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Relationship Between Triglyceride-Glucose Index and Microvascular Complications in Hospitalized Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Aim: The increasing prevalence of diabetes mellitus (DM) brings about a rise in nephropathy, retinopathy, and neuropathy, which are microvascular complications of diabetes. The triglyceride-glucose (TyG) index is a convenient indicator of insulin resistance. It is related to microvascular and macrovascular complications among nonhospitalized patients with diabetes. However, it is unclear if the TyG index poses risks for vascular complications of type 2 DM in hospitalized patients. This study aims to investigate possible relations between this index and the risk of microvascular complications in hospitalized patients with type 2 DM.

Material and Methods: The present study included 420 type 2 DM patients who were hospitalized in our clinic between February 2019 and May 2022. The TyG index was measured as fasting triglycerides mg/dL × fasting glucose mg/dL/2. The presence of microalbuminuria (MAU), diabetic neuropathy, chronic kidney disease (CKD), and retinopathy (DR) were evaluated. The data were analzed using IBM SPSS 22.0 statistical software. The level of statistical significance was taken as $p<0.05$.

Results: Among the patients (164 males, 256 females), the median age was 61 years (20-91).. Diabetic nephropathy, retinopathy, and neuropathy rates were 34.0%, 35.4%, and 50.5%, respectively. Patients with diabetic nephropathy had significantly higher TyG index values (9.67±0.84) compared to those without (9.48±0.75, $p=0.019$). No significant associations were found between the TyG index and retinopathy or neuropathy.

Conclusion: High TyG index values were associated with diabetic nephropathy in hospitalized patients with T2DM. The TyG index may be a useful, easy-to-measure marker for early detection and prevention of diabetic nephropathy in clinical settings.

Keywords: *Triglyceride-glucose index, Diabetic retinopathy, Diabetic nephropathy, Diabetic neuropathy*

Hastanemizde Yatan Tip 2 Diyabetli Hastalarda Trigliserid/Glukoz İndeksi ile Diyabetin Mikrovasküler Komplikasyonları Arasındaki İlişki

ÖZ

Amaç: Diyabetes melitusun (DM) prevalansındaki artış, diyabete bağlı mikrovasküler (nefropati, retinopati ve nöropati) komplikasyonların artışını da beraberinde getirmektedir. Trigliserid/glukoz indeksi (TyG) insülin direncini yansıtmakta kullanışlı bir göstergedir. Ayakta tedavi alan diyabetli hastalarda mikrovasküler ve makrovasküler komplikasyonlar ile arasındaki ilişki gösterilmiştir. Ancak yatan hastalarda bu ilişki net değildir. Hospitalize olan tip 2 diyabetli hastalarda trigliserid/glukoz indeksi ile diyabetin mikrovasküler komplikasyonları arasındaki olası ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntemler: Bu çalışmaya Şubat 2019-Mayıs 2022 tarihleri arasında tip 2 DM nedeniyle yatırılan toplam 420 hasta dahil edildi. Trigliserid/glukoz indeksi açlık trigliserid mg/dl × açlık glukoz mg/dl/2 formülüne göre hesaplandı. Her bir hasta için mikroalbuminüri,

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kronik böbrek hastalığı (KBH), diyabetik nöropati ve retinopati (DR) varlığı değerlendirildi. Verilerin analizinde IBM SPSS 22 yazılımı kullanıldı. Anlamlılık değeri p<0,05 olarak kabul edildi.

Bulgular: Hastaların 256'sı (%61,0) kadın, 164'ü (%39,0) erkekti. Ortanca yaş 61 (20-91) yıl olarak hesaplandı. Hastaların %34,0'ünde nefropati, %35,4'ünde retinopati ve %50,5'inde nöropati saptandı. TyG indeksi diyabetik nefropatili hastalarda nefropatisi olmayan hastalara göre anlamlı derecede yüksekti (9,67±0,84 vs 9,48±0,75, p=0,019). Retinopati ve nöropatinin TyG indeksi ile ilişkisi yoktu.

Sonuç: Yüksek TyG indeksi, tip 2 DM'li hastalarda nefropati varlığıyla ilişkilidir ve pratikte diyabetik nefropatinin erken tespiti ve önlenmesi için ucuz, ölçümü kolay bir belirteç olarak kullanılabilir.

