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The relationship one-hour glycemia level at oral glucose tolerance test and non-alcoholic fatty liver disease

Oral glukoz tolerans testinde 1. saat glukoz seviyesi ve non-alkolik yağlı karaciğer hastalığı

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Abstract

Objective: The etiology of non-alcoholic fatty liver disease (NAFLD) is still not clearly defined. Carbohydrate metabolism disorder including prediabetes to overt diabetes constitutes the main stone of the NAFLD. However; data on the relationship between glycemic disorders and NAFLD is scarce. Recent studies show that alanine transaminase (ALT) and gamma-glutamyl transferase (GGT) levels can be predictor factors for NAFLD. The relationship between hepatic test and prediabetes has not been defined clearly, yet. Therefore; we evaluated whether the intermediate stages of oral glucose tolerance test have association with NAFLD and with hepatic function test.

Materials and Methods: 75 gr oral glucose loading test and hepatic function levels were evaluated in 367 participants. Hepatosteatosis level were assessed with ultrasonographic evaluation.

Results: Grade of hepatic steatosis was positively correlated with age, body mass index (BMI), 60. min blood glucose, ALT, GGT and weakly positively correlated with fasting blood glucose, 0. min blood glucose. In lineer regression analysis, 60. min blood glucose after glucose loading were obtained to be an independent risk factor for NAFLD regardless of age, BMI.

Conclusion: NAFLD is extremely common in people with carbohydrate metabolism disorder and is mainly associated with glucose levels. The 60. min blood glucose levels after post challenge test might have been a role in etiopathogenesis of NAFLD. ALT and GGT levels are also associated with glucose levelsat one-hour glucose loading and hepatosteatosis degree.

Keywords: One-Hour Glucose Levels; Oral Glucose Tolerans Test; Non-Alcoholic Fatty Liver Disease; Hepatic Function Test.

Öz

Amaç: Non-alkolik yağlı karaciğer hastalığının (NAYKH) etyolojisi henüz net aydınlatılamamıştır. Prediyabetten diyabete karbohidrat metabolizma bozuklukları NAYKH'nın temelini oluşturmaktadır. Ancak, NAYKH ve glisemik bozukluklar arasındaki ilişkiye dair yayınlar yetersiz kalmaktadır. Yakın zamanda yapılan çalışmalarda alanin transaminaz (ALT) ve gama-glutamil transferaz (GGT)'nin NAYKH için belirteç olduğu gösterilmiştir. Hepatik testlerle prediabet arasındaki ilişki de yeterince tanımlanmamıştır. Bu nedenle, çalışmamızda oral glukoz tolerans testinde ara basamaklarının NAFLD ve hepatik fonksiyon testleri ile ilişkili olup olmadığı değerlendirildi.

Gereç ve Yöntemler: 75 gr oral glukoz tolerans testi ve hepatik fonksiyon testleri 367 hastada değerlendirildi. Hepatosteatoz seviyesi ultrasonografi ile değerlendirildi.

Bulgular: Hepatosteatoz yaş, BMI, 60. dk kan glukozu, ALT, GGT ile pozitif korelasyon göstermektedir. Açlık kan glukozu ve 0. dk kan glukozu ile zayıf pozitif korelasyon göstermektedir. Lineer regresyon analizinde, 60. dk glukoz NAYKH için bağımsız bir risk faktörü olarak saptanmıştır.

Sonuç: NAYKH karbonhidrat metabolizma bozukluğu olan kişilerde sık rastlanmaktadır ve temel olarak glisemi düzeyleri ile ilişkilidir. NAYKH etyolojisinde glukoz tolerans testi 60. dk glukoz seviyelerinin rolü olabilir. ALT ve GGT seviyeleri de çalışmamızda 1.saat glukoz düzeyleri ve hepatosteatoz seviyeleri ile ilişkilendirilmiştir.

Anahtar Kelimeler: 1. Saat Glukoz Düzeyi; Oral Glucoz Tolerans Testi; Non-Alkolik Yağlı Karaciğer Hastalığı; Hepatik Fonksiyon Testi.

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INTRODUCTION

Prediabetes, a silent condition with no clinical symptoms, reflects a carbohydrate metabolism dysfunction. Fasting blood glucose, 2 hour glucose tolerance test and glycosylated hemoglobin values have been used to identify the states. The evidences on the association between prediabetes, regardless of which test you choose, and cardiovascular disease have been growing at a great pace (1-3). Additionally, it has been recently shown that persons with prediabetes defining with fasting blood glucose 100 to 125 mg/dl exhibit a significantly elevated hospitalization risk compared to those without diabetes (4). Furthermore; a pro-inflammatory diet related mortality has been increased in subjects with prediabetes identifying with glycosylated hemoglobin percentage 5.7 to 6.4 (5).

