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Is there a correlation between blood glucose curve and the insulin resistance during oral glucose tolerance test in females suffering from polycystic ovary syndrome?

Da li postoji korelacija oblika glikemijske krive i rezistencije na insulin u toku testa oralnog opterećenja glukozom kod žena obolelih od sindroma policističnih jajnika?

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Abstract

Background/Aim. Insulin resistance occurs in approximately 60–80% of women with polycystic ovary syndrome (PCOS) and in 95% of obese women with PCOS. Previous studies have shown that the shape of the glucose curve obtained during an oral glucose tolerance test (OGTT) may be useful as a metabolic screening parameter and could give insight into the future risk of diabetes mellitus type II. The aim of this study was to determine the frequency of insulin resistance according to the Homeostasis model assessment of insulin resistance (HOMA-IR) and indirect assessment method of insulin resistance based on insulinemias during the oral glucose tolerance test (OGTT) (here in after "insulinemias during the OGTT"), as well as, frequency of glucose curve shapes (monophasic, biphasic, triphasic) in patients with PCOS. Also, the aim of research was testing the correlation between glucose curve shape and peak time of glucose during the OGTT with presence of insulin resistance in patients with PCOS. **Methods.** Patients were observed according to the following parameters: presence of insulin resistance, glucose curve shape and peak time of glucose and insulin during the OGTT. **Results.** The observed prevalence of insulin resistance in the PCOS group according to the HOMA-IR > 2.5 was 66.19% and according to insulinemias during the OGTT was 78.42%. The shape of the glucose curve was monophasic in 293 (70.26%), biphasic in 56 (13.43%) and triphasic in 68 (16.31%) of patients. There was statistically significant difference in the frequency of insulin resistance, according to glucose curve shape, only when it was defined by insulinemias during the OGTT ($p = 0.005$). **Conclusion.** According to results of the study, the most patients with PCOS have a monophasic shape of glucose curve. When we take frequency of insulin resistance in account, we notice approximately the same frequency in all types of curves, when it is defined by the HOMA-IR. On the other hand, when insulin resistance is defined by insulinemias during the OGTT, resistant patients with PCOS mostly have triphasic glucose curve shape.

Key words:
polycystic ovary syndrome; glucose tolerance test; blood glucose, insulin resistance.

Apstrakt

Uvod/Cilj. Učestalost insulinske rezistencije u grupi bolesnica sa sindromom policističnih jajnika (PCOS) kreće se od 60% do 80%, dok u populaciji gojaznih žena sa PCOS iznosi čak 95%. Ranija istraživanja su pokazala da oblik glikemijske krive u toku testa oralnog opterećenja glukozom (OGTT) može biti koristan metabolički skrining parametar za rizik od nastanka dijabetesa melitusa tip II. Cilj rada bio je odrediti učestalost insulinske rezistencije prema homeostaznom modelu procene insulinske rezistencije (HOMA-IR) i metodom indirektne procene insulinske rezistencije na osnovu insulinemija u toku OGTT (u daljem tekstu "vrednosti insulinemija u toku OGTT"), kao i učestalost oblika glikemijske krive (monofazne, bifazne, trifazne) u populaciji bolesnica sa PCOS. Takođe, cilj studije je bio ispitivanje povezanosti oblika glikemijske krive, kao i vremena glikemijskog pika u toku OGTT sa insulinemijama, sa prisustvom insulinske rezistencije u populaciji žena sa PCOS. **Metode.** Bolesnice smo posmatrali u odnosu na prisustvo insulinske rezistencije, oblik glikemijske krive i u odnosu na vreme glikemijskog i insulinskog pika u toku OGTT. **Rezultati.** Učestalost insulinske rezistencije na osnovu HOMA-IR > 2,5 iznosila je 66,19%, dok je na osnovu vrednosti insulinemija u toku OGTT iznosila 78,42%. Monofazni oblik glikemijske krive

