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ORIGINAL ARTICLE

Prevalence of insulin resistance and impaired glucose tolerance in a sample of obese spanish children and adolescents

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Abstract The prevalence of obesity in children has increased in developed countries in the last decades. It is associated with alterations in glucose metabolism that may be present in childhood. To assess the frequency of glucose metabolism alterations and insulin resistance and their possible determinants in a sample of obese children from Valladolid (Spain), we retrospectively studied 100 obese children and adolescents (11.59 ± 2.73 years). Anthropometric measures, biochemical parameters, and oral glucose tolerance test (OGTT) were performed. Insulin resistance was evaluated with fasting insulin, HOMA index, and insulin values in OGTT. Impaired glucose tolerance was found in 15% of the sample, and was the most frequent of glucose metabolism alterations. Impaired fasting glucose was found in 2%. No case of type 2 diabetes was found. Acanthosis nigricans was present in 22%, with predominance in females, but not all presented insulin resistance. The prevalence of insulin resistance was 29% when HOMA index was used, and 50% when the insulin response in OGTT was used. Not all patients with impaired glucose tolerance had a pathological HOMA index, and not all with pathological HOMA index presented insulin resistance when insulin values in OGTT were used. Higher 2-h post-OGTT insulin levels were found in children with impaired glucose tolerance. It is paramount to identify young people with glucose regulation alterations for early, intensive intervention to prevent or at least postpone the onset of type 2 diabetes. OGTT is a screening tool necessary to fulfill this objective.

Keywords Impaired glucose tolerance · Insulin resistance · Obesity

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Introduction

The prevalence of obesity in children has increased and reached an epidemic proportion in developed countries in the last decades. This has led to a worldwide increase in the rate of glucose metabolism alterations in this age group [1]. The occurrence of T2DM in obese children of European origin appears to be a rare event, and impaired glucose tolerance (IGT) prevalence shows great variation among different studies. The onset of T2DM is thought to follow a progression through a phase of altered glucose metabolism or prediabetes states, including insulin resistance, impaired fasting glucose (IFG), and IGT. The process, which may take decades in adults, appears to be accelerated in youth [2]. Screening at-risk obese children and adolescents for abnormalities in glucose homeostasis is therefore of extreme importance to prevent or at least postpone the onset of diabetes in subjects with IFG and/or IGT. The aim of our work was to evaluate the frequency of glucose metabolism alterations and insulin resistance and their possible determinants in obese children from Valladolid (Spain).

Methods

Study population

It was a retrospective review of 100 patients between 5 and 18 years of age with obesity and who had an OGTT

performed between January and December of 2008 at Pediatric Endocrinology Unit of the Clinic Universitary Hospital of Valladolid (Spain). All the subjects were referred from their primary care pediatric consultant and the reason for referral was, in all cases, the presence of excess body weight. Exclusion criteria were the presence of endocrine disorders or genetic syndromes, including syndromic obesity, and the presence of underlying chronic diseases. Informed consent was obtained from parents before any testing procedure and ethical approval was obtained.

Clinical parameters

Height was measured without shoes to the nearest 0.1 cm using a wall-mounted stadiometer (Harpender®), and weight was measured in underwear to the nearest 0.1 kg using a medical balance scale (Seca®). The degree of obesity was quantified using body mass index (BMI) and BMI-standard deviation score (BMI-SD). Obesity was defined according to the 2008 Spanish growth charts [3], 1988 Orbegozo's Foundation Spanish growth charts [4] (when BMI was higher than 97th percentile or ≥2 BMI-SD according to sex and age) and using the criteria proposed by Cole et al. [5], when BMI was higher than the age and sex specific equivalent to 30 kg/m^2 in adults. Pubertal development stages were determined according to Tanner [6], and the children were divided in two groups: prepubertal (Tanner's stage I) and pubertal (Tanner's stages ≥ II). Acanthosis nigricans was sought in all patients. Systolic and diastolic blood pressure was measured three times after rest and the average of these measurements was used. Our patients and their families were asked about familial history of obesity and diabetes.

