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Insulin resistance and impaired glucose tolerance in obese children and adolescents

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In developed countries, obesity prevalence has strongly increased in the last decades. This has also been observed in children and adolescents. Until recently, type 2 diabetes mellitus was considered very rare among children and adolescents; however, in the last decades, some cases have been observed mainly in obese adolescents of some minority populations. The aim of our study was to assess the prevalence of type 2 diabetes, impaired glucose tolerance (IGT) and insulin resistance, and the metabolic features, in obese children and adolescents. We have studied 95 obese children and adolescents, 53 males and 42 females, aged 4-16 years. The prevalence of IGT in obese children and adolescents studied was 7.4%; there was not any child with type 2 diabetes. Fasting glucose and insulin serum concentrations did not show significant differences between obese children with or without IGT; however, 120 minutes after an oral glucose tolerance test, glucose and insulin serum concentrations showed statistically significant differences between both groups. Insulin resistance is defined as a HOMA index higher than 4. The prevalence of insulin resistance in obese children studied was 35.8%. Trygliceride serum concentrations were higher and HDL-C serum concentrations were lower in obese children with IGT than in those without IGT, but the differences were not statistically significant. IGT and insulin resistance are frequent in obese children and adolescents; early treatment in obese children and adolescents with IGT constitutes a strategy of reversing progression to β-cell failure and in preventing type 2 diabetes.

Key words: Obesity, Insulin resistance, Impaired glucose tolerance, Children, Nutrition.

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In developed countries, obesity prevalence has strongly increased in the last decades (22). This has also been observed in children and adolescents (15, 29). In Spain, we have conducted studies, which have shown a trend towards elevated obesity prevalences in children and adolescents (3, 23). Overweight adolescents appear to have an increased risk of obesity-related mortalities and morbidities later in life, regardeless of their adult weight status (20). The persistence of obesity from childhood into adulthood also may favor an early onset of diabetes, as suggested by the recent trend of the early onset of type 2 diabetes in individuals who have suffered from obesity since childhood (12).

Until recently, type 2 diabetes mellitus was considered very rare among children and adolescents. In recent years there has been series of reports indicating an increasing incidence of early-onset type 2 diabetes, with a documented age of diagnosis as low as 3.5 years among Pima Indians (5, 11). A case study from Cincinati reported 54 children and adolescents with type 2 diabetes; 37 (69%) of the patients were African American, and 35 (65%) had at least one first-degree relative with type 2 diabetes (21). SINHA *et al.* (26) has determined the prevalence of impaired glucose tolerance (IGT) in obese children, documenting IGT in 25 % of 55 obese children, aged 4 to 10 years, and in 21 % of 112 obese adolescents, aged 11 to 18 years. In addition, clinically asymptomatic, or silent, type 2 diabetes was found in 4 of the 112 obese adolescents (4 %).

There were not a lot of data in European children and adolescents regarding frequency of abnormalities of glucose homeostasis. In the United Kingdom the prevalence of type 2 diabetes of those under 18 years has been estimated as being 0.038/1000 (10). In 710 grossly obese Italian children, of European origin, INVITTI *et al.* (14) observed that the prevalence of IGT was 4.5 % and that of type 2 diabetes of 0.1 %. In Germany, the prevalence of type 2 diabetes in obese children has been estimated as 1.56% and in Hungary of 1.93% (16).

The aim of our study was to assess the prevalence of IGT and insulin resistance with the main metabolic features, in obese children and adolescents.

Patients and Methods

We have studied 95 obese children and adolescents (53 males and 42 females). The children were aged 4-16 years, with a mean age of 10.78±2.53 years. The study was conducted at the Endocrinology Unit, Department of Paediatrics, University Hospital of Zaragoza (Spain). Among them, 94.7% of the children were of Spanish-Caucasian origin, 3.2% were Hispanics and 2.1% Gypsies. Furthermore, 40.4% of the children were pre-pubertal, 20.2 were in Tanner 2 stage, 12.8% in Tanner 3, 8.5% in Tanner 4 and 18.1% in Tanner 5 pubertal stage. With the exception of obesity, the children had no apparent disease and were not taking any kind of medication. None of the obese children had a history of endocrine, nutritional, growth or renal problems. Patients with other causes of secondary obesity were excluded. Parents, or the children's guardians, were informed by letter about the nature and purpose of the study. After receiving their written consent, the children were considered for inclusion in the study. The study was approved by the Ethics Committee of the University Hospital, Zaragoza, Spain.

