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ELEVATED 1 HOUR GLUCOSE DURING ORAL GLUCOSE TOLERANCE TEST- A NEW PARAMETER OF IMPAIRED METABOLISM

Flavia Diugan ✉, ***Maria Mota***

University of Medicine and Pharmacy, Craiova, Romania

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Abstract

Background and aims: *Recently, large scale studies emphasized the idea of an excess of metabolic and cardiovascular risk in patients currently considered to have normal glucose tolerance but showing an elevated 1 hour glucose (≥155mg/dl) during oral glucose tolerance test (OGTT).* ***Material and Methods****: 75 subjects with normal glucose tolerance or impaired glucose tolerance were completely investigated. We evaluated the clinical and biological markers associated to insulin resistance and we calculated the cardiovascular risk of the subjects using the SCORE charts.* ***Results and Discussions:*** *Our data found statistically significant correlations between subjects with normal glucose tolerance and elevated 1 hour glucose and the following markers of insulin resistance: triglycerides to HDL- cholesterol ratio (TG/HDL-chol), Homeostatic Model Assessment (HOMA-IR), The Quantitative Insulin Sensitivity Check Index (QUICKI), fasting insulin, fasting glucose to fasting insulin ratio. Also, the subjects with elevated 1 hour glucose had a greater cardiovascular risk compared to subjects with 1 hour glucose <155 mg/dl.* ***Conclusions:*** *This study identifies a category of subjects currently considered as normal glucose-tolerant individuals but with a special metabolic profile, an increased cardiovascular risk and an increased risk of developing diabetes.*

key words: *1 hour glucose - OGTT, insulin resistance, cardiovascular risk*

Background and aims

We are currently talking of a "pandemic "of diabetes globally. Whatever were the reasons that led to this situation (high prevalence of obesity in both adults and children, poor and unbalanced nutrition, increased life expectancy, ageing, etc.) the consequences are serious and diabetes is now a real public health problem. Diabetes and its complications are a real economic and social burden, generating huge costs of care.

These data are even more frightening as the number of patients diagnosed with diabetes is in reality almost doubled by that of patients with undiagnosed diabetes or pre-diabetes [1].

But there is also encouraging news, data from large-scale studies that demonstrated that prevention methods applied in the early stages of impaired glucose tolerance have the effect of reducing the progression to diabetes, improving the lipid profile and lowering the cardiovascular risk. Thus, it is correct to say that the key to reducing morbidity and mortality associated with diabetes and its complications is detecting it in

✉ Str Nicolae Balcescu nr 54, Craiova, Jud Dolj, Romania. Tel: 0752204050;
corresponding author e-mail: dinuflv@yahoo.com

its early stages, especially in the stage of impaired glucose metabolism (impaired glucose tolerance-IGT/ impaired fasting glucose-IFG) and applying early prevention measures. IFG and IGT are entities proven to have a major risk for the future development of diabetes and to positively correlate to cardiovascular risk. These risk categories have been extensively studied and there is no doubt that there are great benefits associated with early intervention on this population [2].

Recently, some large studies emphasized the idea of an excess of metabolic and cardiovascular risk in patients currently considered to have normal glucose tolerance but showing elevated 1 hour glucose during oral glucose tolerance test (OGTT) [3,4].

Several studies have investigated the hypothesis that subjects with normal glucose tolerance and elevated 1 hour glucose during OGTT represent an intermediate category of patients with impaired glucose metabolism: insulin resistance and reduced sensitivity to glucose of the β cells. The cardiovascular risk and subsequent development of diabetes in this population was found to be equal to that of the patients diagnosed with IGT [5].

The aim of the present study was to investigate the hypothesis that elevated 1 hour glucose during OGTT can identify subjects that are considered to have normal glucose tolerance according to current definitions but have a particular metabolic profile. These patients could benefit from therapeutic interventions similar to those applied to patients with IGT. For this, we evaluated the relationship between elevated 1 hour glucose and clinical and biological markers of insulin resistance as well as cardiovascular risk in subjects with normal glucose tolerance under current definitions. According to data from the literature, we agreed to a cut off value for 1 hour glucose of 155 mg/dl [4,6].

Material and Methods

The study was conducted between January and August 2015 and the subjects were selected from patients who presented to the outpatient consultations at Diab Clinique Craiova.

