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Original article

Time of the Peak, Shape of the Curve and Combination of These Glucose Response Characteristics During Oral Glucose Tolerance Test as Indicators of Early Beta-Cell Dysfunction in Obese Adolescents

Sabolić et al. OGTT Indicators of Beta-Cell Dysfunction

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What is already known on this topic?
Oral glucose tolerance test (OGTT) is traditionally used to define glucose tolerance status based on 2-hour plasma glucose level. There is growing evidence that glucose curve characteristics, such as time of the glucose peak and shape of the glucose curve, may serve as indicators of beta-cell dysfunction.

What this study adds?
Late glucose peak, as well as monophasic glucose curve during OGTT, disclose impairement of beta-cell function in obese adolescents with normal glucose tolerance (NGT). Moreover, a combination of these glucose curve characteristics strongly predicts low oral disposition index (oDI).

Abstract
Objective: Characteristics of the glucose response during oral glucose tolerance test (OGTT) may reflect differences in insulin secretion and action. We aimed to examine whether timing of the glucose peak, shape of the glucose curve and their combination could be indicators of beta-cell dysfunction in obese/severely obese adolescents with normal glucose tolerance (NGT).
Methods: Data from 246 obese/severely obese adolescents who completed OGTT were reviewed. Out of 184 adolescents with NGT, 174 could be further classified into groups based on timing of the glucose peak (early/30 minutes vs late/≥60 minutes) and shape of the glucose curve (monophasic vs biphasic). Groups were compared with respect to insulin sensitivity (whole body insulin sensitivity index, WBISI), early-phase insulin secretion (insulinogenic index, IGI) and beta-cell function relative to insulin sensitivity (oral disposition index, oDI).
Results: Late glucose peak (p=0.004) and monophasic glucose curve (p=0.001) were both associated with lower oDI after adjustment for age, sex, puberty stage and body mass index (BMI) z-score. Among obese/severely obese adolescents with NGT, those with coexistent late glucose peak and monophasic glucose curve had lower oDI than those with early glucose peak and biphasic glucose curve (p=0.002). Moreover, a combination of late glucose peak and monophasic glucose curve was the most powerful predictor of the lowest oDI quartile (OR: 11.68, 95% CI: 3.048-44.755, p<0.001).
Conclusion: Late timing of the glucose peak, monophasic shape of the glucose curve and in particular combination of those characteristics during OGTT may indicate early beta-cell dysfunction in obese/severely obese adolescents with NGT.
Keywords: Oral glucose tolerance test, beta-cell dysfunction, obese adolescents

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Introduction

Oral glucose tolerance test (OGTT) has been used traditionally to diagnose dysglycemia, according to fasting and 2-hour post-load glucose thresholds (1,2). However, even obese individuals with initially normal glucose tolerance (NGT) can eventually develop prediabetes and progress to type 2 diabetes (3-5). Impaired insulin secretion relative to insulin sensitivity, reflecting an early defect in beta-cell function, presents a key patophysiologic feature in those with the highest risk for disease progression (5). Finding the predictors of beta-cell dysfunction in obese normoglycemic adolescents might be important for timely prevention of diabetes in youth (5,6). In recent years it has been studied whether some features of the glucose response during OGTT, including time of the glucose peak and shape of the glucose curve, could be used as predictors of insulin secretion relative to insulin sensitivity.

Time of the glucose peak was found to be a reliably reproducible variable of the OGTT (7). It's role in prediction of beta-cell dysfunction has been studied in adult population (8-10). Delayed timing of post-load glucose peak >30 minutes was associated with declining beta-cell function, worsening glucose tolerance over time (8) and a greater likelihood of prediabetes and diabetes (9,10). To our knowledge, association of glucose peak time and beta-cell function in youth has not been thoroughly investigated. So far, time of the glucose peak has been explored as potential predictor of beta-cell function and prediabetes risk in post-pubertal overweight/obese adolescent girls of diverse ethnicity (11) and recently in overweight/obese white and black adolescents (12).

On the other hand, monophasic glucose curve shape has already been investigated as an early marker of beta-cell dysfunction and a risk predictor for type 2 diabetes in adults (13-15), pregnant women (16) and adolescents (17-19). As well, monophasic glucose curve predicted the risk for progression to type 1 diabetes among autoantibody-positive relatives of people with type 1 diabetes; moreover the risk in the monophasic group was increased with delayed timing of the glucose peak (20).

As time of the glucose peak and shape of the glucose curve reflect differences in insulin secretion and action, they deserve further investigation and validation in different populations, including obese youth. Their joint ability to detect impaired beta-cell function is not sufficiently explored.

Therefore the aims of the present study were: 1) to investigate time of the glucose peak and shape of the glucose curve as independent predictors of beta-cell dysfunction and; 2) to explore their joint ability to detect impaired beta-cell function in obese/severely obese adolescents.

Materials and Methods

Participants

This retrospective analysis included data from 246 adolescents aged 10-18 years, referred for obesity to Department of Pediatric Endocrinology at the University Hospital Center Sestre milosrdnice, who subsequently completed 2-hour OGTT from January 2016 to March 2018. None of them was previously treated for obesity. Subjects taking any medication or having any systemic or endocrine disease, as well as those fulfilling the OGTT criteria for prediabetes or diabetes (1,2) were excluded (n=62). Out of 184 adolescents with NGT, 174 could be classified based on both, time of the glucose peak and shape of the glucose curve, and their data were further analysed.

