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The effect of puberty on insulin resistance in obese children

S. Pilia[1], M.R. Casini[1], M.L. Foschini[1], L. Minerba[2], M.C. Musiu[1], V. Marras[1], P. Civolani[1], and S. Loche[1]

[1]Pediatric Endocrinology Unit, Microcitemico Hospital, ASL Cagliari; [2]Department of Public Health, University of Cagliari, Cagliari, Italy

ABSTRACT. ***Objective:*** **Insulin resistance (IR) increases during puberty in normal children. IR is the first adverse metabolic event of obesity, and the marker of the metabolic syndrome. We aimed to study the effect of puberty on IR in obese and normal-weight children.** ***Design:*** **Cross-sectional evaluation of fasting glucose, insulin concentrations, and homeostasis model assessment of IR (HOMA-IR) in obese and control children throughout puberty.** ***Patients and methods:*** **We recruited 424 obese children (207 pre-pubertal and 217 pubertal divided in Tanner stages 2-3, 4, and 5) and estimated IR using the HOMA-IR index. Data were compared to those obtained in 123 healthy normal-weight children (40 pre-pubertal and 83 pubertal divided in Tanner stages 2-3, 4, and 5).** ***Results:*** **In the obese children mean HOMA-IR increased progressively across Tanner stages, and was significantly higher in all groups (pre-pubertal and Tanner stages 2-3, 4, and 5) of obese than in control children. HOMA-IR was significantly correlated with BMI.** ***Conclusions:*** **HOMA-IR in obese children increases at puberty more than in normal-weight children and does not return to pre-pubertal values at the end of puberty.**

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INTRODUCTION

In the last decades obesity and overweight in children and adolescents have reached alarming proportions. It is estimated that about 8-10% of children worldwide are obese (1-4). Increased risk factors for heart disease as well as Type 2 diabetes are thus occurring with increased frequency in overweight youths (5, 6). Impaired glucose tolerance (GT) has been demonstrated in as many as 25% of obese pre-pubertal children, and shown to be correlated to insulin resistance (IR) and fasting hyperinsulinemia (7). In addition, IR and hyperinsulinaemia co-exist in pre-adolescent children with moderate-to-severe obesity and with a relatively short duration of the obese state (8). In both adults and children, the importance of visceral obesity in the pathogenesis of IR is documented by several reports (9-12), and the risk of developing metabolic and cardiovascular complications in obese children is correlated to the distribution of the fat mass rather than to body mass index (BMI). In fact, obese children with more abdominal fat are those more likely to become obese adults (13, 14).

A number of studies have demonstrated that normal-weight children have transient IR at puberty (15-18), in the period of rapid growth. The hormonal changes as well as changes in body composition that occur during puberty favor development of IR with compensatory hyperinsulinemia. According to previous reports (18), IR increases at Tanner stage 2 (onset of puberty), peaks at Tanner stage 3, and returns to near pre-pubertal levels at Tanner stage 5 (end of puberty). Girls have been reported to be more insulin resistant than boys at all Tanner stages (19). Furthermore, Hoffmann et al. (19) have demonstrated that early pubertal girls are more insulin resistant than boys and compensate with increased insulin secretion. IR is generally related to BMI and adiposity, but the physiological and transient IR that occurs during puberty in non-obese children is not completely explained. Klein et al. (20) have shown in a longitudinal study that in adolescent girls homeostasis model assessment of IR (HOMA-IR) and fasting insulin levels increased during puberty, and BMI was significantly and positively correlated with insulin levels.

Although several studies have documented the increase in IR associated with puberty in normal children, none has studied IR in obese children across puberty. In this study we evaluated IR cross-sectionally by means of the HOMA index in a large number of pre-pubertal and pubertal obese children. Data were compared to those obtained in age-matched normal-weight children.

