Triglyceride-Glucose Index is a Reliable Predictor of Metabolic Disorder in Gallstones

Trigliserit-Glikoz İndeksi Safra Taşlarında Metabolik Bozukluğun Güvenilir Bir Göstergesidir

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ABSTRACT

Objective: The risk of gallstones is increased in fatty liver, overweight, and metabolic syndrome. The hyperinsulinemic-euglycemic clamp method is considered the best method for insulin resistance (IR); but it is a time consuming and expensive procedure. As an alternative strategy, in this study, we would like to demonstrate the triglyceride-glucose (TyG) index as the predictor of the development of gallstone disease associated with metabolic disorders.

Methods: The TyG was investigated in our study with 1484 patients between the ages of 18-75 who underwent follow-up and/or cholecystectomy due to gallstones. The serum fasting blood glucose and triglyceride levels of the patients were measured in the biochemistry laboratory of our hospital. The bile ducts and gallstones of all patients were evaluated with the Philips Affiniti 50 (The Philips Affiniti 50 Ultrasound; Philips North America Corporation 3000 Minuteman Road M/S 109 Andover, MA 01810, USA) ultrasonography device used by radiologists in the radiology clinic of our hospital. The data obtained were evaluated in SPSS, and p<0.05 was considered significant.

Results: Our study includes 1484 (980 female, 504 male) patients. The plasma glucose (124.6±24.5 mg/dL), triglyceride (198.3±36.8 mg/dL), insulin (16.5±5.6 uIU/mL), and Homeostasis Model Assessment of IR 4 level (8±1.2), were at statistically and significantly higher levels in the patients than in the control group (p=0.001). It was found that the basal TyG was associated with the primary endpoint incidence of gallstones at significant levels. The

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Amaç: Yağlı karaciğer, obezite ve metabolik hastalıklarda safra kesesi taşı görülme riski artmıştır. Hiperinsülinemik-glisemik klemp yöntemi insülin direnci (IR) için "altın standart" bir yöntem olarak kabul edilmektedir, ancak zor ve maliyetlidir. Alternatif bir yöntem olarak daha hızlı ve daha düşük maliyetli biyokimyasal ölçüm olan trigliseride-glukoz (TyG) indeksi, metabolik bozukluklarla ilişkili olan safra kesesi taşı hastalığı tanısında yararlı olabilir. Bu çalışmanın amacı safra kesesi taşı tanısında TyG indeksinin etkinliğini değerlendirmektir.

Yöntemler: Çalışmada, safra kesesi taşı ile takip ve/veya kolesistektomi yapılan 18-75 yaş aralığında olan 1484 olgularda TyG indeksi araştırıldı. Hastaların serum açlık kan glukoz ve trigliserid düzeyleri hastanemiz biyokimya laboratuvarında ölçüldü. Tüm hastaların safra yolları ve safra taşları hastanemiz radyoloji kliniğinde radyologlar tarafından kullanılan Philips Affiniti 50 (The Philips Affiniti 50 Ultrasound; Philips North America Corporation 3000 Minuteman Road M/S 109 Andover, MA 01810, USA) ultrasonografi cihazı ile değerlendirildi. Elde dilen veriler SPSS'de değerlendirildi, p<0,05 anlamlı kabul edildi.

Bulgular: Araştırmaya toplam 1484 (980 kadın ve 504 erkek) hasta alındı. Çalışmamızdaki biyokimyasal parametrelerden açlık safra kesinde taş saptanan olgularda plazma glukoz 124,6 mg/dL, trigliserid 198,3±36,8 mg/dL, insülin 16,5±5,6 uIU/mL, IR'nin Homeostatik Modeli Değerlendirmesi 4,8±1,2 seviyesi kontrol grubuna göre hepsi istatistiksel olarak anlamlı yüksekti (p=0,001). Bazal TyG indeksi, primer sonlanım noktası safra kesesi taşı insidansı ile önemli ölçüde ilişkili olduğu saptandı. Tek değişkenli

ABSTRACT

TyG was related with hazard ratio 1.65 as a continuous variable in univariate analysis (95% confidence interval 1.15-1.98; p<0.001).

Conclusion: High TyG scores were associated with gallstone disease, and it can be used as an identifying marker for screening people who have gallstone disease and as an indication for therapeutic precautions.