The target population was represented by subjects over 18 years old that were not previously diagnosed with diabetes and to whom OGTT was performed in order to assess their metabolic status. All participants agreed and signed an informed consent. The exclusion criteria were: subjects previously diagnosed with diabetes or those who were diagnosed with diabetes after the OGTT had been performed, subjects with fasting plasma glucose ≥ 110 mg /dl (patients with IFG according to the World Health Organization), subjects who had medical conditions or received medications that interfered with insulin secretion, insulin resistance or lipid levels and pregnant or breast-feeding women.

After applying the inclusion and exclusion criteria we identified a study group of 75 patients (39 men and 36 women), 25 subjects (13 men and 12 women) for each of the 3 groups: Group 1A (subjects with normal glucose tolerance and 1 hour glucose < 155mg/dl), Group 1B (subjects with normal glucose tolerance and 1 hour glucose ≥ 155mg/dl) and Group 2 (subjects with IGT: subjects with 2 hour glucose ≥140mg/dl regardless of 1 hour glucose). All participants were completely evaluated at enrollment.

All subjects were questioned regarding their background (age, gender, residence, occupation, level of exercise, smoker status, lifestyle), reasons for referral to physician, family history (especially a history of cardiovascular diseases and diabetes), physiologic and pathologic personal history (focusing on cardiovascular and metabolic diseases, polycystic ovarian syndrome and other conditions associated with insulin resistance etc.).

The clinical exam included evaluation of: weight, height, waist circumference (WC), hip circumference, blood pressure.

In terms of laboratory investigations, we used the following devices: Pentra ES60 for the complete blood count and Siemens Advia 2400 for the biochemical determination. We calculated LDL- cholesterol using the Friedewald formula [7]. Fasting insulin was determined by chemiluminiscence, using Imulite 1000- Siemens. All parameters were determined from venous blood drawn in a fasting state.

The 75 g glucose OGTT was performed taking into consideration all the necessary precautions: it was performed in the morning, after at least 8 hours of fasting (overnight fast); all subjects had a free diet, with a minimum content of 150 g carbohydrates/ day for 3 days before the test and an usual level of physical activity for 24 hours prior to the test. Any medication, the presence of fever or other conditions that could influence the OGTT were recorded; the participants were not allowed to smoke and were kept at rest during the test [8].

After all the necessary data were obtained, we evaluated some of the most relevant parameters correlated to insulin resistance and we calculated the cardiovascular risk of the studied subjects.

Insulin resistance was evaluated using clinical markers: body mass index (BMI ≥ 30 kg/m²), WC (WC≥ 80 cm in women and WC ≥ 94 cm in men), waist-to-hip ratio (≥ 0.85 in women and ≥ 0.90 in men), waist-to-height ratio (≥ 0.5) and biological markers: triglycerides to HDL- cholesterol ratio (TG/HDL- chol ≥ 3); Homeostatic Model Assessment [HOMA- IR= (Fasting Insulin (mU/l) × Fasting Glucose (mmol/l) / 22,5 ≥ 2,5]; The Quantitative Insulin Sensitivity Check Index [QUICKI= 1/(log Fasting Insulin + log Fasting Glucose) < 0,357]; fasting insulin (>16.3 mU/l); fasting glucose–to-fasting insulin ratio (< 4.5). We evaluated and compared the glycemic control of the subjects in the 3 groups using glycated hemoglobin (HbA1c).

The cardiovascular risk of each patient included in the study was estimated using the SCORE model for European countries with increased risk, using the following data: age, sex, smoking / non-smoking status, total cholesterol, systolic blood pressure [9]. It assesses the risk of fatal cardiovascular disease of the subjects over the next 10 years.

Statistical analysis: Data processing have used Microsoft Excel software (Microsoft Corp, Redmond, WA, USA) together with XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France), IBM SPSS Statistics 20.0 software (IBM Corporation, Armonk, NY, United States). The obtained information were stored in Microsoft Excel files and then statistically processed in order to analyze the relationship between clinical and laboratory data.

We used Excel (Pivot Tables, Functions-Statistical, Chart and Data Analysis module) for the secondary processing of data (descriptive analysis of the group based on various parameters). In order to achieve complex statistical tests (Chi square test / Fisher exact test, Student test) we used the XLSTAT module or SPSS. In order to characterize the numerical data from the analysis, we used fundamental statistical indicators: arithmetic mean and standard deviation.

