Comparison Between β-Cell Function and Insulin Resistance Indexes in Prepubertal and Pubertal Obese Children

Gabriele Guzzaloni, Graziano Grugni, Giuliana Mazzilli, Dario Moro, and Francesco Morabito

Several methods have been developed to assess insulin resistance (IR), insulin secretion, and sensitivity: some of them, such as the homeostasis model assessment (HOMA) for IR (HOMA IR) and for insulin secretion (HOMA β cell) and the quantitative insulin sensitivity check index (QUICKI) are based on fasting levels of glucose (fasting G) and insulin (fasting I); others, such as the pancreatic insulin response to glucose (IRG) and the insulin sensitivity index (ISI) are derived from the glycemic and insulinemic responses to the oral glucose tolerance test (OGTT). The aim of the study was to compare these indexes in a large group of prepubertal and pubertal obese subjects and verify whether the data from fasting samples were enough for evaluating IR and insulin secretion or if OGTT was mandatory. A total of 405 obese subjects (221 boys and 184 girls) was studied. Ninty-three were prepubertal (Tanner stage I), 98 early pubertal (stage II to III) and 214 late pubertal (stage IV to V). In each subject, a 120-minute OGTT was performed, and the glycemic (mean blood glucose [MBG]) and insulinemic (mean serum insulin [MSI]) responses, expressed as AUC/120, as well as IRG and ISI were calculated. The fasting I/fasting G ratio (FIGR), HOMA IR, HOMA β cell, and QUICKI were then measured. FIGR and HOMA IR increased in both sexes during puberty, but in girls, the increase was already evident from stage I to stage II to III, while in boys, it was evident only from stage II to III to stage IV to V. QUICKI decreased in girls at the onset of puberty and was lower than in boys in stage II to III; on the other hand, HOMA β cell did not show any variation. IRG increased throughout puberty, although it was higher in boys than in girls in stages II to III and IV to V, while ISI decreased at the onset of puberty in boys; HOMA IR correlated with MSI and IRG, and HOMA β cell with MSI in pubertal subjects only. In conclusion, the indexes deriving from fasting samples, such as FIGR and HOMA IR, proved to be enough for evaluating IR in prepubertal and pubertal obese subjects, as did QUICKI for insulin sensitivity, However, OGTT is still useful for assessing insulin secretion, because IRG is more sensitive in depicting the pubertal variations of IR than HOMA β cell.

INSULIN RESISTANCE (IR) is a feature of obesity and hallmarks normal pubertal development. Of the various methods developed for assessing IR, many are very costly and disliked by patients, so that they cannot be used for large-scale investigations. Therefore, as a surrogate for a direct measure of IR, fasting I,[1] as well as its ratio with fasting G (FIGR) have been used, at least in subjects without insulin secretion deficiency.[2] Based on fasting I and fasting G, the homeostasis model assessment (HOMA) for evaluating both IR (HOMA IR) and pancreatic insulin secretion (HOMA β cell)[3] were introduced, as was more recently, the quantitative insulin sensitivity check index (QUICKI).[4] Moreover, based on the results of the oral glucose tolerance test (OGTT), the insulinemic pancreatic response to glucose (IRG), as a measure of insulin secretion, and the insulin sensitivity index (ISI) were obtained, both well correlated with the estimations derived from the clamp technique.[5,6] In a previous study of obese adolescents, we observed a correlation between FIGR, IRG, and body mass index (BMI) on the one hand, and an increase of IRG during pubertal development on the other.[7]

The present investigation was conducted to assess the indexes of IR and insulin secretion in a group of prepubertal and pubertal obese subjects and to compare those based on fasting I and fasting G with those derived from glycemic and insulinemic responses to OGTT and to clarify whether the assessments obtained from fasting samples could be clinically sufficient for evaluating IR.

SUBJECTS AND METHODS

A total of 405 Caucasian obese subjects (BMI > 2 SD for chronological age, according to Rolland-Cachera[8]), 221 boys and 184 girls were studied: prepubertal (stage I according to Tanner, 93 subjects, 58 boys and 35 girls), early pubertal (stage II to III, 98 subjects, 65 boys and 33 girls) and late pubertal (stage IV to V, 214 subjects, 98 boys and 116 girls) (Table 1).

