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Glucose tolerance and insulin sensitivity markers in children and adolescents with excess weight

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Abstract. – OBJECTIVE: Type 2 diabetes mellitus (T2DM) and obesity are alarmingly increasing in children and adolescents. Hence, predictors for early metabolic abnormalities in childhood are urgently needed. We investigated glucose tolerance in children and adolescents with obesity, markers of insulin sensitivity between males and females and the potential association between the parameters measured during an OGTT (glucose, insulin, c-peptide) and prediabetes or stages of puberty.

PATIENTS AND METHODS: Glucose tolerance in 89 children and adolescents with excess weight, aged 4-19 years, from Western Greece was studied. A 3-hour OGTT was performed and fasting glucose (FG), fasting insulin (FI), 1/FI, FG/FI, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), ISI Matsuda index and Insulinogenic index (IGI30), were also calculated.

RESULTS: No significant differences were observed in glucose values between males and females. Insulin and c-peptide concentrations were higher in the girls at several time points. FG/FI was significantly higher in the boys. Girls with obesity may be at higher risk for future insulin resistance.

CONCLUSIONS: Better surveillance of pubertal girls with obesity is crucial and can be achieved using additional information provided by an OGTT, since they appear to be at a higher risk for beta-cell exhaustion. During the OGTT, not only are the baseline and 2-hour glucose and insulin measurements useful for predicting future metabolic risks and development of T2DM in children and adolescents with obesity, but additional time measurements may also be helpful.

Key Words:
Children, HOMA-IR, Type 2 diabetes mellitus, Obesity, Oral glucose tolerance test (OGTT).

Introduction

Type 2 diabetes mellitus (T2DM) in children and adolescents is emerging as a new disease with rising prevalence over the last two decades[1-4]. Similarly, obesity is alarmingly increasing in children and adolescents worldwide[5].

T2DM is usually preceded by a milder metabolic disturbance known as prediabetes and represented by impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). According to the American Diabetes Association (ADA), IFG is defined as a fasting glucose of 100-125 mg/dl, IGT as a 2-hour glucose of 140-199 mg/dl on an Oral Glucose Tolerance Test (OGTT)[6] and T2DM as a fasting glucose of >125 mg/dl, or a 2-hour glucose of ≥200 mg/dl on an OGTT, or a random glucose of ≥200 mg/dl with the classic diabetes symptoms[7]. It is well established that T2DM is characterized by insulin resistance during the initial phase[8]. Interestingly though, with progression of time insulin resistance is superseded by beta cell dysfunction and exhaustion[8]. On the other hand, obesity in children and adolescents is defined as a BMI above the 95th percentile for age and sex according to the Centers for Disease Control and Prevention (CDC) age- and gender-specific criteria[9].

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Since the number of children and adolescents with obesity is rapidly growing, markers that would serve as predictors for early metabolic abnormalities and the development of diabetes are urgently needed. Such markers have been described in adults and youth and include: i) markers of glucose response during an OGTT: fasting, 1-hour and 2-hour glucose concentrations, that have been associated with beta-cell function impairment[10,11], and ii) fasting indices and OGTT-related markers of insulin sensitivity.

The aims of this study were to investigate: (1) glucose tolerance in children and adolescents with obesity from Western Greece through the assessment of possible differences in the glucose, insulin and c-peptide response curves during an OGTT, (2) markers of insulin sensitivity between male and female children and adolescents and (3) the potential association between the parameters measured during an OGTT (glucose, insulin, c-peptide) and prediabetes or stages of puberty.

Patients and Methods

Eighty-nine children and adolescents with obesity (BMI: >95th centile for gender and age), 45 girls, aged 4-19 years old, were enrolled in the study from the Outpatient Clinic of Paediatric Endocrinology of the University Hospital of Patras in Greece. The present study was conducted from June 2016 to December 2017. Subjects included had failed to lose at least 5% of their body weight following a diet within a 12-month period and had an OGTT during this period. There was no bias regarding the recruitment process. The research was approved by the Research Ethics Committee of the Hospital and was performed according to the ethical standards of the Helsinki Declaration, as revised in 1983. Informed consent was obtained from the parents of the children involved in the study and informed assent was obtained from children over 7 years of age.