Analytic parameters

Fasting glucose, fasting insulin, cholesterol (total, LDL, HDL), triglycerides, HbA1c, and transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] were measured in all subjects. Laboratory tests were performed at the central laboratory of the hospital. All patients underwent an OGTT which was performed according to clinical recommendations for children. After an overnight fast of 10–12 h, at approximately 8:00 am a baseline extraction was made, and then 1.75 g of glucose per kilogram of body weight were given orally, up to a maximum of 75 g. Venous blood samples were obtained after 0, 30, 60, 120 min to measure plasma glucose and insulin. Subjects were classified according to the latest American Diabetes Association (ADA) [7] diagnostic criteria in normal glucose tolerance (NGT), IFG, IGT and affected by T2DM. IFG was defined as a fasting plasma glucose level of 100–125 mg/dl (5.5–6.0 mmol/l), IGT as a fasting plasma glucose level < 126 mg/dl (7 mmol/l) and 2-h post-OGTT plasma glucose level of 140–199 mg/dl (7.8–11.1 mmol/l) and T2DM was defined as fasting glucose level of 126 mg/dl (7 mmol/l) or higher or 2-h plasma glucose level of more than 200 mg/dl (11.1 mmol/l). Insulin sensitivity was estimated by QUICKI index (1/(log fasting glucose + log fasting insulin). To estimate insulin resistance, the homeostasis model assessment for insulin resistance (HOMA-IR) [fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5] and insulin values in OGTT (peak and 120 min values) were used. Insulin resistance was defined if the insulin peak was higher than 150 μU/ml or insulin value at 2 h higher than 75 μU/ml [8]. Fasting insulin, HOMA, and QUICKI indexes were compared with national reference values attending at age, sex, and pubertal stage, and were considered pathological if were higher than 2 SD (HOMA index, fasting insulin) or lower than 2 SD (QUICKI index) [9].

Statistical analyses

All results are expressed as mean [with 95% confidence intervals (CI)] and standard deviation (SD), or percentage. The Student's t test was carried out for between-groups comparison of means, after checking normal distribution of variables (Kolmogorov–Smirnov test), and we determined correlations between quantitative variables with the Pearson's correlation coefficient. Chi-square test was used to compare proportions. All analyses were performed using SPSS for Windows V11, and statistical significance was accepted at $P < 0.05$ level.

Results

Patients characteristics

A total of 100 subjects were recruited. Table 1 provides clinical characteristics of the patients, Table 2 provides anthropometric and laboratory data, and Table 3 provides differences between pubertal and prepubertal children. There were 44 males and 56 females (ratio male/female 0.78). The median age was 11.59 years, slightly high in boys. Most patients were of Caucasian origin (95%). 66% had a family history for type 2 diabetes (mostly in 2nd degree relatives) and 12% for type 1 diabetes. 21% recognized family history of obesity, but parent's BMI was above 25 kg/m^2 in more than half of the sample. 100% of the sample had a BMI ≥ 2 SD when 1988 Orbegozo's Foundation Spanish growth charts were used and therefore were obese, whereas 67% were obese when 2008 Spanish growth charts were used (the rest of the samples were overweight).

Table 1 Clinical characteristics of obese children

Characteristics	Boys ($n = 44$)	Girls ($n = 56$)	Total ($n = 100$)	P value
Age (years ± SD)	12.19 ± 2.27	11.12 ± 2.97	11.59 ± 2.73	0.044
Ethnicity (%)				
Caucasian	95.5	94.6	95	0.853
Hispanics	4.54	5.35	5	
Obesity in family (%)	22.7	19.6	21	0.521
BMI mother (kg/m^2)	29.53 (26.83–32.23)	29.91 (28.07–31.75)	29.73 (28.15–31.31)	0.815
BMI father (kg/m^2)	29.48 (27.46–31.5)	28.75 (26.85–30.65)	29.07 (27.69–30.45)	0.604
Type 2 diabetes in family (%)	61.36	69.64	66	0.386
Parents (%)	6.81	17.85	13	0.103
Second degree relative (%)	61.36	62.5	62	0.907
Tanner stage (%)				
Prepubertal (%)	36.4	32.1	34	0.658
Pubertal (%)	63.6	67.9	66	
Acantosis nigricans (%)	15.9	26.8	22	0.011