Anahtar Sözcükler: *Trigliserit-glikoz indeksi, Diyabetik retinopati, Diyabetik nefropati, Diyabetik nöropati*

INTRODUCTION

Diabetes mellitus (DM) is rapidly rising globally, particularly in developing countries. This increase is accompanied by a surge in diabetes-related microvascular complications, including nephropathy, retinopathy, and neuropathy (1). Diabetic nephropathy, the leading cause of end-stage renal disease, is the most common microvascular complication (2). This complication stands out as the most significant reason for blindness among people who work actively in the Western world (3). In patients with diabetic retinopathy, regulation of modifiable risk factors may positively affect the progression of the disease. Diabetic neuropathy is seen in 26% of patients 5 years after the diagnosis of DM and in 41% after 10 years. Asymmetric sensory changes occur in approximately half of patients with clinical DM (4).

Insulin resistance, which arises from metabolic abnormalities, is a primary contributing factor for type 2 DM. Chronic hyperglycemia and insulin resistance can lead to vascular damage, highlighting the importance of monitoring insulin resistance for preventing type 2 DM and its complications (5). Traditional methods like hyperinsulinemic euglycemic clamps to measure insulin resistance are expensive and time-consuming (6). As an alternative method, the homeostasis model assessment of insulin resistance (HOMA-IR) is extensively utilized in clinical settings (6). However, insulin and c-peptide assays are expensive and may not be available in all laboratories. Therefore, easier and more applicable methods are needed. The triglyceride-glucose (TyG) index can be obtained by values of fasting triglyceride and glucose used to detect insulin resistance. This index has a better predictive performance than the HOMA-IR and hyperinsulinemic-euglycemic glucose clamp (7,8).

Studies have explored the link between the TyG index and vascular damage. However, the predictive power of the TyG index for microvascular complications in hospitalized patients, who often have elevated glucose and triglyceride levels, remains unclear. Existing research on this topic is scarce. The present study aims to investigate the potential association between microvascular complications and the TyG index in hospitalized patients with type 2 DM.

MATERIALS and METHODS

This retrospective study was conducted between February 2019 and May 2022 by reviewing medical records of patients hospitalized for management of hyperglycemia and evaluation of diabetes-related complications.. Patients with type 1 DM, pregnant women, and patients aged below 18 were not accepted into the study. The glucose and lipid values of the patients were measured after 8 hours of fasting at night. The data on age, gender, fasting glucose, anti-diabetic drugs, lipid-lowering drugs, low-density (LDL) and high-density lipoprotein (HDL), triglyceride, total cholesterol, and HbA1c values of each patient were collected. The TyG index was calculated for each patient using the formula: fasting triglyceride (mg/dl) × fasting glucose (mg/dl) / 2 (5,6). The correlation between the TyG index and microvascular complications of diabetes was investigated.

For neuropathy examination, the pinprick test, light touch perception using 10-g monofilament, vibration threshold using a 128 Hz tuning fork, and ankle reflexes were evaluated. Patients who were found to have symmetrical, asymmetrical, or focal diabetic neuropathy and who use drugs for neuropathic pain were recorded as having diabetic neuropathy. To assess retinopathy, an ophthalmologist used an ophthalmoscope to examine the retina according to the International Classification of Diabetic Retinopathy established by the American Academy of Ophthalmology. Patients diagnosed with proliferative or non-proliferative diabetic retinopathy were categorized as having retinopathy. Following the American Diabetes Association guidelines, urinary albumin excretion was measured to assess nephropathy. Accordingly, our study recorded urine albumin/creatinine ratio <30 mg/gr as no nephropathy, and ≥30 mg/gr was recorded as high urinary albumin excretion and diabetic nephropathy. Chronic kidney disease (CKD) was defined as eGFR ≤ 60 mL/min per 1:73 m^2.

Statistical Analysis

Data analyses were performed using IBM SPSS 22.0 software. Descriptive statistics included numbers and percentages for categorical variables, and mean±standard deviation

or median and first and third quartiles (IQR) for the numerical variables. The Kolmogorov-Smirnov test was utilized to determine the conformity to normal distribution in the study groups. For two independent group comparisons, the T-test was employed when the condition of normal distribution was met. Additionally, the Mann-Whitney U test was utilized when this condition was not met. For the comparison of categorical variables, the chi-square test was employed. Statistical significance level was accepted as $p<0.05$. A power analysis was conducted following the methods of Liu et al. (9). We used the G*Power 3.1.9 software for the power analysis (α err=0.05, power 95%; effect size: 0.425; total sample size: 290 patients). We completed the study with 420 patients after accounting for exclusions and drop-outs.