A 3-hour Oral Glucose Tolerance Test (OGTT) was performed to all the patients. After the administration of oral glucose at the dose of 1.75 g/Kg (max: 75 g), blood samples were obtained at T=0, T=15 (for 48 subjects who were randomly selected), T=30, T=60, T=90, T=120 and T=180 min. Glucose, insulin and c-peptide concentrations were measured at all time points.

Prediabetes was defined as either IFG or IGT. IFG was defined as plasma glucose between 100 and 125 mg/dl at T=0 min and IGT as plasma glucose between 140 and 199 mg/dl at T=120 min. At the baseline (T=0 min), biochemical tests were also performed (Table I).

OGTT data were used to calculate fasting indices and OGTT-derived surrogate estimates of insulin sensitivity: mean fasting glucose (FG), mean fasting insulin (FI), 1/FI, FG/FI, Homeostatic Model Assessment of Insulin Resistance [HOMA-IR = I_0*G_0/22.5 [I_0: Fasting insulin (μIU/ml), G_0: Fasting glucose (mmol/L)], Quantitative insulin sensitivity check index (QUICKI=1/[log(I0)+log(G0)], ISI Matsuda index (calculated

Table I. Epidemiological, biochemical and insulin-sensitivity markers in boys (N=44) and girls (N=45) who underwent an OGTT. Median values [lower and upper quartiles] are provided. Mann-Whitney U test was performed for Age, BMI and BMI-SDS variables. Univariate analysis of variance (ANOVA) was applied for all other markers adjusted for Tanner stage and BMI-SDS. Statistical significance is shown in bold characters.

Markers	Boys	Girls	*p*-value
Age (years)	11.4 [9.9, 14.0]	12.0 [10.3, 14.6]	0.448
BMI (kg/m^2)	25.9 [22.2, 29.8]	26.8 [24.5, 29.2]	0.421
BMISDS (kg/m^2)	2.0 [1.6, 2.5]	2.0 [1.5, 3.0]	0.557
IGF-1 (ng/ml)	327 [234, 532]	676 [362, 876]	0.046
TSH (μIU/ml)	1.69 [1.10, 2.04]	1.40 [0.80, 2.08]	0.345
HbA1c (%)	5.2 [4.8, 5.6]	5.2 [4.8, 5.4]	0.525
Total Cholesterol (mg/dl)	157 [142, 186]	158 [141, 180]	0.766
LDL (mg/dl)	91 [76, 121]	100 [85, 121]	0.896
HDL (mg/dl)	45 [39, 60]	45 [38, 54]	0.758
Triglycerides (mg/dl)	58 [46, 101]	67 [53, 108]	0.464
SGOT (mg/dl)	23 [22, 32]	22 [20, 25]	0.816
SGPT (mg/dl)	22 [18, 29]	17 [14, 24]	0.694
Uric acid (mg/dl)	4.6 [3.2, 5.4]	4.4 [3.4, 5.4]	0.690
Urea (mg/dl)	28 [24, 32]	26 [23, 30]	0.522
Creatinine (mg/dl)	0.64 [0.60, 0.82]	0.60 [0.60, 0.70]	0.068

using WEB calculator) and Insulinogenic index at T=30 min ($IGI_{30=}(I_{30}-I_0)/(G_{30}-G_0)$. I_{30}, I_0, G_{30} and G_0: insulin and glucose concentrations at T=0 and 30 min, respectively). Oral Disposition Index (oDI) was calculated using the formula $oDI=(\Delta I_{0-30}/\Delta G_{0-30}) \times (1/\text{fasting insulin})$ (Table II).

Fasting plasma glucose was assessed by the hexokinase method with the use of a biochemical analyzer (Olympus AU 600, Dallas, Texas, TX, USA). Insulin concentrations were measured with the Electro-Chemiluminescence immunoassay (ECLIA) method and the Roche E170 Immunology Analyser (Holliston, Massachusetts, MA, USA) was used for the process. C-peptide was determined by radioimmunoassay (RIA) (Merck KGaA, Darmstadt, Germany).