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u toku OGTT je imalo 293 (70,26%), bifazni 56 (13,43%), a trifazni oblik krive 68 (16,31%) bolesnica. Statistički značajna razlika u pogledu učestalosti insulinske rezistencije u odnosu na oblik glikemijske krive registrovana je kada je insulinska rezistencija bila definisana na osnovu vrednosti insulinemija u toku OGTT (p = 0,005). **Zaključak.** Prema rezultatima studije, većina bolesnica sa PCOS ima monofazni oblik glikemijske krive. Kada govorimo o učestalosti insulinske rezistencije u odnosu na oblik krive, uočava se približno ista učestalost kada insulinsku rezistenciju definišemo po HOMA-IR. S druge strane, kada insulinsku rezistenciju definišemo na osnovu vrednosti insulinemija u toku OGTT, bolesnice sa insulinskom rezistencijom većinom imaju trifazni oblik glikemijske krive.

Ključne reči:
jajnik, policistični, sindrom; glukoza, test tolerancije; glikemija; insulin, rezistencija.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting 6–10% of reproductive-aged women [1–3]. Beside the reproductive dysfunction, androgenic excess and polycystical structure of ovaries, which stands for the basic parameters that define this syndrome, the special attention should be paid to metabolic aspect of this complex disorder. PCOS is a significant risk factor in the occurrence of glucose intolerance (IGT), metabolic syndrome and diabetes mellitus type II in females [4, 5]. The frequency of insulin resistance in a group of patients with PCOS varies from 60–80%, while in a group of obese women with PCOS it goes up to 95% [6, 7].

The oral glucose tolerance test (OGTT) with determining the level of insulinemia is used as an accepted clinical method in assessing the occurrence of insulin resistance. It is most commonly used in patients suffering from PCOS. Earlier studies showed that the shape of glucose curve during the OGTT can be used as a useful metabolic screening parameter [8] for a risk of occurring diabetes mellitus type II [9]. Monophasic glucose curve shape goes in favour of the worsening of insulin sensitivity and the damage of beta cells [10], while the more complex shapes of glucose curve are correlated with the better glucose tolerance [11].

The aims of this study were: to determine the frequency of insulin resistance in a population of females, suffering from PCOS according to the Homeostasis model assessment of insulin resistance (HOMA-IR) and according to indirect assessment method of insulin resistance based on insulinemias during the OGTT (here in after "insulinemias during the OGTT"); to determine the frequency of the shape of the glucose curve (monophasic, biphasic and triphasic) in a population of females suffering from PCOS; to examine the presence of the correlation between the glucose curve shape and the insulin resistance during the OGTT with determining the level of insulinemias in patients suffering from PCOS; to examine the possible correlation between the time of the glycemic peak during the OGTT with determining the level of insulinemias and the presence of insulin resistance in population of females suffering from PCOS.

Methods

Totally 417 female patients were included in this retrospective study, that were hospitalized on the Department of Gynecological Endocrinology, Clinic for Gynecology and Obstretics, Clinical Center of Serbia, in a period from January 1st, 2017 until December 31st, 2018. Patients were hospitalized due to the plan, regarding the further examination of irregular menstrual cycles or due to the clinical signs of hyperandrogenism. During the hospitalization patients were completely examined, including physical examination, ultrasound examination and laboratory analysis. The blood was taken from each patient in order to determine the basic hormonal status (follicle stimulating hormone – FSH, luteinizing hormone – LH, prolactin, estradiol, progesterone and testosterone) and androgen status (androstendione, 17-OH-progesterone, dehydroepiandrosterone sulfate – DHEA-S, sex hormone binding globulin – SHBG). The OGTT with determining the level of insulinemias was carried out. Patients' data were collected from medical histories.

