Trigliserit/Glikoz İndeksi (TyG) ve Trigliserit/HDL-Kolesterol Oranı (TG/HDL-c) Gestasyonel Diyabeti Tahmin Edebilir mi?

Can Triglyceride/Glucose Index (TyG) and Triglyceride/HDL-Cholesterol Ratio (TG/HDL-c) Predict Gestational Diabetes Mellitus?

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ABSTRACT

AIM: We investigated whether measurement of triglyceride/glucose index (TyG) and triglyceride/HDL-cholesterol ratio (TG /HDL-c) in the first trimester can predict gestational diabetes mellitus (GDM).

MATERIAL AND METHOD: Twenty-five patients with GDM and 52 women without GDM with normal glycemic control during pregnancy were included in the study as a control group. Both insulin-controlled diabetes and diet-controlled diabetes were included in the diagnosis of GDM. Fasting glucose and plasma lipid profiles including TG, HDL-c, TyG index, and TG /HDL-c measured in the first trimester were analyzed.

RESULTS: Triglyceride values (mean 133±40 mg/dL in the gestational diabetes group, 100±54 mg/dL in the control group), TyG index (15.0±8.9 in the mean gestational diabetes group, 8.8±5.0 in the control group), and TG/HDL-C ratio (mean 3.3±2.6 in the gestational diabetes group and 1.9±2.6 in the control group) was found to be significantly higher in the GDM group (p=0.01, p=0.01, p=0.01, respectively). The optimal cutoff value for TyG index was 10.4, sensitivity was 76%, specificity was 77%, and area under the receiver characteristic curve (AUC) was 0.765 to predict GDM (p < 0.001). The optimal cutoff value for the TG /HDL-C ratio was 2.3, sensitivity was 76%, specificity was 69, AUC 0.697 to predict GDM (p=0.005).

CONCLUSION: TyG and TG/HDL-C ratio measured in the first trimester are thought to predict GDM better than fasting plasma glucose.

Keywords: Gestational diabetes mellitus, first trimester, pregnancy, Triglyceride/Glucose Index, Triglyceride/HDL-Cholesterol Ratio

ÖZET

AMAÇ: Birinci trimesterde trigliserid/glukoz indeksi (TyG) ve trigliserid/HDL-kolesterol oranı (TG /HDL-c) ölçümünün gestasyonel diyabetes mellitusu (GDM) tahmin edip edemeyeceğini araştırdık.

GEREÇ VE YÖNTEM: Gebelikte GDM'li 25 hasta ve glisemik kontrolü normal olan GDM'siz 52 hasta kontrol grubu olarak çalışmaya alındı. GDM tanısına hem insülin kontrollü diyabet hem de diyet kontrollü diyabet dahil edildi. İlk trimesterde ölçülen TG, HDL-c, TyG indeksi ve TG /HDL-c'yi içeren açlık glukoz ve plazma lipid profilleri analiz edildi.

BULGULAR: Trigliserit değerleri (ortalama gestasyonel diabetes grubunda 133±40 mg/dL, kontrol grubunda 100±54 mg/dL), TyG indeksi (ortalama gestasyonel diabetes grubunda 15,0±8,9, kontrol grubunda 8,8±5,0) ve TG/HDL-K oranı (ortalama gestasyonel diabetes grubunda 3,3±2,6 kontrol grubunda 1,9±2,6) GDM grubunda anlamlı olarak daha yüksek bulundu(sırasıyla p=0.01, p=0.01, p=0.01) GDM'yi öngörmek için TyG indeksi için optimal kesme değeri 10,4, duyarlılık %76, özgüllük %77 ve ROC analizinde eğri altında kalan alan (AUC) 0,765 idi (p < 0,001). GDM'yi öngörmek için TG/HDL-K oranı için optimal kesme değeri 2,3, duyarlılık %76, özgüllük 69, AUC 0,697 idi (p=0,005).

SONUÇ: İlk trimesterde ölçülen TyG ve TG/HDL-C oranının GDM'yi açlık plazma glukozundan daha iyi öngördüğü düşünülmektedir.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, birinci trimester, gebelik, Trigliserit/Glikoz İndeksi, Trigliserit/HDL-Kolesterol Oranı.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a glucose intolerance that begins during pregnancy and is the most common endocrinological disorder in pregnancy. Due to physiologic changes that occur during normal pregnancy, there is decreased insulin sensitivity, hyperinsulinemia, and mild postprandial hyperglycemia to meet increasing maternal and fetal demands, especially beginning in the second trimester. In the last trimester, maternal serum triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol levels increase significantly. Elevated maternal TG levels interfere with placental lipase activity and facilitate the transfer of metabolites that are stored as fat in the fetus. [1],[2]