Sedentary lifestyle due to an innovative technology, easy access to high glycemic index food due to attractive food industry and drug habits including antibiotics, antidepressants, antihypertensives cause deterioration of insulin secreting and signaling pathways and all those result in disruption of carbohydrate metabolism.

Common cause of chronic liver disease in the community is non-alcoholic fatty liver disease (NAFLD), consisting of pure steatosis to steatohepatitis and cirrhosis (6,7). NAFLD is found to be mainly associated with obesity, type 2 diabetes, dyslipidemia (8-10). Due to the effect on cardiovascular and liver-related mortality, as well as overall mortality, NAFLD becomes a significant importance, currently (7,11). Therefore, defining etiopathogenesis clearly and taking preventive care for causal etiologies are the main stone of the NAFLD therapy.

MATERIALS and METHODS

A total of 367 individuals carrying high risk for glucose metabolism disorder such as impaired blood glucose, polycystic ovary syndrome and obesity were enrolled the study. The study was conducted between January 2014 and June 2014. No patients had clinical evidence of advanced liver or renal disease, cardiovascular events, or recent history of acute illness. Patients who had chronic liver disease (alcohol abuse or intake _20 g/day, viral hepatitis, autoimmune hepatitis, and use of hepato-toxic drugs) were excluded fom the study.

Participants were also excluded from the study if they had used confounding medications, including oral contraceptive agents, antilipidemic drugs, hypertensive medications, and insulin-sensitizing drugs, within 3 months before enrollment. The protocol was approved by the local ethics committee. All participants gave written informed consent.

All participants underwent a 75 g oral glucose tolerance test (OGTT) after an 8-h fast and carbohydrate-free diet on 3 days. Blood samples were obtained from all participants five times during the OGTT (before and 30, 60, 90 and 120 min after oral glucose tolerance test).

Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Waist circumference was measured in a standing position at the level of the umbilicus.

Information on daily alcohol consumption, smoking status, and use of medications (including also hepatotoxic drugs such as glucocorticoids, amiodarone, methotrexate, or antineoplastic drugs) were obtained from all participants by a questionnaire (12). All participants were abstainer.

Venous blood was drawn in the morning after an overnight fast. Plasma liver tests and other biochemical blood measurements were determined by Standard laboratory procedures.

Serology for viral hepatitis B and C was assessed in all participants. The participants who had positive serology for hepatits B and C were excluded from the study. The glucose levels were evaluated with enzymatic heksokinase method (Roche, Hitachi Cobas c system). Aspartate transaminase (AST), alanine transaminase (ALT) and gamma-glutamyl transferase (GGT) levels were measured by kinetic method (Roche, Hitachi). Levels of total-cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride (TG) were determined with enzymatic colorimetric assays by Roche Hitachi reagents. LDL cholesterol (LDL) was calculated by the Friedewald equation.

Hepatic ultrasonography scanning was performed in all participants with Hitachi-Aloka 7 MHZ probe in our clinic. The diagnosis of hepatic steatosis was made on the basis of characteristic sonographic features (6,13, 14). It is known that ultrasonography has a sensitivity of 90% and a specificity of 95% in detection of moderate and severe hepatic steatosis (6,13). Semiquantitative sonographic scoring for the degree of hepatic steatosis was recorded as following 0=absent;1=mild; 2=moderate and 3=severe.

Statistical Analyses

Collected data was entered to SPSS version 15. The data were shown as mean ± SD. Normally distributed variables were compared using One-way Anova test. Data that were not normally distributed were compared by the Kruskall-Wallis test. Pearson correlation coefficient analysis was used to determine the correlation between the values. Logistic regression analysis was used to determine the association between blood glucose levels and NAFLD severity.
p value lower than 0.05 was accepted as statistically significant.

RESULTS

367 patients with increased risk for type 2 diabetes mellitus were evaluated. Of the patient's 270 (73.6%) were female, 97 (26.4%) were male. Mean age was 43.23±15.96 and mean BMI was 30.39±8.33. The clinical and biochemical values were given in table 1. Grade of hepatic steatosis was positively correlated with age, body mass index, 60. min blood glucose, ALT, GGT and weakly correlated with fasting blood glucose, 0. min

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blood glucose (table 2). 60.min blood glucose level was also found to be positively correlated with age, hepatic steatosis degree, HbA1C levels, total cholesterol, TG, LDL, aspartate transaminase (AST), alanine transaminase (ALT) and gamma-glutamyl transferase (GGT) levels (table 3). In lineer regression analysis, 60. min blood glucose after 75-g oral glucose tolerance test were obtained to be an independent risk factor for NAFLD regardless of age, BMI (unstandardized beta coefficient:0.01, p:0.007; model included: age, BMI, ALT, GGT, HbA1C, fasting and 0.min blood glucose level).