The diagnosis of PCOS was established based on the Rotterdam criteria [12]. For establishing the diagnosis two out of the following three criteria were necessary to be fulfilled: hyperandrogenism – clinical symptoms (hirsutismus and/or acne) and/or confirming biochemical analysis (increased levels of testosterone and/or androstenedione); chronic anovulation – oligomenorrhea/amenorrhea; polycystic morphology of ovaries – at least 12 follicles with diameter 2–9 mm and volume of at least one ovary should be greater than 10 mL.

Patients, diagnosed with some other endocrinological disease (hyperprolactinaemia, hyper/hypothireoidism, Cushing syndrome, nonclassic adrenal hyperplasia) and also the patients, who were using oral contraceptive therapy or drugs that could affect the metabolism of glucose and have an impact on insulin sensitivity were excluded from this study. All stated data was collected from the medical histories of patients.

The OGGT was performed as follows: first of all, the basic sample for glycemia and insulin level was taken from patients. Hereupon, patients drank a standard 75 g glucose solution, and samples were taken for determining glycemia and insulin at 0, 30, 60, 120 and 180 minutes.

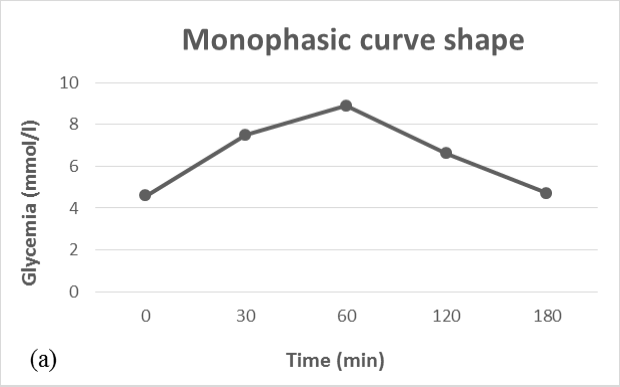
Insulin resistance was defined in 2 different ways. The first way of determining the insulin resistance was by using the HOMA-IR. It was calculated using the following formula: fasting glycemia (mmol/L) × fasting insulinemia (μIU/mL)/22.5 [13]. The borderline of the HOMA-IR was from 2.5 and it was taken from the basic research. Values above mentioned one were defined as insulin resistance.

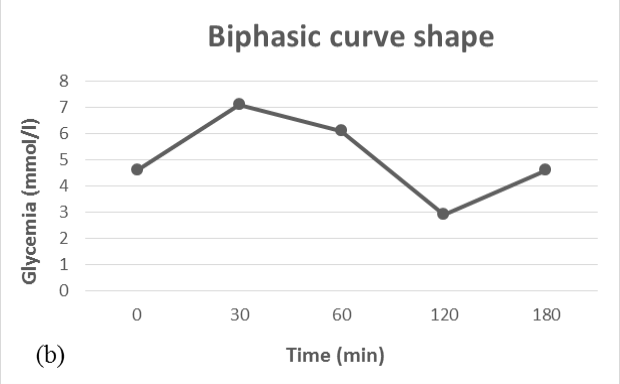
The second indicator of insulin resistance was defined based on borderline values for insulin in 0 minute

(I0 > 22.1 μIU/mL), 60 minute (I60 > 130 μIU/mL) and in 120 minute (I120 > 30 μIU/mL), that were given in Greenspan's Basic & Clinical Endocrinology [14]. We will refer to this method in the text as "indirect assessment method of insulin resistance based on insulinemias during OGTT" ("insulinemias during OGTT").

The glucose curve shape

Monophasic shape of the glucose curve is characterized by the glycemic peak between the 30th and the 120th minute, as well as the significant decrease in glycemia values from minimum 0.25 mmol/L between the 120th and the 180th minute upon starting the OGTT (G180–G120 < -0.25 mmol/L) [8] (Figure 1a).