Thyroidal, adrenal, and gonadal diseases were ruled out by appropriate analyses, particularly with regard to congenital adrenal hyperplasia and ovarian hyperandrogenism, by adrenocorticotrophic hormone (ACTH) and gondadtropin-releasing hormone (GnRH)-analog stimulations.

After fasting overnight, between 8 AM and 9 AM, each subject underwent the following examinations: fasting G (mg/dL, glucose oxidase-paraminophenazone method), fasting I (μU/mL, immunofluorimetric method) as well as glycemic (mean blood glucose [MBG], mg/dL) and insulinemic (mean serum insulin [MSI], μU/mL) responses to a 120-minute OGTT with 75 g glucose, and expressed as area under the curve (AUC/120'), obtained by the trapezoidal method.

Based on the foregoing, FIGR was the ratio between fasting I (pmol/L) and fasting G (mmol/L)[2]; HOMA IR was calculated according the following formula: fasting I (μU/mL) × fasting G (mmol/L)/22.5, while HOMA β cell = 20 × fasting I (μU/mL)/fasting G (mmol/L) – 3.5,[3] and QUICKI = l/log fasting I + log fasting G.[4]

As previously reported,[6] IRG (μU/mL/min) was the ratio between insulin (μU/mL/min) and glucose net increase areas (mmol/L/min) in the first 30 minutes of OGTT, while ISI (mg/L^2/mmol × mU/min) was calculated as $75/120 + (G_0' - G_{120'}) \times 0.19 \times$ body weight/120 × MBG/log MSI.

The statistical analysis was performed by analysis of variance (ANOVA) and Student's *t* test, as appropriate, and linear regression, after logarithmic transformation of the values, to normalize the distribution. Thus, the data were expressed as median and interval between

From the Divisione Auxologia, Ospedale San Giuseppe, Istituto Auxologico Italiano, IRCCS, Verbania Intra, Italy.

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Address reprint requests to Gabriele Guzzaloni, MD, Divisione Auxologia, Ospedale San Giuseppe, Istituto Auxologico Italiano, IRCCS, PO Box 1, 28921, Verbania Intra, Italy.

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Table 1. Clinical Features of the Subjects

	Stage I		Stage II to III		Stage IV to V	
	Boys (n = 58)	Girls (n = 35)	Boys (n = 65)	Girls (n = 33)	Boys (n = 98)	Girls (n = 116)
Age (yr)	11.5 (9.6-12.4)	9.5 (8.1-10.2)	13 (12.1-13.8)	11.7 (10.5-12.2)	15.3 (14.9-15.9)	15.9 (14.4-17)
BMI	30.4 (27.8-34.3)	29.9 (28.3-33)	31.1 (29-35.4)	30 (28.1-33)	37 (34.6-40.9)	34.7 (32-38)
BMI-SDS	5.7 (4.7-7.3)	6.4 (5.3-7.7)	5.2 (4.3-6.1)	5.1 (4.2-5.8)	5 (5.6-6.5)	5 (4.2-5.7)

NOTE. Median, first, and third quartile in parentheses.

the first and third quartile. Zero hypothesis was discarded for values of P less than .05.

RESULTS

Fasting Samples

Fasting G did not change during puberty, while fasting I increased from stage I to stage II to III in girls (Figs 1 and 2). FIGR and HOMA IR increased in both sexes during puberty, but in girls, this was already evident in stage II to III, while in boys, it became evident in stage IV to V only (Figs 3 and 4). On the other hand, HOMA β cell did not show any variation throughout pubertal development (Fig 5). QUICKI decreased from stage I to stage IV to V in both sexes (Fig 6).

In stage II to III, FIGR was higher in girls than in boys (28.7 [21.4 to 41.6] *v* 21.1 [16.1 to 32.8], $P < .05$) and QUICKI lower (0.313 [0.273 to 0.304] *v* 0.327 [0.309 to 0.344], $P < .05$). Fasting G, fasting I, FIGR, and HOMA IR did not show any difference between the sexes.