Ethics

The study protocol was approved by the Ethics Committee of the University Hospital Center Sestre milosrdnice (approval number: 251-29-11-20-01-3). The requirement for informed consent was waived due to the retrospective nature of the study.

Anthropometric measurements

Body weight was measured using a digital weighting scale to the nearest 0.1 kg, with subjects wearing only underwear. Standing height was measured with Harpenden stadiometer to the nearest 0.1 cm. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Obesity was defined as BMI ≥ 95th percentile for age and sex (21). Subjects were further classified as either obese if having a BMI ≥95th percentile and <120% of the 95th percentile for age and sex or severely obese if having a BMI ≥ 120% of the 95th percentile for age and sex or an absolute BMI ≥ 35 kg/m2 (22), whichever was lower. The BMI z-score was calculated using US reference values (21). The pubertal stage was assessed using Tanner criteria (23).

Oral glucose tolerance testing

After 10-12 h overnight fast, a standard OGTT was performed with ingestion of the glucose load, 1.75 g/kg body weight, up to 75 g of glucose. Venous blood samples for measurement of plasma glucose and serum insulin were obtained at 0, 30, 60, 90 and 120 minutes. NGT was defined as fasting glucose < 5.6 mmol/l and 2 h glucose < 7.8 mmol/l (1).

Classification of the glucose response – time of the glucose peak, shape of the glucose curve

With respect to timing of the first glucose peak during OGTT, glucose response was dichotomized as maximal glucose occuring at 30 or ≥ 60 minutes (excluding 120 minutes due to inapplicability for the shape classification stated below). The glucose peak was considered either early (at 30 minutes) or late (≥ 60 minutes).

Shape of the glucose curve was classified as monophasic or biphasic (24). Monophasic curve was characterised by an increase of glucose to a maximum between 30-90 minutes, followed by a decrease until 120 minutes. The curve was classified as biphasic if glucose peaked at 30 or 60 minutes, followed by a nadir and a second peak by 120 minutes. The upward or downward change in plasma glucose between the time points was defined as glucose difference of ≥ 0.2 mmol/l to minimize fluctuations in glucose concentrations, which may be caused by the method of glucose

analysis, rather than physiological reasons. Ten subjects with NGT who could not be classified according to the aforementioned criteria were excluded from further analysis (inability to determine glucose peak time (n=3), curve shape (n=3) or peak time and curve shape (n=2), incessant increase (n=1) and paradoxical glucose response (n=1)).

Calculations derived from OGTT

Insulin sensitivity was assessed using the Matsuda index, an established measure of whole-body insulin sensitivity (WBISI), which has been validated against the euglycaemic-hyperinsulinaemic clamp, and calculated as: WBISI = 10 000/√[(fasting glucose (mmol/l/l) x 18.02 x fasting insulin (mIU/l)) x (mean glucose (mmol/l) x 18.02 x mean insulin (mIU/l))] (25).

Early-phase insulin secretion was assessed using the insulinogenic index (IGI), which was calculated as the ratio of the incremental change of plasma insulin (mIU/l) to that of plasma glucose (mmol/l) during the first 30 minutes after glucose ingestion, as: $IGI = \Delta Insulin_{30}/\Delta Glucose_{30} \times 18.02$ (26).

In addition, in order to assess beta-cell function relative to insulin sensitivity, oral disposition index (oDI) was calculated as the product of WBISI and IGI. As a surrogate estimate of beta-cell function relative to insulin sensitivity, oDI can be applied to obese adolescents in studies where the applicability of clamp studies is limited due to feasibility, cost and labor intensiveness (27).

Protocol

Subjects were initially grouped based on whether time of the glucose peak occured early (at 30 minutes, P_{30}) or late (≥ 60 minutes, $P_{\geq 60}$). Those two groups were compared with respect to WBISI, IGI and oDI.

Participants were subsequently grouped according to shape of the glucose curve as either monophasic (M) or biphasic (B) and compared with respect to WBISI, IGI and oDI.

Subjects were finally stratified into four groups, those with: (1) early glucose peak and monophasic curve shape ($P_{30}M$); (2) early glucose peak and biphasic curve shape ($P_{30}B$); (3) late glucose peak and biphasic curve shape ($P_{\geq 60}B$); (4) late glucose peak and monophasic curve shape ($P_{\geq 60}M$). Groups were compared with respect to WBISI, IGI and oDI.

Analytical methods

Plasma glucose concentration was determined by the hexokinase method on the Abbott Architect c8000 chemistry analyzer (Abbott Diagnostics, USA). Serum insulin was assessed by the electrochemiluminesence immunoassay (ECLIA) on the Cobas E601 analyzer (Roche Diagnostics, Germany).

Statistical analysis

Statistical analysis was performed using SPSS 25.0.0.1. (SPSS Inc. 2017).

Descriptive statistics was used to describe the basic features of the sample in the study, using relative frequencies for categorical variables, and mean and standard deviation for continuous variables. Since some variables deviated from normal distribution, non-parametric descriptive parameters, median and interquartile range were also calculated. Normality of distribution was tested using Shapiro-Wilk test. To test statistical significance of differences between obese and severely obese group of participants, independent samples t-test and chi-square were calculated. ANOVA and ANCOVA adjusted for age, sex, Tanner stage and BMI SDS were used to determine the association of glucose peak timing, glucose curve shape and combined glucose curve features with insulin sensitivity, early-phase insulin secretion and beta-cell function relative to insulin sensitivity. Logistic regression was used to explore relationship between predictor variables and the lowest oDI quartile. P-values <0.05 were considered statistically significant.

