THE COMPARISON OF GLYCATED HEMOGLOBIN AND HOMEOSTASIS MODEL ASSESSMENT VALUES TO 30, 60 AND 90-MIN GLUCOSE LEVELS DURING OGTT IN SUBJECTS WITH NORMAL GLUCOSE TOLERANCE

POREDENJE VREDNOSTI GLIKOLIZIRANOG HEMOGLOBINA I MODELDA HOMEOSTAZE SA NIVOIMA GLUKOZE POSLE 30, 60 I 90 MINUTA TOKOM OGTT KOD SUBJEKATA SA NORMALNOM TOLERANCIJOM GLUKOZE

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Summary

Background: The subjects with impaired glucose tolerance have an increased risk for future type 2 diabetes (T2DM); however, a significant number of individuals who develop T2DM have normal glucose tolerance (NGT) at baseline. The study aims to compare glycated hemoglobin (HbA1C) and homeostasis model assessment (HOMA-IR) levels to 30, 60 and 90-min glucose levels in subjects with NGT.

Methods: A 75-g oral glucose tolerance test (OGTT) at 0, 30, 60, 90 and 120-min was performed in 1118 subjects without known T2DM. Blood samples were also drawn for fasting insulin and HbA1C levels.

Results: Forty percent of the subjects with NGT had increased post-challenge values above the determined optimal glucose levels (10.2, 10.3 and 8.9 mmol/L at 30, 60 and 90-min, respectively). Compared to the subjects with NGT whose glucose levels were below the determined optimal values at 30, 60 and 90-min, we found significantly elevated HbA1C and HOMA-IR levels in the subjects with NGT whose glucose levels were above the determined optimal values (p<0.001).

Conclusions: We conclude that the subjects with NGT have different HbA1C and HOMA-IR levels considering glucose levels measured earlier than at 2-h during OGTT. Further well-designed prospective studies are needed to define the significance of 30-min, 60-min and 90-min glucose levels in the prediction of disease in subjects with T2DM.

Keywords: diabetes mellitus, glycated hemoglobin, homeostasis model assessment, normal glucose tolerance, oral glucose tolerance test

Kratak sadržaj

Uvod: Osobe sa poremećajem tolerancije glukoze izložene su povećanom riziku za dobijanje dijabetesa tipa 2 (T2DM), međutim, značajan broj pojedinaca koji dobiju T2DM ima u početku normalnu toleranciju glukoze (NGT). Cilj ove studije bio je da se uporede nivoi glikoliziranog hemoglobina (HbA1C) i modela homeostaze (HOMA-IR) sa nivoima glukoze posle 30, 60 i 90 minuta kod osoba sa NGT.

Metode: Test oralne tolerancije glukoze (OGTT) sa 75 g glukoze urađen je u 0, 30, 60, 90 i 120. minuto kod 1118 subjekata bez T2DM. Uzorci krvi su takođe uzeti radi mjeranja nivoa insulinina i HbA1C.

Rezultati: Četrdeset odsto subjekata sa NGT imalo je povišene nivoj posle testa u odnosu na utvrđene optimalne nivoj glukoze (10,2, 10,3 i 8,9 mmol/L posle 30, 60 i 90 minuta). U poređenju sa subjektima sa NGT kod kojih su posle 30, 60 i 90 minuta nivoj glukoze bili ispod utvrđenih optimalnih vrednosti, otkrili smo značajno povišene nivo HbA1C i HOMA-IR kod subjekata sa NGT čiji su nivoj glukoze bili ispod utvrđenih optimalnih vrednosti (p<0,001).

Zaključak: Zaključujemo da subjekti sa NGT imaju različite nivo HbA1C i HOMA-IR s obzirom na nivo glukoze izmerene pre drugog sata tokom testa oralne tolerancije glukoze. Potrebne su nove, pažljivo osmišljenе prospektivne studije kako bi se definisao značaj nivoa glukoze posle 30, 60 i 90 minuta u predikciji bolesti kod osoba sa T2DM.

Ključne reči: dijabetes melitus, glikolizirani hemoglobin, model homeostaze, normalna tolerancija glukoze, test oralne tolerancije glukoze
Introduction

The prevalence of diabetes mellitus is increasing worldwide, and it is expected that the number of adults with diabetes will reach 552 million by 2030 (1). Diabetes is characterized by the development of microvascular complications in the retina, renal glomerulus and peripheral nerves. As a consequence of the microvascular pathology, diabetes is the leading cause of blindness, end stage renal disease and a variety of debilitating neuropathies (2).