OGTT

Eighteen subjects of 405 (4.4%) fulfilled the actual criteria of impaired glucose tolerance (ie, glucose plasma values at 120 minutes during OGTT = 140 mg/dL), 2 in stage I (1 boy and 1 girl), 1 (girl) in stage II to III, and 15 in stage IV to V (5 boys and 10 girls): this subgroup of patients was numerically too small for a separate statistical evaluation. MBG did not change during puberty (Fig 7), while MSI increased in girls (Fig 8). IRG increased during puberty in boys (Fig 9), paralleling the decrease of ISI (Fig 10), but in girls, the increase of IRG was not significant, while the behavior of ISI in girls was similar to that of boys.

Girls had higher values of ISI than boys in stage II to III (12.6 [10.9 to 24.8] *v* 11.3 [8.9 to 27.7], $P < .05$) and boys in stage IV to V (17.4 [11.9 to 25.7] *v* 16.8 [12.7 to 20.1], $P < .0001$). MBG and MSI did not show any differences between the sexes.

Correlations Between the Variables

Positive correlations were found between HOMA IR and MSI, HOMA IR and IRG, as well as between HOMA β cell and IRG in all groups of subjects; HOMA β cell correlated with MSI in pubertal subjects only; QUICKI correlated negatively with IRG in all pubertal stages and with MSI only in stage IV to V. Lastly, a positive correlation was found between QUICKI and ISI in stage I (Table 2).

BMI correlated positively with FIGR in all pubertal stages, strongly in stage I and weakly in stage IV to V; no correlations between BMI and HOMA β cell or ISI were found; correlations with the other indexes were weak and variable in each pubertal stage (Table 3).

DISCUSSION

Obesity and puberty are characterized by IR, which in turn, plays a key role in the development of diabetes.[9,10] However,

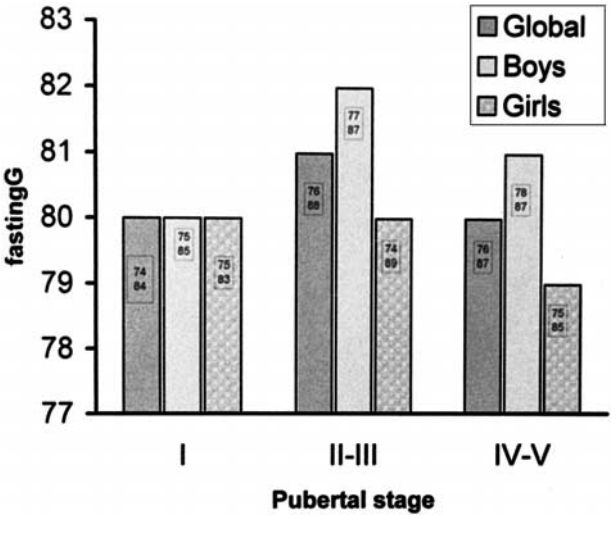

Fig 1. Modifications of fasting G, as median, 1st, and 3rd quartile (squares in the columns) during puberty.

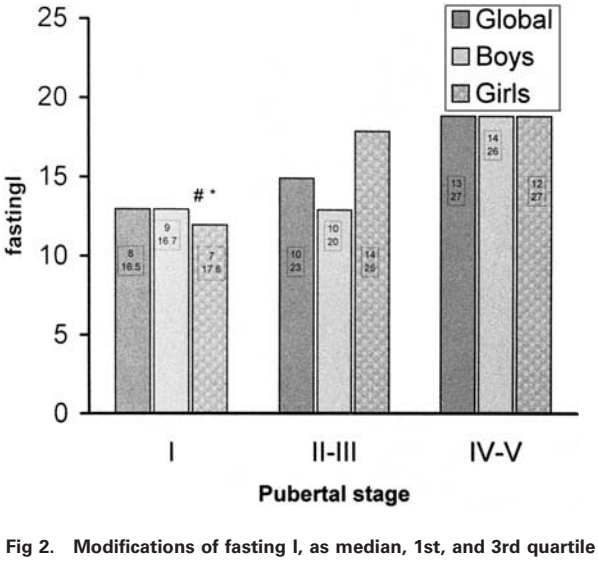

Fig 2. Modifications of fasting I, as median, 1st, and 3rd quartile (squares in the columns) during puberty ($^{\#}P < .0001$ *v* II to III; $^{*}P < .0001$ *v* IV to V).

