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Original Article

Isolated first hour hyperglycemia in oral glucose tolerance test is associated with insulin resistance

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ABSTRACT

Aims: To investigate metabolic and hemogram derived inflammatory markers in patients with isolated hyperglycemia on 1st hour of oral glucose tolerance test.

Methods: The subjects undergone 75 g OGTT for any reason were enrolled to the present retrospective cross sectional study. Plasma glucose, insulin and hemogram derived inflammatory markers, including mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) of the subjects in isolated hyperglycemia group compared to those in healthy controls.

Results: Mean PLR of the isolated hyperglycemia and control groups were 106.4±28.8% and 121.4±38%, respectively (p=0.043). Mean HOMA–IR values of patients and controls were 4.09±2.84 and 3.02±2.2, respectively (p=0.027). Plasma glucose at 1st hour was significantly correlated with fasting insulin (r=0.286; p=0.018) and HOMA-IR (r=0.32; p=0.007).

Conclusion: We think that isolated 1st hour hyperglycemia in OGTT should not be classified as normal since it is associated with increased fasting insulin and HOMA-IR levels. However, studies with larger cohort are needed to confirm our results.

Keywords: Isolated hyperglycemia, oral glucose tolerance test, insulin, HOMA-IR, platelet to lymphocyte ratio

INTRODUCTION

Subjects were considered to have prediabetes when their glucose levels on fasting and at 2nd hour in oral glucose test do not meet the criteria to establish diabetes mellitus diagnosis but yet, too high to consider as normal. There is no international consensus on the definition of prediabetes. Impaired fasting glucose (IFG) is defined as fasting plasma glucose levels between 100-125 mg/dl, and 2-hour plasma glucose levels <140 mg/dl, while impaired glucose tolerance (IGT) is defined as fasting plasma glucose levels <100 mg/dl, and 2-hour plasma glucose levels between 140-199 mg/dL.[1]

Although international guidelines have changed over the years to reduce the threshold for the diagnosis of diabetes and prediabetes, according to the current definitions of prediabetes, the beta-cell function is greatly impaired at the time of diagnosis, thus it is recommended that attention should be focused on early identification of individuals with prediabetes. Since it is found that beta-cell function progressively decreases even at glucose levels below the threshold values for IFG or IGT, more sensitive diagnostic methods are needed to identify individuals at risk for Type 2 diabetes mellitus (DM). [2,3]

The relationships between prediabetes and increased risk of early forms of diabetic kidney disease, diabetic neuropathy, macrovascular disease, and diabetic retinopathy have been well established in data in literature.[4] Therefore, early diagnosis of prediabetes and prevention of its possible complications are essential.

No current international guidelines for prediabetes diagnostic criteria include plasma glucose one hour after oral glucose tolerance test (OGTT). However, recent studies have shown that individuals with elevated plasma glucose levels after standard OGTT are at high risk for diabetes development, micro-macrovascular complications, and mortality.[5,6]

High serum glucose levels at first hour in OGTT were also reported to be associated with obesity, hypertension, hypercholesterolemia, metabolic syndrome, diabetic retinopathy, left ventricular diastolic dysfunction, and an

increase in carotid artery intima thickness and, therefore, atherosclerosis.[7-9]

Platelets have many bodily functions and they have essential role in thrombosis, progression of atherosclerotic lesions and plaque destabilization. They contain many mediators of coagulation, inflammation, and atherosclerosis and they release these substances when necessary.[10] A hemogram marker, mean platelet volume (MPV) is considered as a marker of platelet activation and refers the size of circulating platelets.[11] Platelet volume is introduced as a marker of platelet function as well activation and may have other functions in inflammatory conditions.[12] MPV has been shown to be higher in prediabetic patients than in normoglycemic subjects. It has also been observed that among the patients with normal fasting glucose, those with more elevated glucose have higher MPV compared to those with lower glucose.[13,14]

Infections and inflammatory stimuli cause an increase in neutrophil count and a reduction in lymphocyte count, which constitutes neutrophil/lymphocyte ratio as a superior marker than its components in diagnosis of inflammatory conditions.[15] NLR is higher in patients with a previous diagnosis of uncomplicated diabetes and newly diagnosed with OGTT compared to subjects with impaired glucose tolerance. It is also higher in people with impaired glucose tolerance than those with normal glucose tolerance.[16]

PLR was found to be the lowest in the newly diagnosed diabetic group and lower in the impaired glucose tolerance group than in the normal glucose tolerance group; however, PLR was higher in the previously diagnosed diabetic group compared to the other groups.[16]

These markers have not been studied in Isolated hyperglycemia at 1-hour on OGTT. In this study, we compared MPV, NLR, and PLR values of patients with isolated 1-hour glucose elevation during OGTT with those with normal glucose tolerance. We also investigated whether early diagnosis of prediabetes and diabetes is possible by assessing this tool.