In our study, we used Chi square test in order to see if there are overall significant differences between the 3 groups and and we used the following interpretation of the results:

- $p < 0.05$: statistically significant result
- $p < 0.001$: statistically highly significant result

Because the three groups were rather small, we used Fisher exact test as an alternative to Chi

square test, for a better precision of the statistical results. Fisher exact test is used to verify if there are nonrandom associations between two categorical variables.

Results

Regarding the clinical markers of insulin resistance, although many studies had analyzed and communicated statistically significant associations between the parameters describing obesity and in particular abdominal obesity and insulin resistance in subjects with elevated 1 hour glucose, we couldn't find any statistically significant correlations in this study.

We used Chi square test for an overall comparison of the three groups and Fisher exact test to compare Group 1B and Group 2.

Neither the BMI (p chi square=0.361, p Fisher exact= 0.778) nor the WC (p chi square=0.521, p Fisher exact= 0.463), the waist-to-hip ratio (p chi square=0.319, p Fisher exact= 0.289) or the waist-to-height ratio (p chi square=0.376, p Fisher exact= 0.349) differed significantly in the group of patients with elevated 1 hour glucose compared to patients in the other two groups. This might be due to the small number of patients in each group and a rather large variability of these parameters in all three studied groups.

Regarding the biological markers of insulin resistance, the situation was different. In this study, both fasting insulin and glucose to insulin ratio differed significantly from patients in the group with 1 hour glucose ≥ 155 mg /dl compared to patients with normal glucose tolerance and 1 hour glucose < 155 mg /dl. However, there were no statistically significant differences in terms of these indicators between the group of patients with high 1 hour blood glucose and the group of patients with IGT (Figures 1 and 2).

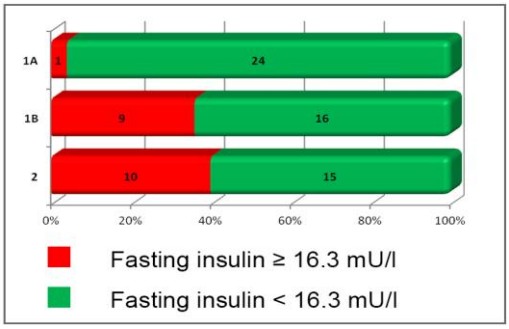

Figure 1. *Fasting insulin levels in the three groups.*
p Chi square= 0.006893 (there are significant differences between the three groups);
p Fisher exact= 1 (there are no significant difference between group 1B and group 2).

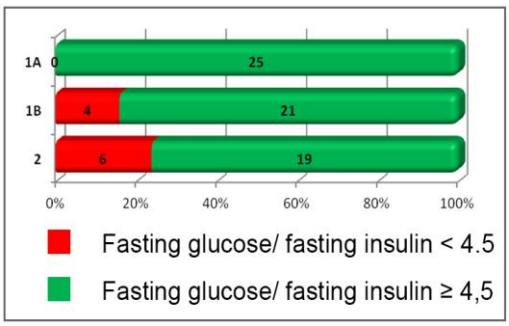

Figure 2. *Fasting glucose-to-Fasting insulin ratio in the three groups.*
p Chi square=0.040 (there are significant differences between the three groups)
p Fisher exact= 0.7252024 (there are no significant differences between group 1B and group 2).

Regarding the HOMA IR and QIUCKI indexes there were also no statistically significant differences between the group of patients with elevated 1 hour glucose and the group of patients with IGT, but significant differences between these 2 groups and the control group (with one hour glucose < 155 mg /dl) (Figures 3 and 4).

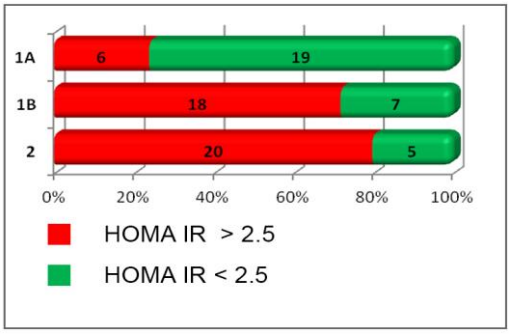

Figure 3. *HOMA IR values in the three groups.*
p Chi square= 0.000078 (there are significant differences between the three groups)
p Fisher exact= 0.742 (there are no significant differences between group 1B and group 2)

