Original article

Insulin resistance and secretion indexes in healthy Italian children and adolescents: a multicentre study

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Abstract. *Background and aim:* To establish normal values of insulin resistance, secretion and sensitivity using respectively HOMA-IR, HOMA-β% and QUICKI indexes in healthy Italian children and adolescents, based on fasting samples. *Methods:* We determined HOMA-IR, HOMA-β% and QUICKI at baseline in 142 healthy subjects from Pediatric Centres, aged 2.7 to 19 years (10.6±3.8, Mean±SD), with different Tanner's pubertal Stages (TS). None had hypo/hyperglycemia (fasting plasma glucose ranging from 3.6 to 5.6 mmol/l), obesity (BMI (kg/m2) 17.9±2.4, M±SD), or family history for diabetes mellitus. *Results:* The HOMA-IR index slightly increases with Tanner's stage. As regards HOMA-β% and QUICKI, a weak variation throughout puberty was observed. No significant correlation was observed between HOMA-IR, HOMA-β%, QUICKI and BMI-SDS or chronologic age. *Conclusions:* Normal values of HOMA-IR, HOMA-β% and QUICKI are useful tools in the clinical and epidemiological practice for baseline screening and follow-up of subjects at risk for type 2 diabetes mellitus. (www.actabiomedica.it)

Key words: Insulin resistance, HOmeostatic Model Assessment (HOMA), QUantitative Insulin-sensitivity ChecK Index (QUICKI), paradigm model, minimal model, type 2 diabetes mellitus, obesity

Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder of heterogeneous etiology with social, behavioural and environmental risk factors unmasking the effects of genetic susceptibility (1). T2DM has become a global problem, both in developing countries, that adopt the so called "westernised lifestyle", and in developed countries in which an association with overweight and obesity has been documented (2). Moreover, age at onset of T2DM is decreasing worldwide, and affected children and adolescents are on the rise (3). This trend is occurring too quickly to be the consequence of increased gene frequency, and the key role of environmental factors, like overeating and sedentary lifestyle, seems to be more realistic (2).

Studies in populations at risk of developing T2DM reported that insulin resistance is an early and primary abnormality detectable in the normoglycemic, pre-diabetic state, and the worsening of insulin resistance leads to fasting hyperglycemia, impaired glucose tolerance and clinical diabetes mellitus. Moreover, a cluster of insulin resistance, obesity, hypertension and hyperlipidemia characterizes the so-called "metabolic syndrome", known as a severe risk

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factor for cardiovascular disease in adulthood (4). Recently, clinical features of the metabolic syndrome have been observed also in U.S. adolescents (5).

Insulin resistance (IR) is characterized by a decreased ability of insulin to stimulate the use of glucose by the muscle and adipose tissue, where the suppression of lipase controlled by insulin is impaired (6). The consequent excessive supply of free fatty acids further affects glucose transportation in the skeletal muscles, and inhibits insulin activity (7). In the liver, insulin resistance leads to increased hepatic glucose production, initially compensated by increased insulin secretion. If the process persists, glucotoxicity may occur, leading to chronic hyperglycemia and clinical diabetes (8).

In order to assess insulin resistance, insulin secretion and insulin sensitivity, methods based on hyperglycemic clamp have been validated both in obese and normal adults (9). In pediatric subjects, euglycemic clamp procedure is cumbersome, time consuming and technically difficult to perform on a large group. HOmeostasis Model Assessment of IR index (HOMA-IR), HOMA of percent β-cell function (HOMA-β%) and QUantitative Insulin-sensitivity ChecK Index (QUICKI) indexes calculated on fasting samples have the advantage of being quicker, simpler, less expensive and cumbersome than those based on minimal models, making them more acceptable to children, and ideal for large and longitudinal studies.

Several indexes based on mathematical modelling of fasting plasma glucose and insulin concentrations, like HOMA-IR, HOMA-β%, and QUICKI have been validated in adult obese patients and healthy controls (10-12).

The aim of our cross-sectional study was to establish normal values of HOMA-IR, HOMA-β%, and QUICKI indexes, calculated on fasting samples, in a healthy population of randomly-selected Italian healthy children and adolescents.

