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Triglycerides-Glucose Index as a Predictor of Stroke Risk in Hemodialysis Patients

Hemodiyaliz Hastalarında İnme Riskinin Belirleyicisi Olarak Trigliserit Glikoz İndeksi

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ÖZET

Arka Plan: Trigliserit-glukoz indeksi (TyG), insülin direncinin basit bir göstergesidir. TyG bağımsız olarak inme oluşumu ile ilişkilidir. Önceki çalışmalar inme ve hemodiyaliz hastalarında TyG arasındaki ilişkiyi araştırmıştır.
Amaç: Hemodiyaliz hastalarında inme ile TyG arasındaki ilişkiyi araştıran bir çalışma yoktur. Bu nedenle, TyG'nin hemodiyalizde inmeyi tahmin edip etmediğini incelemek istedik.
Yöntemler: Altı aydan uzun süredir hemodiyaliz tedavisi gören 149 son dönem böbrek hastalığı (ESKD) hastasını retrospektif olarak inceledik. Hastalar MR görüntüleri ve kliniklerine göre inmeli ve inmesiz olarak gruplara ayrıldı. İnme için bağımsız belirleyicileri belirlemek için ikili lojistik regresyon analizi yapıldı.
Bulgular: Ortalama TyG değeri 9,13 ± 0,74 idi ve inmeli hastalarda anlamlı olarak yüksekti (p= 0,003). Medyan değerin üzerinde olan grupta inmeli hasta sayısı daha yüksekti (OR= 1,981, p= 0,039). İki değişkenli korelasyon analizinde, TyG değeri C-reaktif protein ile pozitif, HDL ile negatif korelasyon gösterdi. Çok değişkenli analizimizin sonucunda yaş ve TyG değerleri inmenin bağımsız belirleyicileriydi.
Sonuç: Çalışmamızda regresyon analizinde TyG indeksinin inme için bağımsız bir belirteç olarak belirlenmesi, TyG indeksinin hemodiyalize giren hastalarda inme için yararlı bir gösterge olduğunu kanıtlamaktadır.

Anahtar Kelimeler: Trigliserit glukoz indeksi, son dönem böbrek hastalığı, hemodiyaliz, inme

ABSTRACT

Backround: The triglycerides-glucose index (TyG) is a simple indicator of insulin resistance. The TyG is independently associated with stroke occurrence. Previous studies have investigated the relationship between the TyG in stroke and hemodialysis patients.
Aim: There is no study investigating the relationship between stroke and TyG in hemodialysis patients. Therefore, we wanted to examine whether the TyG predicts stroke in hemodialysis
Methods: We retrostprctively analyzed 149 end-stage kidney disease (ESKD) who had been on hemodialysis for more than six months were included. The patients were divided into groups, stroke, and non-stroke, according to their MR images and clinics. Binary logistic regression analysis was performed to identify independent predictors for stroke.
Results: The mean TyG value was 9.13 ± 0.74 and significantly higher in patients with stroke (p= 0.003). The number of patients with stroke was higher in the group above the median value (OR= 1.981, p= 0.039). In the bivariate correlation analysis, the TyG value was positively correlated with C-reactive protein and negatively associated with HDL. As a result of our multivariable analysis, age and TyG values were independent predictors of stroke.
Conclusion: The determination of the TyG index as an independent predictor for stroke in the regression analysis in our study proves that the TyG index is a helpful indicator for stroke in patients undergoing hemodialysis.

Key words: Triglyceride glucose index, end-stage kidney disease, hemodialysis, stroke

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INTRODUCTION

The risk of stroke increases sevenfold in the first year of dialysis treatment, and these patients are four to ten times more at risk than in the normal population (1). Accelerated atherosclerosis and malnutrition-inflammation due to uremia, anticoagulants used during dialysis, are blamed for the increased risk of stroke, especially in dialysis patients (2). These uremia-specific factors trigger endothelial dysfunction, platelet aggregation, and vascular calcification and increase the risk of cerebrovascular disease.

It is known that insulin resistance leads to the emergence and recurrence of ischemic stroke. The increase in platelet adhesion, activation, and aggregation is among the reasons accused in this hypothesis (3). The triglyceride glucose index (TyG index), which is more readily applicable, less costly, and reliable, has been suggested in recent studies and has been determined to overlap with (HIEC) and HOMA IR. The TyG index has been associated with the progression of renal failure and also increased cardiovascular death in this group. As expected, increased TyG index has been shown to be associated with increased stroke. An increased TyG index is associated with mortality and poor prognosis in patients with acute ischemic stroke (4).