Results

Demographic characteristics of study participants

There were no statistically significant differences between the groups of obese (n=76) and severely obese (n=98) adolescents with respect to age (P=0.127), sex (P=0.357) and puberty stage (P=0.929) (Table 1).

OGTT-derived indices of insulin sensitivity, secretion and beta-cell function in obese vs severely obese adolescents

The group of severely obese adolescents had significantly lower WBISI (P=0.002) and oDI (P=0.019) than the obese group. At the same time, there was no difference in IGI (P=0.420) between the groups (Table 1).

Prevalence of glucose curve characteristics with respect to time of the glucose peak and shape of the glucose curve

Early glucose peak and monophasic glucose curve were the prevalent morphological features identified, irrespective of the degree of obesity, while the most common curve characteristics with combined features were biphasic curve with early glucose peak and monophasic curve with late glucose peak (Table 2).

Among the participants, 57.5% (100/174) had a glucose peak at 30 minutes and 42.5% (74/174) at ≥60 minutes. Glucose curve was monophasic in 55.7% (97/174) and biphasic in 44.3% (77/174) of subjects. A biphasic curve with glucose peak at 30 minutes was identified in 36.2% (63/174), a monophasic curve with glucose peak at ≥60 minutes in 34.5% (60/174), a monophasic curve with glucose peak at 30 minutes in 21.3% (37/174), and a biphasic curve with glucose peak at ≥60 minutes in 8% (14/174).

In adolescents with glucose peak at 30 minutes, 63% (63/100) had biphasic glucose curve. In individuals with glucose peak at ≥60 minutes, 81.1% (60/74) had monophasic glucose curve.

In subjects with biphasic curve, 81.8% (63/77) had glucose peak at 30 minutes, while in those with monophasic curve, 61.9% (60/97) had glucose peak at ≥60 minutes.

More frequent association of early glucose peak and biphasic curve, as well as association of late glucose peak and monophasic curve was observed in both, obese and severely obese adolescents (Table 2).

Relationship of glucose curve characteristics and OGTT-derived indices

Time of the glucose peak

After adjustment for age, sex, puberty stage and BMI z-score, glucose peak at ≥60 minutes was associated with lower oDI (P=0.004) (Figure 1A, Table 3). There was no statistically significant difference in WIBSI between the groups with glucose peak at 30 and ≥60 minutes (P=0.302), while a trend towards lower IGI with glucose peak at ≥60 minutes did not reach statistical significance (P=0.057) (Table 3).

Shape of the glucose curve

No difference between the groups with monophasic and biphasic glucose curve was observed with respect to WBISI (P=0.784) after adjustment for age, sex, puberty stage and BMI z-score (Table 3). However, adolescents with monophasic curve had lower IGI (P<0.001) and oDI (P=0.001) (Table 3, Figure 1B).

Time of the glucose peak and shape of the glucose curve as combined glucose curve characteristics

Among four groups with combined glucose curve characteristics ($P_{30}M$, $P_{30}B$, $P_{\geq 60}B$ and $P_{\geq 60}M$), after adjustment for age, sex, puberty stage and BMI z-score, significant differences were found for IGI (P=0.001) and oDI (P=0.004). $P_{30}M$ group had lower IGI than $P_{30}B$ group, while $P_{\geq 60}M$ group had both, lower IGI and lower oDI than $P_{30}B$ group (Figure 2).

Time of the glucose peak and shape of the glucose curve as predictors of low oDI

Among adolescents with oDI in the first (lowest) quartile, the proportion of those having glucose peak at ≥60 minutes was significantly higher than among adolescents with oDI in the third or fourth quartile, whose predominant glucose peak time was 30 minutes (χ^2=10.281, df=3, P=0.016) (Figure 3A).

With regard to the shape of the glucose curve, proportion of subjects with monophasic glucose curve was significantly higher among adolescents with oDI in the first quartile, while participants with biphasic glucose curve were more prevalent among adolescents with oDI in the third or fourth quartile (χ^2=17.135, df=3, P=0.001) (Figure 3B).

According to logistic regression, when age, sex, puberty stage and BMI z-score were included in the model, probability to have oDI in the lowest quartile was almost three times higher in adolescents with late (vs early) glucose peak (OR: 2.96, 95% CI: 1.3339-6.526, p=0.007), almost five times higher in subjects with monophasic (vs biphasic) glucose curve (OR: 4.91, 95% CI: 1.856-12.977, P=0.001), and almost twelve times higher in participants with combination of late glucose peak and monophasic glucose curve (vs combination of early glucose peak and biphasic glucose curve) (OR: 11.68, 95% CI: 3.048-44.755, p<0.001).

Discussion

This study indicates that morphological characteristics of the glucose response during OGTT, including time of the glucose peak, shape of the glucose curve and combination of these features, may be informative of impaired beta-cell function in obese/severely obese youth with NGT.

There was no statistically significant difference in the prevalence of glucose curve characteristics, including time of the glucose peak, shape of the glucose curve or both features combined, between otherwise demographically comparable groups of obese/severely obese adolescents. Through the literature search, we found no similar data comparing the prevalence of glucose curve characteristics in subjects with different obesity classes.

As expected, severely obese adolescents had lower WBISI, reflecting lower insulin sensitivity (28,29). Insulin secretion expressed as IGI did not differ significantly between the groups. However, beta-cell function was worse in severely obese adolescents, which is consistent with previous findings (30,31).