Subjects and methods

Study population

This cross-sectional study was performed in 142 subjects, 85 males and 57 females, aged 2.7 to 19 years (10.6 ± 3.8 years, Mean ± SD) recruited in different Italian Pediatric Diabetes Units belonging to the Italian Society of Pediatric Endocrinology and Diabetes (ISPED). Detailed medical and family histories were obtained for all subjects, who were referred for auxological evaluation, and major illnesses were excluded. They were in good health and they were not following a weight loss diet or an intense exercise programme. None of the subjects was pregnant or had a chronic illness like diabetes mellitus, liver, kidney or heart failure or was taking drugs that might affect glucose homeostasis. Family history was negative for diabetes mellitus.

Clinical characteristics of the enrolled subjects are reported in Table 1.

Clinical monitoring/Laboratory testing

In all subjects height, weight, body mass index and pubertal stage according to Tanner were recorded (13, 14). Measurements were taken with the subject wearing only light indoor clothing and barefoot. Height was measured with a portable Harpender stadiometer using Tanner technique. Weight was measured with a standardized portable scale. Body Mass Index (BMI) was calculated as follows: weight (Kg)/height (metres^2). Obesity was defined as BMI higher than 97th percentile for age (15).

BMI was calculated and BMI SDS score (BMI-SDS) was computed for each subject using the LMS method: BMI SDS=[(BMI/M)^L - 1]/(LxS) (16); the Italian data were used as reference standards (17).

The pubertal development stages were clinically assessed by trained research personnel using Tanner's staging criteria (13, 14). Subjects were divided into different Tanner stages according to pubic hair development in boys and to breast and pubic hair development in girls.

After overnight fasting for 12±1 hours, all subjects of each Centre underwent blood sampling withdrawals for assay of glucose, insulin, and anti β-cell autoantibodies. Blood samples were immediately processed or centrifuged at +4°C, the fractions were separated and plasma was stored at −20°C until analysis. Plasma glucose levels were measured using glucose oxidase technique (Glucose Autoanalyzer). Since insulin values may considerably vary among different

laboratories, all measurements were simultaneously performed at the Parma University Laboratory by radioimmunoassay using a commercial kit (Radim Kit, Rome, Italy). The inter- and intra-assay coefficients of variation were 8.2% and 6.9% for low values and 7.0% and 6.0% for high values, respectively. As immunological markers of type 1 diabetes mellitus, anti-islet cell antibodies (ICA) were detected through indirect immunofluorescence technique and anti-glutamic acid decarboxylase antibodies (GADA) were detected through radioligand assay with recombinant human GAD 65 antibody.

In order to detect insulin sensitivity we evaluated HOMA-IR using the following formula: fasting plasma insulin in mU/l x FPG in mmol/l/22.5 (10), and QUICKI as $1/(\log_{10}$ fasting plasma insulin in mU/l + $\log_{10}$ glucose in mg/dl) (11). In order to evaluate pancreatic β-cell function, we measured HOMA-β% as (20 x fasting insulin in mU/l)/(fasting glucose in mmol/l – 3.5) (10).

Informed consent and Ethics Committee

Informed consent was obtained after oral or written information was given. The Ethics Committees of all participating Pediatric Units approved the study.

Statistical methods

Quantitative variables (i.e.: HOMA-IR) were reported either as means and standard deviations (SD) or medians and quartiles or in Table 3 and 4 as percentiles (from the 2.5th to the 97.5th). Descriptive statistics for qualitative variables were reported in terms of absolute frequencies and percentages. Comparison of quantitative variables (ex: HOMA-IR, HOMA-β% and QUICKI) between the two groups of subjects (ex: males vs females) was performed using the non parametric Mann-Whitney U test and comparison of quantitative variables among groups of subjects (ex: pubertal Tanner's stages) was performed by means of non parametric analysis of variance (Kruskal-Wallis test); Dunn's test was applied to explore *post-hoc* differences between pairs of groups. Correlations among quantitative variables were evaluated using Spearman's correlation coefficients.

For all statistical tests, a p value less than 0.05 was considered as statistically significant. The statistical package "Statistica" (StatSoft Corp., Tulsa, OK) was used for all the analyses.

Results

Clinical characteristics

In all subjects, fasting plasma glucose (FPG) was < 5.6 mmol/l, personal and family histories were negative for obesity and diabetes mellitus. Autoantibodies against β-cells were negative in all subjects. The mean fasting indexes of insulin resistance, secretion and sensitivity are reported in Table 1.