In the girls, Tanner stages for breast development were assessed. Tanner stages in the boys were correlated with testicular volume as follows: Tanner I: < 4 ml, Tanner II: 4-8 ml, Tanner III: 10-12 ml, Tanner IV: 15-20 ml, Tanner V: 20-25 ml.

Statistical Analysis

Statistical analysis was performed using the SPSS Statistical Software Package (IBM, Armonk, NY, USA). Median and corresponding lower and upper quartile values (or interquartile range) were considered, due to small number of patients and lack of normality (Kolmogorov-Smirnov normality test, $p<0.05$) of parameters' distributions, especially when splitting the sample in subcategories such as gender, stages of puberty and prediabetes.

To study statistically significant differences for each parameter measured during an OGTT (i.e., glucose, insulin and c-peptide for 7 different time points) with respect to gender, stages of puberty and prediabetes (yes/no), appropriate statistical tests were applied (Friedman's two-way ANOVA by Ranks for related samples or ANOVA for repeated measures, depending on parameters' distributions).

To study statistically significant differences with respect to gender for each epidemiological marker (i.e., age, BMI and BMISDS), an appropriate non-parametric statistical test was applied (Mann-Whitney U test for unpaired data). For each biochemical and insulin marker or for fasting indices and OGTT-derived estimates for insulin sensitivity, univariate ANOVA statistical tests were applied adjusted for Tanner stage and BMI-SDS.

Finally, to study statistically significant differences with respect to Tanner stage for fasting indices and OGTT-derived estimates for insulin sensitivity, appropriate statistical tests were applied (Kruskal-Wallis one-way ANOVA for k=5 samples or univariate ANOVA, depending on indices' distributions) adjusted for gender and BMI-SDS.

In all cases, the level of statistical significance was set to $\alpha=0.05$. In case of multiple pair-wise comparisons (i.e., among Tanner stages), Bonferroni adjustment was applied.

Results

Comparisons in the OGTT Parameters Between Children and Adolescents According to Gender

Among the different parameters that were assessed, statistically significant difference was only found in IGF-1 between the girls (higher values) and the boys (lower values), adjusted for Tanner stage and BMI-SDS (Table I). Goodman and Kruskal tau (based on chi-square approxima-

Table II. Fasting indices and OGTT-derived estimates for insulin sensitivity in boys (N=44) and girls (N=45) who underwent an OGTT. Median values [lower and upper quartiles] are provided. Univariate analysis of variance (ANOVA) was applied for all indices adjusted for Tanner stage and BMI-SDS. Statistical significance is shown in bold characters.

Indices	Boys	Girls	*p*-value
Fasting insulin (FI) (μIU/ml)	7.10 [4.10, 11.30]	10.08 [5.93, 15.15]	0.195
Fasting glucose (FG) (mg/dl)	81 [77, 88]	76 [72, 83]	0.337
FG/FI	11.22 [6.88, 20.53]	7.09 [5.42, 11.58]	0.045
HOMA-IR	1.60 [0.85, 2.10]	1.95 [1.10, 3.00]	0.300
1/FI	0.15 [0.09, 0.25]	0.10 [0.07, 0.16]	0.059
QUICKI	0.36 [0.34, 0.39]	0.34 [0.32, 0.38]	0.489
ISI Matsuda index	6.47 [4.07, 10.11]	4.73 [3.15, 7.18]	0.644
Insulinogenic index (II)	0.87 [0.28, 1.87]	1.13 (0.37, 1.85]	0.634
Disposition index (DI)	0.11 [0.04, 0.23]	0.11 (0.04, 0.20]	0.230

tion) showed a statistically significant difference in pubertal distribution between boys and girls (τ=0.129, p=0.023<0.05). The measured glucose, insulin and c-peptide concentrations of the boys and girls of the studied population during the OGTT are shown in Figures 1, 2 and 3.

Glucose

Median glucose values during the OGTT showed no statistically significant differences between the boys and the girls at all time points (Figure 1).

Insulin

Median insulin values were higher in the girls compared to the boys from T=60 min to T=180 min. The differences were statistically significant at T=60 min and T=90 min, while no statistically significant interactions exist among gender, Tanner stage and BMI-SDS (Figure 2).