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, estimated to account for 85–90% of diabetes (3). T2DM is often asymptomatic in its early stages and can remain undetected for several years. Increasing evidence shows that half of those with T2DM are not aware of their morbidity (4). Recent clinical trials have demonstrated that lifestyle intervention and pharmacological therapy in high-risk individuals reduce the incidence of T2DM. It is therefore important to identify the high-risk subjects for the purpose of early intensive lifestyle counseling or even pharmaceutical treatment (5–7).

There is no consensus on what the most accurate screening test for detection of diabetes is. The most widely used screening tests are the fasting plasma glucose (FPG) test and the oral glucose tolerance test (OGTT). According to the current diagnostic criteria for diabetes of the World Health Organization (WHO) (8) and American Diabetes Association (ADA) (9), fasting plasma glucose should be ≥7.0 mmol/L or 2-h plasma glucose ≥11.1 mmol/L. Moreover, impaired glucose tolerance (IGT), a risk factor of diabetes, is described by 2-h plasma glucose ≥7.8 mmol/L and <11.1 mmol/L.

The subjects with impaired glucose tolerance have high risk for progression to T2DM; however, approximately 40% of individuals who develop T2DM have NGT at baseline (10). The determination of IGT is based only on the 2-hour post-challenge glucose level of OGTT. The importance of 30-min, 60-min or 90-min glucose levels of OGTT has not been clearly defined. A few studies reported that the plasma glucose concentration at 1-h of OGTT is a strong predictor of future risk of T2DM (11, 12).

Hemoglobin A1c (HbA1C) is an indirect measure of the mean blood glucose level over the previous 2–3 months. The HbA1C assay provides a reliable measure of chronic glycemia (13). Randomized controlled trials and observational studies have shown that HbA1C is a good predictor of microvascular complications including retinopathy, micro- or macroalbuminuria and peripheral neuropathy (14–16). It is also suggested that the HbA1C assay helps to predict the likelihood of developing diabetes in the future (9, 17, 18).

Insulin resistance plays an important pathophysiological role in the development of diabetes. Homeostasis model assessment (HOMA), a model of interactions between glucose and insulin, has been used to assess insulin resistance and beta-cell function. Homeostasis model of insulin resistance (HOMA-IR) is defined by the product of the fasting glucose and fasting insulin divided by a constant (19). Numerous previous studies have shown that in several populations high HOMA-IR values were associated with an increased prevalence of both impaired glucose tolerance (IGT) and T2DM (20–22).

The present study primarily aimed to evaluate the serum glucose levels at 30-min, 60-min and 90-min during OGTT in subjects with NGT. Secondly, we intended to compare HbA1C and HOMA-IR levels to 30, 60 and 90-min glucose levels in the subjects with NGT.

Materials and Methods

A total of 1118 subjects without known T2DM were enrolled in the study. The exclusion criteria were designed to reject any possible cause that would affect the results of OGTT: history of chronic gastrointestinal diseases associated with malabsorption, liver or kidney failure, chronic pancreatitis, current infection, history of any malignant disease, history of alcohol abuse, active menstruation, and using drugs that could influence glucose metabolism such as steroids. Morbid obesity (body mass index ≥40 kg/m² or ≥35 kg/m² with hypertension) was also an exclusion criterion. In addition, pregnant women were excluded. This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

OGTT was performed in all subjects after 10–12 hours of overnight fasting. Each subject was informed to consume at least 250 g of carbohydrates in their meals for at least 3 days before the test. Blood samples were drawn into dry tubes at 0, 30, 60, 90 and 120 min during OGTT for measurement of glucose levels and fasting insulin levels. Samples were centrifuged at 1,000 g for 10 min to obtain serum. Serum samples were analyzed within an hour after blood sampling. For measurement of HbA1C, whole blood samples were collected into tubes containing K₂-EDTA at 0 min.

Serum glucose levels were analyzed via the enzymatic (glucose oxidase) colorimetric assay method on a Roche Hitachi Modular P analyzer. Serum insulin levels were measured using the Access Ultrasensitive Insulin chemiluminescent immunoassay from Beckman Coulter. HOMA-IR was computed by the product of the fasting glucose (mmol/L) and fasting insulin (mIU/mL) divided by 22.5. The denominator of 22.5 is a normalizing factor. The product of normal fasting plasma insulin of 5 mIU/mL and normal fasting plasma glucose of 4.5 mmol/L of a normal healthy individual is 22.5.
The HbA1c assay was carried out using high-performance liquid chromatography (HPLC) with boronate affinity technology on a Primus Ultra 2 analyzer. This system’s results are certified as traceable to the DCCT/NGSP and IFCC reference methods.

