different comorbidities such as carbohydrate metabolism impairment, lipid panel abnormalities, vitamin D deficiency, hypertension and non-alcoholic steatohepatitis[9].

In order to optimise healthcare resource management, it is extremely important to be familiar with predictors of the onset of these obesity-associated comorbidities. In particular, we believe that analysis of those factors in childhood could be important due to the potential for reversibility. Therefore, we established the following objectives: a) to analyse the prevalence of obesity-related comorbidities in a sample of obese children and adolescents and b) to study various factors linked to the presence of comorbidities.

Material and methods

Ours was a descriptive study of patients diagnosed with childhood obesity between January 2018 and December 2020 on a Childhood Obesity Unit at a tertiary hospital.

Sample size calculation

For an estimated prevalence of comorbidities associated with obesity in adolescence of 25%[9], a minimum of 113 subjects would need to be included with a precision (β) of 8% and a level of significance (α) of 95% (Ene 2.0® program), paired by sex and with a similar number of subjects in prepuberty, early puberty, mid-puberty and late puberty.

Inclusion criteria

Children 6–18 years of age with a body mass index (BMI) >2 standard deviation scores (SDS) above the mean according to Spanish reference tables[10], with no chronic disease prior to diagnosis of obesity and no ongoing treatment with corticosteroids, antidepressants, antipsychotics and/or anti-epileptic drugs were included. Subjects with suspected syndromic signs and symptoms were excluded.

Study variables

- *Anthropometric data:* weight (kg), height (cm), BMI (absolute value and SDS for age and sex according to reference tables[10]) and waist circumference (cm and SDS according to reference tables[11]).
- *Body composition:* body fat (% and kg) measured using impedance analysis (Tanita 3000®).
- *Tanner stage*[12,13]*, age at menarche and calendar of menstrual cycles.*
- *Systolic blood pressure (SBP) and diastolic blood pressure (DBP):* mmHg, taking the mean of three measurements.
- Clinical biochemistry results after 12 h of fasting: glucose (mg/dl), HbA1c (%), insulin (μIU/mL), total cholesterol (mg/dl), triglycerides (TGs) (mg/dl), high-density lipoprotein cholesterol (HDL-C) (mg/dl), low-density lipoprotein cholesterol (LDL-C) (mg/dl), aspartate aminotransferase (AST) (IU/l), alanine aminotransferase (ALT) (IU/l), 25-hydroxy vitamin D (ng/mL), thyroid-stimulating hormone (TSH) (μIU/mL), free thyroxine (T4) (ng/dl), C-reactive protein (CRP) (mg/dl), creatinine (mg/dl) and uric acid (mg/dl).
  - Homeostatic model assessment (HOMA) calculation: baseline insulin (μIU/mL) × baseline glucose (mmol/l) / 22.5.
- Presence of sleep apnoea–hypopnoea syndrome (SAHS), idiopathic intracranial hypertension or polycystic ovary syndrome.