Tables 2 reports the descriptive statistics of the 3 indexes, HOMA-IR, HOMA-β% and QUICKI, grouped by sex and by Tanner pubertal stage and reports the analysis of the difference among groups. Values of the three above mentioned indexes were not different in

Table 1. Clinical characteristics of enrolled subjects (N = 142)

General characteristics			
		N (%)	
Sex:	Males	85 (59.9)	
	Females	57 (40.1)	
Tanner's stage:	1	73 (51.4)	
	2-3	45 (31.7)	
	4-5	24 (16.9)	
		Mean (SD)	Median (Min - Max)
Age (years)		10.6 (3.8)	10.8 (2.7 - 19.0)
BMI (kg/m^2)		17.9 (2.4)	17.0 (14.2 - 24.5)
BMI-SDS (LMS)		-0.35 (0.8)	-0.42 (-1.94 - 1.74)
Fasting indexes of IR and secretion indexes			
		Mean (SD)	Median (Min - Max)
FPG (mmol/l)		4.68 (0.38)	4.72 (3.55 - 5.55)
FPI (mU/l)		7.11 (4.28)	6.15 (1.00 - 23.00)
HOMA-IR		1.49 (0.91)	1.32 (0.21 - 5.39)
HOMA-β %		144.1 (142.2)	107.5 (17.2 - 1078.2)
QUICKI		0.37 (0.04)	0.37 (0.30 - 0.52)

SD: Standard Deviation; Min-Max: Minimum and Maximum values

males and females (Table 2). Values of HOMA-IR index were significantly higher in subjects in Tanner's Stage 4 and 5 with respect to subjects in Tanner's Stage 1 (Dunn's test; $p<0.05$) (Table 2). Analogously, HOMA-β% index increased with Tanner's stage: subjects in Tanner's Stage 4 and 5 had significantly higher values either with respect to subjects in Tanner's Stage 1 (Dunn's test; $p<0.01$) or with respect to subjects in Tanner's Stage 2 and 3 (Dunn's test; $p<0.05$). QUICKI statistically decreased throughout puberty; in particular, subjects in Tanner's Stage 4 and 5 had significantly lower values of QUICKI index as compared to subjects in Tanner's Stage 1 ($p<0.05$) (Table 2).

Table 3 reports the percentiles (from the 2.5th to the 97.5th) of the indexes HOMA-IR, HOMA-β% and QUICKI grouped by pubertal Tanner's Stage.

The percentiles (from the 2.5th to the 97.5th) of the same indexes grouped by pubertal Tanner's Stage and by sex are reported in Table 4.

No correlation was observed neither among the three indexes of IR and secretion (HOMA-IR, HOMA-β% QUICKI) and BMI-SDS ($r_S = 0.076$, $r_S = 0.078$ and $r_S = -0.076$, respectively) nor among the three indexes of IR and secretion and chronological age ($r_S = 0.27$, $r_S = 0.23$ and $r_S = -0.27$, respectively).

Discussion

This study was aimed at establishing normal values of fasting insulin resistance, insulin secretion and insulin sensitivity using respectively HOMA-IR, QUICKI and HOMA-β% in a representative group of Italian healthy children and adolescents. We are aware that the sample size could be limited, but all enrolled subjects were characterized by normal fasting plasma glucose, normal BMI-SDS and no family history of obesity and diabetes mellitus.

Table 2. Descriptive statistics of HOMA-IR, HOMA-β% and QUICKI indexes in 142 healthy Italian children and adolescents, grouped by sex and pubertal Tanner's Stage (TS)

	N	Min-max	Mean (SD)	Median	P
Grouped by sex					
HOMA-IR					
Males	85	0.21-3.61	1.37 (0.73)	1.27	0.28#
Females	57	0.37-5.39	1.65 (1.10)	1.40	
HOMA-β%					
Males	85	17.2-781.4	130.4 (124.7)	102.4	0.07#
Females	57	24.6-1078.2	164.6 (163.9)	127.4	
QUICKI					
Males	85	0.32-0.52	0.38 (0.04)	0.37	0.28#
Females	57	0.30-0.46	0.37 (0.04)	0.36	
Grouped by pubertal Tanner's Stage (TS)					
HOMA-IR					
TS 1	73	0.21-2.89	1.26 (0.61)	1.28	0.015##
TS 2-3	45	0.29-5.39	1.58 (1.09)	1.20	
TS 4-5	24	0.42-4.36	1.99 (1.08)	1.71	
HOMA-β%					
TS 1	3	17.2-781.4	117.4 (112.5)	100.2	0.001##
TS 2-3	45	24.1-1078.2	155.0 (181.5)	100.4	
TS 4-5	24	32.8-487.4	205.0 (121.9)	183.9	
QUICKI					
TS 1	73	0.33-0.52	0.38 (0.04)	0.37	0.015##
TS 2-3	45	0.30-0.48	0.37 (0.42)	0.37	
TS 4-5	24	0.31-0.45	0.36 (0.03)	0.35	