Prevalent features of the glucose response in our sample of obese/severely obese adolescents with NGT were early glucose peak and monophasic glucose curve. According to studies published so far, early glucose peak was detected in minority of obese postpubertal adolescent girls with NGT or prediabetes (34/88) (11) and in approximately half of obese black and white adolescents with NGT or impaired glucose tolerance (IGT) (142/278) (12). A higher proportion of subjects with early glucose peak in current study (100/174) is probably due to normotolerant glucose status of included adolescents and is in agreement with cross-sectional analyses that have linked later time of the glucose peak with impaired glucose tolerance and type 2 diabetes (7,32). With regard to the prevalence of monophasic glucose curve, our findings are in line with formerly published data for obese adolescents with NGT (33). The prevalence of combined glucose curve characteristics involving time of the glucose peak and shape of the glucose curve has not been thoroughly investigated. According to our results, 71% of participants had either early glucose peak with biphasic curve or late glucose peak with monophasic curve. In the study of Chung and others, normotolerant or prediabetic adults with glucose peak >30 minutes more often had monophasic glucose curve (78%), while those with glucose peak at 30 minutes had an equal chance of having either biphasic or monophasic curve (54% vs 45%) (9). In the present study, adolescents with late glucose peak more frequently had monophasic glucose curve as well (81%), but in subjects with early glucose peak a higher prevalence of biphasic curve was detected (63%). As younger persons are more likely to be characterized by a biphasic glucose response (19,24), our results suggesting a stronger association of early glucose peak and biphasic glucose curve may be atributed to younger age and normotolerant glucose status of included subjects. In nondiabetic Latino adolescents, the biphasic group exhibited a higher percentage of „early responders“ compared with the monophasic group (57% vs 32%) (18), and this trend was even more pronounced in our sample (82% vs 38%).

The time point after an oral glucose load at which the peak glucose concentration occurs has recently been shown to represent a reliably reproducible parameter of the OGTT, with 76% agreement on triplicate testing performed at three different days (7). As well, time to glucose peak has already emerged as a potential predictor of beta-cell function in adults, while only scarce data related to adolesents currently exist. In adults, cross-sectional studies have linked a late glucose peak during OGTT with beta-cell dysfunction, impaired glucose tolerance and type 2

diabetes (7,9,10). A longitudinal study comprising 532 women in the first year postpartum, revealed that both a shift of the glucose peak to a later time point and a consistently delayed glucose peak were associated with declining beta-cell function and worsening of glucose tolerance status over a 9 month period (8). In adults with newly diagnosed type 2 diabetes, time to glucose peak during OGTT was assessed before and after 4 weeks of intensive insulin therapy; a resultant improvement of beta-cell function was associated with a shift of the glucose peak to an earlier time point (7). Regarding adolescent population, 54 overweight/obese postpubertal girls with late glucose peak had lower insulin sensitivity index (ISI) (P=0.004) and oDI (P<0.001) than 34 girls with earlier glucose peak (11). Nolfe et al. also supported the concept that the more quickly the plasma glucose concentration returned to or below the fasting glucose level following glucose ingestion, which was associated with earlier glucose peak, the lower was the risk for future diabetes (33). In the present study, participants with late glucose peak had lower oDI than subjects with early glucose peak (P=0.002). Our findings are in agreement with cross-sectional analyses linking delayed glucose peak with early defect in beta-cell function (8-12).

Significance of glucose curve shape was first established in adults. Beta-cell function adjusted for insulin resistance was found to be significantly lower in non-diabetic individuals with monophasic glucose curve; moreover a monophasic glucose response was more prevalent among subjects with IGT than in individuals with NGT (13). Another study linked monophasic glucose curve shape with increased risk for type 2 diabetes; over a 7-8 years follow-up, the conversion rate to type 2 diabetes in prediabetic adults with monophasic glucose curve was twice as big as the conversion rate of subjects with biphasic glucose response (14). Although questions regarding the curve shape stability were initially raised, recent data suggest that it is high (34). In EGIR-RISC cohort, 70% of participants presented with monophasic OGTT-glucose curve shape both at baseline and 3 years later (15). Besides that, persistence over time of monophasic shape and switch from biphasic to monophasic shape was associated with increased risk of impaired glucose metabolism (15). Cross-sectional studies in adolescents (17,18), including clamp studies in obese youth of both sexes and all pubertal stages (19), found a monophasic glucose curve shape to be associated with significantly worse beta-cell function relative to insulin sensitivity. In our study, after adjustment for age, sex, puberty stage and BMI z-score, subjects with monophasic glucose response had lower oDI (P=0.001) reflecting poorer β-cell function, which is in accordance with findings of other studies performed in youth (17-19).

The glucose curve shapes observed within a 2-hour window during OGTT are partialy influenced by the time of the first glucose peak. Subjects with early peak are more likely to have biphasic, while those with late peak more often have monophasic curve shape. Cree-Green et al. found that peak glucose time was more predictive of β-cell function than shape of the glucose curve (11). Similar findigs were published in an adult cohort with increased risk for type 2 diabetes (9).

To our knowledge, significance of combined glucose curve features in detection of beta-cell dysfunction have not been investigated. Thus, we further categorised subjects according to the combination of both features, time of the glucose peak and shape of the glucose curve. Adolescents with late glucose peak and monophasic curve shape had **lower** oDI than those with early peak and biphasic curve shape (P=0.002). **Moreover,** a combination of late glucose peak and monophasic glucose curve proved to be the strongest predictor of poor beta-cell function, as reflected by the highest risk of oDI in the lowest quartile (OR: 11.68, 95% CI: 3.048-44.755, p<0.001). We found no data in the literuture highlighting the fact that glucose normotolerant adolescents with the combination of late glucose peak and monophasic glucose response during OGTT, are at increased risk for poor beta-cell function.