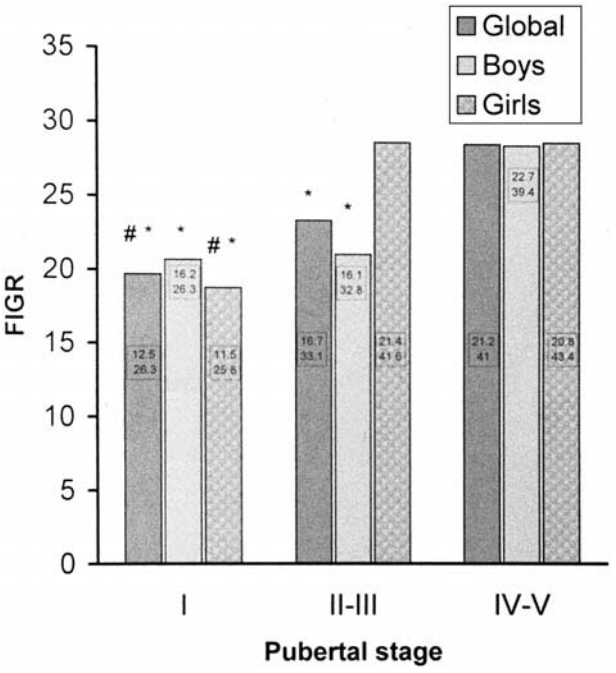

Fig 3. Modifications of FIGR, as median, 1st, and 3rd quartile (squares in the columns) during puberty (#$P < .0001$ *v* II to III; *$P < .0001$ *v* IV to V).

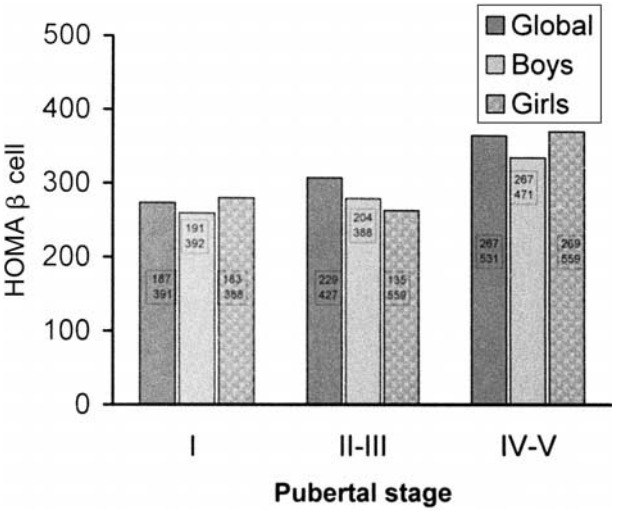

Fig 5. Modifications of HOMA β cell, as median, 1st, and 3rd quartile (squares in the columns) during puberty.

reliable and inexpensive indexes are required for revealing IR directly or indirectly by evaluating insulin sensitivity in large-scale studies. For this purpose, some measurements have been introduced, based on fasting I and fasting G, and well correlated with those obtained by the clamp technique, which is considered the gold standard, but is technically very complex for routine use.[1-4]

However, these indexes have so far been used only in adults: HOMA IR was reported to be 1.0 in young Caucasian healthy subjects of the original British study[3] and from 2.1 up to 2.7 in non-Hispanic whites and Mexican-Americans in the San Antonio Heart study[11]; QUICKI 0.382 ± 0.007 (mean ± SE) in lean and 0.331 ± 0.010 in obese subjects.[4] On the other hand, the values of FIGR in obese adolescents were higher than 22, suggestive of IR.[9] In the absence of a control group, these data indicate that HOMA IR was more able than FIGR to show IR in our sample, even before puberty; both showed an increase of IR during pubertal development, probably due to the contribution of physiologic IR, which occurred in stage II to III, in