P: Mann-Whitney U test; ## P: Kruskal Wallis test

Table 3. Percentiles of HOMA-IR, HOMA-β% and QUICKI indexes in healthy Italian children and adolescents, grouped by pubertal Tanner's Stage (TS) (N=142)

	N	2.5th	5th	10th	25th	Median	75th	90th	95th	97.5th
HOMA-IR										
TS 1	73	0.28	0.42	0.55	0.74	1.28	1.67	2.11	2.20	2.69
TS 2-3	45	0.37	0.38	0.57	0.81	1.20	1.87	3.08	3.61	4.02
TS 4-5	24	0.42	0.73	0.79	1.08	1.71	2.59	3.63	3.64	4.36
HOMA-β%										
TS 1	73	32.8	43.3	48.9	67.8	100.2	131.3	157.0	192.1	683.9
TS 2-3	45	24.6	34.4	41.2	55.0	100.4	163.7	259.4	523.4	548.8
TS 4-5	24	32.8	51.2	55.5	113.7	183.9	265.0	403.4	421.8	487.4
QUICKI										
TS 1	73	0.33	0.34	0.34	0.35	0.37	0.40	0.43	0.45	0.49
TS 2-3	45	0.31	0.32	0.32	0.35	0.37	0.40	0.42	0.46	0.46
TS 4-5	24	0.31	0.32	0.32	0.33	0.35	0.38	0.40	0.40	0.45

Table 4. Percentiles of HOMA-IR, HOMA-β% and QUICKI indexes in healthy Italian children and adolescents, grouped by sex and pubertal Tanner's Stage (TS)

	N	2.5th	5th	10th	25th	Median	75th	90th	95th	97.5th
Males (N=85)										
HOMA-IR										
TS 1	46	0.28	0.40	0.45	0.65	1.19	1.64	2.11	2.20	2.44
TS 2-3	27	0.29	0.62	0.68	0.90	1.13	2.13	2.76	3.08	3.61
TS 4-5	12	0.73	0.73	0.79	1.12	1.68	2.41	2.47	2.72	2.72
HOMA-β%										
TS 1	46	32.8	43.3	45.1	64.6	89.6	118.7	133.3	154.7	683.9
TS 2-3	27	24.1	36.1	41.2	63.2	98.4	163.7	249.1	363.4	523.4
TS 4-5	12	51.2	51.2	57.2	111.1	165.0	232.2	261.5	403.4	403.4
QUICKI										
TS 1	46	0.33	0.34	0.34	0.35	0.37	0.41	0.44	0.45	0.49
TS 2-3	27	0.32	0.32	0.33	0.34	0.38	0.39	0.41	0.42	0.48
TS 4-5	12	0.33	0.33	0.33	0.33	0.35	0.38	0.40	0.40	0.40
Females (N=57)										
HOMA-IR										
TS 1	27	0.51	0.55	0.61	0.92	1.36	1.71	2.12	2.20	2.89
TS 2-3	18	0.37	0.37	0.38	0.61	1.38	1.82	4.02	5.39	5.39
TS 4-5	12	0.42	0.42	0.88	1.08	1.91	3.50	3.64	4.36	4.36
HOMA-β%										
TS 1	27	38.1	46.6	56.5	75.2	122.1	154.8	184.7	192.1	232.5
TS 2-3	18	24.5	24.5	34.4	53.2	112.8	171.1	548.8	1078.2	1078.2
TS 4-5	12	32.8	32.8	55.5	132.8	236.7	316.3	421.8	487.4	487.4
QUICKI										
TS 1	27	0.33	0.34	0.34	0.35	0.36	0.39	0.42	0.43	0.43
TS 2-3	18	0.30	0.30	0.31	0.35	0.36	0.42	0.46	0.46	0.46
TS 4-5	12	0.31	0.31	0.32	0.32	0.35	0.38	0.39	0.45	0.45

Since pubertal development starts at different chronological ages, an accurate staging of puberty is essential before evaluating insulin resistance and secretion indexes in all subjects. In our healthy subjects, the lowest levels of insulin resistance and secretion indexes have been found in prepubertal children, while the highest levels were observed during pubertal development. Similar results have been reported in normal values of first-phase insulin response in healthy controls (18). Insulin sensitivity decreases as children enter puberty, because of increased secretion and peripheral action of growth hormone/IGF1 axis and gonadal steroids (19). Similar results have been found in our healthy subjects as regards QUICKI.