GDM has many complications such as polyhydramnios; this is a clinical condition that requires to be closely monitored as it leads to many foetal (birth trauma, macrosomia, intrauterine growth retardation) and maternal complications (increased caesarean section rates and preeclampsia). For this reason, the World Health Organization (WHO), the International Association of Diabetes and Pregnancy Study Groups (IADPSG), and the American Diabetes Society recommended screening pregnant women with a one- or two-step oral glucose tolerance test (OGTT).[3]

Previous studies have shown that the triglyceride glucose index (TyG) is beneficial in the early detection of patients at risk for diabetes mellitus.[4] This index is significantly related to the risk of developing acquired type 2 diabetes.5 It has been shown that the ratio of triglycerides to HDL cholesterol (TG /HDL-C) may be beneficial for glycemic control in normal weight patients with type 2 diabetes.[6]

In this study, we investigated whether the TyG and TG/HDL-C ratio measured in the first trimester could be indicative of gestational diabetes mellitus associated with worsening glucose metabolism in the advanced weeks of pregnancy.

MATERIAL AND METHOD

This was a monocentric retrospective cohort study. The Institutional Review Board approved the study protocol with decision number 21/04/2022/05/28, and the principles of the Declaration of Helsinki were followed.

Patients diagnosed with gestational diabetes in the second trimester after triglycerides, glucose, and HDL cholesterol were measured in the first trimester were enrolled in the study within the five-year period between March 1, 2017, and March 31, 2022. During this period, patients in whom triglyceride, glucose, and HDL cholesterol levels were measured in the first trimester and who then had a normal pregnancy outcome were also used as a control group. At our hospital, we diagnose GDM using the 2-step scheme. According to these criteria, a 50 g OGTT test is performed in all pregnant women between 24 and 28 weeks of gestation, and a 100 g Oral Glucose Tolerance Test (OGTT) is performed without checking fasting status in those patients who have a blood glucose level of 140 mg/dl or more in the first hour to diagnose the disease. According to Carpenter and Coustan's criteria, GDM is diagnosed when patients exceed two thresholds.7 In these patients, diet is first initiated. These patients were switched to a low glycemic index, low carbohydrate diet consisting of vegetables, legumes, fruits, and high fiber cereals to support fetal growth while limiting postprandial glucose elevation and achieving adequate pregnancy weight gain. If there is no improvement after two weeks of fasting and postprandial blood glucose monitoring, insulin is started in these patients so that the diagnosis of GDM includes insulin-regulated diabetes mellitus and diet-regulated diabetes mellitus. Multiple pregnancies, pregnant women with gestational diabetes mellitus, pregnant women with additional comorbidities such as hypertension, thyroid disease, pregnant women who did not receive care in our hospital in the first trimester or who received care in our hospital in the first trimester but delivered in another hospital were excluded from the study.

In each patient, age, parity, smoking, use of assisted reproductive techniques, fasting blood glucose (FPG), first trimester systolic and diastolic blood pressure, HDL cholesterol (HDL-c), and triglycerides were determined. Gestational age was calculated using the first day of the last menstrual period, and sagittal head-breech distance measured in the first trimester was confirmed by ultrasound. The values of venous blood samples taken from the patient during hospitalization as part of routine clinical practice were included in the study. TyG was calculated according to the following formula: $TyG = Ln [TG (mg/dl) FPG (mg/dl)/2]$.[8]

Statistical analyzes of the study were performed using the SPSS 23.0 program. The descriptive statistics of the categorical variables

in the data set are reported with mean and standard deviation, and the descriptive statistics of the continuous variables are reported with median, minimum, and maximum values. The conformity of the continuous variables to the normal distribution was examined using the Shapiro-Wilk test. The chi-square test was used to analyze the difference between categorical variables, and the Kruskal-Wallis and Mann Whitney U tests were used for numerical variables. p<0.05 were considered statistically significant. Univariate logistic regression analysis was conducted and Receiver Operating Characteristic (ROC) curve was obtained.

RESULTS

There were 25 patients in the GDM group and 52 in the control group. The clinical and disease characteristics of these patients are shown in

Patients	Gestational Diabetes (n: 25)	Control Group (n: 52)	p
Age (years)	32.6± 4.7	30.7 ± 4.5	0.10
Parity			0.81
0	13 (52%)	27 (51.9%)	
1-2	9 (36%)	21 (40.4%)	
> 2	3 (12%)	4 (7.7%)	
BMI (kg/m²)	27.1±3.3	26.5 ± 3	0.69
Smoking	3 (12%)	5 (9.6%)	0.94
Assisted reproduction	3 (12%)	8 (15.4%)	0.15
Triglycerides (mg/dL)	133±40	100±54	**0.01**
HDL cholesterol (mg/dL)	57±13	56±14	0.88
Fasting plasma glucose (mg/dL)	91±17	87±9	0.12
Triglycerides/glucose index	15.0±8.9	8.8±5.0	**0.01**
Triglycerides/HDL cholesterol ratio	3.3±2.6	1.9±2.6	**0.01**

Chi-square test. Data are shown as (mean (min-max)), (mean±SD) or (n,%).