RESULTS

The study sample consisted of 420 patients in total. Of these patients, 256 (61.0%) were female and 164 (39.0%) were male. The median age was 61 years (20–91), and the median duration for diabetes was 12.0 years (1–42). The data on nephropathy, retinopathy, and neuropathy were analyzed in 415, 412, and 418 patients, respectively. Nephropathy was observed in 141 (34.0%), retinopathy in 146 (35.4%), and neuropathy in 211 patients (50.5%) (Table 1).

Table 1: Demographical features and laboratory findings of patients.

Demographical and Laboratorial Parameters	Findings (n=420)
Age (year) *	61 (20–91)
Gender (male/female) n(%)	164(39.0) / 256 (61.0)
Duration of diabetes (years)*	12.0 (1–42)
Hypertension (n=355)	266 (74.9)
Diabetic nephropathy (n=415)	141 (34.0)
Diabetic retinopathy (n=412)	146 (35.4)
Diabetic neuropathy (n=418)	211 (50.5)
HbA1C (%±SD)	9.91±2.31
Total cholesterol (mg/dl)*	175 (80–790)
Triglyceride (mg/dl)*	168 (41–2189)
LDL cholesterol (mg/dl)*	101 (18–453)
HDL cholesterol (mg/dl)*	38 (15–103)
Fasting glucose (mg/dl)*	161.0 (37–640)
Triglyceride-glucose index±SD	9.54±0.79
Creatinine (mg/dl)*	0.79 (0.39–9.9)
Uric acid (mg/dl)* (n=371)	5.10 (1.40–13.40)

*Data are presendet as median (minimum.-maximum). SD, standart deviation. **LDL:** Low-density lipoprotein, **HDL:** High-density lipoprotein, **HOMA-IR:** Homeostasis model assessment for insulin resistance, **HbA1c:** Glycosylated hemoglobin

Patients with diabetic nephropathy had significantly higher TyG index values compared to those without nephropathy ($p = 0.019$). The TyG index value was 9.67±0.84 in patients with diabetic nephropathy, while it was 9.48±0.75 in patients without nephropathy. The TyG index was similar in those with and without retinopathy and those without neuropathy. The TyG index was 9.65±0.82 in diabetic retinopathy patients and 9.50±0.77 among patients without retinopathy ($p=0.078$). Furthermore, we observed a TyG index value of 9.62±0.83 in patients with diabetic neuropathy and 9.47±0.74 in patients without neuropathy ($p=0.051$) (Tables 2-4).

When the patients were grouped according to their HbA1c levels, higher rates of diabetic retinopathy and neuropathy were detected among patients with HbA1c ≥ 9 than those with HbA1c<9 ($p=0.002$ and $p=0.003$, respectively). There was no significant difference in nephropathy prevalence between the two HbA1c groups ($p = 0.724$). The mean Ty/G index was 9.22±0.76 in patients with HbA1c< 9% and 9.73±0.74 in patients with HbA1c ≥ 9% ($p<0.001$) (Table 2).

Table 2: The correlation between the TyG index and diabetic retinopathy.

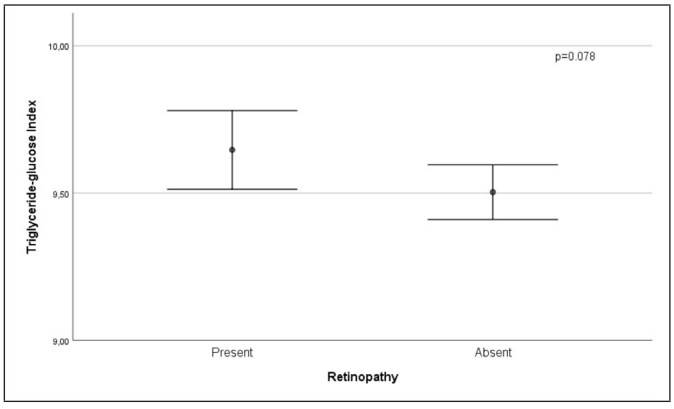
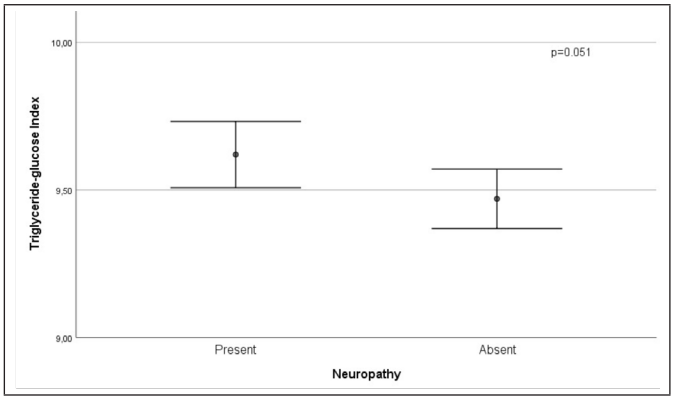


Table 3: The correlation between the TyG index and diabetic neuropathy.