Definitions

- *Hypertension:* mean of three determinations of SBP and/or DBP above the 95th percentile for age, sex and height[14].
- *Carbohydrate metabolism impairment:*
  - Insulin resistance[15]:
    a Prepubertal: baseline insulin >15°μIU/mL and/or HOMA > 3.5.
    b Pubertal: baseline insulin >25°μIU/mL and/or HOMA > 4.5.
  - Prediabetes[16]:
    a HbA1c 5.7%–6.4%.
    b Impaired fasting glycaemia: blood glucose levels 100—125 mg/dl.
    c Carbohydrate intolerance: blood glucose levels 140—199 mg/dl 120 min after oral overload.
  - Type 2 diabetes mellitus: obesity plus any of the following criteria, after having ruled out type 1 diabetes mellitus[16]:
    a HbA1c ≥6.5%.
    b Venous fasting blood glucose levels ≥126 mg/dl.
    c Blood glucose levels ≥200 mg/dl 120 min after oral overload.
- *Dyslipidaemia:* TGs >95th percentile and/or HDL-C <5th percentile for age and sex[17].
- *Hyperuricaemia:* uric acid >7 mg/dl[18].
- *Vitamin D deficiency:* 25-hydroxy vitamin D < 20 ng/mL[19].
- *Non-alcoholic fatty liver disease:* ALT levels >35 IU/l[20] together with ultrasound suggestive of hepatic steatosis (after having ruled out other causes of hypertransaminasaemia).
- *Non-autoimmune subclinical hypothyroidism:* TSH above the upper limit of normal for age, normal free T4 and negative thyroid autoimmunity[21].
- *Sleep apnoea–hypopnoea syndrome*: Apnoea–Hypopnoea Index >5, along with witnessed episodes of snoring and/or apnoea[22].
- *Idiopathic intracranial hypertension:* headache, papilloedema, cerebrospinal fluid pressure >25 cmH_2O following lumbar puncture and neuroimaging with no space-occupying lesions[23].
- *Polycystic ovary syndrome:* a) clinical and/or biochemical hyperandrogenism; b) menstrual cycle abnormalities taking into account time elapsed since menarche; c) ruling out of other causes of hyperandrogenism[24].
- *Metabolically healthy obese:* no carbohydrate metabolism impairment, dyslipidaemia, hyperuricaemia or hypertension.

Statistical analysis

In the descriptive analysis, qualitative variables are shown in frequency tables and quantitative variables are shown in terms of mean and 95% confidence interval. The Kolmogorov–Smirnov test was used to confirm whether the data had a normal distribution. Variables that did not follow a normal distribution were logarithmically transformed. The overall prevalence of comorbidities was analysed. In addition, rates of comorbidities were studied based on age, stage of puberty, sex, BMI and body composition using the following statistical tests: χ^2, Student's t and analysis of variance (ANOVA). A p value <0.05 was considered significant. Statistical analysis was performed using the software program SPSS version 25.0®.

Ethical and legal considerations

The study was conducted with the approval of the Independent Ethics Committee at our hospital (no. TFG012-21, 8 February 2021) in accordance with the Declaration of Helsinki and in compliance with current Spanish legislation.

Results

Sample description

A total of 158 obese children with a mean age at diagnosis of 12.48 years (12.05–12.91) and a BMI (Z-score) >3.24 SDS (3.04–3.44) were included. Of the 158 patients, 76 (48.1%) were boys and 82 (51.9%) were girls. The distribution by stage of puberty was: 44 in Tanner stage 1 (30 boys and 14

Table 1 Data on anthropometric measurements, body composition, blood pressure and biochemical variables at diagnosis.

Variable	Mean	95% confidence interval
Age (years)	12.37	11.90–12.84
BMI (kg/m^2)	30.59	29.82–31.36
BMI (Z-score)	3.28	3.08–3.47
Height (Z-score)	1.02	0.83–1.20
Waist circumference (cm)	98.34	96.30–100.38
Waist circumference (Z-score)	2.52	2.38–2.66
Body fat (%)	39.74	38.62–40.87
SBP (mmHg)	111.64	109.74–113.54
SBP (Z-score)	0.46	0.30–0.62
DBP (mmHg)	71.62	70.26–72.99
DBP (Z-score)	0.82	0.72–0.92
Glucose (mg/dl)	86.32	85.01–87.63
HbA1c (%)	5.24	5.11–5.37
Insulin (μIU/mL)	25.60	22.77–28.45
HOMA	5.47	4.9–6.04
Cholesterol (mg/dl)	154.65	150.08–159.22
Triglycerides (mg/dl)	104.54	94.32–114.77
HDL-C (mg/dl)	44.38	42.96–45.80
LDL-C (mg/dl)	91.71	87.48–95.94
AST (IU/l)	24.27	22.08–26.45
ALT (IU/l)	27.11	22.66–31.57
25-hydroxy vitamin D (ng/mL)	18.21	17.31–19.11
Uric acid (mg/dl)	5.55	5.14–5.96
Free T4 (ng/dl)	1.21	1.18–1.23
TSH (μIU/mL)	2.88	2.63–3.14

girls), 16 in Tanner stage 2 (12 boys and four girls), 23 in Tanner stage 3 (13 boys and 10 girls), 19 in Tanner stage 4 (9 boys and 10 girls) and 56 in Tanner stage 5 (12 men and 44 women).