BMI: Body Mass Index, HDL: High-density lipoprotein

Table 1. Clinical and disease characteristics of patients and control group

The mean age of patients in the GDM group was 32.6 ± 4.7 years, and 30.7 ± 4.5 years in the control group. Reproduction was assisted in 12% (n=3) of patients in the GDM group and in 15.4% (n=8) of patients in the control group. BMI, HDL, cholesterol, and fasting plasma glucose levels didn't differ significantly between the two groups. Triglycerides (133±40 mg/dL vs. 100±54 mg/dL), TyG index (15.0±8.9 vs. 8.8±5.0) and TG /HDL-C ratio (3.3±2.6 vs. 1.9±2.6) were significantly higher in the GDM group (p=0.01, p=0.01 and p=0.01, respectively).

The perinatal and neonatal outcomes of the groups are compared in

Table 2. Perinatal and neonatal outcomes of study population and control group

Patients	Gestational Diabetes (n: 25)	Control Group (n: 52)	p
Gestational age at delivery (weeks)	36.6±2.4	38.1±1.9	**0.01**
Preterm delivery	8 (32%)	7 (13.5%)	**0.04**
Neonatal birthweight	3300±663	3282±582	0.90ᵃ
Percentile	68±22	60±18	
>90th percentile	8 (32%)	4 (7.7%)	
<10th percentile	0	3 (5.8%)	
Preeclampsia	4 (16%)	5 (9.6%)	0.41
Cesarean delivery	16 (64%)	27 (51.9%)	0.34
Primary cesarean delivery	9 (56.3%)	12 (44.4%)	0.45
Neonatal intensive care unit admission	5 (20%)	3 (5.8%)	0.06

Kruskal Wallis test. Data are shown as (mean±SD) or (n,%).

ᵃ Chi-square significance. The number of patients with a neonatal

birthweight of >90th percentile in the gestational diabetes group is higher than control group **(p=0.02)**.

Gestational age at delivery was significantly lower in the GDM group

and preterm birth was significantly higher in this group (p=0.01 and 0.04, respectively). The number of patients with a neonatal birth weight of > 90th percentile was higher in the gestational diabetes group than in the control group (p=0.02). Cesarean section rates and neonatal intensive care unit (NICU) admissions were statistically similar between groups but generally higher in the GDM group.

Table 3. Area Under the ROC Curve (AUC), OR, sensitivity and specifity by the optimized cut-off values and diagnostic data of first trimester triglycerides dependent indexes and fasting plasma glucose in predicting gestational diabetes mellitus.
Logistic regression models obtained from forward stepwise selection. AUC, Area Under the Curve, CI: Confidence interval, HDL, High-density lipoprotein, OR, Odds ratio.

	AUC (95%	Cut	OR	Sensitivity(%)	Specificity(%)	P value
Triglyceride/glucose index					77	<0.001
Triglycerides/HDL cholesterol ratio					69	0.005
Triglycerides					73	0.001
Fasting plasma glucose					76	0.32
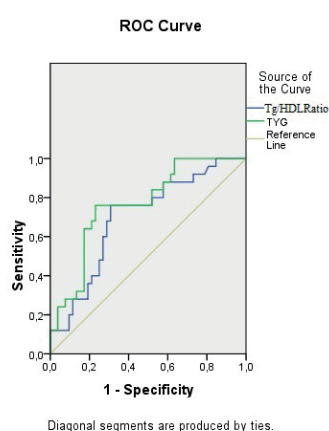
ROC Curve

Source of the Curve
Tg/HDLRatio
TYG
Reference Line

Diagonal segments are produced by ties.

Table 3 shows tri... d fasting plasma glucose for predic... lue for TyG index was 10.4, sensiti... %, area under the receiver operating... 0.765 (p<0.001). The optimal cut o... 3, sensitivity was 76%, specificity w... 5, Table3,

Figure 1. A ROC curve was drawn to show the predictive roles of TyG and TG/HDL-C ratio. Univariate logistic regression analysis was conducted

The optimal cut off value for triglycerides was 111 mg/dl, sensitivity 68%, specificity 73%, AUC was 0.660 (p=0.001). The optimal cut off value for fasting plasma glucose was 93 mg/dl, sensitivity 48%, specificity 76%, AUC was 0.570 (p=0.032).