Groups of hepatosteatosis

Age, BMI, 60.min blood glucose, ALT and GGT levels were significantly different between hepatosteatosis groups ($p<0.05$, table 4). The lineer increase was observed in terms of age, BMI, 60.min blood glucose, ALT and GGT levels as the hepatosteatosis level increase. However lineer elevation in 0.min. plasma glucose levels were disrupted at the 2.hepatostetosis level (table 4).

Table 1. The clinical characteristics and biochemical values of the cases

Variable	Mean±S.D
Age, years	43.23±15.96
BMI, kg/m^{22}	30.39±8.33
Waist circumference, cm	96.73±17.20
Fasting glucose, mg/dl	95.87±15.69
Fasting insülin, uIU/mL	14.23±12.32
0.min. glucose, mg/dl	92.32±11.71
60.min glucose, mg/dl	138±41.16
120.min. glucose, mg/dl	110.77±37.88
HOMA-IR	2.91±1.83
HbA1c, %	5.86±1.46

BMI: body mass index; HOMA-IR: homeostasis model assessment insulin resistance ind

Table 2. The correlation between demographic, biochemical values and hepatosteatosis

Variable	r	p
Age, years	0.350	<0.001
BMI, kg/m^2	0.414	<0.001
Fasting glucose, mg/dl	0.255	0.014
Fasting insülin, uIU/mL	-	0.751
0.min.glucose, mg/dl	0.281	0.044
60.min.glucose, mg/dl	0.391	0.004
90.min.glucose, mg/dl	-	0.100
120.min. glucose, mg/dl	-	0.069
HbA1C, %	0.395	0.001
Total cholesterol, mg/dl	-	0.676
Triglyceride, mg/dl	-	0.158
HDL, mg/dl	-	0.599
LDL, mg/dl	-	0.769
AST, U/L	-	0.117
ALT, U/L	0.309	0.003
GGT, U/L	0.456	<0.001

BMI: body mass index; HDL: high density lipoprotein cholesterol; LDL: LOW density lipoprotein cholesterol; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma glutamyl transferase

Table 3. The correlation between demographic, biochemical values and 60.min blood glucose

Variable	r	p
Age, years	0.485	<0.001
BMI, kg/m^2	-	0.116
Hepatic steatosis grade, mg/dl	0.391	0.004
Total cholesterol, mg/dl	0.306	0.002
Triglyceride, mg/dl	0.269	0.008
HDL, mg/dl	-	0.599
LDL, mg/dl	0.284	0.005
HbA1C, %	0.506	<0.001
AST, U/L	0.284	0.006
ALT, U/L	0.330	0.001
GGT, U/L	0.281	0.006

BMI: body mass index; HDL: high density lipoprotein cholesterol; LDL: Low density lipoprotein cholesterol; AST:Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma glutamyl transferase

Table 4. Comparison of mean rank values including fasting glucose, 0.min glucose, 60. min glucose, ALT and GGT levels in hepatosteatosis group.

Hepatosteatosis	Age	BMI	0.min glucose	60.Min glucose	ALT	GGT
			Mean Rank			
0	41.65	25.22	21.64	20.00	36.69	33.61
1	65.27	36.63	30.30	28.30	45.32	42.27
2	76.84	46.67	25.50	37.79	46.18	44.59
3	70.19	53.33	48.00	42.50	72.17	78.40
p	<0.001	0.007	0.129	0.027	0.020	0.002

BMI: body mass index; HDL: high density lipoprotein cholesterol; LDL: LOW density lipoprotein cholesterol; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma glutamyl transferase

DISCUSSION

In the present study, we investigated the relationship between NAFLD, serum liver enzyme levels and intermediate stages of oral glucose tolerance test. We found the 60.min glucose levels were associated with hepatosteatosis level and with ALT and GGT levels.

Hyperglycemia are strongly associated with NAFLD. Furthermore; NAFLD has been found to be associated with uncontrolled diabetes (15). However; before overt diabetes development as well as in prediabetes stage there is limited data on the association with NAFLD and glucose levels.

The obvious pathogenesis of NAFLD is not clear and is thought to be related to glucose levels causing the start of inflammatory process and oxidant stress. Therefore, in etiopathogenesis of NAFLD, hyperglycemia is the most relevant factor. Furthermore, in individuals with NAFLD seem prone to develop impaired carbohydrate metabolism varying from a condition of prediabetes to overt diabetes (16-18). The coincidence of NAFLD and impaired carbohydrate metabolism disorders tend to be an increasing trend.