Keywords: Triglyceride-glucose index, metabolic disorder, gallstones

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analizde, sürekli bir değişken olarak TyG indeksi, risk oranı 1,65 (%95 güven aralığı 1,15-1,98; p<0,001) ile ilişkilendirildi.

Sonuç: Yüksek TyG skorları safra taşı hastalığıyla ilişkilendirilmiştir ve safra taşı hastalığı olan kişileri taramak için tanımlayıcı bir belirteç ve terapötik önlemler için bir gösterge olarak kullanılabilir.

Anahtar Sözcükler: Trigliserid-glukoz indeksi, metabolik hastalıklar, safra taşı

Introduction

Gallstones are common in the world. The prevalence of gallstones has a frequency of 10-15% in developed countries (1). If we identify the chain of events that result in the formation of gallstones, many studies were conducted in the past to elucidate the factors and mechanisms responsible for the nucleation of crystals (2). There are some theories about gallstone formation. But the most accepted theories are the changes in bile composition (oversaturation of calcium bilirubinate, pigment and cholesterol stones), increased crystal nucleation in the presence of mucin and similar factors, and slowing of bile flow (3).

The risk of especially gallstones is increased in fatty liver, obesity and metabolic diseases (4). It has been reported in recent years that metabolic disorders are associated with diseases such as fatty liver, type 2 diabetes mellitus (DM), metabolic syndrome, and hyperlipidemia (5,6). Insulin resistance (IR) is the predictor of the onset of these diseases, and is a widely used marker (7). It is already known that IR is a key factor in the pathogenesis of metabolic abnormalities (8). The hyperinsulinemic-euglycemic clamp (HEC) method is considered as the best method for IR; however, it is a difficult process and costly. As an alternative strategy, we would like to investigate the triglyceride-glucose (TyG) index which is a faster and low-cost biochemical measurement tool, as the predictor of the development of gallstone disease associated with metabolic disorders for the first time.

Methods

The TyG index was investigated in our study with 1484 patients, who were between the ages of 18-75, who underwent follow-up and/or cholecystectomy due to gallstones in our general surgery clinic between 2010-2021. Patients who were pregnant, who had acute inflammation, alcohol use, history of cancer, renal or infectious hepatitis (anti-HCV positive), and liver cirrhosis were excluded from the study. Those who had a history of DM or newly diagnosed diabetic patients, those who used triglyceride-reducing medication (statins, fibrates, omega-3, thiazolidinedione, or insulin) were also excluded from the study.

The demographic characteristics of the patients, their biochemical data, ultrasonographic examination reports of the bile ducts were collected from the patient files and electronic records. The serum fasting blood glucose and triglyceride levels of the patients were measured in the biochemistry laboratory of our hospital. Plasma glucose (cut-off level 70-100 mg/dL) was determined with the glucose oxidase method. The triglyceride (cut-off level 0-150 mg/dL) level was determined with the enzymatic method. Fasting plasma was calculated by using glucose and insulin (cut-off level 0-25 uIU/mL) and Homeostasis Model Assessment for IR (HOMA-IR) [HOMA-IR: fasting insulin (uIU/mL) x fasting glucose (mg/dL)/405] (9). The TyG index was calculated with the formula in [fasting TGs (mg/dL) x fasting glucose (mg/dL)/2] and using fasting triglyceride and glucose (10). The biliary tract and gallstones of all patients were evaluated with the Philips Affiniti 50 (The Philips Affiniti 50 Ultrasound; Philips North America Corporation 3000 Minuteman Road M/S 109 Andover, MA 01810, USA) ultrasonography (US) device used by radiologists in our hospital's radiology clinic. Philips Affiniti 50 brand US device is a well-equipped device that provides radiologists with new levels of clinical knowledge by providing easy examination with advanced organ modeling, image sectioning and proven quantification.

This study was conducted in accordance with the ethical rules with the approval of Medicana International Samsun Hospital Clinical Research Ethics Committee (decision no: 7136, date: 20.05.2021). All participants were informed before the study and were included in the study after their consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

The data was transferred to IBM SPSS Statistics 22 (IBM, Armonk, NY, USA) and processed. Frequency distribution (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation) for numerical variables were provided while assessing the study data. The Kolmogorov-Smirnov test was used to determine if numerical variables followed a normal distribution. For normal distribution variables, independent sample t-test was employed to see if there was a difference between the two groups. For variables that did not fit a normal distribution, the Mann-Whitney U test was utilized. To assess the association between two category variables, the chi-square test was performed. In addition, the cut-offs for the variables were determined using receiver operating characteristic

(ROC) analysis. The statistically significant two tailed p-value was considered as <0.05.