DISCUSSION

This study examined maternal TyG index and TG /HDL-C ratio in first-trimester pregnancies and showed that an increase in TyG index and TG /HDL-C ratio in the first trimester may predict GDM. In addition, the optimal cut-off values and diagnostic data for estimating GDM are for TyG index: first trimester cut-off: 10.4, sensitivity: 76%, specificity: 77%, AUC: 0.765, and for TG /HDL-C ratio: first trimester cut-off: 2.3, sensitivity: 76%, specificity: 69%, AUC: 0.697, and better than fasting plasma glucose sensitivity.
There are studies showing that TyG index may be elevated in pregnant women with GDM .[9]-[13] First, Pazhohan et al. showed that there was a significant association between the increase in FPG, triglycerides, TG /HDL-C ratio and TyG index and the risk of GDM.[10] Liu et al. found the first trimester TyG index to be higher in the GDM group, and the risk of developing GDM was 3.53-fold higher in high tertiles compared to reference tertiles.[9] Sánchez-García et al. did not find a significant association between the TyG index and GDM in the first trimester. They showed that the TyG index in the second trimester has a high sensitivity and negative predictive value for the diagnosis of GDM and can be used as a screening strategy to reduce the need for an OGTT.[11] However, in the first trimester study of the same team, GDM and TyG index were not significantly associated .[12] Recently, a cohort study by Kim et al examined the association between pre-pregnancy TyG index and GDM and found a significant association in primiparous women.[13] In a meta-analysis by Song et al, women with the highest TyG index independently have a higher risk of GDM.[14] In our study, we examined the TyG index in the first trimester in GDM and controls. Although fasting plasma glucose was similar in both groups, we found that the TyG index was higher in the GDM group. We also found that the TyG index in the first trimester had a sensitivity of 76% and a specificity of 77% with a cut-off value of 10.4

for the detection of GDM. Although our results are similar to other studies, we believe that the differences in the results of the studies are due to the differences in the study population such as maternal age, race, ethnic differences, geographic characteristics, and BMI. The common feature of insulin resistance and GDM is dyslipidemia characterized by hypertriglyceridemia associated with decreased HDL-C.[15] TG/HDL-C ratio is a lipid parameter and a predictor of metabolic syndrome.[16] Giannini et al. found correlations between the TG /HDL-C ratio and insulin sensitivity measured by the hyperinsulinemic euglycemic clamp method.[17] However, there are very few studies in pregnant women. We found that TG and TG /HDL-C ratio in the first trimester were higher in the GDM group. Pazhohan et al. found that TG /HDL-C ratio was 3.01 and 3.87 times higher in the GDM group in the second and third tertiles, respectively .[10] Similarly, Liu et al. showed that the TG /HDL-C ratio was associated with a 2.38-fold higher risk of GDM in the high tertile.[9] We demonstrated that a cut-off value of 2.3 can predict GDM with 76% sensitivity and 69% specificity. However, it should be noted that there are confounding factors for these values such as racial and ethnic differences, etc.
Gestational diabetes is known to be associated with adverse pregnancy outcomes. Pregnant women with GDM are at high risk for adverse outcomes such as maternal polyhydramnios, preterm delivery, hyperemesis gravidarum, and neonates are at high risk for macrosomia, neonatal hypoglycemia, hyperbilirubinemia, interventional or cesarean delivery, shoulder dystocia, and birth trauma.[18,19] In our study, it was found that prematurity was higher in the GDM group. Also, as expected, the number of LGA infants and NICU admission were significantly higher in neonates with GDM. The cesarean section rate was higher than the rates recommended by WHO in both groups .[20] This might be related to the fact that we are a tertiary center. Moreover, according to the Organization for Economic Co-operation and Development (OECD) 2020 data, the cesarean section rate in Turkey is 57.3%, which is quite high.[21] The increase in constant monitoring, doctors' fear of malpractice, and mothers' mistaken belief that cesarean delivery is safer for the baby are some of the reasons for this situation.
Our study has some limitations. Our data are retrospective and our sample size is relatively small and includes only the Turkish population. We do not have data on continuous glucose monitoring in pregnant women, and we are not sure whether they are following their diet properly and whether our results reflect specific time periods.

CONCLUSION

In conclusion, an elevated TyG index in the first trimester may predict GDM. In addition, our study shows that a high TG / HDL-C ratio in the first trimester may also predict GDM. However, not only population-based retrospective studies but also randomized controlled prospective studies with large samples should be performed to draw definite conclusions on this issue.

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