C-peptide

Median c-peptide values were higher in the girls from T=60 min to the end of the OGTT. Statistical significance was found at T=90 min and T=120 min, while no statistically significant interactions exist among gender, Tanner stage and BMI-SDS (Figure 3).

Fasting Indices and OGTT-Derived Estimates for Insulin Sensitivity

No statistically significant differences were observed in the fasting glucose and fasting insulin concentrations between the boys and the girls. FG/FI was significantly higher in the boys compared to the girls, while no statistically significant interactions exist among gender, Tanner stage and BMI-SDS. Other fasting indices, as well as OGTT-derived surrogate estimates of insulin sensitivity, did not demonstrate statistical significance (Table II).

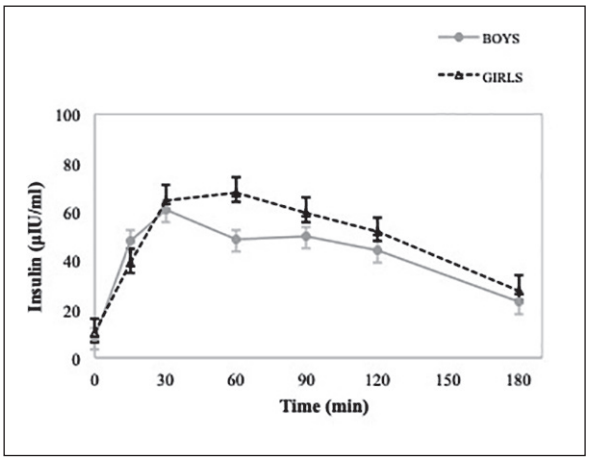

Figure 2. Median insulin values during OGTT in boys and girls. Statistical significance is depicted with * (p<0.05).

OGTT Parameters Between Children and Adolescents According to the Presence of Prediabetes and Pubertal Status

Presence of Prediabetes

Among the studied patients with obesity, seven had prediabetes (9%), 3 IFG and 4 IGT. These patients exhibited significantly higher glucose

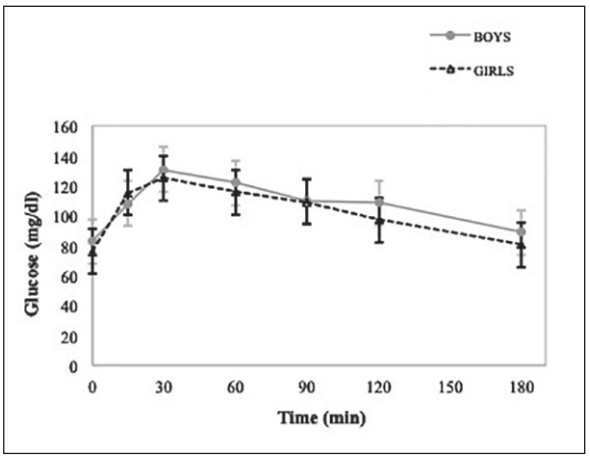

Figure 1. Median glucose values during OGTT in boys and girls. No statistically significant differences were noticed.

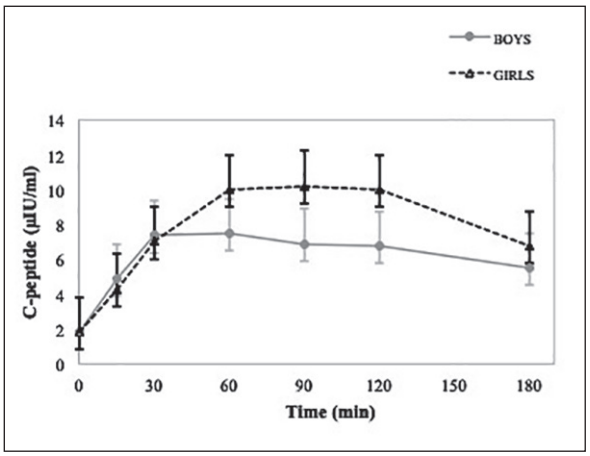

Figure 3. Median c-peptide values on the first OGTT in boys and girls. Statistical significance is depicted with # (p<0.05).

concentrations at T=60, 90, 120 and 180 min, and higher insulin concentrations at T=30, T=60 and T=90 min, compared to patients without prediabetes. No statistically significant interactions exist among prediabetes, gender, Tanner stage and BMI-SDS. Furthermore, no statistically significant differences in c-peptide concentrations were obtained when comparing patients with the presence of prediabetes and those without prediabetes.