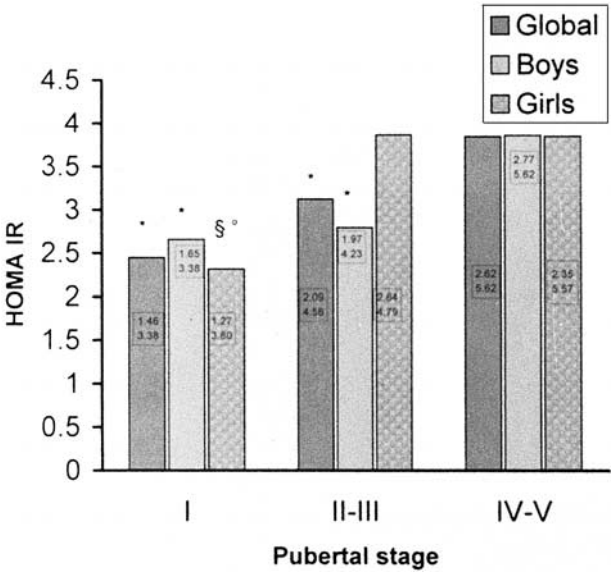

Fig 4. Modifications of HOMA IR, as median, 1st, and 3rd quartile (squares in the columns) during puberty (§$P < .01$ *v* II to III; °$P < .01$ *v* IV to V; *$P < .0001$ *v* IV to V).

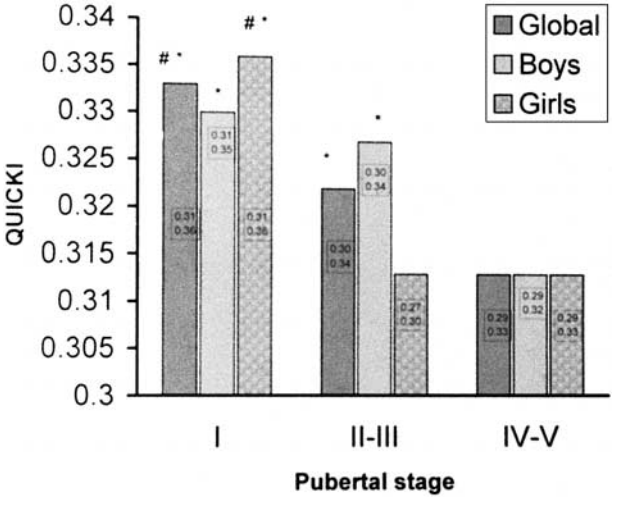

Fig 6. Modifications of QUICKI as median, 1st, and 3rd quartile (squares in the columns) during puberty (#$P < .0001$ *v* II to III; *$P < .0001$ *v* IV to V).

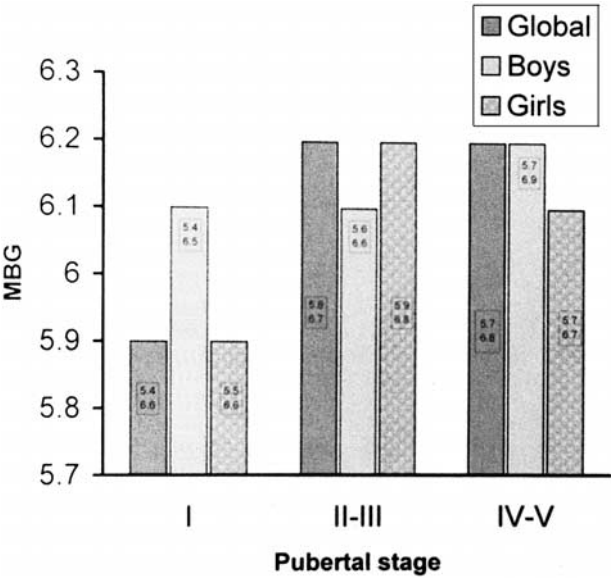

Fig 7. Modifications of MBG as median, 1st, and 3rd quartile (squares in the columns) during puberty.

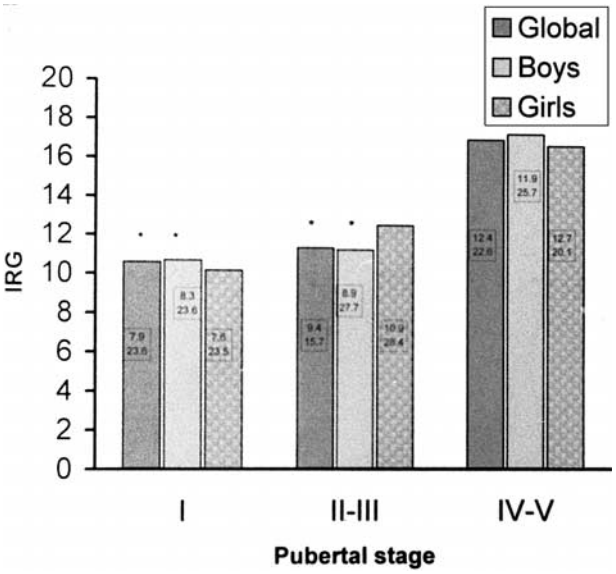

Fig 9. Modifications of IRG as median, 1st, and 3rd quartile (squares in the columns) during puberty (*$P < .0001$ *v* IV to V).