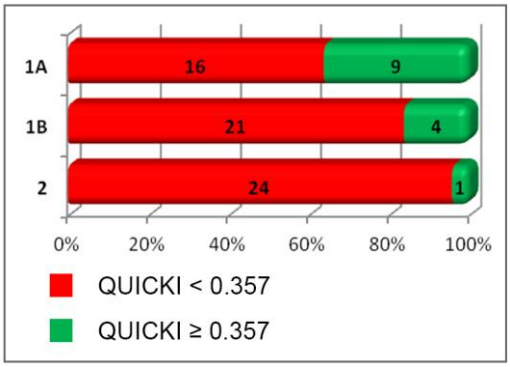

Figure 4. *QUICKI Index values in the three groups.*
p Chi square= 0.014 (there are significant differences between the three groups)
p Fisher exact=0.349 (there are no significant differences between group 1B and group 2)

In terms of the HbA1c, we analyzed the mean values of this parameter in the three groups using the ANOVA test and we obtained a p value of 7.26×10^{-8} (statistically highly significant) indicating that there is a statistically highly significant overall difference between the three groups. We used the test Fisher's LSD (Fisher's Least Significant Difference) in order to identify the pairs that differed and observed that Group 1A had a significant lower HbA1c than Group 1B (p=0.024) and Group 1B had a significant lower HbA1c than Group 2 (p=0.032). The fact that the subjects in group 2 (subjects that had been diagnosed with IGT during the OGTT) had higher HbA1c than those in groups 1A and 1B is not surprising. What it is notable, however, is the statistically significant difference between patients in group 1B and the control group (Figure 5).

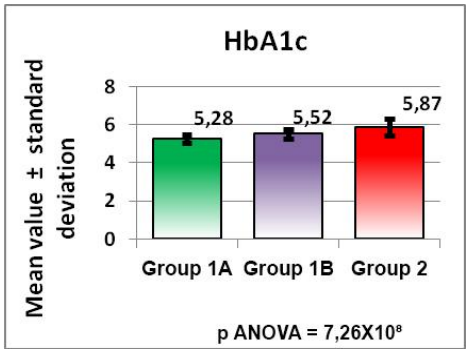

Figure 5. *HbA1c: mean values in the three groups*

When comparing the average value of cardiovascular risk (evaluated using the SCORE

charts for European countries) between the three groups we identified a significant overall difference, the ANOVA test result being p = 0.034. When continuing the analysis using the post-hoc Fisher's LSD test, in order to find the matching pairs that differed from each other, we found that the average value for subjects in group 1A differed significantly from that of the subjects in group 1B (p= 0.032) and group 2 (p= 0,044). Surprisingly, we found that the cardiovascular risk of the subjects in group 1B (with elevated 1 hour glucose) was higher than the cardiovascular risk of the subjects in group 2 (subjects with IGT) (p=0.043) (Figure 6).

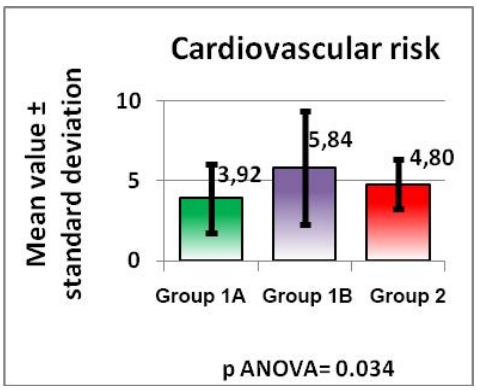

Figure 6. *Cardiovascular risk: mean values in the three groups*

Discussions

This study has argued in favor of the association between some specific markers of insulin resistance and a form of altered carbohydrate metabolism that is still unrecognized and still framed as normal glucose tolerance.

Our findings support the results of many other studies published in recent years that have highlighted the increased value of 1 hour glucose during OGTT in assessing alterations in the glucose metabolism. In several studies 1 hour glucose is considered to be even more important than 2 hours glucose in the early detection of impaired glucose tolerance and, as a consequence, in the early prevention of diabetes.

Two large-scale longitudinal studies, San Antonio Heart Study [6] and Botnia Study [4], conducted on large numbers of patients, emphasized the theory that 1 hour glucose is better correlated to insulin resistance and insulin secretion than 2 hours glucose or fasting glucose. In addition, they demonstrated that 1 hour glucose above the threshold of 155 mg /dl is associated more strongly with the risk of diabetes.