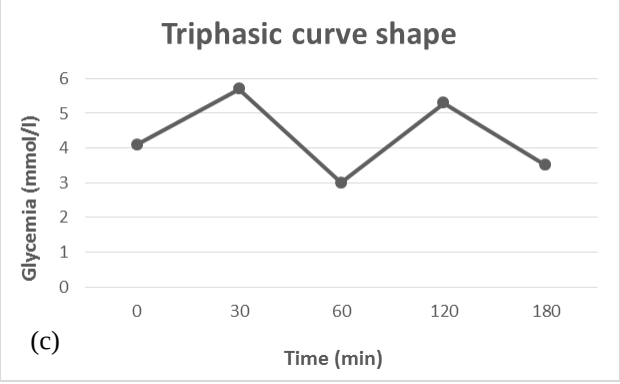


Fig. 1 – The glucose curve shape: (a) Monophasic curve shape; (b) Biphasic curve shape; (c) Triphasic curve shape.

Biphasic shape of glycemic curve is characterized by peak of glycemia in the 30th or the 60th minute, as well as the significant increase in glycemia values between the 120th and the 180th minute (G180–G120 > 0.25 mmol/L). If the peak is reached in the 30th minute, one should have in mind the significant increase of glycemia between 60th and 180th minute (G180–G60 > 0.25 mmol/L) [8, 15] (Figure 1b).

Triphasic shape curve is characterized by peaks in the 30th and 120th minute, as well as the negative peak in the 60th minute. The significant decrease in glycemia values between the 120th and the 180th minute criterion has to be fulfilled (G180–G120 < -0.25 mmol/L) [8, 15] (Figure 1c).

The shape of the curve that is described as unclassified occurs when insignificant changes of glycemia values between the 120th and the 180th minute (< 0.25 mmol/L) are noticed. The patients with this glucose curve shape were excluded from the study.

Statistical analysis

The database was created in Microsoft Office Excel. Statistical data analysis was done using SPSS software 20.0 (Statistical Package for the Social Sciences) for Windows (SPSS Inc., Chicago, IL, USA). For statistical data processing, methods of descriptive and analytical statistics were used. Relative numbers and arithmetic meanings were used from descriptive statistical methods. To test the significance of the difference in arithmetic meanings, the *t*-test and ANOVA were used, while the χ^2 test was used to test the significance of the frequency difference. In case the necessary condition for using the mentioned tests were not fulfilled, the appropriate nonparametric tests were applied: Kruskal-Wallis test and Mann-Whitney test.

Results

Study group consisted of 417 patients suffering from polycystic ovary syndrome. Monophasic shape of glucose curve obtained through the OGTT had 293 (70.26%), biphasic 56 (13.43%) and triphasic shape of glucose curve had 68 (16.31%) patients. By comparing the mean values of body mass index (BMI) in patients with monophasic (23.68 ± 5.09 kg/m^2), biphasic (22.12 ± 3.55 kg/m^2) and triphasic (22.41 ± 4.6 kg/m^2) shape of glucose curve we found the statistically significant difference between these groups ($p < 0.05$). However, these correlations showed no signs of clinical significance, due to the fact that the mean values of BMI in all three groups of patients belong to a group of normally nourished patients.

The frequency of insulin resistance based on the HOMA-IR > 2.5 amounts to 66.19% (276 out of total 417 patients). The majority of women with insulin resistance had a monophasic shape of glucose curve. Elaborately, 198 patients with insulin resistance had a monophasic glucose curve shape, which represents 67.58% of the total number of patients with monophasic shape curve. Additionally, a triphasic shape of glucose curve, that was noticed in 41 patients (60.29% from a total number of patients with triphasic glu-

cose curve shape) was on the second place. Finally, biphasic glucose curve shape was seen in 37 patients with insulin resistance (66.07% of patients with biphasic shape of glucose curve obtained during OGTT). There was no statistically significant difference in comparison between the frequency of insulin resistance and the shape of glucose curve ($p > 0.05$) (Figure 2a).