METHODS

Ethics

The approval of Ethics Committee of Kırıkkale University, dated 02.10.2018 and numbered 02.10.2018 was obtained before the study, and it was conducted in accordance with the Declaration of Helsinki.

Study Cohort

From January 1, 2016 to December 31, 2017, patients who underwent a 75-gram standard oral glucose tolerance test (OGTT) in the Internal Medicine/Endocrinology Clinic at the Kırıkkale University Faculty of Medicine Hospital were selected to participate in the study if they had an isolated 1-hour glucose elevation (≥155 mg/dl). Patients who met the exclusion criteria or whose visceral fat index (VFI) data were not available were excluded, leaving 50 patients included in the study. A control group of 48 healthy individuals with normal glucose tolerance (NGT) and matching demographic characteristics was selected based on the OGTT.

The inclusion criteria for the study were adult male or female patients over the age of 18, who had undergone a 75-gram standard OGTT and had normal fasting plasma glucose levels and 2-hour plasma glucose levels.

The exclusion criteria for the study were patients under the age of 18, with a diagnosis of diabetes, thyroid dysfunction, kidney failure, liver failure, use of antidepressants, cerebrovascular disease, cardiovascular disease, use of any medication, previously diagnosed glucose intolerance (diabetes/pre-diabetes), use of oral antidiabetic or diabetogenic medications, diagnosis of hypertension or use of hypertension medications, cancer or hematologic disease, smoking or alcohol consumption, and pregnant patients.

The following were measured using retrospective data from the biochemistry laboratory of our hospital: fasting plasma glucose (using GLUC Hk Gen.3,800 tests by Cobas C kit, UV test hexokinase method), total cholesterol (by Cobas Integra CHOL 2 Hico 400 tests kit), triglyceride (TG Gen.3 200 tests, Cocas C, enzymatic colorimetric method with Integra kit), high-density lipoprotein (HDL-C Gen.3, 200 tests, Cobas C, homogeneous enzymatic colorimetric method with integrated kit), LDL cholesterol level (using Friedewald's formula [LDL=Total cholesterol- (VLDL + HDL); VLDL=TG/5] when triglyceride level was under 400 mg/dl).

In our study, there was no patient and control group with triglyceride levels above 400 mg/dl. C-reactive protein (Cobas C 501 particle surface expanded immunoturbidimetric assay) and insulin (Insulin Elecsys 100 T. kit) were tested with electrochemiluminescence method using cobas®e601 brand device and original Roche diagnostic kits (Roche Diagnostic GmbH, Sandhofer Strasse 116, D-68305 Mannheim).

Hemogram parameters (hemoglobin, white blood cell, platelet, neutrophil, lymphocyte, MPV, PDW) were measured by flow cytometric impedance method on an automatic whole blood count device (Mindray BC 6800, Shenzhen, China). Simply division of neutrophils by lymphocytes and platelets by lymphocytes was used in calculation of NLR and PLR, respectively.

HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) score was calculated using [plasma fasting glucose x plasma fasting insulin level] / 405 formula.

Values above HOMA-IR ≥2.7 were considered insulin resistance.

Statistical Analysis

Data were analyzed using IBM Statistical Package for Social Sciences 21.0 (Chicago, IL, USA). Descriptive statistics are given as a number, percentage, mean, and standard deviation. The chi-square test was used to compare categorical variables between groups. Kolmogorov-Smirnov test, Shapiro-Wilks test, and histograms were used in normality analysis of study variables.

The t-test was used in independent groups to compare the numerical variables that fit the normal distribution among the independent groups. The Mann-Whitney U test was used to compare the numerical variables that did not fit the normal distribution among the independent groups. Pearson correlation analysis was performed for variables that conform to the normal distribution, and Spearman correlation analysis was used for variables that do not, in correlation analysis. For the analysis of the relationship between two variables, For statistical significance, $p < 0.05$ was taken as the limit value.