Even if in many studies the clinical markers of insulin resistance were significantly correlated to elevated 1 hour glucose, in our study we couldn't find this association. Still, the biological markers of insulin resistance (fasting insulin, fasting glucose to insulin ratio, HOMA IR, QUIKI index) significantly correlated to 1 hour glucose ≥ 155mg/dl when compared to subjects with normal glucose tolerance and 1 hour glucose below this threshold. Moreover, we couldn't find any significant differences when we evaluated insulin resistance by these parameters between subjects with elevated 1 hour glucose and subjects with IGT. Considering the fact that insulin resistance is an important factor in the development of diabetes and also knowing the importance of the early prevention, these data should stop us from overlooking a form of glucose intolerance that is yet not recognized and to whom the prevention measures do not apply.

Our findings are in accordance with three other important studies that investigated this theory: the studies conducted by De Pergola et al. [10], Joshipua et al. [11] and the RISC study [12]. In all these studies elevated 1 hour glucose strongly correlated to insulin resistance evaluated by high fasting insulin and increased HOMA IR index. In addition, De Pergola found a significant association between elevated 1 hour glucose and waist circumference and fasting glucose levels. In the RISC Study subjects with

1 hour glucose ≥155mg/dl had higher BMI, larger WC, higher insulin secretion and lower insulin sensitivity than subjects with 1 hour glucose < 155mg/dl.

Another reference study that evaluated the metabolic profile and cardiovascular risk in patients with 1 hour glucose ≥ 155 mg /dl is the GENFIEV study [13]. Its results clearly demonstrated the following: subjects with 1 hour glucose ≥ 155 mg /dl were more insulin resistant and had an increased cardiovascular risk objectified by: higher HOMA IR index, higher BMI, larger WC and higher values of HbA1c, higher systolic blood pressure, an abnormal lipid profile and higher carotid intimate- media thickness when compared to subjects with 1-hour glucose < 155 mg /dl and subjects with IGT. Our study's findings are consistent with these results.

Given the undeniable value of these indicators in the assessment of insulin resistance [14-18] we have arguments to support the idea of categorizing these subjects with elevated 1 hour glucose during OGTT in a special category of patients with a particular metabolic profile. Thus, 1 hour glucose could become at least as important as 2 hours glucose.

Regarding the cardiovascular risk assessed by the SCORE charts applicable to high risk European countries (including Romania), we observed a statistically significant difference between subjects from the groups with elevated 1 hour and 2 hours glucose compared to subjects in the control group. Moreover, the cardiovascular risk of the subjects with high 1 hour glucose, subjects that according to the current definitions are considered to have normal glucose tolerance, was higher than that of subjects with IGT.

A recent study led by Lind M et al [19] investigated the occurrence of acute cardiovascular events in a group of 504 individuals who were enrolled in Finnish Diabetes Prevention Study, determining their relationship with HbA1c, fasting blood glucose, 1 hour and 2 hours glucose during OGTT. The follow-up period was 13 years and the results have shown that HbA1c and both 1 hour and 2 hours glucose, but not fasting glucose correlated with cardiovascular risk.

In the recent years, the importance of elevated 1hour glucose and its consequences has been of an increasing interest. Thus, Bergman et al. published this year the results of a study on 2138 adults without diabetes at baseline from the Israel Study of Glucose Intolerance, Obesity and Hypertension [20] that completed a 2-hour, 100g OGTT between 1979 and 1984 and were followed for all cause mortality for 33 years. Although Bergman and al. used a 100g OGTT instead of the usual 75 g OGTT, they established the same cutoff value for 1 hour glucose, 155 mg/dl. The results of this study showed that elevated1 hour glucose (≥ 155mg/dl) was a reliable predictor of pre-diabetes risk and it was accompanied by a 28% increase in mortality risk. In addition, an increase in 1 hour glucose above 200 mg /dl was associated with increased mortality in a follow up study of the Erfurt Male Cohort Study [21]. It showed that 1 hour glucose during OGTT ≥ 200mg/dl was associated with a mortality risk 1.5 times higher than that of individuals with 1 hour glucose below this threshold.

Conclusions

This study showed that 1 h OGTT glucose ≥ 155 mg/dl identifies a category of subjects currently enrolled as glucose tolerant but with a special metabolic profile and an increased cardiovascular risk. They could be identified through OGTT and could benefit from various methods of lifestyle optimization which proved effective in reducing the cardiovascular risk and the progression to diabetes in prediabetic patients.

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