The frequency of insulin resistance according to insulinemias during the OGTT amounts to 78.42% (327 out of total of 417 patients). The majority of patients with insulin resistance had a monophasic shape of glucose curve. Elaborately, 231 patients had insulin resistance, which represented 78.84% from the total of patients with monophasic shape of glucose curve. Triphasic glucose curve shape, that was noticed in 60 patients (88.23% from a total number of patients with triphasic shape of glucose curve) was on the second place. Finally, biphasic shape of glucose curve was determined in 36 patients with insulin resistance (64.28% of patients with biphasic shape of glucose curve obtained during OGTT). There was a statistically significant difference noticed in comparison between the frequency of insulin resistance and the shape of glucose curve ($p = 0.005$) (Figure 2b).

Regarding the time of the glycemic peak, from the total number of 293 patients with monophasic curve, 146 (49.83%) had a peak time in the 30th minute, 139 (47.44%) in the 60th minute and 8 (2.73 %) in the 120th minute (Figure 3a). When talking about patients with a biphasic curve, from the total number of 56 patients, 44 (78.57%) had a peak time in the 30th minute, 11 (19.64%) had a peak in the 60th minute and 1 (1.79%) in the 180th minute (Figure 3b). As for patients with triphasic glycemic curve, from a total number of 68, 66 (97.06%) patients had a peak time of the 30th minute and 2 (2.94%) in the 120th minute (Figure 3c). There was no statistically significant difference in the frequency of insulin resistance compared to the glycemic time ($p > 0.05$). The same holds true for all criteria of insulin resistance (Figure 3).

Fig. 2 – The frequency of insulin resistance in the group of patients with monophasic, biphasic and triphasic glucose curve shape, when the insulin resistance is defined according to the homeostasis model assessment of insulin resistance (HOMA-IR) > 2.5 (a) and according to insulinemias during the oral glucose tolerance test (OGTT) (b). (-)IR patients without insulin resistance; (+)IR patients with insulin resistance.