RESULTS

Fifty patients and forty-eight healthy people were included in the study. Of the 50 patients, 66.0% (n=33) of subjects were female, and 34.0% (n=15) of those were male. Among the 48 healthy people, 68.8% (n=33) of individuals were female, and 31.2% (n=15) of those were male. There was no statistically significant difference between the two groups in terms of gender (p=0.772). The mean age was 45.2±13.3 years in the patient group and 44.4±13.3 years in the control group. There was no statistically significant difference between the groups regarding age (p= 0.775)

The weight, height, and BMI did not statistically differ between the two groups (p=0.685, 0.787, and 0.647, respectively) (**Table 1**). The patients' mean plasma glucose levels after OGTT for the 0-hour, 1-hour, and 2-hour were 92.2±5.8 mg/dl, 178.4±18.9 mg/dl, 115.2±16.0 mg/dl, respectively. The control group's mean plasma glucose levels after OGTT were 92.0±8.2 mg/dl at the 0-hour, 116.5±20.7 mg/dl at the 1-hour, and 97.9±16.9 mg/dl at the 2-hour. In the patient group, plasma glucose values at the first hour (p <0.001) and at the second hour (p <0.001) were significantly higher than the control group. Fasting plasma glucose was not significantly different among study groups (p=0.210) (**Table 2**).

Table 1. Results of anthropometric measurements

Variable name	Patient group (n=50) *	Control group (n=48) *	p value **
Age (years)	45.2±13.3	44.4±13.3	0.775
BMI (kg/m²)	32.4±8.0	31.7±7.3	0.647
Weight (kg)	88.7±21.2	86.0±16.9	0.685
Height (m)	1.657±0.083	1.652±0.087	0.787

* Mean±standard deviation is given.
** p <0.05 was taken as the limit value of significance.

Table 2. OGTT results

Variable name	Patient group (n=50) *	Control group (n=48) *	p value **
OGTT 0-hour (mg/dl)	92.2±5.8	92.0±8.2	0.210
OGTT 1-hour (mg/dl)	178.4±18.9	116.5 ±2 0.7	**<0.001**
OGTT 2-hour(mg/dl)	115.2±16.0	97.9±16.9	**<0.001**

* Mean±standard deviation is given.
** p <0.05 was taken as the limit value of significance.

There was no statistically considerable difference between the two groups in terms of HbA1c (p=0.44). The mean fasting insulin value was 17.7±12.0 µIU/ml in the patient group and 13.5±9.6 µIU/ml in the control group. Fasting insulin levels were significantly higher in the patient group (p=0.041). The mean HOMA–IR values of patients and controls were 4.09±2.84 and 3.02±2.2, respectively. The HOMA – IR values were found to be significantly higher in the patient group than in the control group (p=0.027). CRP was not statistically different between study and control groups (p=0.814). See in **Table 3**.

Table 3. HbA1c, fasting insulin, HOMA–IR and CRP results

Variable name	Patient group (n=50) *	Control group (n=48) *	p value **
HbA1c (%)	5.5±0.3	5.7±0.6	0.440
Fasting insulin (µIU/ml)	17.7±12.0	13.5±9.6	**0.041**
HOMA–IR	4.09±2.84	3.02±2.25	**0.027**
CRP (mg/L)	2.78±2.12	2.37±1.33	0.814

* Mean±standard deviation is given.
** p <0.05 was taken as the limit value of significance.

Hemoglobin of healthy subjects was 14±1.7 g/dl. Blood hemoglobin level in study group was not statistically different than the controls (p=0.112). Mean WBC was higher in OGTT group (8240±1607/mm³) compared to control subjects (7519±1861/mm³) (p=0.013). The numbers of neutrophils of study and control groups were 4908±1404/mm³, and 4497±1327/mm³, respectively (p=0.114). Lymphocyte count was 2626±718 / mm³ in OGTT group and 2255±597/mm³ in control group. There was a considerable statistical difference between each group (p=0.008). The two groups did not significantly differ regarding platelet count (p=0.518). There was no statistically significant difference between the two groups in terms of MPV (p=0.814). NLR was not significantly different between study and control groups (p=0.29). The platelet-lymphocyte ratio (PLR) was 106.4±28.8% in study group and 121.4±38% in control group (p=0.043). **Table 4** shows hemogram parameters study groups.

Table 4. Complete blood count values of the study population

Variable name	Patient group (n=50) *	Control group (n=48) *	p value **
Hemoglobin (g/dl)	14.6±1.8	14.0±1.7	0.112
White blood cell count (count/mm³)	8240±1607	7519±1861	**0.013**
Neutrophil count (count/mm³)	4908±1404	4497±1327	0.114
Lymphocyte count (count/mm³)	2626±718	2255±597	**0.008**
Platelet count (count/mm³)	266645±55931	258847±60474	0.518
MPV (fL)	9.94±1.28	10.0±1.10	0.814
PCT (%)	0.25±0.05	0.24±0.07	0.671
NLR (%)	2.03±0.95	2.09±0.72	0.290
PLR (%)	106.4±28.8	121.4±38.0	**0.043**

* Mean±standard deviation is given.
** p <0.05 was taken as the limit value of significance.