Weight and height were measured and the body mass index (BMI) was calculated as the ratio of weight by height^2. Obesity

was defined by using the IOTF reference standards (4), when BMI was higher than the corresponding value of 30 kg/m^2, in each age and sex group.

Blood pressure was measured three times by the same examiner with a mercury sphygmomanometer. First, fourth, and fifth Korotkoff phases were recorded each time. Finally, we have considered the mean of the three measurements for each child.

Blood was obtained by vein puncture between 8:00 a.m. and 9:30 a.m., after overnight fasting. All assays were performed at the Department of Biochemistry, University Hospital of Zaragoza. Glucose, triglycerides and high density lipoprotein-cholesterol (HDL-C) serum concentrations were determined by enzymatic colorimetric assay on a Roche/Hitachi MODULAR P analyser. Insulin was determined by immunometric assay with a Immulite analyser. Subjects underwent an oral glucose tolerance test with a glucose dose of 1.75 g/kg, up to a maximum of 75 g glucose in 250 ml water. Samples were drawn at baseline and after 120 minutes for determination of glucose and insulin concentrations.

Impaired glucose tolerance was defined as fasting plasma glucose level of less than 126 mg/dl and a two-hour plasma glucose level of 140 to 200 mg/dl; type 2 diabetes was defined as a fasting glucose level of 126 mg/dl or higher or a two-hour plasma glucose level of more than 200 mg/dl (28). Insulin resistance was determined by homeostatic model assessment (HOMA index) (17) and calculated as the product of the fasting plasma insulin level (in microunits per millilitre) and the fasting plasma glucose level (in millimoles per litre), divided by 22.5. Lower insulin-resistance values indicate a higher insulin sensitivity, whereas higher values indicate a lower insulin sensitivity.

Mean values of blood pressure and metabolic variables were compared between obese children with and without IGT, by using the unpaired *t*-test.

Results

The prevalence of IGT in the obese children and adolescents studied was 7.4%; there was not any children with type 2 diabetes. Fasting glucose and insulin serum concentrations did not show significant differences between obese children with or without IGT; however, 120 minutes after an oral glucose tolerance test, glucose and insulin serum concentrations showed significant differences between both groups (Fig. 1 and 2).

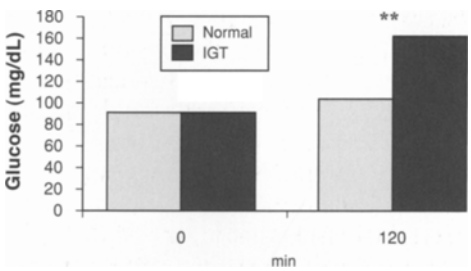

Fig. 1. *Plasma glucose during an oral glucose-tolerance test in 95 obese children* (IGT: Impaired glucose tolerance). P = 0.035 at 120 minutes between obese children with and without IGT.

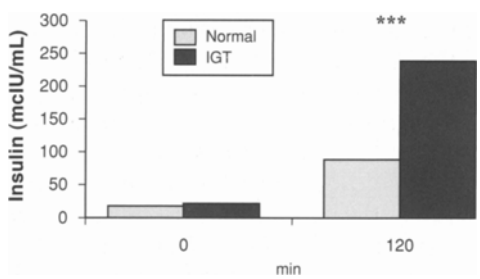

Fig. 2. *Plasma insulin during an oral glucose-tolerance test in 95 obese children* (IGT: Impaired glucose tolerance). P < 0.001 at 120 minutes between obese children with and without IGT.

The HOMA distribution in the obese children and adolescents studied was compared with the values obtained in 74 non-obese children and adolescents from the same Health Area covered by the University Hospital of Zaragoza. In figure 3, the distribution of HOMA index values in both groups can be seen. If we consider a value of 4 as the cut-off point to define the presence of insulin resistance, the prevalence was 4.1% in non-obese children and 35.8% in obese ones.

Systolic and diastolic blood pressure measurements revealed no significant differences between obese children with and without IGT. Systolic blood pressure mean values were 119.29 and 121.91 mm Hg, respectively, and diastolic blood pressure mean values were 64.29 and 69.16 mm Hg, respectively.