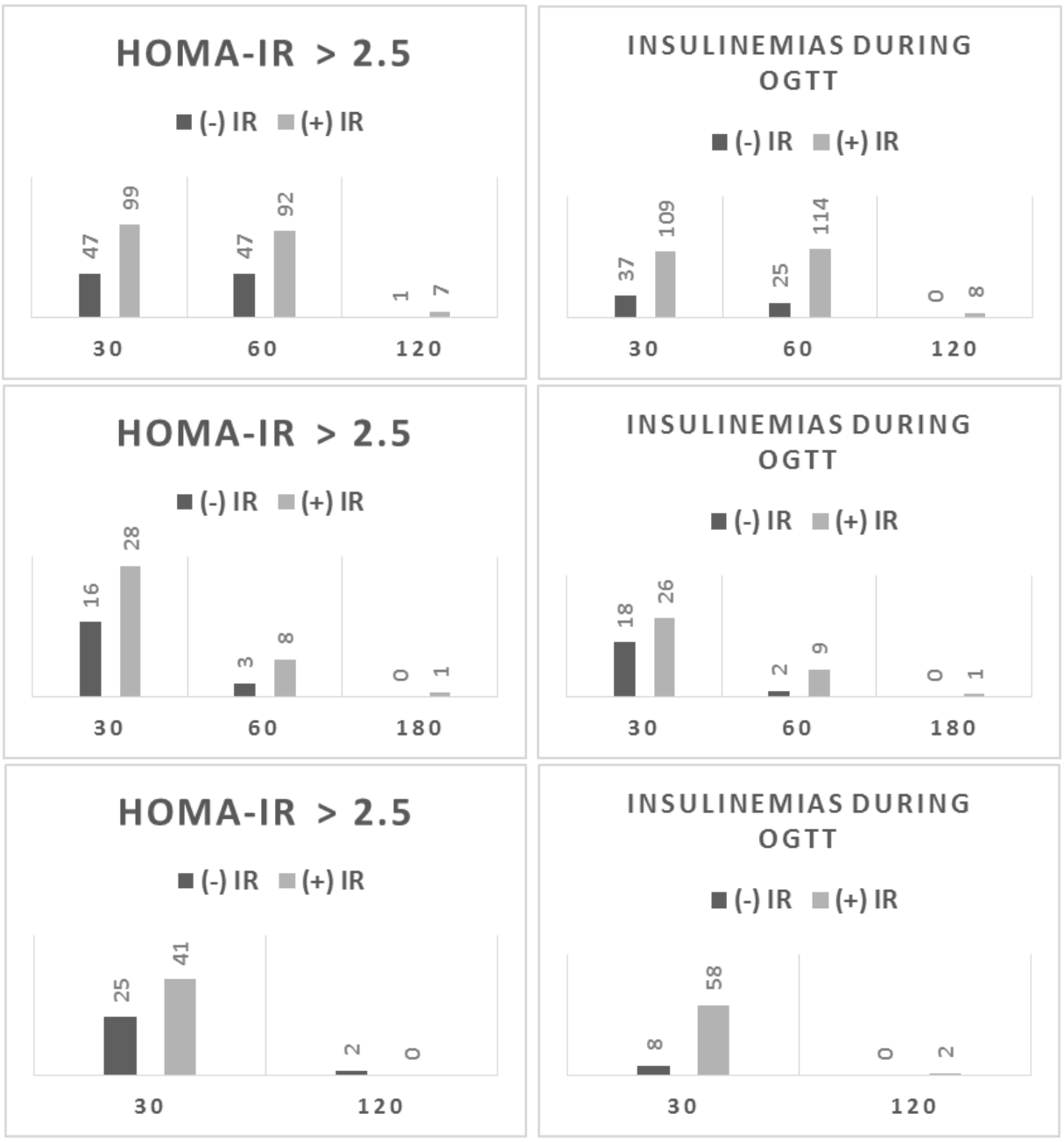


Fig. 3 – The frequency of insulin resistance (IR) in patients with glycemic peak in the 30th, 60th, 120th, 180th minute, when insulin resistance is defined according to the homeostasis model assessment of insulin resistance (HOMA-IR) > 2.5 and according to insulinemias during oral glucose tolerance test (OGTT).
(-)IR patients without insulin resistance; (+)IR patients with insulin resistance.

There was no statistically significant difference regarding the frequency of insulin resistance compared to the time of insulin peak, when it was defined according to the HOMA-IR > 2.5 ($p > 0.05$) (Figure 4a).

There was statistically significant difference regarding the frequency of insulin resistance compared to the time of insulin peak, when it was defined according to insulinemias during the OGTT ($p = 0.002$) (Figure 4b).

When comparing the areas underneath the monophasic, biphasic and triphasic glucose curves (AUCglu) no statistical significance was found ($p > 0.05$). The same holds true for comparing the areas underneath the AUCglu of patients that were suffering from insulin resistance and the ones who were not (especially for the HOMA-IR > 2.5 and according to insulinemias during the OGTT) ($p > 0.05$).

When comparing the areas underneath the insulinemia curve (AUCins) of patients with monophasic, biphasic and triphasic shapes of glucose curves no statistical significance were calculated ($p > 0.05$). When compared the surface underneath the AUCins of patients with insulin resistance and

Fig. 4 – The frequency of insulin resistance (IR) in patients with insulin peak in the 30th, 60th, 120th and 180th minute, when insulin resistance is defined according to the homeostasis model assessment of insulin resistance (HOMA-IR) > 2.5 (a) and according to insulinemias during the oral glucose tolerance test (OGTT) (b).
(-)IR patients without insulin resistance; (+)IR patients with insulin resistance.

the ones without it and when insulin resistance was defined according to the HOMA-IR > 2.5, no statistical significant difference was found ($p > 0.05$). There was a statistically significant difference in the AUCins in patients with insulin resistance and the ones without insulin resistance, when insulin resistance was defined according to insulinemias during the OGTT ($p = 0.003$).