Results

A total of 1484 (980 female, 504 male) patients were included in the present study. The mean age of the patients was 54±12.5 (18-75). The biochemical parameters used in our study, the plasma glucose (124.6±24.5 mg/dL), triglyceride (198.3±36.8 mg/dL), insulin (16.5±5.6 uIU/mL), and HOMA-IR 4 level (8±1.2) were at statistically and significantly higher levels in the patients than in the control group (p=0.001). The clinical data, demographic characteristics, and biochemical data of the cases are shown in Table 1.

The fasting plasma glucose and triglyceride levels were found to be higher at statistically significant levels in the group with gallstones when compared to the group without gallstones in our study (p=0.001). It was found that the basal TyG index was associated with the primary endpoint incidence of gallstones at significant levels. The TyG index was associated with hazard ratio (HR) 1.65 as a continuous variable in univariate analysis [95% confidence interval (CI) 1.15-1.98; p<0.001]. The cut-off value of the TyG index was 4.82 for gallstone disease. Area under the ROC curve (AUROC)=0.789 (95% CI 0.783-0.795). The ≥4.82 TyG Index value identified gallstone disease with a sensitivity of 74.2% and a specificity of 72.5% (Figure 1). The TyG index value was accepted as 4.49; the intersection point with IR with a sensitivity of 82.6% and specificity of 82.1% in previous studies (AUC=0.889, 95% CI: 0.854-0.924) (11).

Discussion

Among the pathogenic factors for gallstones, genetic predisposition, hepatic oversecretion of cholesterol, oversaturated bile, oversaturation and inflamation in the gallbladder, and altered bowel microbiota are mentioned in previous studies (12). The pathophysiology of this disease are associated with IR, overweight, metabolic diseases, and DM (13,14). Gallstones are among the consequences of metabolic disorders. In this respect, using tests and markers to predict metabolic diseases may be predictive for gallstones from the consequences of metabolic diseases.

IR was used as an important tool for metabolic disorders for many years (15). The HEC is the best test for IR measurement. However, it cannot be used commonly in clinical settings because of the complexity of the test process (16). Metabolic disorders are related with the chronic increases in plasma glucose and triglycerides. It was reported in recent studies that the TyG index is associated with IR that is measured with the HEC test at significant levels. It was shown that it performs better than the HOMA-IR evaluation (17,18). In the present study, it was found that the HOMA-IR level was higher in gallbladder stone disease. We can speculate that some gallstones are the result of metabolic diseases.

The pathogenesis of gallstones has not yet been fully understood. New risk factors continue to be identified in addition to previous risk factors (19). In this respect, one of the most important risk factors is IR. Many previous studies showed that non-insulin-dependent diabetic patients have a risk factor in this regard (20).
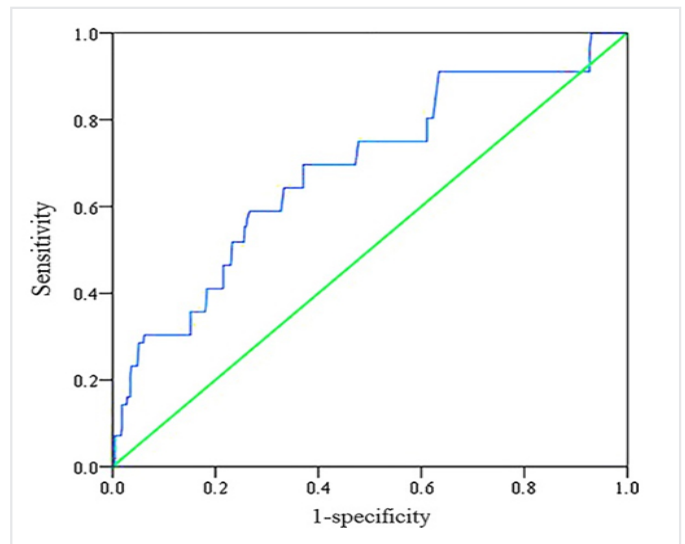
Figure 1. The ROC curves of the triglyceride-glucose index, as a marker for predicting gall stone disease. The AUC of ROC curves of the triglyceride-glucose index to predict gall stone disease (AUC) 0.789 (%95 CI 0.783-0.795; p=0.001).