Taking into account IR indexes, the HOMA model was first described in 1985 by Matthews (10) to assess insulin sensitivity and β-cell function from fasting plasma glucose and insulin levels in normal adults. The HOMA model represents a so-called "paradigm model", i.e. a physiologically based structural model with theoretical solutions adjusted to population norms (20). By contrast, the "minimal model" uses a curve fitting equations limited to a small number of variables and requires a significant time series of data (21), which are not suitable for a large number of pediatric subjects.

QUICKI provides another reproducible and robust estimate of insulin sensitivity, similar to HOMA-IR except that QUICKI transforms the data of fasting plasma glucose and insulin by taking both the logarithm and the reciprocal of the glucose-insulin product. Since distribution of fasting insulin values is skewed, data transformation is aimed at generating a better fit than other indexes (11). In a study aimed at evaluating insulin sensitivity from basal values and from an oral glucose tolerance test, QUICKI results strongly correlated with OGTT measures (22). Therefore, in subjects at risk of T2DM, like overweight or obese youths, and offspring of affected parents, HOMA-IR and QUICKI can be employed to evaluate longitudinal changes of insulin sensitivity and secretion, or to assess the efficacy of early prevention and intervention programs (23). In fact, untreated young patients with T2DM show microalbuminuria at the time of diagnosis (24) and are at risk of premature cardiovascular disease (25-29).

Several studies compared the validity of fasting insulin sensitivity and secretion indexes compared with the estimates obtained from the minimal model (30-33). In particular, in a group of normal glucose tolerant children, 81% of whom were obese, fasting indexes of insulin resistance and secretion were significantly related with the corresponding clamp-derived ones (30). Arslanian found a close correlation between insulin sensitivity and β-cell indexes obtained by euglycemic-hyperinsulinemic clamp technique and by simple estimates using fasting glucose and insulin values in a large group of children and adolescents, with various degrees of pubertal development, glucose tolerance and policystic ovary syndrome (31). Similarly, Conwell concluded that baseline HOMA-IR and QUICKI data are closely correlated with values obtained by frequently sampled intravenous glucose tolerance test (FSIVGTT) (32). As a measure of insulin resistance in obese youths, HOMA-IR seems more reliable than the fasting glucose/insulin ratio and QUICKI (33).

Moreover, a recent study performed in obese children and adolescents reported that the power of indexes based on fasting values of glucose and insulin for the assessment of insulin sensitivity was sex dependent and influenced by pubertal stage, making these indexes not suitable for screening procedures (34).

As regards Italian pediatric patients, in obese subjects with different degrees of pubertal development, HOMA-IR, HOMA-β% cell and QUICKI values based on fasting levels of plasma glucose and insulin were compared with those obtained from OGTT. HOMA-IR increased in both sexes during pubertal development, HOMA-β% showed no variations, and QUICKI decreased in girls at the onset of puberty. The authors concluded that indexes obtained from fasting samples are useful tools for assessing insulin sensitivity and secretion in prepubertal and pubertal obese subjects (35).

HOMA-IR and QUICKI are primarily indexes of hepatic but not peripheral insulin action, and recent data do not indicate one to be better than the other (36). On the other hand the specificity and sensitivity of surrogate indexes of insulin sensitivity like QUICKI were poor and they cannot be considered accurate predictors (37).

Minimizing the development of insulin resistance secondary to obesity in childhood and adolescence is mandatory. In particular, insulin resistance should be carefully considered since it precedes the complications of metabolic syndrome, and influences the risk for obesity-related metabolic co-morbidities (38-40). Follow-up studies evaluating insulin resistance in childhood and adolescence are important because of the increasing prevalence of obesity, metabolic syndrome, impaired glucose tolerance and T2DM in youths (41-43).

Our data may prove informative to develop strategies that seek to target the early-life risk factors for diabetes, like insulin resistance, and may be useful for follow-up studies.

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