Although trygliceride serum concentrations were higher (95.29 and 84.40 mg/dL, respectively) and HDL-C serum concentrations lower (41.40 and 49.73 mg/dL, respectively) in obese children with IGT than in those without IGT, differences were not statistically significant.

Discussion

Type 2 diabetes is an important problem among all US populational groups, especially in some ethnic minorities' (6). This seems to be not the case in European children and adolescents. However, IGT and insulin resistance seems to be present in an important number of children and adolescents, mainly in those with exogenous obesity. We have observed that 7.4% of our obese patients showed IGT; this prevalence is similar to that observed in Italian obese children. In clinical and epidemiologic studies, insulin resistance is widely assessed by using the HOMA index (13); however, there is no agreement on the best cut-off value to define insulin resistance in children and adolescents. With data from our laboratory, we have estimated that from a statistical point of view, a HOMA index of 4 could be accepted as the cut-off point. Taking into consideration this value, the prevalence of insulin resistance in our sample of obese

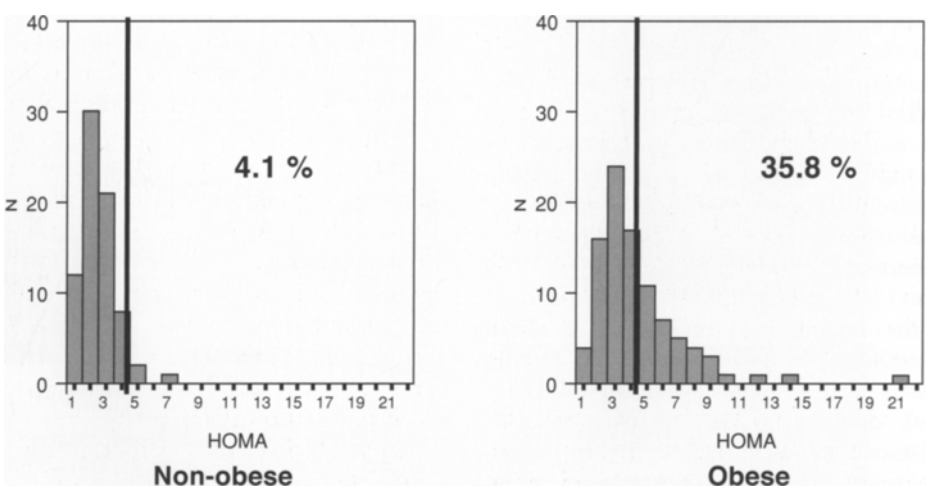

Fig. 3. *HOMA index in obese and non-obese children and adolescents.*

children and adolescents would be of 35.8%.

Glucose homeostasis depends on the balance between insulin secretion by the pancreatic β-cells and insulin action. For hyperglycemia to develop, insulin resistance alone is not sufficient and inadequate β-cell insulin secretion is necessary. There has been considerable debate about whether insulin resistance or insulin hyposecretion is the primary defect in type 2 diabetes in adults. The clinical characteristics in children with type 2 diabetes suggests that the initial abnormality is impaired insulin action, later accompanied by β-cell failure. The failure of the β-cell to continue to hypersecrete insulin underlies in the transition from insulin resistance (with compensatory hyperinsulinemia and normoglycemia) to clinical diabetes (with overt fasting hyperglycemia and increased hepatic glucose production). The results observed in our study point in the same direction.

Insulin transduction signals are highly complex mechanisms, which are only partly elucidated. Several molecular mechanisms have been shown to be potentially involved in the pathogenesis of insulin resistance (25). There is a substantial amount of evidence that lipids are tightly involved in insulin resistance of obese individuals. High body fat mass is associated with increased whole body lipolysis and plasma free fatty acid concentrations. Several hypotheses link increased fatty acid concentrations with insulin-mediated glucose disposal in skeletal muscle, the major glucose-utilising tissue. It has been proposed that intracellular fatty acyl CoA may directly inhibit muscle glucose transport by impairing insulin signaling (8). Impaired muscle lipid oxidation, possibly related to a low muscle oxidative capacity, as often observed in insulin resistant individuals, would lead to accumulation of muscle fatty acyl CoA and insulin resistance (24).