Glucose tolerance status was defined according to the OGTT criteria of ADA: 2-h post-challenge glucose $\geq 11.1$ mmol/L as T2DM; 2-h post-challenge glucose 7.8–1.0 mmol/L as IGT; 2-h post-challenge glucose $\leq 7.8$ mmol/L as normal glucose tolerance (NGT).

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS 15.0, SPSS Inc., Chicago, IL, USA) in computerized media. Variables are presented as means $\pm$ SD. In order to divide the subjects with NGT into subgroups, the sensitivity and specificity of 30-min, 60-min and 90-min glucose values to detect IGT were determined by receiver operating characteristic (ROC) curve analysis. The significance of the mean differences was tested by ANOVA. If the ANOVAs revealed significant differences, post hoc pair-wise comparisons with Tamhane adjustments were used to identify the differences. Non-parametrically distributed variables were compared using the Mann-Whitney test. P values less than 0.05 were considered to be statistically significant.

Results

The present study included 1118 subjects in whom 75-g OGTT was performed. The mean age of participants was 46.7±12.6 years, and 67.9% were women.

Using the OGTT diagnosis criteria for T2DM, out of 1118 participants, 754 had NGT, 284 had IGT, and 80 had DM.

The mean HbA1C levels were 5.45±0.41%, 5.68±0.41% and 5.98±0.45% for NGT, IGT, and T2DM respectively. As expected, HbA1C levels of DM group were significantly higher than those of IGT and NGT groups ($p<0.001$). It was also found that HbA1C levels were elevated in the subjects with IGT compared to the subjects with NGT ($p<0.001$) (Table I).

Similar to HbA1C, HOMA-IR values were found to be significantly higher in T2DM group than NGT group (mean HOMA-IR: 3.5±1.8 and 2.6±1.9 respectively, $p=0.001$). It was also found that the subjects with IGT had higher HOMA-IR values than the subjects with NGT (mean HOMA-IR: 3.4±2.3 vs. 2.6±1.9, $p<0.001$) (Table I).

In order to divide the subjects with NGT into subgroups, the sensitivity and specificity of 30-min, 60-min and 90-min glucose values to detect IGT were determined by receiver operating characteristic (ROC) curve analysis. ADA criterion for detecting IGT was used as the »gold standard«. The areas under curves for IGT were 0.715 (95% CI: 0.682–0.747), 0.823 (95% CI: 0.797–0.850) and 0.909 (95% CI: 0.890–0.928) for 30-min, 60-min and 90-min glucose values, respectively (Table II) (Figure 1).

Table I Laboratory characteristics and gender distribution of the subjects classified by ADA criteria (*=$p<0.001$ vs. both NGT and IGT, **=$p<0.001$ vs. NGT, ***=$p=0.001$ vs. NGT, ¶=$p<0.001$ vs. NGT).

|                          | Normal Glucose Tolerance | Impaired Glucose Tolerance | Type 2 Diabetes Mellitus |
|--------------------------|--------------------------|----------------------------|--------------------------|
| Sex (male/female)        | 754                      | 284                        | 80                       |
| Fasting Glucose (mmol/L) | 246/508                  | 83/201                     | 29/51                    |
| 2-h glucose levels (mmol/L) | 5.61±0.49               | 5.99±0.49                  | 6.27±0.38                |
| Insulin (pmol/L)         | 72.2±45.1                | 87.5±56.2                  | 86.8±42.3                |
| HbA1C (%)                | 5.45±0.41                | 5.68±0.41**                | 5.98±0.45*               |
| HOMA-IR                  | 2.6±1.9                  | 3.4±2.3¶                   | 3.5±1.8***               |

Table II Area Under the Curve characteristics of 30-min, 60-min and 90-min glucose levels for IGT.

| Test Result Variables | Area | Std. Error | Significance | 95% Confidence Interval |
|----------------------|------|------------|--------------|-------------------------|
|                      |      |            |              | Lower Bound | Upper Bound |
| Glucose level at 30-min | 0.715 | 0.017      | <0.001       | 0.682       | 0.747       |
| Glucose level at 60-min | 0.823 | 0.014      | <0.001       | 0.797       | 0.850       |
| Glucose level at 90-min | 0.909 | 0.010      | <0.001       | 0.890       | 0.928       |
The optimal glucose value with the maximal sum of sensitivity and specificity for 30-min was 10.2 mmol/L. For 60-min and 90-min, the optimal glucose values were 10.3 mmol/L and 8.9 mmol/L, respectively (Table III).