MATERIALS AND METHODS

Four hundred and twenty-four obese non-diabetic children and 123 healthy normal-weight children were included in the study. All subjects were recruited from the Pediatric Endocrinology Unit of the Ospedale Regionale per le Microcitemie in Cagliari, Italy, from January 2005 to November 2006. Obesity was defined as BMI>95th centile for sex and age according to the Italian 2006 growth reference charts (21). The study was approved by the local Ethics Committee and informed consent was obtained from the children and/or from their legal guardians. Two hundred and seven obese children were pre-pubertal (112 boys, age 3.7-13.2 yr and 95 girls, age 4.6-11.5 yr) and 207 were pubertal (49 boys, age 9.3-17.8 yr and 47 girls, age 7.3-13.4 yr, Tanner stage 2-3; 20 boys, age 11.6-17.7 yr and 24 girls, age 9.7-14.2 yr, Tanner stage 4; 11 boys, age 14-17.6 yr and 66 girls, age 9.9-18.5 yr, Tanner stage 5). None had dysmorphic syndromes and all subjects were free of medications. None had diabetes, 45 patients had impaired fasting glucose, but normal GT after oral GT test. All were included in the study. The control group comprised 20 pre-pubertal boys (age 5.0-13.0 yr) and 20 pre-pubertal girls (age 4.0-10.0 yr), 20 boys (age 12.0-15.0 yr) and 20 girls (age 7.0-17.0 yr) in Tanner stage 2-3, 7 boys (age 13.0-17.0 yr) and 13 girls (age 9.0-16.0 yr) in Tanner

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Correspondence: S. Loche, MD, Servizio di Endocrinologia Pediatrica, Ospedale Regionale per le Microcitemie, Via Jenner, 09121 Cagliari, Italy.

E-mail: sloche@mcweb.unica.it

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stage 4, and 7 boys (age 14.0-17.0 yr) and 16 girls (age 12.0-17.0 yr) in Tanner stage 5.

Assessment of anthropometry and pubertal status

Weight was measured in light indoor clothing using a calibrated electronic scale (Seca, Italy). Height was measured using a calibrated wall-mounted stadiometer. Pubertal development was assessed by the same staff members using the criteria of Marshall and Tanner (22, 23).

Biochemical assays

Measurement of fasting serum insulin and glucose were performed from venous blood sampling in the morning between 08:00 and 09:00 h after fasting overnight. Blood glucose levels were measured using the glucose-oxidase method. Blood insulin levels were measured using a commercial radioimmunoassay (Adaltis, Italy). Sensitivity was 0.3 μU/ml with intra- and inter-assay coefficient of variation of 2.3% and 3.5%, respectively. In our laboratory, normal fasting insulin concentrations are 4.3-19.9 μU/ml. IR was estimated using the HOMA-IR index calculated according to the formula: fasting blood glucose (mmol/l) × fasting insulin (μU/ml)/22.5.

Statistical analysis

Statistical analyses were performed using the SPSS 10.0 package (SPSS, Inc. Chicago, IL, USA). Data are presented as mean±SE. BMI-SD score (BMI-SDS) were calculated using the Growth Analyzer software (Novo Nordisk) and were derived from the Italian data of Luciano et al. (24). Unpaired Student t-test was used to compare two groups. Differences between HOMA mean values between obese and controls in different groups, relating to gender, were investigated by multifactorial analysis of variance test. Spearman's coefficient was used for correlation analyses. $p<0.05$ was considered significant.

RESULTS

Mean BMI-SDS for the different groups of obese subjects are reported in Table 1. Mean fasting serum glucose was similar between obese subjects and controls at any stage of pubertal maturation (Table 2). Mean insulin concentrations were significantly higher in all groups of obese subjects than in controls, and were significantly higher in any pubertal stage than in pre-puberty (Table 2). There was a trend to higher insulin concentrations in pubertal *vs* pre-pubertal control children of both sexes, although the difference did not reach statistical significance (Table 2).

Mean HOMA-IR was significantly higher in obese subjects than in controls, and was significantly higher in either Tanner stage 2-3, 4, and 5 pubertal obese subjects of both sexes than in pre-pubertal ones (Fig. 1). There was a trend to increased HOMA values with puberty in control subjects. Only in Tanner stage 5 control girls were mean HOMA values significantly higher than in pre-puberty, Tanner stage 2-3 and 4. Mean HOMA-IR was not statistically different between boys and girls, either obese or normal weight (Table 2).

In the obese subjects there was a significant correlation between BMI-SDS and HOMA-IR (r=0.2044, $p<0.0001$) as well as between BMI-SDS and insulin (r=0.2059, $p<0.0001$).

In the obese subjects HOMA-IR increased during puberty more than in the control group at any Tanner stage. In fact, the mean HOMA-IR increase between pre-puberty and Tanner stage 2-3, 4, and 5 was 12.7%, 2%, and 27%, respectively in controls and 29.4%, 41.6% and 38.8%, respectively in obese children.