Table 2 Anthropometrics and laboratory parameters of obese children

	Boys ($n = 44$)	Girls ($n = 56$)	Total ($n = 100$)	P value
BMI (kg/m^2)	28.92 (27.96–29.88)	27.59 (26.71–28.47)	28.17 (27.51–28.83)	0.046
BMI-SD*	4.19 (3.81–4.57)	3.72 (3.42–4.02)	3.93 (3.69–4.17)	0.062
BMI-SD**	2.53 (2.26–2.80)	2.49 (2.27–2.71)	2.51 (2.34–2.68)	0.791
Total cholesterol (mg/dl)	158.15 (149.51–166.79)	153.68 (145.40–161.96)	155.65 (149.67–161.63)	0.461
LDL (mg/dl)	88.73 (80.73–96.73)	89.1 (81.24–96.96)	88.94 (83.32–94.56)	0.641
HDL (mg/dl)	46.54 (41.60–51.48)	47.94 (44.36–51.52)	47.34 (44.40–50.28)	0.949
Triglycerides (mg/dl)	114.27 (87.63–140.91)	88.58 (78.54–98.62)	99.74 (86.68–112.8)	0.051
Fasting glucose (mg/dl)	85.95 (84.29–87.61)	85.68 (83.6–87.76)	85.80 (84.44–87.16)	0.843
Fasting insulin (μU/ml)	14.58 (12.46–16.70)	14.18 (12.54–15.82)	14.35 (13.05–15.65)	0.764
Fasting insulin-SD	+2.03 (1.33–2.73)	+1.06 (0.64–1.48)	+1.49 (1.09–1.89)	0.017
Glucose 120′ (mg/dl)	116.27 (109.85–122.69)	114.1 (108.18–120.02)	115.06 (110.72–119.4)	0.623
Insulin peak in OGTT (μU/ml)	155.12 (105.04–205.2)	132.24 (105.28–159.2)	142.20 (115.68–168.72)	0.396
Insulin 120′ (μU/ml)	106.18 (70.82–141.54)	102.59 (74.57–130.61)	104.13 (82.21–126.05)	0.872
HbA1c (%)	5.47 (5.37–.57)	5.47 (5.40–5.54)	5.47 (5.41–5.53)	0.950
HOMA-IR	3.08 (2.65–3.51)	3.06 (2.68–3.44)	3.07 (2.79–3.35)	0.962
SD-HOMA	+1.72 (1.08–2.36)	+0.95 (0.51–1.39)	+1.29 (0.91–1.67)	0.049
QUICKI	0.33 (0.32–0.34)	0.33 (0.32–0.34)	0.33 (0.32–0.34)	0.781
SD-QUICKI	−3.14 (−2.89)–(−3.39)	−2.87 (−2.63)–(−3.11)	−2.99 (−2.16)–(−2.82)	0.135

* 1988 Orbegozo's Foundation Spanish growth charts, ** 2008 Spanish growth charts. Data are expressed as 95% mean confidence interval

Only 82% met Cole's criteria for obesity. Using 1988 Orbegozo's Foundation Spanish growth charts 43% of the sample had a BMI higher than 4 SD, while only 7% had a BMI higher than 4SD when the other national charts were used, presenting most of the sample (41%) a BMI between 2 and 3 SD. Acanthosis nigricans was found in 22% of the sample. Levels of AST and ALT were normal in all patients. High systolic blood pressure (>Pc 95th adjusted for age and gender) was found in 5% of the sample, but diastolic blood pressure was normal in all patients. There were no significant differences between boys and girls for any of these factors, except in age. We found a significant higher SD-BMI in prepubertal children.