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval

Table 1. The relation between clinical, demographic, biochemical characteristics and TyG index values of the participants of both groups

Parameters	Gallstones (n=1484)	Non-gallstones (n=256)	p-value
Age	58.5±12.4	59.1±11.5	0.592
Female, sex (%)	980 (66.03%)	175 (68.35%)	0.494
Fasting plasma glucose (mg/dL)	124.6±24.5	102.5±18.3	0.001
Triglycerides (mg/dL)	198.3±36.8	156.9±24.7	0.001
Insulin (uIU/mL)	16.5±5.6	9.5±1.1	0.001
TyG index	5.06±0.04	4.81±0.03	0.001
HOMA-IR	4.8±1.2	2.3±0.7	0.001

Data are expressed as mean±SD, median or number (%). TyG index: Triglyceride-glucose index, HOMA-IR: Homeostasis model assessment of insulin resistance

In these studies, it was reported that the most important risk was that IR might be the primary factor playing roles in the formation of gallstones (21,22). The relation between gallstones and metabolic syndrome and/or IR syndrome is the subject of recent reports (22,23). However, there are very few data on the relation with IR. It was found in our study that the fasting plasma glucose and insulin values, which are among the metabolic parameters, were statistically higher in the patients compared to the control group. We also detected IR in the group with gallstones.

It was reported in previous studies that the risk factors for cholesterol gallstones were increased waist circumference and central fat deposition. It was shown that these two factors are frequently related with hyperlipidemia (especially hypertriglyceridemia and low-high-density lipoprotein concentrations) (24,25). These increased bile cholesterol concentrations and gallbladder mucin secretion caused by hypertriglyceridemia may constitute the basic steps in the pathogenesis of gallstones (26-28). We showed in our study that the triglyceride level is significantly higher. It might be the preliminary finding of metabolic gallstones.

It was shown in recent studies that the TyG index can predict the incidence of fatty liver disease (29). It was shown that it is the definition and predictor of metabolic syndrome (30). It was also shown to be a risk determinant and predictor in prediabetes, diabetes, coronary syndrome, hypertension, macrovascular complications and obesity, which are the reflections of IR and/or metabolic diseases, and these diseases are strongly associated with the TyG index (31-34). Some gallstones are detected in patients with metabolic syndrome associated with hyperinsulinemia, hypertriglyceridemia, and high glucose levels. IR, metabolic syndrome, and gallstones were investigated very little in previous studies, and the data are very inadequate in this respect. The relation between the TyG index and gallstones was not investigated until now. Our study is the first one in this regard. It was determined in our study that the incidence of gallstone disease, which is the primary endpoint and the TyG index were significantly associated. As a continuous variable, the TyG index was associated with HR 1.65 in univariate analysis (95% CI 1.15-1.98; p<0.001). The cut-off value of the TyG index was 4.82 for gallstone disease. AUROC=0.789 (95% CI 0.783-0.795). The TyG index ≥4.82 identified gallstone disease with a sensitivity of 74.2% and a specificity of 72.5%. We showed that there is a strong relation between gallstone disease and the TyG index.

Conclusion

When the findings of this study were evaluated, it was found that high TyG index scores were associated with gallstone disease. We showed that the TyG index is a definition and predictor of gallstone disease. For this reason, it can be used as an identifying marker for screening people who have gallstone disease and as an indication for therapeutic precautions.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the ethical rules with the approval of Medicana

International Samsun Hospital Clinical Research Ethics Committee (decision no: 7136, date: 20.05.2021).

Informed Consent: All participants were informed before the study and were included in the study after their consent was obtained.

Authorship Contributions

Surgical and Medical Practices: Ö.K.O., E.A., Concept: Z.E., E.A., H.E., Design: Z.E., Ö.K.O., E.A., H.E., Data Collection or Processing: E.A., Analysis or Interpretation: Z.E., Ö.K.O., E.A., H.E., Literature Search: Z.E., Ö.K.O., H.E., Writing: Z.E., H.E.

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