Study Limitations

In the current study, time of the glucose peak and shape of the glucose curve were determined by a single OGTT. **Although recent studies in adults suggest glucose response pattern reproducibility and persistance over time (7,15), youth-specific investigation of glucose curve characteristics are needed.** In addition, our classification of glucose curve response was based on 2-hour OGTT with standard 30-minutes sampling intervals. By using more frequent sampling intervals, it could be possible to capture more details and probably provide better information on beta-cell function. Another drawback of this study was the inability to assign all the adolescents with NGT to either early/late glucose peak or monophasic/biphasic glucose response group, due to the criteria needed for glucose response classification. However, the number of unclassified subjects was small (n=10, 0.05%). Finally, factors which could influence the gastric emptying or differences in pre-test carbohydrate loading were not assessed in the present study.

Prospective longitudinal studies in obese adolescents are needed to confirm the predictive value of the glucose curve morphology with respect to deterioration of beta-cell function and progression from NGT to prediabetes or type 2 diabetes. Also, it should be explored whether lifestyle interventions in obese adolescents with poor beta-cel function could shift glucose peak to an earlier time point and/or glucose curve shape from monophasic to biphasic.

Conclusion

Early identification of subjects with high risk for type 2 diabetes among obese adolescents requires studies that focus on the initial stages of the disease, before the onset of any alterations in glucose tolerance. The present study confirms that obese adolescents with late glucose peak, as well as those with monophasic glucose response during OGTT, although normoglycemic, have reduced beta-cell function relative to insulin sensitivity. The risk of impaired beta-cell function is even more pronounced in obese youth with the aforementioned glucose curve features combined, making them a target population for intensive lifestyle intervention.

Authorship Contribution

Study design, data collection and analysis, first draft of the manuscript: Lavinia La Grasta Sabolić

Clinical care and implementation of the study, literature search: Marija Požgaj Šepec

Study design contribution, critical revision of the manuscript: Maja Cigrovski Berković, Gordana Stipančić

All authors approved the manuscript in its final version.
Lavinia La Grasta Sabolić is the guarantor of this work, had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Demographic characteristics of study participants and OGTT-derived indices of insulin sensitivity, secretion and beta-cell function

	Obese n = 76 (43.7%)	**Severely obese** n = 98 (56.3%)	**P-value**	**Total** n = 174 (100%)
BMI (kg/m^2)	29.50 ± 2.31 (24.5-36)	35.55 ± 4.74 (28-51.7)	<0.001	32.8 ± 4.8 (24.5-50.9)
BMI z-score	1.94 ± 0.16 (1.61-2.21)	2.41 ± 0.19 (2.08-3.05)	<0.001	2.21 ± 0.29 (1.61-3.05)
Age (years)	14.19 ± 2.12 (10-18)	13.72 ± 1.98 (10-17.6)	0.127	13.92 ± 2.05 (10-18)
Sex – M/F	30 (39.5) / 46 (60.5)	46 (46.9) /52 (53.1)	0.357	76 (43.7) / 98 (56.3)
Tanner stage				
I	8 (10.5)	10 (10.2)		18 (10.3)
II	16 (21.1)	19 (19.4)		35 (20.1)
III	7 (9.2)	13 (13.3)	0.929	20 (11.5)
IV	12 (15.8)	13 (13.3)		25 (14.4)
V	33 (43.4)	43 (43.9)		76 (43.7)
WBISI	2.49 ± 1.16 (0.67-6.52)	1.98 ± 0.95 (0.35-7.90)	0.002	2.20 ± 1.08 (0.35-6.52)
IGI	2. 44 ± 1.32 (0.03-6.52)	2.63 ± 1.66 (0.44-9.61)	0.420	2.55 ± 1.52 (0.03-9.61)
oDI	5.20 ± 2.23 (0.09-11.06)	4.42 ± 2.06 (0.60-11.68)	0.019	4.76 ± 2.16 (0.09-11.68)

Data are reported as n (%), mean ±SD (range); M – male, F – female; BMI – body mass index, WBISI – whole body insulin sensitivity index, IGI - insulinogenic index, oDI - oral disposition index
P-values: chi-square for categorical variables, independent t-test for continuous variables

Table 2: Prevalence of glucose curve characteristics in obese vs severely obese adolescents

Glucose curve characteristics	**Obese** n = 76	**Severely obese** n = 98	**P-value***
P_{30}	46 (60.5)	54 (55.1)	
$P_{\geq 60}$	30 (39.5)	44 (44.9)	0.537
M	41 (53.9)	56 (57.1)	
B	35 (46.1)	42 (42.9)	0.759
P_{30}M	18 (23.7)	19 (19.4)	
P_{30}B	28 (36.8)	35 (35.7)	
$P_{\geq 60}$B	7 (9.2)	7 (7.1)	0.727
$P_{\geq 60}$M	23 (30.3)	37 (37.8)	

Data are reported as n (%); P_{30} - glucose peak at 30 minutes, $P_{\geq 60}$ - glucose peak at ≥60 minutes, M - monophasic glucose curve, B - biphasic glucose curve
***significance of differences between obese and severely obese adolescents in each glucose curve characteristics frequency**: chi-square statistics (Fisher's exact test for 2x2 tables)