Table 3 Differences between prepubertal and pubertal children

	Prepubertal ($n = 34$)	Pubertal ($n = 66$)	P value
Boys/girls (ratio)	16/18 (0.88)	28/38 (0.74)	0.658
BMI	26.45 (25.39–27.51)	29.06 (28.32–29.80)	<0.001
BMI-SD*	4.31 (3.83–4.79)	3.73 (3.47–3.99)	0.026
BMI-SD**	2.82 (2.48–3.16)	2.35 (2.17–2.53)	0.010
Fasting glucose (mg/dl)	85.32 (83.22–87.42)	86.04 (84.26–87.82)	0.622
Fasting insulin (μU/ml)	13.19 (10.87–15.51)	14.95 (13.39–16.51)	0.202
SD-Fasting insulin	+2.10 (1.38–2.82)	+1.17 (0.71–1.63)	0.028
HOMA-IR	2.88 (2.37–3.39)	3.17 (2.83–3.51)	0.338
SD HOMA	+2.01 (1.29–2.82)	+0.92 (0.50–1.34)	0.008
Glucose 120′ (mg/dl)	110.5 (102.4–118.6)	117.41 (112.39–122.43)	0.132
Insulin 120′ (μU/ml)	96.67 (58.65–140.69)	106.18 (80.10–132.26)	0.785
Insulin peak in OGTT (μU/ml)	113.81 (82.87–144.75)	155.42 (119.68–191.16)	0.145

* 1988 Orbegozo's Foundation Spanish growth charts, ** 2008 Spanish growth charts. Data are expressed as 95% mean confidence interval

Table 4 Physical and biochemical characteristics of children with or without IGT

	NGT ($n = 85$)	IGT ($n = 15$)	P value
Boys (*n*/%)/girls (*n*/%)	37 (43.5)/48 (56.5)	7 (46.7)/8 (53.3)	0.821
Age (yr ± SD)	11.52 ± 2.66	12.07 ± 3.04	0.471
Prepubertal/Pubertal (%)	35.3/64.7	26.7/73.3	0.515
BMI	28.06 (27.33–28.79)	28.83 (27.43–30.23)	0.406
BMI-SD*	3.89 (3.63–4.15)	4.16 (3.54–4.78)	0.438
BMI-SD**	2.46 (2.28–2.64)	2.75 (2.27–3.23)	0.244
Type2DM in family (%)	64.7	73.33	0.515
Fasting glucose (mg/dl)	85.35 (83.93–86.77)	88.33 (84.03–92.63)	0.123
Fasting insulin (μU/ml)	14.10 (12.70–15.50)	15.78 (12.30–19.26)	0.361
SD fasting insulin	1.40 (0.96–1.84)	1.96 (1.02–2.90)	0.329
Insulin 120′ (μU/ml)	84.85 (65.71–103.99)	195.40 (123.44–267.36)	<0.001
Insulin Peak in OGTT (μU/ml)	133.28 (104.68–161.74)	183.81 (115.29–252.33)	0.148
Glucose 120′ (mg/dl)	108.29 (105.05–111.53)	153.4 (147.3–159.5)	<0.001
HOMA-IR	2.98 (2.68–3.27)	3.58 (2.70–4.46)	0.141
SD-HOMA	1.19 (0.79–1.59)	1.87 (0.71–2.97)	0.208
QUICKI index	0.33 (0.32–0.34)	0.34 (0.31–0.37)	0.730
SD-QUICKI	−2.99 (−3.18)–(−2.80)	−2.96 (−3.38)–(−2.54)	0.897
Triglycerides (mg/dl)	99.04 (84.42–113.66)	103.66 (75.64–131.68)	0.801
Total cholesterol (mg/dl)	152.62 (147.04–158.20)	172.8 (149.78–195.82)	0.015
LDL cholesterol (mg/dl)	86.65 (81.47–91.83)	102.71 (79.27–126.15)	0.045
HDL cholesterol (mg/dl)	47.48 (44.2–50.76)	46.5 (40.22–52.78)	0.816
Acantosis nigricans (%)	20	33.33	0.250
IFG (%)	1.18	6.66	0.001