Data on anthropometric measurements, body composition, blood pressure and clinical chemistry appear in Table 1.

Mean age at menarche in adolescent girls was 11.37 years (11.04–11.70).

Prevalence of comorbidities

The different comorbidities found in our sample are presented in order from highest prevalence to lowest prevalence: 25-hydroxy vitamin D deficiency (64.2%), insulin resistance (45.1%), dyslipidaemia (32.2%), hyperuricaemia (18.5%), hypertension (HTN) (15%), polycystic ovary syndrome (9.3% among women in Tanner stage 5), non-alcoholic fatty liver disease (8.2%), subclinical hypothyroidism (6.9%), prediabetes (6.8%), SAHS (6.2%), idiopathic intracranial hypertension (1.2%) and type 2 diabetes (0.6%).

A total of 13.4% could be considered metabolically healthy obese individuals.

Predictive factors for comorbidity

Table 2 reports the relationship between, on the one hand, age, sex, BMI Z-score and body fat percentage and, on the other hand, rates of comorbidities in our sample. Obese patients above the median age showed a significantly higher prevalence of hypertension and hyperuricaemia. In addition, a higher prevalence of non-alcoholic fatty liver disease was found among male patients. Furthermore, patients with a BMI Z-score above the median had higher rates of insulin resistance, HTN and non-alcoholic fatty liver disease than those below the median. Finally, those with a body fat percentage above the median had a higher prevalence of HTN.

Table 3 compares biochemical parameters by tertiles of age, BMI Z-score and body fat percentage. Age was associated with decreased 25-hydroxy vitamin D and HDL-C levels and increased HOMA and uric acid levels. BMI Z-score was positively correlated with HOMA. Finally, body fat percentage was associated with increased HOMA and decreased HDL-C.

Table 4 compares the same biochemical parameters by sex and Tanner stage. We found male sex to be associated with higher AST and ALT levels than female sex. Moreover, more advanced stages of puberty were correlated with significantly lower 25-hydroxy vitamin D and HDL-C levels and higher HOMA and uric acid levels.

Discussion

We report a descriptive study on the frequency of different comorbidities associated with childhood obesity. We also evaluated the impact of possible risk factors such as age, BMI, body composition and stage of puberty on the onset of these disorders.

In our sample, the most prevalent comorbidity was vitamin D deficiency, which affected 64% of our patients. Previously, our group found a high prevalence of vitamin

Table 2 Rates of comorbidities based on age, sex, BMI and body fat.