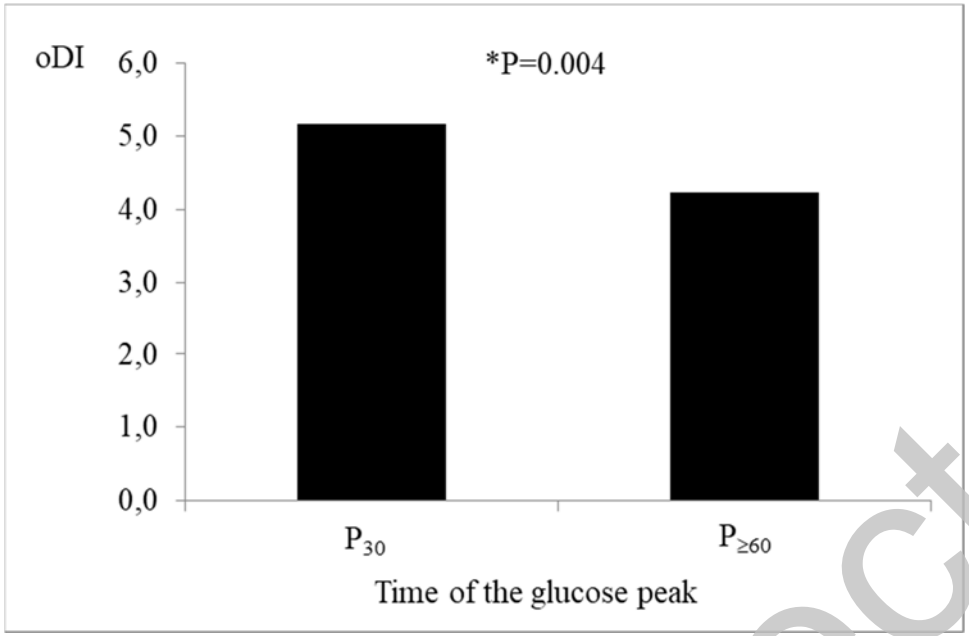
Table 3. OGTT-derived indices in groups with **early vs late glucose peak and biphasic vs monophasic glucose curve**

OGTT-derived indices	**Time of the glucose peak**			**Shape of the glucose curve**		
	P_{30}	$P_{\geq 60}$	*P-value	B	M	*P-value
WBISI	2.30±1.13 **(0.66-7.9)**	2.08±1.00 **(0.35-4.94)**	0.302	2.21±1.06 **(0.66-5.13)**	2.20±1.10 **(0.35-7.9)**	0.784
IGI	2.76±1.62 **(0.62-9.61)**	2.27±1.32 **(0.44-7.13)**	0.057	3.04±1.72 **(0.77-9.61)**	2.16±1.21 **(0.44-7.13)**	<0.001
oDI	5.23±2.16 **(1.23-11.68)**	4.15±2.02 **(0.68-10.57)**	0.004	5.44±2.07 **(1.64-11.3)**	4.25±2.10 **(0.68-11.68)**	0.001

B

Data are reported as mean ±SD **(range)**; WBISI – whole body insulin sensitivity index, IGI – insulinogenic index, oDI – oral disposition index, P_{30} – glucose peak at 30 mintues, $P_{\geq 60}$ – glucose peak at ≥60 minutes, M – monophasic glucose curve, B – biphasic glucose curve
***** after adjustment for age, sex, puberty stage and BMI z-score