While the relevance of the TyG index to stroke in patients with CKD has been shown in different studies, there is very little literature data investigating this situation in hemodialysis patients. Therefore, in this study, we wanted to investigate the relationship between the triglycerides-glucose index and stroke in hemodialysis patients.

METHODS

Hemodialysis modality included conventional 4-h HD three times a week with polysulfone dialyzers. A mean blood flow rate of 250 ml/min (range 200–300 ml/min) was obtained during dialysis sessions. Dialysate fluid composition included 140 mEq/l of sodium, 1–4 mEq/l of potassium, three mEq/l of calcium, 1.8 mEq/l of magnesium, and 33 mEq/l of bicarbonate.

Patients were evaluated for ischemic or hemorrhagic stroke with clinical and MR imaging (axial T1-, T2- and proton density-weighted, slice thickness 5 mm, interslice spacing 1.5 mm on 1.5 T MRI scanners). As a result of the evaluation, 80 patients (both known and newly diagnosed) were included in the cerebrovascular disease group. The exclusion criteria were: (1) being under the age of 18, (2) the presence of active infection, (3) autoimmune disease, (4) malignant disease, (5) the presence of non-stroke cerebrovascular disease, and (6) patients with uncontrolled hypertension and diabetes.

Biochemical analyses

Venous blood samples for biochemical analyses were drawn after an overnight fast between 8.00 p.m. and 8.00 a.m at a single midweek dialysis session. Serum glucose levels were determined using an oxidase-based technique at Roche/Hitachi Modular System (Mannheim, Germany). Serum creatinine, urea, calcium, albumin, uric acid, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and phosphorus (P) were determined using a Synchron LX20 system (Beckman Coulter, USA) with original Beckman reagents. HDL-C levels were determined by a direct enzymatic method without precipitation. LDL-C levels were calculated using the Friedewald Formula (5). Serum C-reactive protein (CRP) levels were measured with an immunoturbidimetric assay using an automated clinical chemistry analyzer.

Definition of triglyceride glucose index

Triglyceride and glucose were obtained to calculate the TyG index. TyG index was calculated by formula Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)]/2 (6).

Statistical analysis

The Statistical Package conducted the statistical analysis for Social Sciences for Windows ver. 18.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard deviation or median and interquartile range (IQR), with a significance level of $p < 0.05$. For dichotomous variables, the frequency of positive occurrences was given along with their corresponding percentages. Statistical comparisons of individual groups were based on Student's t-test for continuous variables, whereas the Spearman test evaluated the correlations between groups. Binary logistic regression analysis was performed to determine independent predictors for cerebrovascular disease. Factors with a p-value of <0.2 were included in the univariate analysis in the regression test, while those that were significant in the univariate analysis were included in the multivariable evaluation.

RESULTS

The laboratory and clinical characteristics of the patients are summarized in Table 1. The mean TyG index value of 149 hemodialysis patients was 9.13 ± 0.74. Patients were divided into two subgroups (group 1: patients with stroke, n= 80 and group 2: patients without stroke, n= 69) according to stroke. TyG index value was significantly higher in patients with stroke (group 1) than in patients without stroke (group 2) (p= 0.003) (Table 1). When the patients were grouped according to the median TyG index value, the number of patients with stroke was higher in the group above the median value (OR= 1.981, p= 0.039) (Figure 1).

In the bivariate correlation analysis, the TyG index value was positively correlated with C-reactive protein (r= 0.313, p= 0.008) and negatively associated with HDL (r= -0.207, p= 0.011) (Figure 2).

We also performed binomial logistic regression analysis

Table 1. Demographic, clinic, and biochemical features of the patients undergoing hemodialysis according to stroke groups