Pubertal Status

Statistically significant differences in fasting insulin concentrations and HOMA-IR between Tanner stages are shown in Figures 4 and 5. No statistically significant differences were obtained in glucose and c-peptide values at T=0 min with respect to Tanner stage.

Other fasting indices, as well as OGTT-derived surrogate estimates of insulin sensitivity did not demonstrate statistical significance among Tanner stages.

Discussion

The OGTT is currently the gold standard for the diagnosis of diabetes. In our experience, the 3-hour OGTT can identify children who have a delayed insulin response and are able to normalize their glucose levels at the 3-hour time-point if they have an abnormal glucose response at the 2-hour point. Other groups have also found that 3 hours is a better duration for an OGTT to capture the full spectrum of glucose and insulin excursions in youth[12,13].

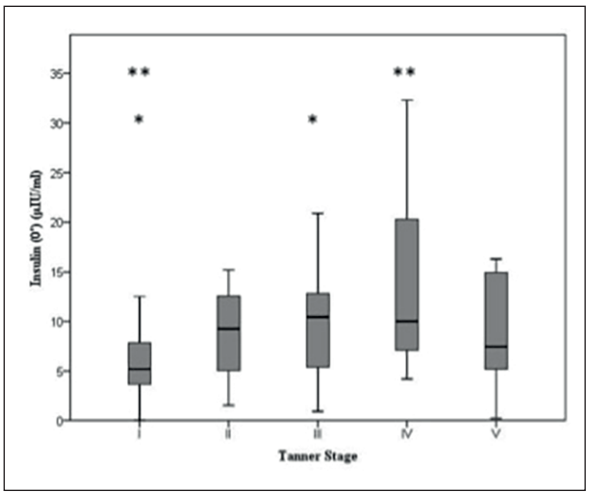

Figure 4. Boxplots for Insulin (t=0 min) with respect to Tanner stage. Statistical significance is depicted with * for Tanner I and Tanner III and with ** for Tanner I and Tanner IV (p<0.01).

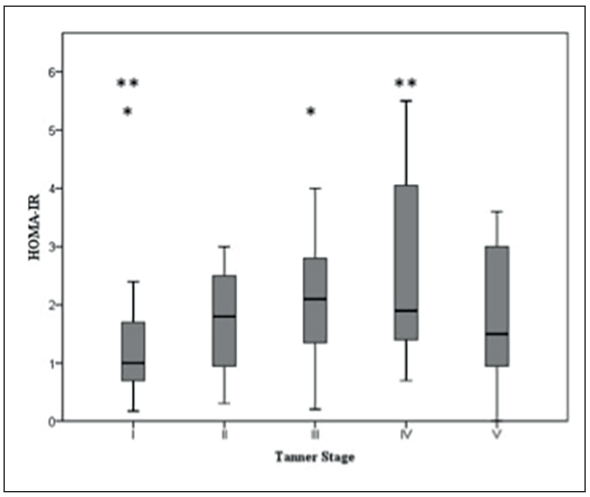

Figure 5. Boxplots for HOMA-IR with respect to Tanner stage. Statistical significance is depicted with * for Tanner I and Tanner III and with ** for Tanner I and Tanner IV (p<0.01).

In the present study, boys and girls with obesity showed similar mean glucose concentrations at all time points during the OGTT. However, the girls showed higher insulin and c-peptide concentrations particularly at T=60 min and T=90 min for insulin and at T=90 min and T=120 min for c-peptide. These findings may possibly suggest that these time points are of clinical significance. According to Kim et al[14], a monophasic glucose curve has been associated with lower insulin sensitivity and poorer beta-cell function in obese youth without diabetes, compared to a biphasic curve. In the present study, the boys exhibited a biphasic glucose and, particularly, insulin curve, as opposed to the girls who exhibited monophasic curves. This observation further suggests that girls with obesity have impaired insulin sensitivity and beta-cell function compared to boys. Increased insulin resistance and impaired metabolic profile were also implied in the girls by the finding of higher IGF-1 concentrations compared to the boys and worse FG/FI. Both have been reported to correlate strongly with clamp insulin sensitivity in obese youth[15].