As shown in **Table 5**, there was no statistically significant correlation between OGTT 1-hour glucose and the number of platelets (r=0.048; p=0.643), MPV (r=-0.014; p=0.895), PCT (r=0.004; p=0.972), NLR (r=-0.064; p=0.540) and CRP (r=0.253; p=0.102).

Table 5. Correlation of complete blood count, CRP, HbA1c, insulin and HOMA-IR results with OGTT 1-hour plasma glucose

Variable name	Correlation coefficient	p value **
Hemoglobin	0.243	**0.018**
White blood cell count	0.318	**0.002**
Neutrophil count	0.217	**0.035**
Lymphocyte count	0.288	**0.005**
Platelet count	0.048	0.643
MPV	-0.014	0.895
PCT	0.004	0.972
NLR	-0.064	0.540
PLR	-0.233	**0.024**
CRP	0.253	0.102
HbA1c	-0.049	0.704
Fasting insulin	0.286	**0.018**
HOMA–IR	0.322	**0.007**

* The correlations of the variables with OGTT 1st hour glucose were examined in all subjects.
** p <0.05 was taken as the limit value of significance.

There was a statistically significant positive correlation between OGTT 1-hour glucose and hemoglobin (r=0.243; p=0.018), white blood cell count (r=0.318; p=0.002),

neutrophil count (r=0.217; p=0.035) and lymphocyte count (r=0.288; p=0.005). There was a statistically significant negative correlation between OGTT 1-hour glucose and PLR (r=-0.233; p=0.024).

No statistically significant correlation was found between OGTT 1st hour glucose and HbA1c (r=-0.049; p=0.704). A statistically significant positive correlation was found between OGTT 1-hour glucose and fasting insulin (r=0.286; p=0.018) and HOMA-IR (r=0.32; p=0.007) values of the study groups.

DISCUSSION

In this study, we investigated the markers of chronic inflammation including MPV, NLR, and PLR in patients with elevated 1st hour during OGTT. The MPV and NLR values were not different in the patient group, and PLR was significantly lower in the patient group in our study. Besides, the number of white blood cells and insulin levels were significantly higher in the patients.

The 155 mg/dl threshold for 1-hour plasma glucose after OGTT was first identified in San Antonio Heart Study (SAHS) over 1611 patients without diabetes. In this study, the patients were followed for an average of 7-8 years. It was shown that plasma glucose elevation after OGTT predicted the risk of type 2 DM (16.7%) that would develop after 7-8 years with higher sensitivity than IGT (threshold 140 mg/dl).[17] When the literature is reviewed, the most comprehensive study is by Bardini et al.[18], including 1062 patients. According to this study, patients were divided into four groups according to whether they were prediabetic and whether their plasma glucose levels were higher than 155 in OGTT. According to the results of the study, significant increases in fibrinogen level and white blood cell count were found in patients with plasma glucose above 155 mg/dl in the first hour compared to the other patients. The number of white blood cells increased in our study similarly.

This study showed that OGTT 1st hour glucose >155 mg/dl is an actual threshold for subclinical inflammation, dyslipidemia, and insulin resistance; therefore, this threshold value should be considered in order to identify patients with high cardiovascular risk.[18]

In addition, previous studies have shown that elevated glucose levels are associated with obesity, hypertension, hypercholesterolemia, metabolic syndrome and left ventricular diastolic dysfunction. It was shown that carotid artery intima thickness increased, the prevalence and incidence of diabetic retinopathy were significantly increased, eGFR was lower, and the high levels of ALT and GGT were associated with elevated 1-hour glucose levels.[7-9,19,20]

In another study of methods for predicting the development of type 2 diabetes, it was shown that the high plasma glucose concentration during the first hour of OGTT was higher in predicting the risk of developing future Type 2 DM compared with HbAlc alone. According to another study, 1-hour plasma glucose concentration during OGTT was found to have a stronger correlation with insulin secretion, insulin resistance, and insulin secretion/insulin resistance index compared with 2-hour plasma glucose concentration, and 1-hour plasma glucose concentration was reported to be more potent in predicting diabetes.[21,22] It is known that MPV and NLR values are increased in prediabetes and diabetes subjects compared to the normal population. In addition, studies have shown that MPV increases in diseases such as DM, acute coronary syndrome, stroke, preeclampsia, and hypercholesterolemia.[23-26]