	Age			Sex			BMI (Z-score)			Body fat (%)		
	≤ median	> median	p	Male	Female	p	≤ median	> median	p	≤ median	> median	p
Vitamin D deficiency	63.2%	65.3%	χ^2 NS	62.7%	65.8%	χ^2 NS	60%	68.4%	χ^2 NS	62.3%	74.6%	χ^2 NS
Insulin resistance	46.5%	43.8%	χ^2 NS	49.3%	41.1%	χ^2 NS	35.6%	54.9%	χ^{2*}	44.8%	46.7%	χ^2 NS
Dyslipidaemia	28.4%	34.2%	χ^2 NS	23.6%	38.5%	χ^2 NS	33.3%	29.3%	^{2} NS	27.9%	37.5%	χ^2 NS
Prediabetes	6.1%	7.6%	χ^2 NS	10.3%	3.6%	χ^2 NS	6.3%	7.5%	χ^2 NS	6%	6.2%	χ^2 NS
Hyperuricaemia	7.1%	29.6%	χ^{2*}	22.9%	10%	χ^2 NS	7.7%	27.6%	χ^2 NS	5.6%	20%	χ^2 NS
Hypertension	9.2%	20.8%	χ^{2*}	13.9%	16%	χ^2 NS	7.6%	23%	χ^{2**}	4.7%	23.8%	χ^{2**}
Non-alcoholic fatty liver disease	8.2%	8.1%	χ^2 NS	13.7%	2.7%	χ^{2*}	1.4%	15.1%	χ^{2**}	3.4%	12.9%	χ^2 NS
SAHS	6.1%	6.3%	χ^2 NS	9%	3.6%	χ^2 NS	5%	7.5%	χ^2 NS	9%	4.6%	χ^2 NS
Metabolically healthy	20.4%	6.3%	χ^{2*}	13.5%	13.3%	χ^2 NS	20.9%	7.4%	χ^{2*}	16.7%	11.4%	χ^2 NS

p: degree of significance; NS: not significant.
* $p < 0.05$.
** $p < 0.01$.

D deficiency in obese children and adolescents compared to the group consisting of normal-weight individuals[19,25]. Various hypotheses have been put forward to attempt to account for the higher prevalence of vitamin D deficiency in the population of obese children and adolescents. One such hypothesis is that this higher prevalence can be explained by lifestyle changes leading to decreased outdoor physical activity and therefore less exposure to sunlight. In addition, vitamin D bioavailability in obese individuals is lower than in normal-weight individuals due to greater deposition in adipose tissue in these individuals[19]. Our study identified age and more advanced stage of puberty as possible risk factors related to higher rates of vitamin D deficiency. These findings may be linked to less physical activity and sun exposure than at younger ages[25]. In sum, we believe that these data point to a need to implement regular screening for vitamin D deficiency in obese patients, particularly adolescents.

The second most common comorbidity among obese individuals was insulin resistance, in 45.1% of patients. These figures were similar to those reported in a Spanish study that included 1300 patients[26]. Factors related to this comorbidity were age, BMI, body fat percentage and stage of puberty. Therefore, it would be advisable to evaluate patients for insulin resistance as of Tanner stage 2 and/or in adolescents over 11.5 years of age. Regardless of age and stage of puberty, it would also be advisable to assess subjects with a BMI > 3.5 SDS and/or a body fat percentage >41.7% for insulin resistance. Unlike the above-mentioned Spanish study wherein 46% of subjects had prediabetes[26], 6.8% of patients in our study met the criteria for prediabetes. The two studies did agree on the prevalence of type 2 diabetes, which was below 1%. The latter finding should incite reflection on the methodology used to screen for carbohydrate metabolism impairment among obese adolescents in our setting.

Our study found a rate of subjects with dyslipidaemia of 32.2%; this was slightly lower than in other studies, such as one conducted in nearly 2,000 Polish children[27], which found rates of dyslipidaemia of 38.2% in girls and 40.5% in boys. These differences are likely due to different criteria in relation to the definition of dyslipidaemia, sample selection, fasting time and numbers of patients included. As in our study, the Polish study found blood HDL levels to be negatively correlated with age, BMI and body fat percentage[27]. Although rates of dyslipidaemia were higher among adolescents, they were not negligible in school-age children; this, added to the well-established relationship between lipid levels and cardiovascular risk, indicates that a lipid panel is necessary in all obese children at diagnosis.