DISCUSSION

Insulin resistance, a condition where body tissues become less responsive to insulin, is linked to dyslipidemia, high blood pressure, and hyperglycemia. Although the clamp method is considered the gold standard of insulin resistance measurement, it is impractical in clinical conditions and requires equipment (10). Therefore, insulin resistance is indirectly measured using specific methods designed for this purpose. The most common method is the homeostasis model assessment of insulin resistance (HOMA-IR), which estimates insulin resistance based on fasting glucose and insulin levels. However, HOMA-IR has limitations due to the variability in individual insulin levels. Standardization of insulin assays is crucial for accurate HOMA-IR measurements (11). According to a study, the TyG index obtained from triglycerides and glucose can be an effective marker in predicting insulin resistance. This study investigated body mass index, hip circumference, triglyceride, glucose, and HOMA-IR and TyG indices in healthy, obese, diabetic, and prediabetic individuals. It revealed that the TyG index overlapped with the hyperinsulinemic-euglycemic clamp technique (8). Several studies have explored the association between the TyG index and metabolic diseases like diabetes and cardiovascular diseases. However, research on the TyG index and microvascular complications in diabetes remains limited. The present study indicated that the TyG index had significant associations with diabetic nephropathy but not with retinopathy or neuropathy.

In a study on 1413 patients with type 2 DM, Srinivasan et al. found a remarkable association between retinopathy and the TyG index when the data were adjusted for blood pressure, smoking, and age. However, the TyG index was similar in those with and without macular edema. However, our study did not significantly associate the TyG index with retinopathy (11).

Table 4: The correlation between the TyG index and diabetic nephropathy.

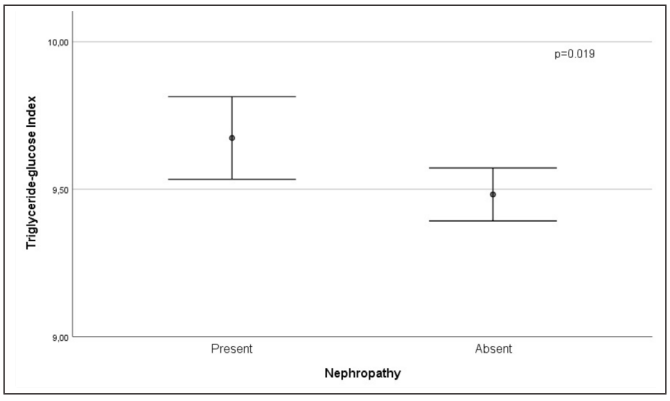


Table 5: Demographical features and laboratory findings in patients with HbA1c<9% and HbA1c ≥ 9%.

	HbA1c<9% (n=153)	HbA1c ≥ 9% (n=267)	p
Age (year±SD)	61.22±11.80	59.00±12.74	0.057
Gender (male/female), n (%)	52/101 (34/66)	112/155 (41.9/58.1)	0.108
Duration of diabetes (years)*	10.50 (0–38)	12.00 (0–42)	0.702
Hypertension (n=355)	98 (81.0)	168 (71.8)	0.058
Diabetic nephropathy (n=415), n(%)	50/152 (32.9)	91/263 (34.6)	0.724
Diabetic retinopathy (n=412), n(%)	38/147 (25.9)	108/265 (40.8)	**0.002**
Diabetic neuropathy (n=418), n(%)	62/152 (40.8)	149/266 (56.0)	**0.003**
HbA1C (%±SD)	7.52±1.09	11.28±1.61	**<0.001**
Total cholesterol (mg/dl)*	173.00 (88–414)	177.0 (80–790)	0.094
Triglyceride (mg/dl)*	158 (41–2189)	175 (50–1269)	0.127
LDL cholesterol (mg/dl)*	97 (18–215)	103 (23–453)	**0.033**
HDL cholesterol (mg/dl)*	38 (21–83)	38 (15–103)	0.587
Fasting glucose (mg/dl)*	122 (41–302)	192 (37–640)	**<0.001**
Triglyceride-glucose index ±SD	9.22±0.76	9.73±0.74	**<0.001**
Creatinine (mg/dl)*	0.77 (0.39–4.03)	0.79 (0.43–9.90)	0.673
Uric acid (mg/dl) (n=371)*	5.20 (1.60–13.40)	5.0 (1.40–10.90)	**0.043**

*Data are presendet as median(minimum.-maximum). SD, standart deviation.