DISCUSSION

Insulin concentrations increase at puberty in normal children as a result of a transient IR (15-19, 25, 26). The effect of puberty on IR has also been studied in pre-pubertal and adolescent obese children (8, 20, 27), but a comparison between obese children and normal-weight subjects has only been reported in obese girls (27). In our study, there was a trend to increased HOMA-IR values with puberty in the control group, although the difference reached statistical significance only in Tanner 5 control girls. Conversely, HOMA-IR values were significantly higher in pubertal Tanner stage 2-3, 4, and 5 obese subjects of both sexes than in pre-pubertal ones. Furthermore, HOMA-IR values in obese boys and girls were always significantly higher than in the control children at any stage of pubertal development. Our results differ from those reported by Moran et al. (18), since in our normal-weight Tanner 5 girls HOMA-IR did not return to near-pre-pubertal levels. These differences could be explained by the fact that Moran et al. (18) evaluated IR by the clamp technique, or to the number of subjects. Our results also differ from those reported by Hoffman et al. (19) since in their study pre-pubertal and early pubertal girls were more insulin resistant than boys. These contrasting results can also be explained by methodological differences, and/or from the sample size.

The hyperinsulinemic-euglycemic clamp is considered the gold standard for the determination of insulin sensitivity (28, 29). A valid alternative is the minimal model analysis of a frequently sampled iv GT test (FSIVGTT) (30-31). The HOMA-IR used in our study, like the quantitative insulin-sensitivity check index, derives estimates of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations, and is reportedly correlated with BMI (32, 33). Some authors found that the

Table 1 - *Mean (±SE) body mass index-SD score (BMI-SDS) in pre-pubertal and pubertal obese boys and girls.*

	Pre-puberty		P 2-3		P 4		P 5	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
BMI-SDS	2.72±0.05[1]	2.96±0.06	2.8±0.07[2]	2.53±0.05	2.9±0.11[3]	2.51±0.11	3.13[3]±0.11	2.68±0.68

[1]$p<0.01$ boys *vs* girls; [2]$p<0.005$ boys *vs* girls; [3]$p<0.01$ boys *vs* girls.

Table 2 - *Mean±SE glucose, insulin and homeostasis model assessment of insulin resistance (HOMA-IR) in pre-pubertal and pubertal obese and controls subjects.*

Pubertal stage	Glucose (mmol/l)		Insulin (μUI/ml)		HOMA-IR	
	Obese	Controls	Obese	Controls	Obese	Controls
Pre-pubertal boys	5.06±0.03 (no.=112)	4.92±0.09 (no.=20)	21.75±1.14[a] (no.=112)	12.84±0.72 (no.=20)	4.93±0.27[a] (no.=112)	2.82±0.17 (no.=20)
Tanner stage 2-3 boys	5.08±0.05 (no.=49)	4.99±0.09 (no.=20)	27.74±1.90[a,b] (no.=49)	15.38±1.30 (no.=20)	6.3±0.45[a,b] (no.=49)	3.4±0.28 (no.=20)
Tanner stage 4 boys	5.06±0.11 (no.=20)	5.32±0.16 (no.=7)	32.53±5.77[a,b] (no.=20)	12.21±2.48[b] (no.=7)	6.99±1.06[a,b] (no.=20)	2.82±0.54 (no.=7)
Tanner stage 5 boys	5.06±0.07 (no.=11)	4.52±0.09 (no.=7)	30.92±4.6[a,b] (no.=20)	15.67±3.26[b] (no.=7)	7.04±1.1[a,b] (no.=11)	3.29±0.67 (no.=7)
Pre-pubertal girls	4.97±0.04 (no.=95)	4.86±0.1 (no.=20)	22.47±1.06[a] (no.=95)	14.67±1.28 (no.=20)	5.01±0.25[a] (no.=95)	3.19±0.29 (no.=20)
Tanner stage 2-3 girls	5.05±0.05 (no.=47)	4.9±0.07 (no.=20)	28.91±1.98[a,b] (no.=47)	15.51±1.47 (no.=20)	6.56±0.48[a,b] (no.=47)	3.36±0.33 (no.=20)
Tanner stage 4 girls	5.12±0.08 (no.=24)	4.71±0.09 (no.=13)	34.68±3.18[a] (no.=24)	15.5±2.26[b] (no.=7)	7.09±0.6[a,b] (no.=24)	3.29±0.52 (no.=13)
Tanner stage 5 girls	5.04±0.05 (no.=66)	4.98±0.09 (no.=16)	29.94±1.58[a,b] (no.=24)	20.78±1.66[b] (no.=66)	6.77±0.39[a,b] (no.=66)	4.33±0.34 (no.=16)

[a]Statistically different *vs* controls; [b]statistically different *vs* pre-pubertal stage.