Uric acid levels increased slightly with age and showed a certain sexual dimorphism in adolescence[18]. However, taking into account the mean value and standard deviation for the calculation of >2 SDs based on age and sex, as of age 10, the cut-off point for defining hyperuricaemia would be 6–7 mg/dl. For this reason, we chose to use 7 mg/dl as a cut-off point, as this is the cut-off point normally used in the adult population. Thus, 18.5% of the patients included in our study showed hyperuricaemia. Focusing on studies with a cut-off point similar to our own revealed the prevalence of hyperuricaemia to range from 0.45% to 26.5% in the general paediatric population. In obese individuals, the prevalence is around 24.4%[18]. Moreover, our study found differences in uric acid levels based on age, BMI Z-score and stage of puberty. With our results, we were unable to discern whether there was a direct relationship between hyperuricaemia and BMI and/or a relationship to poor eating habits. We suspect that the older the age, the worse the nutritional habits. Therefore, it would be advisable to conduct prospective studies collecting nutritional surveys to attempt to link intake to blood uric acid levels. Meanwhile, determination thereof starting in adolescence could be recommended.

The prevalence of HTN in the general paediatric population, using the classic criteria published in 2004 by the Task Force[14], was between 1.5% and 8%[28]. This percentage climbed to 25% in obese adolescents[28]. Overall, 15% of our patients had HTN. Taking into account the median age of our sample, the prevalence was higher in children above the median (20.8% versus 9.2%). Therefore, we believe that age and possibly time since onset of obesity are linked to a higher prevalence of HTN. In addition, higher rates of HTN were seen in children with higher BMI and body fat values. This points to a close relationship between the chronic inflammatory state presented by obese adolescents and the onset of HTN. Given its non-invasive nature, it is absolutely advisable to measure blood pressure in the follow-up of obese patients of all ages. HTN should be confirmed by averaging at least three measurements in a suitable environment for this purpose.

Another obesity-related complication is non-alcoholic fatty liver disease. The prevalence among obese children and adolescents varies depending on the selection criteria used, be they clinical chemistry and/or imaging tests. Although the most accurate test for diagnosis remains liver biopsy, it is not a routine test in regular clinical practice in paediatrics. Our sample showed a lower prevalence than that reported by a Spanish group in 2015 in which up to 19.66% of individuals with overweight or obesity had hypertransaminasaemia (ALT > 35 IU/l)[20]. A recent meta-analysis found a prevalence of non-alcoholic fatty liver disease of 34.2% in obese children and adolescents versus 7.6% in the general paediatric population[29]. We found a higher prevalence of this disorder in male patients (13.7% versus 2.7%), but did not find a relationship to age or stage of puberty. Thus, there is speculation as to the existence of other determining factors, apart from sex steroids, to account for this sexual dimorphism as of pre-puberty[29]. We also found the prevalence of non-alcoholic fatty liver disease to be higher in individuals with a BMI above the median (1.4% versus 15.1%). In summary, it seems advisable to determine transaminase levels in initial testing in all obese patients. Subsequent follow-up, in which liver imaging test results will be assessed, will depend on the patient's initial transaminase levels, degree of obesity and sex.

Of our patients, 13.4% were classified as metabolically healthy; the predictive factors found in them were age and BMI. It is difficult to make comparisons to other studies as there is no consensus as to the criteria for considering a patient to be a metabolically healthy obese patient in any age group, despite various attempts made in expert meetings[30]. Thus, today, there is no consensus for establishing biochemical parameters, anthropometric measurements or lifestyle factors to consider obese individuals metabolically healthy. In this regard, we believe that the paediatric population requires different criteria based on age and stage

Table 3 Comparison of biochemical data considering tertile of age, BMI and body fat.