* 1988 Orbegozo's Foundation Spanish growth charts, ** 2008 Spanish growth charts. Data are expressed as 95% mean confidence interval

Glucose tolerance status

Two percent of the sample presented IFG. The two patients were girls, both with acanthosis nigricans, and one of them had also IGT. IGT was present in 15% of the sample. No silent diabetes was diagnosed. Compared with subjects with NGT, patients with IGT had significantly higher 2-h postload insulin values, total and LDL cholesterol values and prevalence of IFG. No significant differences were found in the other parameters. (Table 4).

Insulin resistance and beta-cell function

When insulin resistance was evaluated through physical markers, acanthosis nigricans was found in 22% of the sample with predominance in girls ($P = 0.001$) and most common location in the neck (86.5%). All of them met criteria for obesity based on the three types of references used. There was a significant association between acanthosis and BMI-SD ($P < 0.001$). 45.5% of patients with acanthosis had HOMA index higher than 2 SD and 59% presented insulin resistance when insulin values in OGTT were used.

Fasting insulin was elevated for age, sex, and pubertal stage (≥2 SD) in 32% of the sample. 71.8% of them presented insulin resistance when insulin values in OGTT were used. Although fasting insulin values were similar in prepubertal than in pubertal children, SD of insulin were considerably higher in prepubertal. There were no differences in fasting insulin between children with NGT and IGT.

HOMA index was higher than 2 SD in 29% of the sample, and 68.9% of them presented insulin resistance when insulin values in OGTT were used. 34.5% of them had acanthosis nigricans. The frequency of IGT in patients with HOMA index higher than 2 SD was 20.7%. Between the children with normal HOMA index (71%), 42.3% of them presented insulin resistance when insulin values at OGTT were used, 16.9% of these patients had acanthosis nigricans, and 12.7% had IGT. There were no differences in HOMA index and SD-HOMA in patients with IGT.

When we analyzed the response of insulin in OGTT, we found that 31% of the sample had an insulin peak higher than 150 μU/ml, 45% a value above 75 μU/ml at 120 min, and 26% had these values high at the same time. The global prevalence of insulin resistance when insulin values at different times of OGTT were used was 50% but curiously only 40% of these patients had a pathological HOMA index. The 2-h postload insulin in OGTT was higher in patients with IFG.

Insulin sensitivity

Impaired insulin sensitivity was defined as a QUICKI index less than 2 SD based on national reference standards, and was present in the most of the sample (93%). There were no significant differences with sex or state of glucose tolerance status.