LDL: Low-density lipoprotein, **HDL:** High-density lipoprotein, **HOMA-IR:** Homeostasis model assessment for insulin resistance, **HbA1c:** Glycosylated hemoglobin.

Few studies have obtained similar results regarding the TyG index in diabetic neuropathy. For example, no correlation existed between diabetic neuropathy and the TyG index in Srinivasan et al. (11). Kwai et al. found no significant relationship between triglyceride levels and changes in axon functions in patients with type 2 DM (12). Presumably, this finding reveals that other mechanisms besides hyperglycemia and high triglycerides affect the development of diabetic neuropathy. Akbar et al. reported a significant variation in the TyG index in type 2 DM patients with and without cardiac autonomic neuropathy (CON). According to this study, the TyG index increased at an early stage in CON. The authors stated that the TyG index, which is an inexpensive and sensitive indicator of CON, could be used as a biomarker and can predict the course of the disease (13).

The TyG index was shown to be connected with a 2-fold increased risk for micro and macroalbuminuria. In the study by Pan et al., the index was highly correlated with albuminuria in hospitalized type 2 DM patients. In particular, this correlation was more significant among patients whose diabetes was poorly controlled and the elderly (5). Another study reported an independent relationship between fasting glucose and triglyceride levels and diabetic nephropathy, as well as a relationship between microalbuminuria and high TyG index (11). Under these findings, patients with nephropathy had significantly higher TyG index values than those without in our study.

Diabetic nephropathy is a multifactorial disease and a major microvascular complication in diabetic individuals. A study including 4721 hospitalized patients with type 2 DM showed a strong correlation between the TyG index and albuminuria level; however, the TyG index was not significantly correlated with GFR (5). This suggests that insulin resistance is more effective in the early stages of diabetic nephropathy, with decreasing effects in the later stages. Interestingly, this study again suggested a higher association of the TyG index with albuminuria in individuals under 60, possibly suggesting that deterioration in beta cell functions and insulin resistance are more important in young people. In contrast, aging-related processes are more dominant in older ages.

According to Liu et al., diabetic nephropathy patients had significantly higher insulin resistance levels than those without diabetic nephropathy, as indicated by the TyG index and HOMA2-IR values. The TyG index (AUC 0.67) had a more significant ROC AUC score than HOMA2-IR (AUC 0.61). The cut-off value for the TyG index was >9.66, with a sensitivity level of 61.7% and a specificity level of 76% for nephropathy. In this study, while the TyG index and albuminuria were correlated, there was no association between GFR and the TyG index (9). Furthermore, the TyG index had a significant correlation with diabetic nephropathy in those with a GFR of 90 mL/min/1.73 m^2 and above but not in those with a GFR below 90 mL/min/1.73 m^2. On the other hand, in the study by Zhao et al. carried out with 2830 elderly individuals, the TyG index was highly correlated with chronic kidney disease and microalbuminuria (14).

To our knowledge, this is the first study in Turkey to investigate the association between the TyG index and microvascular complications in hospitalized patients with type 2 diabetes. However, it has certain limitations. Firstly, it was designed retrospectively, and the data were gathered from patients at a single hospital. We could not evaluate CON or other types of autonomic neuropathy. In addition, measuring the TyG index in hospitalized patients could be affected by hypoglycemic agents, lipid-lowering drugs, diet, and exercise compared to the outpatient clinic. The results of our study should also be evaluated in this context.

In conclusion, our study revealed that the TyG index and diabetic nephropathy were significantly associated among type 2 DM patients. The TyG index can serve as an easily accessible and reproducible marker with a lower cost to detect and prevent diabetic microvascular complications. Further studies with larger samples consisting of type 2 DM patients will better determine the potential uses of this promising marker.

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Author Contributions

Abbas Ali Tam contributed to the conception and design of the study. **Sevgül Fakı, Nurcan İnce, Feride Pınar Altay, Gülsüm Karaahmetli, Mehdi Houssein** prepared the manuscript and analyzed the data, **Oya Topaloğlu, Reyhan Ersoy, Bekir Çakır** contributed to writing –review & editing supervision. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethical Approval

The ethical approval was granted as per the Helsinki Declaration (Number: E.Kurul-E1-22-2682, Date: 15/06/2022).

Peer Review Process

Extremely and externally peer-reviewed.

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