	Age (years)				BMI (Z-score)				Body fat (%)			
	1st tertile (<11.66)	2nd tertile (11.66—14)	3rd tertile (>14)	*p*	1st tertile (<2.69)	2nd tertile (2.69—3.5)	3rd tertile (>3.5)	p	1st tertile (<37.7)	2nd tertile (37.7—41.7)	3rd tertile (>41.7)	*p*
25-hydroxy vitamin D (ng/mL)	18.62 (17.10—20.15)	19.44 (17.56—21.33)	16.64 (15.14—18.13)	ANOVA* Post-hoc: 2—3*	18.71 (17.05—20.36)	18.57 (16.77—20.37)	17.37 (16.05—18.65)	ANOVA NS	18.86 (16.99—20.73)	17.55 (16.09—19.02)	17.26 (15.54—18.98)	ANOVA NS
HOMA	4.42 (3.55—5.30)	6.08 (4.99—7.17)	5.54 (4.67—6.41)	ANOVA* Post-hoc: 1—2*	5.04 (4.08—6.01)	4.72 (3.96—5.48)	6.66 (5.48—7.84)	ANOVA* Post-hoc: 2—3*	5.47 (4.37—6.56)	4.55 (3.73—5.37)	6.53 (5.32—7.74)	ANOVA* Post-hoc: 2—3*
TGs (mg/dl)	105.57 (86.62—124.71)	112.33 (89.30—135.35)	95.10 (83.26—106.94)	ANOVA NS	114.66 (91.10—138.22)	102.76 (85.78—119.74)	95.94 (85.25—106.63)	ANOVA NS	116.05 (91.15—140.94)	105.70 (84.22—127.17)	100.07 (86.96—113.18)	ANOVA NS
HDL-C (mg/dl)	45.96 (43.42—48.50)	45.50 (42.67—48.33)	41.38 (39.34—43.41)	ANOVA* Post-hoc: 1—3*	44.98 (42.57—47.40)	45.32 (42.67—47.97)	42.88 (40.45—45.32)	ANOVA NS	46.86 (43.66—50.05)	43.79 (41.44—46.13)	41.86 (39.40—44.31)	ANOVA* Post-hoc: 1—3*
AST (IU/l)	27.73 (23.50—31.96)	23.28 (20.49—26.07)	22.13 (17.34—26.92)	ANOVA NS	23.22 (20.29—25.45)	24.63 (20.28—28.97)	24.98 (20.31—29.65)	ANOVA NS	23.59 (20.81—26.37)	26.38 (21.13—31.63)	23.45 (18.49—28.41)	ANOVA NS
ALT (IU/l)	28.89 (19.31—38.47)	25.10 (19.89—30.32)	27.85 (18.26—37.44)	ANOVA NS	21.29 (18.97—23.60)	28.64 (18.93—38.35)	31.64 (22.30—40.98)	ANOVA NS	23.17 (20.55—25.79)	29.21 (18.80—39.62)	30.29 (19.14—41.44)	ANOVA NS
Uric acid (mg/dl)	4.67 (4.14—5.20)	6.30 (5.44—7.15)	6.06 (5.41—6.70)	ANOVA** Post-hoc: 1—2** 1—3**	5.46 (4.63—6.30)	5.49 (4.95—6.03)	5.66 (4.75—6.58)	ANOVA NS	6.02 (5.07—6.97)	4.95 (4.28—5.61)	5.91 (5.11—6.71)	ANOVA NS

p: degree of significance; NS: not significant.
* $p < 0.05$.
** $p < 0.01$.

Table 4 Comparison of biochemical data considering sex and stage of puberty.