Discussion

Childhood obesity has experienced an important increase in the last years all over the world [1]. It has been associated with the rising prevalence of many metabolic complications (IGT, IFG, T2DM). Many of them are already present during childhood and tend to persist into adulthood [10]. The prevalence of IGT is highly variable in the different studies and countries (10–30%). In our study, the prevalence of IGT was 15% and the prevalence of IFG was 2%. Other Spanish studies showed a prevalence of IGT between 2.25 and 22.2%, and Guijarro et al. reported a higher prevalence of IFG (7.51%) [11–13]. The prevalence of IGT reported in other countries like Hungary, Iran, and Israel was very similar [14–16]. However, our prevalence of IFG and IGT was higher than in neighbor countries such as Italy [17–19], and lower than in Australia and USA [2, 20]. No case of diabetes was found in our sample. The prevalence of DM reported in Europe is low (0–1.5%) [10] and these data contrast with those reported in USA [20]. In our study, there were no differences in glucose tolerance status between pubertal and prepubertal, as is reflected in other studies [16, 19, 21]. Obese children with IGT had significantly higher 2-h postload OGTT insulin levels, total and LDL cholesterol, but no other significant differences were found, as it was previously described [11, 12, 16, 17, 19, 22]. Recently, some authors have reported a relationship between liver enzyme markers and insulin resistance in obese children according to indirect and direct measures. Wang and Zhang [24, 25] described that ALT is an early indication of insulin resistance, and Abe et al. [26] described that elevated glutamic pyruvic transaminase (GPT) levels were superior to fasting blood glucose as a marker for defining metabolic syndrome. In our sample, levels of AST and ALT were normal in all patients according to our cut-off values. In contrast, Gronbaek et al. [27] reported that about 50% of obese children have ALT elevated values using a cut-off value of 25 IU/l, but they were unable to demonstrate significant correlations with insulin sensitivity and the metabolic syndrome. Not all patients with acanthosis nigricans showed insulin resistance when compared with analytical parameters. Recent consensus of experts about insulin resistance concluded that acanthosis nigricans can point to the likelihood of insulin resistance but cannot define it [23]. To assess insulin resistance, fasting insulin was measured, although we know that it is not an optimal tool, and not always is well correlated with insulin resistance in children. It was pathological in 32% of the sample and most of them had criteria of insulin resistance when insulin values in OGTT were evaluated. We evaluated insulin resistance with HOMA index and insulin response (peak and 120 min) in the OGTT [8, 9]. The prevalence of insulin resistance was different with the two methods, and there were patients with HOMA index fewer than 2 SD who met criteria of insulin resistance when we considered insulin values in OGTT and not all patients with insulin resistance when we

evaluated insulin response in OGTT had pathological HOMA index. We compared the results of HOMA index and fasting insulin to national values, because as far as we know there are no international values universally accepted [23]. We have used adult criteria in the response of insulin in OGTT but there are not known criteria about this in children [8, 18]. On the other hand, we cannot compare our results of insulin resistance with other author's results, because each one used a different criterion to define these disorders. As far as we know, there is only one study which used insulin values in OGTT and they considered that insulin resistance was present if fasting insulin was higher than 25 mUI/l and 120 min value higher than 45 mUI/l [14]. Using these values they found that 89.3% of their sample had insulin resistance, a percentage higher than ours. An agreement upon the definition of insulin resistance in children and adolescents should be reached among investigators and age-dependent cut-off levels should be applied. The decision on whether to perform an OGTT in young people is being increasingly faced by clinicians and there are no evidence-based guidelines as to when one should be performed. According with other authors, we think that it is necessary the realization of OGTT in obese children to identify certain situations, which could be the previous steps of T2DM as insulin resistance, IFG, and IGT. Transition from IGT to diabetes in adults is usually a gradual phenomenon occurring over 5–10 years [28]. The early presentation of T2DM in youth raises the possibility of an accelerated pathophysiological process in these youngsters, compared with adults thus shortening the transition time between IGT and diabetes [28]. In contrast to the vast literature about metabolic predictors of deterioration of glucose tolerance in adults, little is known about this process in children and adolescents. Longitudinal studies are required to determine the sequence of events involved in the transitions from normal to impaired glucose tolerance and to diabetes. Kleber and Weiss followed the evolution of obese patients in which an OGTT has been made [29, 30]. They described that subjects who eventually developed diabetes gained a significant amount of weight and increased their BMI, whereas those who reverted to NGT on average maintained their weight and BMI [28].

In conclusion, the prevalence of glucose metabolism alterations (IFG, IGT, DM2) in obese children living in Valladolid (Spain) is close to that reported in other European countries. The evidence that 15% of obese children have IGT suggests that glucose metabolism disorders are common in them and should be investigated in order to prevent or at least postpone the onset of type 2 diabetes.

Conflicts of interest The authors declare no conflict of interest.

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