In the present study the levels of hepatosteatosis exibited a lineer association with 60.min plasma glucose. However lineer elevation in 0.min. plasma glucose levels were disrupted at the grade 2 hepatostetosis level. This could not be explained with the present findings. The

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group was consisted of the cases with increased risk for diabetes such as PCOS, obesity, not still diabetes, it might be a reason for the discordance between 0.min. glucose levels and the degree of hepatosteatosis.

In a prospective population-based study fatty liver disease was found to be weakly associated with fasting blood glucose in consistent with our results and to be a major determinant of diabetes development with a 5 fold hazard ratio (9). In a recent study conducted in patients with NAFDL, patients exibited both impaired fasting glucose (glucose levels were 100 to126 mg/dl) and an HbA1c level of 5.7-6.4% had higher incidence for diabetes evaluted by oral glucose tolerance test. The ratio was 22.8%. Therefore, in those patients oral screening test should be done (19).

The studies evaluating the one-hour post-load glucose levels after glucose tolerance test are still scarce. In a study evaluating 1000 participants with OGTT the one-hour post-load plasma glucose levels were found to be associated with elevated ALT, GGT levels, but not AST in consistent with our study (20). In a recent study evaluating the intermediate stages of glucose levels with oral glucose tolerance test, the one hour glucose levels was found to be a stronger predictor of type 2 diabetes than impared fasting glucose. The hazard ratio risk of one-hour glucose levels for type 2 diabetes was found to be 4.02, on the contrary the hazard ratio risk of isolated impaired fasting glucose remained at 1.91 (21).

One-hour post-load hyperglycemia by a 75g oral glucose tolerance test as a novel risk factor of atherosclerosis (22). In the light of these evidences post-load one-hour glucose levels have association with increased hepatic transaminase levels consisted with the present results, and also have association with the increased risk of diabetes mellitus and cardiovascular disease.

Besides the association between NAFLD and glucose levels, higher ALT and GGT levels suggesting as predictor factors for NAFLD are also found to be associated with increased diabetes risk. In a follow-up study from Japan 1804 non-diabetic participants were followed for 9 years. 135 participants developed diabetes during follow-up period. In participants at higher ALT and GGT quartiles had the higher risk for diabetes development compared to those at lower quartiles. Author concluded that ALT and GGT levels are strong predictors of diabetes (23). In a recent study evaluating almost 17000 participants, GGT and ALT were found to be associated with development of metabolic syndrome (24).

In addition, ALT and GGT were found to be related to cardiometabolic risk factors including increased LDL cholesterol levels, systolic blood pressure, waist circumference, waist-hip ratio (25). Furthermore; there has been growing evidence on association of ALT and GGT levels with cardiovascular disease and mortality. Additionally; it has been also shown ALT and GGT levels have linear association with endothelial dysfunction (26). Patients with non-alcoholic steatohepatitis diagnosed with liver biopsy had impaired endothelial dysfunction including lower flow-mediated dilatation and higher carotid artery intima-media thickness. In a community-based prospective study, higher levels of ALT and mainly GGT, were associated with development of AF risk. Author concluded the mechanisms of this association was not clear and need to further evaluation (27). In a 9-year follow-up study GGT was found to be related to development of HF in men aged<70 years (28).

In patients with type 2 diabetes, low levels of ALT are associated with an increased risk of all-cause mortality, in particular non-cardiovascular mortality, compared to normal levels of ALT, while risk again starts to increase when levels are above normal. Low levels of ALT and also increased ALT levels above the normal limits have recently shown to be related to increased all-cause mortality in patients with type 2 diabetes (29).

In a study evaluating almost 15000 patients ALT levels were found to be related to mortality from liver disease, but not to be associated with all-cause mortality; however elevated GGT levels were observed to be associated with all-cause mortality including liver disease, neoplasm, and diabetes but not to be associated with cardiovascular disease (30).

These effects on cardiovascular and liver-related disease and mortality, as well as overall mortality, bring NAFLD to the main control point of the metabolic pathways, currently.

NAFLD was also found to be an independent risk factor for diabetic retinopathy and chronic kidney disease (31). However; there is limited evidence suggesting that NAFLD may be a predicted factor for long-term hyperglycemia complications.

In the lights of these evidences NAFLD defining with ultrasonography and elevated hepatic function test, and prediabetes are predictive values for cardiovascular morbidity and mortality. The one-hour post-load blood glucose levels might have been a role in etiopathogenesis of NAFLD. Therefore, definition of etiopathogenesis clearly and taking preventive care for causal etiologies should be the main stones of the NAFLD therapy.

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