Glucose concentrations at T=60 min have been reported to be better associated with beta-cell function and sensitivity to glucose compared to the rest time points of an OGTT[14]. In young

adults and adolescents with obesity, elevated serum glucose concentrations at T=60 min of the OGTT, which may be the result of insulin resistance and changes in the beta-cell function, probably identify patients at increased risk for developing metabolic syndrome[16-18]. Our observation of increased insulin and c-peptide concentrations at T=60 min of the OGTT in the girls may be suggestive again of increased insulin resistance, putting them at risk for future beta-cell dysfunction, even before impaired fasting glucose or impaired glucose tolerance develops. Noticeably, the mean glucose concentrations at T=60 min in the girls never reached the cut-off value of 155 mg/dl that has been reported by Tfayli et al[19] as a predictor of future development of T2DM. In addition, our patients with impaired fasting glucose or impaired glucose tolerance (prediabetes), had significantly higher glucose concentrations during the first, but also during the second and third hours of the OGTT. This may be an indication that not only the baseline or 2-hour glucose measurements during an OGTT are important for predicting increased risk for T2DM, but also higher glucose measurements at T=60 min and T=180 min during the OGTT may serve as predictors for potential heightened risk for future development of T2DM.

Moreover, it is well described that mid-puberty (Tanner stages III-IV) is associated with a marked decrease in insulin sensitivity in youth with obesity and normal weight, particularly in females[20,21]. Interestingly, obese individuals exhibit greater insulin resistance during puberty compared to lean individuals. Whereas insulin resistance during puberty recovers at completion of puberty, this is not the case when obesity co-exists[22]. Our results showed a significant increase in HOMA-IR in mid-puberty (Tanner III and particularly Tanner IV) compared to prepuberty. Also, in children with progressed puberty (Tanner IV and Tanner V), baseline insulin concentrations (T=0 min) were found significantly higher compared to those in the prepubertal children (Tanner I). This again probably reflects the "physiological" insulin resistance of puberty, which is enhanced by obesity (Figure 2).

Limitations of the study include the different pubertal distribution by sex (i.e., different numbers of boys and girls at each Tanner stage), which was minimized in part by the multiple linear models used. Also, the fact that this study represents one time point in a cross-sectional study, given the poor reproducibility of the OGTT in youth reported in the literature. Additional limitations include the fact that the effect of macronutrient content in the diet and physical activity on insulin sensitivity and secretion has not been accounted for, and that a small number of patients had measurement of c-peptide values.

Conclusions

Our study shows that a very small proportion of the studied children and adolescents with obesity (9%) had prediabetes (IFG or IGT). Also, parameters such as the female gender, obesity, prediabetes and progressed pubertal staging, all of which pose a heightened risk for future T2DM or metabolic disease, are associated with disturbed glucose, insulin or c-peptide concentrations at different time points during an OGTT. Our findings support, from a different perspective, the existing knowledge regarding the need for better surveillance of pubertal girls with obesity, since they may be at a higher risk for beta-cell exhaustion. This is suggested by the increased IGF-1 concentrations and FG/FI ratio observed in girls with obesity compared to boys. Also, by additional and novel information that can be provided by an OGTT, including increased insulin and c-peptide concentrations at several time points and the monophasic character of the glucose curve in girls with obesity compared to boys. It should be noted, though, that most of the girls (75%) were at a more progressed Tanner stage (III-V) compared to the boys (59%). In addition, in the children with prediabetes, our findings that glucose and insulin was significantly higher at several time points, suggests that not only T=0 min and T=120 min but all the time points may also be useful for the diagnosis of prediabetes. Our findings emphasize the utility of the OGTT as a diagnostic tool that can possibly provide us with more information than we officially utilize and can be further exploited by physicians for guiding the prevention and treatment approaches in youth with excess body weight.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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