HOMA-IR is a valid method of measurement of insulin sensitivity in non-diabetic children and adolescents (34-36), while others found that this surrogate method offers no advantages over fasting insulin (37-39). However, albeit with limitations, HOMA-IR is considered a reliable method to measure IR in epidemiological studies, or in studies involving a large number of non-diabetic subjects (39). In fact, FSIVGTT and the hyperinsulinemic-euglycemic clamp technique (28-31), are time-consuming, invasive, expensive, labor intensive, require experienced personnel, and are technically difficult to perform in children.

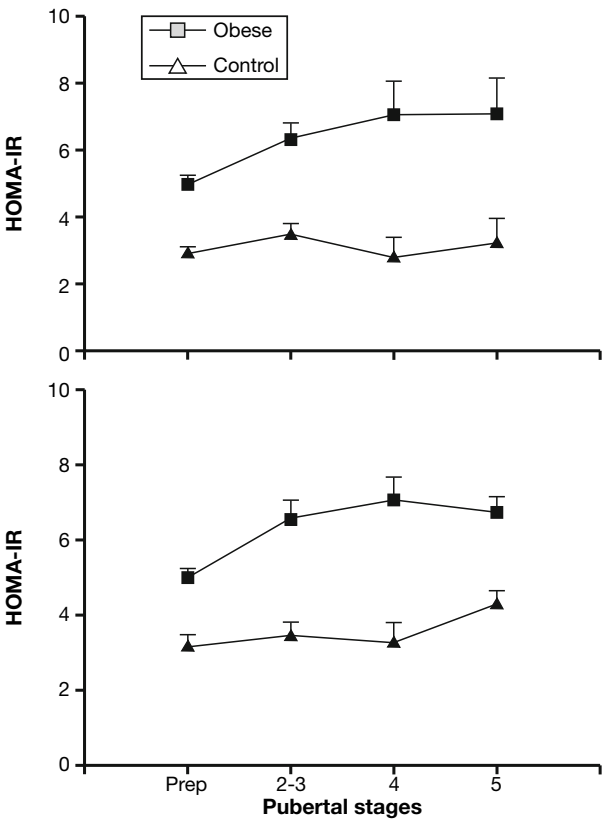

Fig. 1 - *Mean homeostasis model assessment of insulin resistance (HOMA-IR) in pre-pubertal (Tanner stage 1) and pubertal (Tanner stage 2-3, 4, and 5) boys (upper panel) and girls (lower panel). HOMA-IR in obese subjects was consistently higher than in control children at any stage of pubertal maturation.*

Although with the above-mentioned limitations, our data document that pre-pubertal and pubertal obese non-diabetic children have a greater degree of IR than normal weight age-matched children at any stage of pubertal maturation. Similar findings have been reported by McCartney et al. (27) in obese girls. However, in their patients, mean HOMA-IR decreased at Tanner stage 5, but remained significantly higher than in controls matched for age and pubertal stage. In accordance with previous reports (19, 20), we found that HOMA-IR and fasting insulin were correlated with BMI. In addition, we have shown that in obese children, HOMA-IR showed a progressive increase with puberty with the highest levels reached at Tanner stages 4 in girls and 5 in boys.

Puberty is associated with changes in hormonal status, metabolism, and body composition (26, 40). During puberty, in fact, differences in adiposity (BMI increases with age), body fat distribution, gonadal and adrenal hormones (27), and in GH/IGF-I axis function (41) in obese *vs* normal-weight adolescents may explain the increased IR in the obese subjects. In addition, it is known that insulin sensitivity is also influenced by a number of adipose tissue-derived cytokines (42). In this regard, it has been shown in healthy children that changes in adipokine levels throughout pubertal development are sex-dependent, suggesting that gonadal function progression and increasing circulating sex steroids may play an important role in adipokine changes (43-46), and hence in insulin sensitivity (27).

In summary, we have confirmed that obese non-diabetic children have higher HOMA-IR values than normal-weight children. In addition, we have shown that in obese children IR worsens with puberty, and does not return to pre-pubertal values at the end of pubertal maturation. These observations may have practical implications in prevention strategies.

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