agreement with data obtained using the clamp technique.[9] Nevertheless, the distribution of FIGR values in stage II to III pointed to greater IR in girls than in boys, a fact not statistically confirmed by HOMA IR. These differences between the sexes were observed, at least in part, in normal weighted subjects by Moran et al[10] by using the clamp technique, but unlike these investigators, we did not observe a progressive increase of IR during midpuberty or a return to the prepubertal value at the end of puberty, either by HOMA IR or FIGR, probably because of the confounding effect of obesity. Nevertheless, in our opinion, there are greater advantages with the use of HOMA IR than with FIGR, from a clinical point of view, because the former identifies IR earlier than the latter.

It must be remembered that fasting I is regarded as a marker of IR rather than of insulin sensitivity, because the relationship between insulin and glucose is nonlinear.[12] In fact, the effect of insulin is not proportional to its serum concentrations, but rather to those observed in the several compartments, remote from circulating insulin. Moreover, FIGR gives no information on the peripheral effects of insulin, because it is influenced by

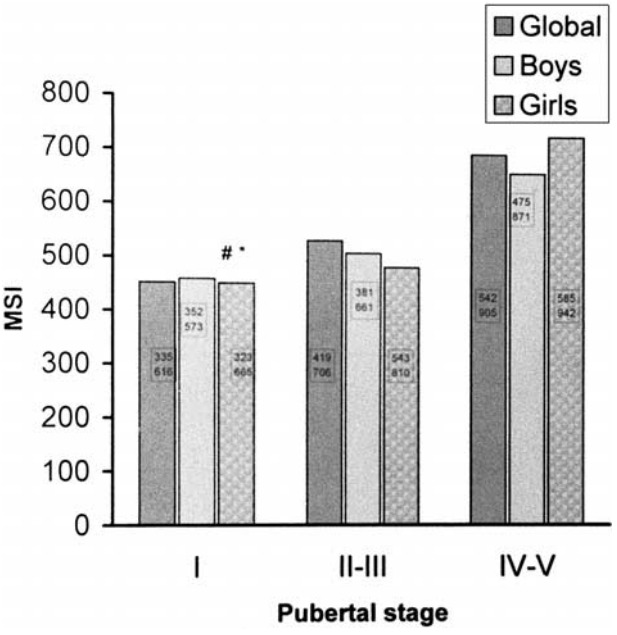

Fig 8. Modifications of MSI as median, 1st, and 3rd quartile (squares in the columns) during puberty (#$P < .0001$ *v* II to III; *$P < .0001$ *v* IV to V).

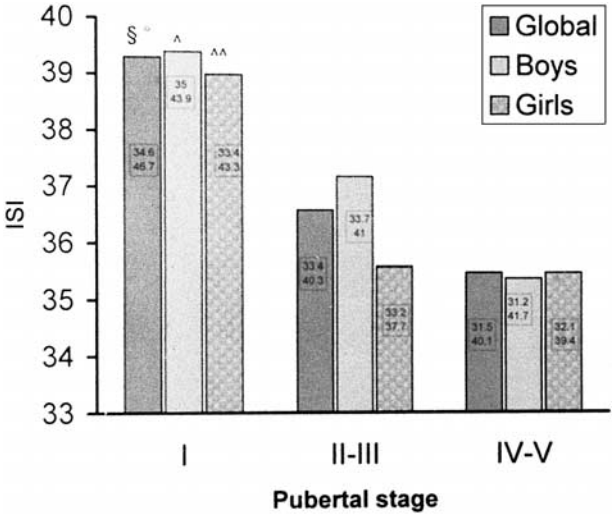

Fig 10. Modifications of ISI as median, 1st, and 3rd quartile (squares in the columns) during puberty (§$P < .01$ *v* II to III; °$P < .01$ *v* IV to V; ^$P < .05$ *v* II to III; ^^$P < .05$ *v* IV to V).