Out of 754 subjects with NGT, 452 had glucose levels below the determined optimal glucose values for 30, 60 and 90-min. The glucose levels of the remaining subjects were above the optimal glucose value or values (only 30-min or both 30-min and 60-min etc.) (Table IV). The subjects with NGT were separated into subgroups according to their glucose levels, as follows:

Group 1: Glucose levels ≤10.2 mmol/L at 30-min, ≤10.3 mmol/L at 60-min and ≤8.9 mmol/L at 90-min.

Table III: The maximal sum of sensitivity and specificity values in the determined 30-min, 60-min and 90-min glucose levels during 2-h OGTT for IGT.

| Test Result Variables | Sensitivity (%) | Specificity (%) |
|-----------------------|----------------|-----------------|
| 10.2 mmol/L in 30-min | 62             | 70              |
| 10.3 mmol/L in 60-min | 75             | 76              |
| 8.9 mmol/L in 90-min  | 83             | 83              |

Table IV: The means of HbA1C and HOMA-IR in the subjects with NGT classified according to glucose levels at 30, 60 and 90-min during OGTT.

| Glucose levels at time points earlier than 2-h | n   | HbA1C (%) | HOMA-IR |
|----------------------------------------------|-----|-----------|---------|
| ≤10.2 mmol/L in 30-min, ≤10.3 mmol/L in 60-min and ≤8.9 mmol/L in 90-min | 452 | 5.35±0.37 | 2.3±1.5 |
| ≥10.2 mmol/L in 30-min                        | 232 | 5.63±0.42 | 3.1±1.9 |
| ≥10.3 mmol/L in 60-min                        | 192 | 5.65±0.42 | 3.1±1.6 |
| ≥8.9 mmol/L in 90-min                         | 136 | 5.68±0.40 | 3.0±1.4 |
| ≥10.2 mmol/L in 30-min and ≥10.3 mmol/L in 60-min | 137 | 5.70±0.43 | 3.2±1.8 |
| ≥10.2 mmol/L in 30-min and ≥8.9 mmol/L in 90-min | 89  | 5.74±0.42 | 3.1±1.4 |
| ≥10.3 mmol/L in 60-min and ≥8.9 mmol/L in 90-min | 113 | 5.71±0.40 | 3.1±1.4 |
| ≥10.2 mmol/L in 30-min, ≥10.3 mmol/L in 60-min and ≥8.9 mmol/L in 90-min | 81  | 5.74±0.43 | 3.1±1.4 |
**Figure 2** Comparison of HbA1C values to 30, 60 and 90-min glucose levels in subjects with NGT (*=p<0.001 vs. group 1).

**Figure 3** Comparison of HOMA-IR values to 30, 60 and 90-min glucose levels in subjects with NGT (*=p<0.001 vs. group 1).
Group 2: Glucose levels ≥10.2 mmol/L at 30-min.
Group 3: Glucose levels ≥10.3 mmol/L at 60-min.
Group 4: Glucose levels ≥8.9 mmol/L at 90-min.
Group 5: Both glucose levels ≥10.2 mmol/L at 30-min and ≥10.3 mmol/L at 60-min.
Group 6: Both glucose levels ≥10.2 mmol/L at 30-min and ≥8.9 mmol/L at 90-min.
Group 7: Both glucose levels ≥10.3 mmol/L at 60-min and ≥8.9 mmol/L at 90-min.
Group 8: Glucose levels ≥10.2 mmol/L at 30-min, ≥10.3 mmol/L at 60-min and ≥8.9 mmol/L at 90-min.

Table IV shows HbA1C levels and HOMA-IR values for each group. As shown in Figure 2, HbA1C levels were found significantly elevated in the subjects with NGT whose glucose levels were above the determined optimal values (Group 2–8) compared to those of the subjects with NGT whose glucose levels were below the determined optimal values at 30, 60 and 90-min (Group 1) (p<0.001). Similarly, compared to those of Group 1, we found significantly elevated HOMA-IR levels in Group 2–8 (Figure 3) (p<0.001).