Parameters	Patients with Storke (n=80) (Mean±SD), Median (IQR) or Frequency (n-%)	Patients without Stroke (n=69) (Mean±SD), Median (IQR) or Frequency (n-%)	p-value
Age (years)	61.75 + 16.17	58.39 + 18.18	0.184
Female/Male	40/40	32/37	0.623
History of DM	31 (39.2%)	30 (42.8%)	0.739
History of HT	51 (64.5%)	48 (68.5%9	0.728
White blood cell count (103/µL))	9.25 (6.61	8.75 (6.87)	0.869
Hemoglobin (gr/dl)	10.52 + 2.37	10.84 + 2.41	0.425
Platelet count (103/mm^3)	203 (196.3)	189.5 (142)	0.025
Glukoz (mg/dl)	158 (131.3)	111 (59.8)	0.142
Urea (mg/dl)	82.5 (88.25)	75 (92.78)	0.947
Creatinine (mg/dL)	4.66 (2.87)	4 (3.03)	0.236
Albumin (g/L)	3.33 + 0.72	3.26 + 0.75	0.547
Calcıum (mg/dl)	8.73 + 0.93	8.9 + 1.21	0.330
Phosphorus (mg/dl)	4.12 + 1.42	4.55 + 1.97	0.132
Parathormone (pg/ml)	107.5 (164.75)	89 (175)	0.702
Uric acid (mg/dl)	5.51 + 2.08	5.59 + 1.54	0.790
CRP (mg/L)	6.45 (6.72)	4.15 (5.5)	0.047
Magnesium (mg/dl)	2.19 + 0.51	2 + 0.35	0.013
LDL - cholesterol (mg/dL)	110 (62)	99 (66.5)	0.271
Triglyceride (mg/dl)	156.5 (117.5)	141.5 (87.3)	0.016
HDL- cholesterol (mg/dL)	36.5 (15.9)	37.5 (16.8)	0.868
TyG index	9.3 + 0.82	8.94 + 0.6	0.003

DM diabetes mellitus, HT hypertension, CRP C-reactive protein, LDL-cholesterol low density lipoprotein cholesterol, HDL-cholesterol high density lipoprotein cholesterol, TyG index Trigliserid glucose index

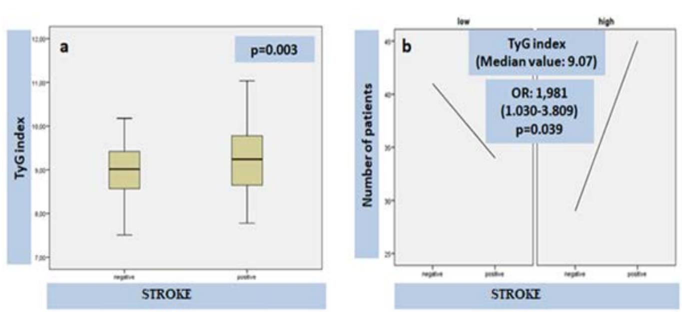

Figure 1. The analysis between TyG index and stroek in the patients undergoing hemodialysis **(a)** Comparison of stroke groups according to the TyG index **(b)** Comparison of patients with stroke according to median TyG index value

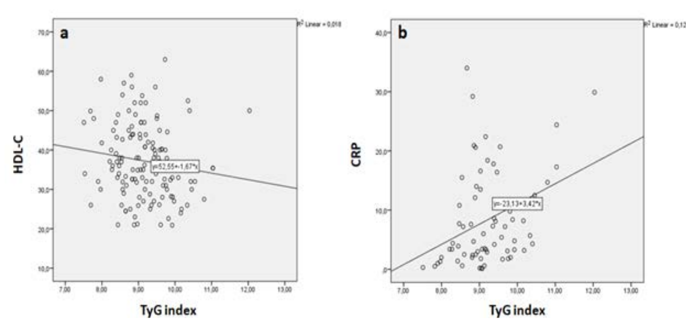

Figure 2. The correlation analyses between TyG index and **(a)** serum level of high density lipoprotein cholesterol and **(b)** C-reactive protein in the patients undergoing hemodialysis

to define variables independently associated with stroke in hemodialysis patients (Table 2). Age, gender, platelet count, glucose, phosphorus, magnesium, C-reactive protein, and TyG index were included in this model. As a result of our multivariable analysis, age and TyG index values were independent predictors of stroke.

DISCUSSION

This study, in which we investigated the relationship of the TyG Index with stroke in hemodialysis patients, had several main findings. Firstly, the TyG index was higher in the group with stroke in hemodialysis patients. Secondly, the number of patients with stroke was higher in the group with the TyG

Table 2. Binomial Logistic Regression Analysis of stroke and other parameters in the patients undergoing hemodialysis

	Univariate Analysis		MultivariateAnalysis	
Parameters	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p-value**
Age (years)	1.022 (1.016-1.031)	**0.033**	1.019 (1.014-1.033)	**0.045**
Gender	1.218 (0.639-2.321)	0.549	-	-
Platelet count (10^3/mm^3)	1.003 (1.00-1.006)	**0.05**	1.003 (0.996-1.010)	0. 345
Glukoz (mg/dl)	1.161 (0.604-2.234)	0.654	-	-
Phosphorus (mg/dl)	0.863 (0.710-1.047)	0.136	-	-
Magnesium (mg/dl)	2.337 (0.933-5.855)	0.070	-	-
CRP (mg/L)	0.999 (0.992-1.005)	0.672	-	-
TyG index	2.027 (1.247-3.296)	**0.004**	2.053 (1.243-3.389)	**0.005**