	Sex			Stage of puberty			
	Male	Female	*p*	Tanner 1	Tanner 2–4	Tanner 5	*p*
25-hydroxy vitamin D (ng/mL)	18.29 (17.01–19.56)	18.15 (16.79–19.51)	Student's t NS	20.06 (18.41–21.70)	17.38 (15.74–19.02)	17.71 (16.19–19.23)	ANOVA* Post-hoc: 1–2*
HOMA	5.43 (4.70–6.17)	5.52 (4.62–6.43)	Student's t NS	4.23 (3.48–4.98)	6.18 (5.15–7.22)	5.66 (4.58–6.73)	ANOVA* Post-hoc: 1–2*
Triglycerides (mg/dl)	103.14 (91.07–115.20)	106.22 (89.23–123.18)	Student's t NS	98.30 (82.31–114.29)	120.27 (98.39–142.14)	94.65 (80.44–108.87)	ANOVA NS
HDL-C (mg/dl)	44.82 (42.82–46.81)	44.36 (42.29–46.43)	Student's t NS	47.07 (44.43–49.72)	44.75 (42.23–47.26)	42.15 (39.85–44.46)	ANOVA* Post-hoc: 1–3*
AST (IU/l)	27.24 (23.05–31.43)	21.22 (19.72–22.72)	Student's t**	26.59 (23.74–29.43)	24.19 (20.44–27.93)	21.96 (17.28–26.64)	ANOVA NS
ALT (IU/l)	34.21 (25.52–42.9)	20.53 (17.96–23.09)	Student's t**	26.17 (22.07–30.27)	28.59 (20.11–37.07)	26.18 (16.96–35.40)	ANOVA NS
Uric acid (mg/dl)	5.69 (5.07–6.31)	5.56 (5.15–5.97)	Student's t NS	4.30 (3.76–4.85)	6.07 (5.49–6.66)	6.18 (5.38–6.97)	ANOVA*** Post-hoc: 1–2**, 1–3***

p: degree of significance; NS: not significant.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

of puberty. In addition, further studies are needed to analyse these patients' actual long-term cardiovascular risk.

Limitations

Our study was not without limitations. These included the study's cross-sectional nature and its lack of a control group. Another limitation was that it was not possible to collect data on race, which could be considered a risk factor in obesity. Furthermore, as liver imaging test results were not available for all patients to assess them for hepatic steatosis, this information was not included in this study. Finally, 25-hydroxy vitamin D levels were not determined during the same season of the year in all patients.

Conclusions

Obese children in our setting were found to have a high frequency of comorbidities. These findings presented us with the challenge of diagnosing these abnormalities earlier taking into account the importance of various risk factors such as age, time since onset of obesity; sex; degree of obesity evaluated using BMI Z-score and body fat percentage; and stage of puberty.

Conflicts of interest

This study received no specific funding from public sector agencies, the commercial sector or non-profit organisations. The authors of this study declare that they have no conflicts of interest.