Discussion

WHO and ADA have published several guidelines for the diagnosis of diabetes since the definition of the diagnostic criteria for diabetes by the National Diabetes Data Group, towards the end of the 1970s. Over this period, there have been significant changes in the diagnostic criteria and classification of diabetes and intermediate hyperglycemia. However, these changes have been limited to fasting blood glucose measurement. The criteria for OGTT have been unchanged and remained restricted to 2h-plasma level. Although the subjects with IGT are generally at an increased risk for future T2DM, ~40% of individuals who develop T2DM have NGT at baseline (10). This may be a result of the fact that the glucose tolerance status is defined mainly by post-challenge 2-h glucose levels. The importance of post-challenge glucose levels other than those at 2-hours, such as 30, 60 or 90-min, has not been clearly defined. A few studies have pointed out the significant role of 1h post-load glucose levels in the prediction of T2DM in the NGT subjects.

A recent study by Abdul-Ghani et al. (11) suggested that the plasma glucose concentration at 1-h during the OGTT is a strong predictor of future risk for T2DM. They determined a cut-off point of 155 mg/dL (8.5 mmol/L) for the 1-h plasma glucose concentration to stratify the subjects into low, intermediate, and high-risk groups for future T2DM. It was also reported that 16.7% of the NGT subjects with a 1-h plasma glucose concentration >8.6 mmol/L developed T2DM within a 7- to 8-year period. Correspondingly, Succurro et al. (12) reported that the NGT subjects with a 1-h post-load glucose value of ≥8.6 mmol/L have an atherogenic profile including intima-media thickness similar to the IGT subjects, suggesting an association of high post-challenge glucose levels other than the 2-h glucose level with the development of atherosclerosis and diabetes mellitus.

In this context, primarily, we investigated the composition of 30, 60 and 90-min glucose levels in the subjects with NGT. It was found that a considerable number of the subjects with NGT had elevated glucose levels prior to 2-h during OGTT. Secondly, we compared HbA1C levels and HOMA-IR values of 8 groups constituted according to their OGTT 30, 60 and 90-min glucose levels.

It is widely accepted that excessive glycation of a variety of proteins, especially advanced glycosylation end products, causes the microvascular complications of diabetes. Glycated hemoglobin is a glycated protein readily available for clinical testing (23). Hence, we analyzed HbA1C levels in order to determine whether the groups differ from each other. Randomized controlled trials and observational studies have shown that HbA1C is a good predictor of microvascular complications (14–16). It is also suggested that HbA1C helps to predict the likelihood of developing diabetes in the future. A report published in 2009 by an International Expert Committee on the role of HbA1C in the diagnosis of diabetes stated that HbA1C can be used to diagnose diabetes (24). The precise lower cut-off point for intermediate hyperglycemia has yet to be defined, although ADA has suggested 5.7–6.4% as the high-risk range (9). Similar cut-off values for intermediate hyperglycemia have been announced by Abdul-Ghani et al. (17). They have shown that HbA1C has a predictive power similar to that of the FPG value and the optimal HbA1C cut-off point to predict future T2DM was 5.6%. In another study, Edelman et al. (18) showed that patients with normal HbA1C have a low incidence of diabetes and may not require re-screening within 3 years, while patients with high-normal HbA1C (5.6%–6.0%) may require follow-up testing sooner than after 3 years.

Compared to the subjects with NGT whose glucose levels were below the determined optimal values at 30, 60 and 90-min, the subjects with NGT whose glucose levels were above the determined optimal values at 30-min, or 60-min, or 90-min, or both 30-min and 60-min, or both 30-min and 90-min, or both 60-min and 90-min, or all at 30, 60, 90-min had significantly elevated HbA1C levels.
betes. HOMA-IR has been suggested as a method to assess insulin resistance (13, 19). Several prospective studies have shown the role of HOMA-IR in predicting future risk of both T2DM and/or IGT in various populations (20–22).

Similar to HbA1C, the subjects with NGT whose glucose levels were above the determined optimal values prior to 2-h had higher HOMA-IR levels than the subjects with NGT whose glucose levels were below the determined optimal values.

This study was a cross-sectional study and we are thus unable to directly determine the relationship of 30-min, 60-min and 90-min post-load glucose levels to the risk for future IGT or T2DM in subjects with NGT. The optimal glucose levels were determined in order to only divide the subjects with NGT into subgroups. These values should be not evaluated as cut-off values. In this context, further well-designed prospective studies are needed to define the significant role of 30-min, 60-min and 90-min post-load glucose levels in the prediction of IGT or T2DM in the subjects with NGT. Thus, a clinician should consider whether there is a group of subjects with NGT who are at an increased risk for future T2DM. Otherwise, a large number of high-risk individuals who would benefit from preventive interventions could be missed (25).

In conclusion, our results show that the subjects with NGT have different HbA1C and HOMA-IR levels according to their glucose values prior to the 2-h glucose level during OGTT.

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