A



B

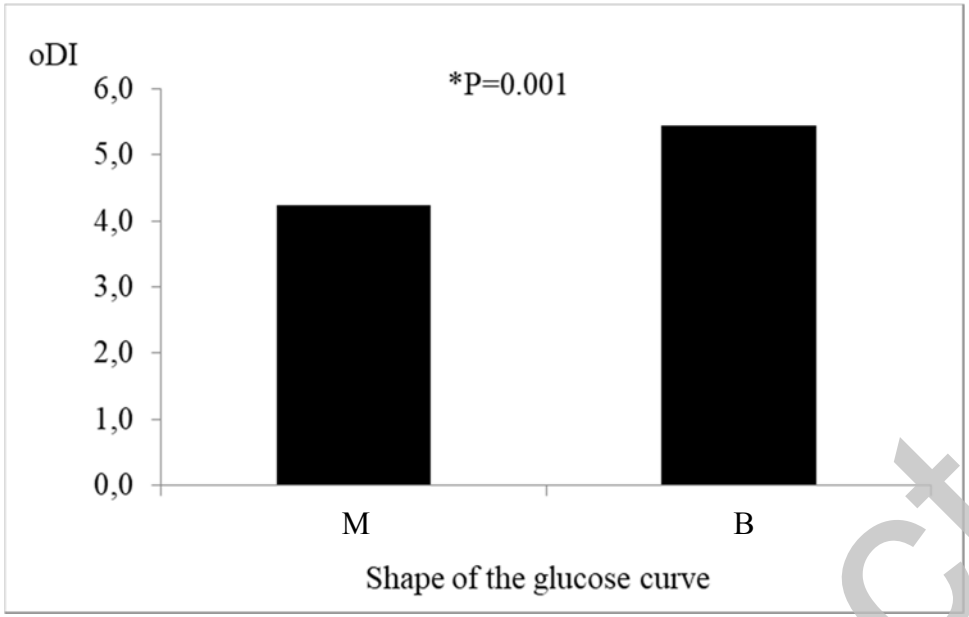
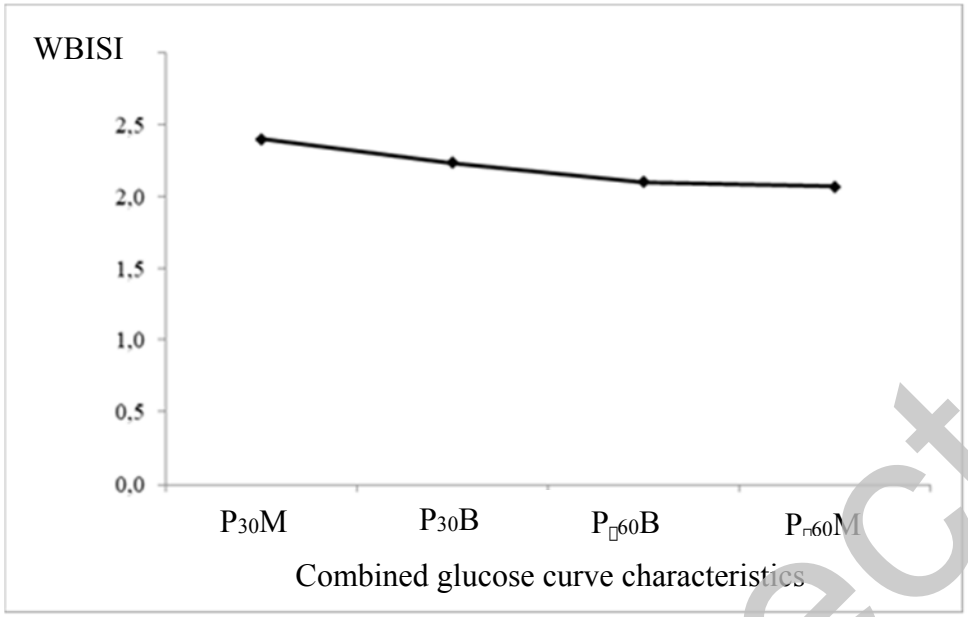


Figure 1. Comparison of average oDI in groups with: (A) early vs late glucose peak; (B) monophasic vs biphasic glucose curve
oDI – oral disposition index, P_{30} – glucose peak at 30 mintues, $P_{\geq 60}$ – glucose peak at ≥60 minutes, M – monophasic glucose curve, B – biphasic glucose curve,
* after adjustment for age, sex, puberty stage and BMI z-score

A



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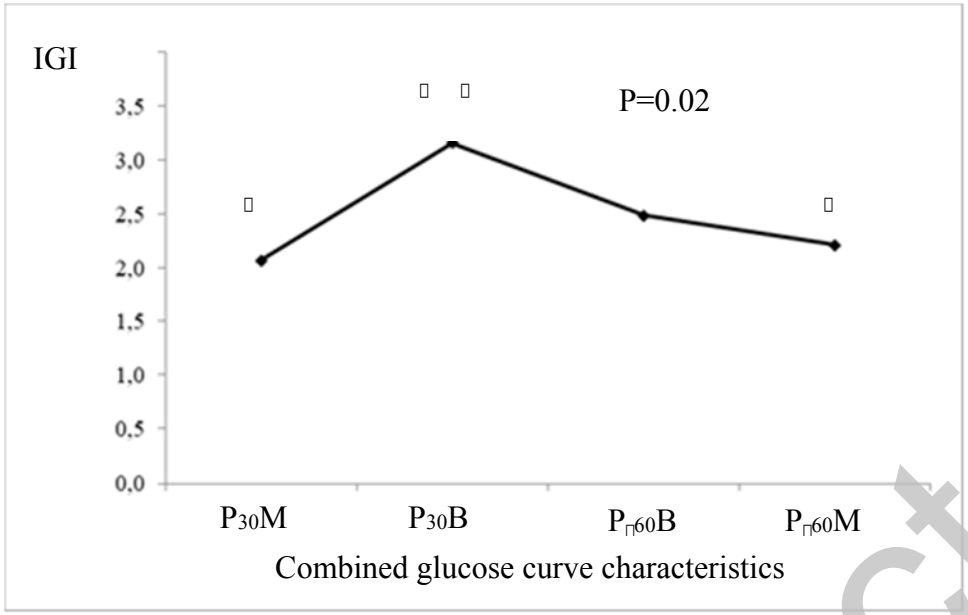