Table 2. Correlations Between the Metabolic Indexes

	Stage I	Stage II to III	Stage IV to V
HOMA IR			
MBG	0.26*	NS	NS
MSI	0.59	0.53	0.46
IRG	0.50	0.50	0.15*
SI	−0.41	NS	−0.19†
HOMA β-cell			
MBG	NS	NS	−0.28
MSI	NS	0.37	0.39
IRG	0.22*	0.44	0.29
QUICKI			
MSI	−0.59	NS	−0.46
SI	0.43	NS	NS
IRG	−0.48	−0.52	−0.21†

Abbreviation: NS, not significant.

*$P < .05$; †$P < .01$; the other correlations showed P values $< .001$.

insulin secretion pulsatility, as well as by stress-induced effects.[13] On the other hand, the determination of insulin levels during OGTT should provide an assessment of insulin sensitivity.[5,6] In fact, the comparison of the values of the third quartile of ISI in our sample with the mean values (± SE) of normal weighted subjects reported in the literature (stage I, 45 ± 3.2; stage II to III, 47.3 ± 2.8; stage IV to V, 69.4 ± 3.8[13];) pointed to a decrease of insulin sensitivity, a fact further supported by the parallel increase of IR indexes and MSI in both sexes during puberty. Nevertheless, QUICKI detected the increase of IR not only at pubertal take-off, but also from mid (stage II to III) and late puberty (stage IV to V), a finding not revealed by using ISI. These data, along with the weak correlation between ISI and QUICKI and the lack of correlation between ISI and BMI, suggest that QUICKI is a more sensitive index for determining IR throughout puberty than ISI, being also easier to calculate.

Taking into account that the hyperinsulinemic response to OGTT arises from an abnormality of early insulin response, with a late compensatory hyperproduction that could interfere with the assessment of insulin secretion, the ratio between the concentrations of insulin and glucose during the first 30 minutes of the OGTT, like that evaluated by IRG, has been suggested as a measurement of insulin secretion.[6,15] In our experience, IRG was much higher than that reported in normal subjects (stage I, 3.5 ± 0.8; II to III, 5.3 ± 0.7; IV to V, 7.4 ± 0.8[13]) and increased during puberty, paralleling the variations of MSI more clearly in boys than in girls, thus confirming the increase of insulin secretion in obese adolescents previously reported by us and others.[7,16] This fact was striking, because the estimation of insulin secretion was not provided by other more complex tests, such as the hyperinsulinemic euglycemic clamp.[11] However, in theory, the phenomenon could also be shown by HOMA β cell, although this index might yield unreliable results if no preliminary correction for insulin resistance was performed, as it was in this study.[11] This fact, along with the wide range of the HOMA β-cell values, might explain why this index did not seem to show any variations in insulin secretion during puberty, suggesting that OGTT is preferable for evaluating insulin secretion, in agreement with other reports.[11,15]

One limitation of this study might be the inclusion of subjects with impaired glucose tolerance, because this condition has been shown to be associated with high IR and low insulin secretion.[11] Nevertheless, taking into account both the small number of such subjects and the purpose of the study, this issue should not confound the interpretation of the results.

In conclusion, OGTT is not necessary for detecting IR in pubertal obesity, since FIGR and HOMA IR are sufficient; however, by using the latter index, IR can be revealed even in prepubertal obese children, and so is preferable to the former. Similarly, with regard to insulin sensitivity, QUICKI is more sensitive than ISI. On the other hand, OGTT is useful in determining insulin secretion, since IRG yields a good estimation of the pubertal variations of IR, being less influenced by interfering factors than HOMA β cell.

Table 3. Correlations with BMI

	Stage I	Stage II to III	Stage IV to V
FIGR	0.34	0.28*	0.15†
HOMA IR	0.38	0.28*	NS
HOMA β-cell	NS	NS	NS
QUICKI	−0.29†	−0.31*	NS
IRG	NS	0.28*	0.19*
SI	NS	NS	NS

$P < .01$; †$P < .05$; the other correlations showed P values $< .001$.

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