References

1. Ghanemi A, Yoshioka M, St-Amand J. Broken energy homeostasis and obesity pathogenesis: The surrounding concepts. J Clin Med. 2018;7:453.
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390:2627–42.
3. Rito AI, Buoncristiano M, Spinelli A, Salanave B, Kunešová M, Hejgaard T, et al. Association between characteristics at birth, breastfeeding and obesity in 22 countries: The WHO European Childhood Obesity Surveillance Initiative - COSI 2015/2017. Obes Facts. 2019;12:226–43.
4. Spinelli A, Buoncristiano M, Kovacs VA, Yngve A, Spiroski I, Obreja G, et al. Prevalence of severe obesity among primary school children in 21 European countries. Obes Facts. 2019;12:244–58.
5. - del Villar-Rubín S, Escorihuela-Esteban R, García-Anguita A, Ortega Moreno L, Garcés Segura C. Valoración de la evolución temporal del sobrepeso desde la edad prepuberal hasta la adolescencia. An Pediatr (Barc). 2013;78:389–92.
6. Geserick M, Vogel M, Gausche R, Lipek T, Spielau U, Keller E, et al. Acceleration of BMI in early childhood and risk of sustained obesity. N Engl J Med. 2018;379:1303–12.
7. Tam CS, Clément K, Baur LA, Tordjman J. Obesity and low-grade inflammation: a paediatric perspective. Obes Rev. 2010;11:118–26.
8. Zorena K, Jachimowicz-Duda O, Ślęzak D, Robakowska M, Mrugacz M. Adipokines and obesity. potential link to metabolic disorders and chronic complications. Int J Mol Sci. 2020;21:3570.
9. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity-assessment, treatment, and prevention: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2017;102:709–57.
10. Carrascosa-Lezcano A, Fernández-García JM, Fernández-Ramos C, Ferrández-Longás A, López-Siguero JP, Sánchez-González E, et al. Estudio transversal español de crecimiento 2008. Parte II: valores de talla, peso e índice de masa corporal desde el nacimiento a la talla adulta. An Pediatr (Barc). 2008;68:552–69.
11. Fernández JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr. 2004;145:439–44.
12. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child. 1969;44:291–303.
13. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45:13–24.
14. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114:555–76.
15. Levy-Marchal C, Arslanian S, Cutfield W, Sinaiko A, Druet C, Marcovecchio ML, et al. Insulin resistance in children: Consensus, perspective, and future directions. J Clin Endocrinol Metab. 2010;95:4189–98.
16. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2021. Diabetes Care. 2021;44 Supl 1:S15–33.
17. Muñoz-Calvo MT. Factores de riesgo cardiovascular en la infancia y adolescencia. In: Tesis doctoral. Universidad Autónoma de Madrid; 1991.
18. Kubota M. Hyperuricemia in children and adolescents: Present knowledge and future directions. J Nutr Metab. 2019;2019:3480718.
19. Gutiérrez-Medina S, Gavela-Pérez T, Domínguez-Garrido MN, Blanco-Rodríguez M, Garcés C, Rovira A, et al. Elevada prevalencia de déficit de vitamina D entre los niños y adolescentes obesos españoles. An Pediatr (Barc). 2014;80:229–35.
20. Guijarro de Armas MG, Monereo-Megías S, et al. Hígado graso no alcohólico en pacientes con sobrepeso y obesidad infantojuvenil. Med Clin (Barc). 2015;144:55–8.
21. Salerno M, Improda N, Capalbo D. Subclinical hypothyroidism in children. Eur J Endocrinol. 2020;183:R13–28.
22. Lloberes P, Durán-Cantolla J, Martínez-García M, Marín J, Ferrer A, Corral J, et al. Diagnóstico y tratamiento del síndrome de apneas-hipopneas del sueño. Arch Bronconeumol. 2011;47:143–56.
23. Mosquera-Gorostidi A, Iridoy-Zulet M, Azcona-Ganuza G, Gembero-Esarte E, Yoldi-Petri ME, Aguilera-Albesa S. Pseudotumour cerebri in children: Aetiology, clinical features, and progression. Neurologia. 2019;34:89–97.
24. Peña AS, Witchel SF, Hoeger KM, Oberfield SE, Vogiatzi MG, Misso M, et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Med. 2020;18:72.
25. Gutiérrez Medina S, Gavela-Pérez T, Domínguez-Garrido MN, Gutiérrez-Moreno E, Rovira A, Garcés C, et al. The influence of puberty on vitamin D status in obese children and the possible relation between vitamin D deficiency and insulin resistance. J Pediatr Endocrinol Metab. 2015;28:105–10.
26. Martos-Moreno GÁ, Martínez-Villanueva J, González-Leal R, Chowen JA, Argente J. Sex, puberty, and ethnicity have a strong influence on growth and metabolic comorbidities in children and adolescents with obesity: Report on 1300 patients (the Madrid Cohort). Pediatr Obes. 2019;14:e12565.

27. Brzeziński M, Metelska P, Myśliwiec M, Szlagatys-Sidorkiewicz A. Lipid disorders in children living with overweight and obesity-large cohort study from Poland. Lipids Health Dis. 2020;19:47.
28. Stabouli S, Redon J, Lurbe E. Redefining hypertension in children and adolescents: A review of the evidence considered by the European Society of Hypertension and American Academy of Pediatrics guidelines. J Hypertens. 2020;38:196–200.
29. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: A systematic review and meta-analysis. PLoS One. 2015;10:e0140908.
30. Iacobini C, Pugliese G, Blasetti Fantauzzi C, Federici M, Menini S. Metabolically healthy versus metabolically unhealthy obesity. Metabolism. 2019;92:51–60.