In a retrospective study of 1876 subjects, the relationship between MPV and plasma fasting glucose levels in the general population was investigated, and MPV was found to be higher in prediabetic patients than in normoglycemic subjects. Moreover, MPV and fasting glucose levels were found to be higher in patients with higher glucose levels than those with low glucose levels, not only in prediabetics but also among patients with normal fasting blood glucose.[13] In the literature, there is only one study, conducted with 48 patients and 48 controls, related to impaired glucose tolerance. As a result of this study, it was found that MPV was significantly higher in the impaired glucose tolerance group than the control group, and MPV was positively correlated with plasma glucose levels at the 2-hour after OGTT in the impaired glucose tolerance group.[14]

In literature, it has been shown that low preoperative PLR may be associated with an increased incidence of postoperative complications regardless of age, BMI, operative procedure, and disease stage, according to studies on PLR.[27] In the previous studies, it was reported that PLR value increased in advanced stages of diabetes despite the decrease in the prediabetic and early diabetic period.[16] From the point of view of PLR, our result was consistent with the previously described decrease in PLR in the prediabetic and early diabetic periods.

In our study, BMI values were above 30 in the control group, similar to the patient group. The fact that MPV, CRP, and NLR values of controls were identical to the patient group may be related to this situation. MPV and CRP values have already been shown to be higher in obese individuals than in normal individuals.[28,29]

When the previous studies were examined, insulin, HOMA-IR, CRP, and white blood cell count were found to be higher in the prediabetic group compared to individuals with normal glucose tolerance.[30-33]

Similar to these results, in our study, insulin levels were remarkably higher in patients with isolated 1-hour elevation during OGTT. We assume that insulin and HOMA-IR levels increase due to the compensatory rise in beta cell function, which begins many years before the diagnosis of diabetes. In fact, in the British Whitehall II study, it was observed that insulin secretion remained constant over the 13-year observation period and showed a remarkable compensatory increase 3-4 years before the diagnosis of diabetes. These results indicate that insulin resistance initiates years before the development of diabetes.[34] Accordingly, we found elevated WBC count in OGTT group compared to controls in present study.

In another study examining the effects of white blood cell levels on the development of diabetes, a total of 352 non-diabetic patients (272 NGT and 80 IGT) were included in the study, and it was found to be significantly higher in patients with IGT (8,470±2,153) than patients with NGT (8,000±1,973).[35]

When 272 patients were prospectively examined, high white blood cell levels predicted progression from NGT to diabetes. Furthermore, in this study, elevated white blood cell levels were shown to be associated with a decrease in insulin sensitivity. Collectively, this data indicates the

role of inflammation in insulin resistance and subsequent development of type 2 diabetes.[35]

It is also thought that activation of the immune system causes a decrease in insulin sensitivity, and its result contributes to developing type 2 diabetes. Interleukin-6 (IL-6), a potent white blood cell differentiation factor, produced primarily on adipose tissue, is associated with insulin resistance.[36,37] Therefore, it can be said that IL-6 can be a factor that increases the white blood cell and causes insulin resistance.[37] Association between inflammation markers (CRP) and prediabetes was well established in the literature. A study consisted of 15,010 adults reported that prediabetic subjects have higher CRP levels than other individuals.[30] There was only a slight increase between prediabetic and diabetic subjects in term of CRP. These findings suggest that onset of diabetes could be related with inflammatory modulation. There are other recent studies supporting the relationship between prediabetes and CRP elevation.[31,32] However, CRP was not significantly different between study and control groups in present work.

In terms of the limitations of the study, firstly, the design of our study was retrospective, and the patients who had isolated 1st hour with standard OGTT between 1 January 2016 and 31 December 2017 were screened.

Therefore, other markers of inflammation, such as IL-6 and high-sensitivity CRP, could not be studied. The other limitation of our study was that the BMI values of the patient and control groups were above 30. The similarity of parameters such as MPV and CRP in the patient and control groups may be related to this situation. On the other hand, when the literature is reviewed, inflammation markers such as MPV, NLR, and PLR have not been studied in patients with isolated 1-hour plasma glucose elevation during oral glucose tolerance test, and this is the first study in this field.

CONCLUSION

Isolated first hour hyperglycemia in oral glucose tolerance test is associated with insulin resistance, therefore, cautiously clinical follow-up is warranted for those subject. Interventions to reduce first hour hyperglycemia in OGTT may yield further benefit in delaying and prevention of overt diabetes. We think that isolated 1st hour hyperglycemia in OGTT should not be classified as normal since it is associated with increased fasting insulin and HOMA-IR levels.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Kırıkkale University Clinical Researches Ethics Committee (Date: 02.10.2018, Decision No: 15/36).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declared that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Data Availability Statement: Data will be made available by the corresponding author on reasonable request.

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