Discussion

The OGTT with determining the level of insulinemias is widely used in clinical praxis, as the most useful method in assessing the presence of insulin resistance. It is mostly used, when patients are suffering from PCOS. Based on the previously acquired data, simple and more practical methods for measuring insulin resistance have been developed. Among them stands homeostasis model assessment of insulin resistance (HOMA-IR) that was used in our current study.

Beside this parameter, in our investigation we used consolidated reference values for insulin in the 0th, 60th, 120th minute of OGTT defined by Greenspan's Basic and Clinical Endocrinology, as indicator of insulin resistance [14].

Due to the fact that there is no consistent method of the OGTT interpretation and that there is no precise way of de-

fining insulin resistance, we wanted to see if the glucose curve shape and the time of glucose peak could be a useful tool in detecting insulin resistance in patients suffering from polycystic ovary syndrome. As far as it is known, based on studying available literature, correlation between glucose curve shape and insulin resistance in women with PCOS is an original idea of this study and it is published in this article for the first time.

Previous research that was performed on this topic, has shown that there is an increased risk of the occurrence of prediabetes in adults with the following morphological characteristics of the glucose curve: the time of glycemic peak after the 30th minute, the glucose concentration in the 60th minute ≥ 8.6 mmol/L and monophasic shape curves [9, 16–18].

It has been observed that most people with normal glucose values and normal insulin sensitivity have peak glycemia in the 30th minute or earlier [15, 19, 20], while on the other hand, the delayed glycemic time (≥ 60 minutes) is observed in adults who are suffering from type II diabetes mellitus [19].

When talking about the time of the glycemic peak of the monophasic curve, an equal number of patients with insulin resistance show an early peak in the 30th minute and a delayed peak at the 60th or the 120th minute.

Based on our results, total insulin response during the OGTT correlates with insulinemias during the test, whereas the HOMA-IR does not correlate. Clinical importance of these two data should be defined and requires further study.

In the study that was engaged in the reproducibility of morphological parameters of the glucose curve during the OGTT, such are the time of the insulin peak, the time of glycemia peak, the shape of the curve, the glucose concentration in 1h after testing, that the time of the glycemic peak proved to be the most reliable parameter [21].

In general, it has been shown that people with biphasic glucose curves have lower BMI, better glucose tolerance, insulin sensitivity, and beta cell function, compared to those patients that are characterized by the monophasic shape of the glucose curve [8, 10, 11].

A more complicated glycemic and insulin response during the 3h-OGTT (that involves a greater number of phases) is associated with better glucose tolerance, beta cell function and greater insulin sensitivity [11].

In our study, the majority of patients were characterized by the monophasic shape of the glucose curve (70.26%), while the frequency of biphasic (13.43%) and triphasic curves (16.31%) was almost identical. Having in mind the results of previous studies that dealt with the shapes of glucose curve in the population of patients with normal glucose tolerance, as well as in the population of patients with impaired glucose tolerance (IGT) and diabetes mellitus, it was expected that the incidence of insulin resistance was the highest in the group of patients with monophasic glucose curve shape, while the more complex shapes of the curve (biphasic and triphasic in our case) should act protective, in the sense of improving the insulin sensitivity. This was not the case in our research. As already mentioned, most patients with PCOS have a monophasic shape of glucose curve, but when the insulin resistance is defined by HOMA-IR, we notice approximately the same frequency. On the other hand, when the insulin resistance is defined by insulinemias during the OGTT, the frequency of insulin resistance in the population of patients with triphasic shape of the glucose curve is as high as 88.23%.

Conclusion

According to results of the study, the most patients with PCOS have a monophasic shape of glucose curve. When we take frequency of insulin resistance into account, we notice approximately the same frequency in all types of curves, when it is defined by the HOMA-IR. On the other hand, when insulin resistance is defined by insulinemias during the OGTT, resistant patients with PCOS mostly have triphasic glucose curve shape. The time of glycemic peak is not related to the frequency of insulin resistance in patients with PCOS, under no criteria of insulin resistance.

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