C

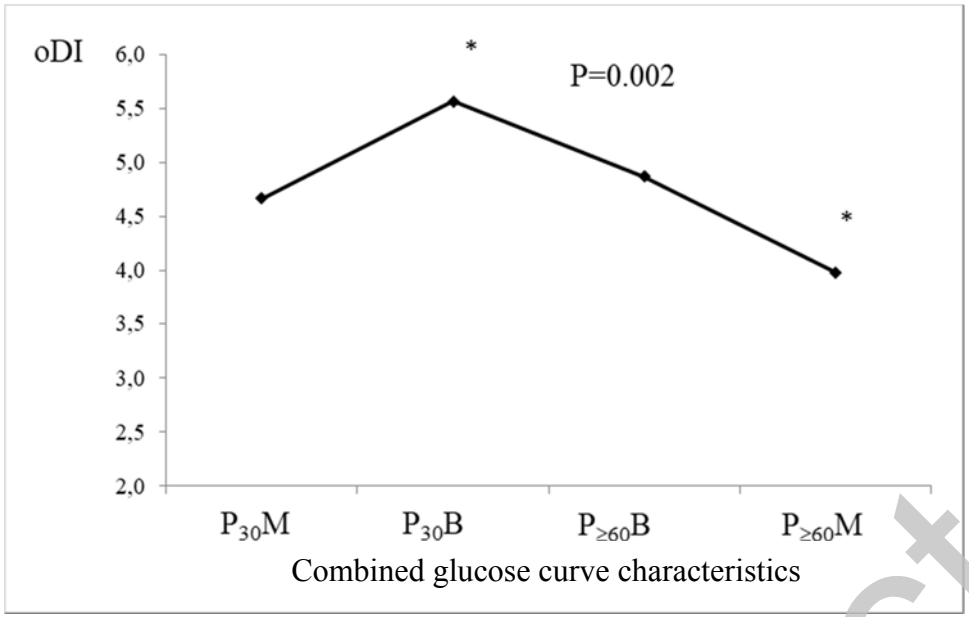
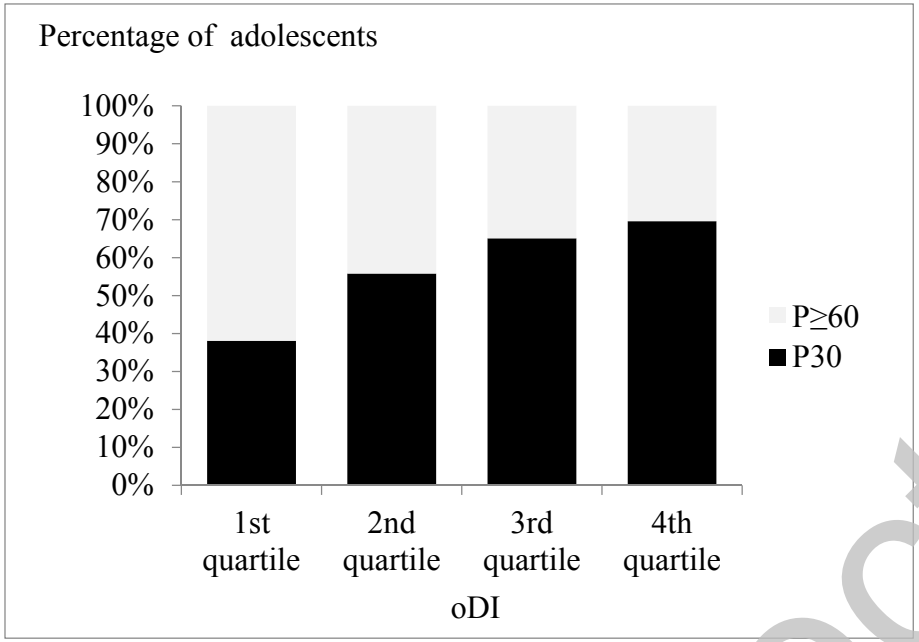


Figure 2. Comparison of average WBISI (A), IGI (B) and oDI (C) in groups with combined glucose curve characteristics
WBISI - whole body insulin sensitivity index, IGI – insulinogenic index, oDI – oral disposition index, $P_{30}M$ – glucose peak at 30 mintues and monophasic glucose curve, $P_{30}B$ – glucose peak at 30 minutes and biphasic glucose curve, $P_{\geq 60}B$ – glucose peak at ≥60 minutes and biphasic glucose curve, $P_{\geq 60}M$ glucose peak at ≥60 minutes and monophasic glucose curve
* statistically significant difference after adjustment for age, sex, puberty stage and BMI z-score

A



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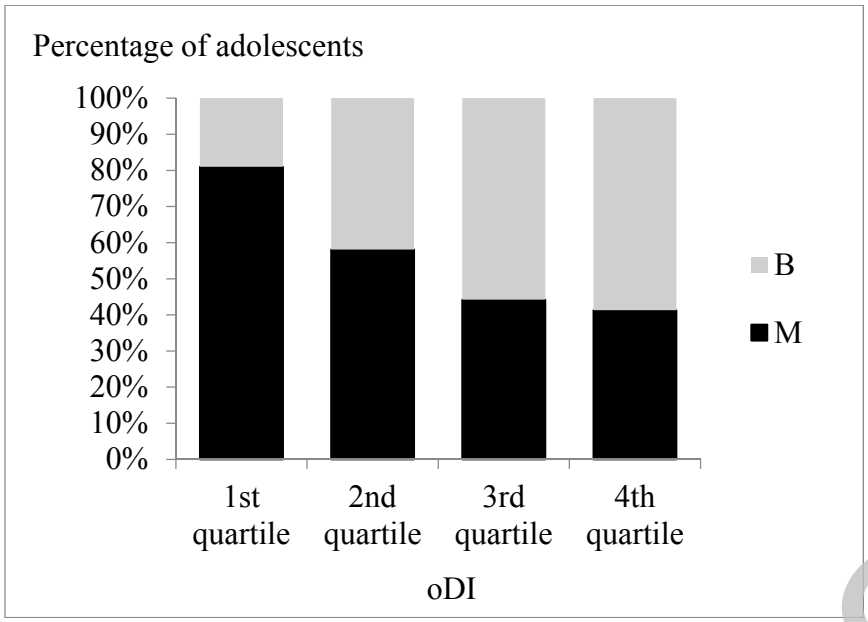

Figure 3. Percentage of adolescents with: (A) early vs late glucose peak in each quartile of oDI; (B) biphasic vs monophasic glucose curve in each quartile of oDI