It has been observed recently that fatty acid may also reduce insulin-mediated glucose disposal through actions exerted at the level of blood vessels. Several conditions such as oral feeding, hyperinsulinemia or mental stress produce skeletal muscle vasodilatation by stimulating the release of NO from endothelial cells. This vasodilatation appears to enhance insulin actions by increasing the delivery of glucose and insulin itself to insulin-sensitive tissues. Infusion of lipids, which leads to elevation of plasma free fatty acid concentrations, impairs endothelial function and reduces insulin actions (27).

Puberty appears to play a major role in the development of type 2 diabetes in children. During puberty, there is increased resistance to the action of insulin, resulting in hyperinsulinemia (2). Both growth hormone and sex steroids have been considered as candidates for causing insulin resistance during puberty. The fact that sex steroids remain elevated after puberty while insulin resistance decreases makes sex steroids an unlikely cause of insulin resistance. Conversely, mean growth hormone levels increase transiently during puberty as insulin action decreases. In addition, administering growth hormone to non-growth-hormone-deficient adolescents is associated with deterioration in insulin action, while testosterone administration has no such effect. Thus, increased growth hormone secretion is most likely responsible for the insulin resistance during puberty, and both growth hormone secretion and insulin resistance decline with completion of puberty.

Type 2 diabetes mellitus is strongly associated with 2 additional cardiovascular disease risk factors: obesity and hyper-

insulinemia. Hyperinsulinemia has been postulated as the critical component of the metabolic syndrome, including insulin resistance, hypertension, hypertriglyceridemia, low high density lipoprotein cholesterol, abnormal blood clotting tendency and chronic inflammation. This syndrome may be present in children before and during puberty (1, 18). In our study we have observed a tendency to high trygliceride and low HDL-C serum concentrations in obese children with IGT. Early diagnosis is imperative to identify comorbidities such as hypertension and dyslipidemia (19).

Accumulative incidence of progression to diabetes ranging from 23 to 63 % is reported among subjects with impaired glucose tolerance followed for 2 years up to 27 years (9). The blood glucose concentration 2h after an oral glucose load is an important predictor of progression to type 2 diabetes mellitus (7). Therefore, subjects with impaired glucose tolerance are an important target group for the prevention of type 2 diabetes mellitus. Early treatment implementation in obese children and adolescents with IGT, constitutes a strategy of reversing progression to β-cell failure and in preventing type 2 diabetes.

B. TRESACO, G. BUENO, L. A. MORENO, J. M. GARAGORRI y M. BUENO. *Resistencia a la insulina e intolerancia a la glucosa en niños y adolescentes obesos.* J. Physiol. Biochem., **59** (3), 217-224, 2003.

La prevalencia de obesidad en los países desarrollados ha aumentado de manera alarmante en las últimas décadas. Esto se ha observado también en niños y adolescentes. Clásicamente, la diabetes tipo 2 se consideraba muy rara en niños y adolescentes; sin embargo, en las últimas décadas, se han observado algunos casos, especialmente en adolescentes obesos de algunas poblaciones minoritarias. El objetivo de nuestro estudio consiste en valorar la prevalencia de diabetes tipo 2, intolerancia a la glucosa (IG) y resistencia a la insulina, y sus principales manifestaciones, en niños y adolescentes obesos. Se estudiaron 95 niños y adolescentes obesos, 53 varones y 42 mujeres, de 4 a 16 años. La prevalencia de IG en los niños y adolescentes obesos estudiados fue de 7.4%; no se detectó ningún niño con diabetes tipo 2. Las concentraciones séricas en ayunas de glucosa e insulina no mostraron diferencias significativas entre los niños obesos con y sin IG; sin embargo, 120 minutos después de la sobrecarga oral con glucosa, las concentraciones séricas de glucosa e insulina mostraron diferencias significativas entre ambos grupos. La resistencia a la insulina se definió cuando el índice HOMA fue mayor que 4. La prevalencia de resistencia a la insulina en los niños obesos estudiados fue 35,8%. Las concentraciones séricas de triglicéridos fueron mayores y las de HDL-C menores en los niños obesos con IG que en aquellos que no la presentaban, pero las diferencias no fueron estadísticamente significativas. La IG y la resistencia a la insulina son frecuentes en niños y adolescentes obesos; el inicio de un tratamiento precoz en los niños y adolescentes obesos con IG puede evitar el deterioro de la función de las células β y contribuir a prevenir la aparición de diabetes tipo 2 en el futuro.

Palabras clave: Obesidad, Resistencia a la insulina, Intolerancia a la glucosa, Infancia, Nutrición.

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