CRP C-reactive protein, TyG index Trigliserid glucose index

index above the median value than in the group with the lower median value. Third, the TyG index was positively correlated with CRP and negatively associated with HDL. Finally, age and TyG index values were independent predictors of stroke. The lipid pattern seen in ESKD patients is high triglyceride levels and decreased high-density lipoprotein (HDL) levels. Our study's negative correlation between the TyG index and HDL is consistent with the CKD lipid pattern. Therefore, current guidelines recommend using lipid-lowering agents in patients with CKD who are not on dialysis, but there are insufficient data on their use in patients undergoing dialysis. (7). In our study, no significant difference was observed between the two groups regarding LDL and HDL cholesterol levels, but triglyceride levels were significantly higher in the stroke group. In addition, those with diabetes mellitus and hypertension were similar between the two groups, and there was no significant difference. Therefore, it may be correct to think that the difference in triglyceride levels between the two groups is related to stroke.

Insulin resistance causes hyperglycemia by affecting the activity and expression of glucose transporters in plasma and hypertriglyceridemia by increasing lipid metabolism, triglyceride synthesis, and release into plasma. Stroke and ESKD cause higher insulin resistance in this group, which may explain why the TyG index and triglyceride levels are higher (8). However, accelerated atherosclerosis due to uremia, malnutrition-inflammation, and anticoagulants are held accountable for ischemic stroke in hemodialysis patients, and it causes platelet aggregation by inducing endothelial dysfunction (1). Studies have shown that insulin resistance contributes to endothelial dysfunction, which causes platelet reactivation and chronic inflammation (9). In addition, it has been demonstrated that improving insulin resistance by providing blood sugar control with insulin-sensitizing treatments reduces thrombosis.

However, studies have shown that thrombocyte activation may develop even under treatment and cause stroke. Yinping et al. in their research, which included 1002 cases of acute ischemic stroke who received antiplatelet therapy, found the TyG index as an indicator of insulin resistance and also found a correlation between high residual on-treatment platelet reactivity (HRPR) and TyG in patients under treatment. The same study observed that as the TyG index increased, the platelet count increased significantly (10). Antiplatelet therapies can reduce aggregation by inhibition of thromboxane A2. However, it has been suggested that insulin resistance may cause activation by activating platelets through different mechanisms other than the thromboxane pathway (11-13). In our study, the higher platelet levels in the stroke group might be higher due to these different pathways and mechanisms, such as increased TyG index and insulin resistance.

Inflammation markers such as CRP and IL-6 TNF alpha were found to be positively correlated with GFR in the Chronic Renal Insufficiency Cohort (CRIC) study (14). In CKD patients, it has been shown that inflammatory cytokines are released not only from lymphocytes but also by the dysfunctional adipose tissue. Previous studies have shown that renal replacement therapies such as hemodialysis are associated with chronic inflammation in patients with CKD and that inflammation markers such as CRP and IL-6 are found to be high in the plasma (15). Qi Mao et al., in their study on patients with non-ST MI, found a positive correlation between the TyG index and CRP and a negative correlation with HDL cholesterol. In this study, patients were grouped according to the median TyG index value, and the CRP (8.4 μg/dl) level was highest in the group with a high TyG index with a median value of >8.85. Likewise, the group with the lowest HDL cholesterol level had the highest TyG index (16).Similarly, in a cohort study investigating the relationship between the TyG index and arterial stiffness in another study conducted in China, CRP levels increased as the TyG index increased (17). In the findings of our study, the CRP level was higher in the group with a high TyG index and showed a positive correlation.Although the whole group was hemodialysis patients, had a similar number of diabetic and hypertensive patients, and did not receive any lipid-lowering treatment, the significant difference in TyG Index, CRP, and HDL between these two groups could be explained by CKD-related uremia and increased inflammation due to hemodialysis itself and stroke. We can associate the increase in inflammation and insulin resistance with increased TyG, increased CRP, and decreased HDL cholesterol, which are biomarkers of insulin resistance.

The risk of cerebrovascular disease is significantly higher in dialysis patients. In the US-based Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) data, the risk of stroke was found to be 10-fold, while ischemic stroke constituted 76% of them (18). Several studies have proven that the TyG index is independently associated with CVD. A higher TyG index indicates all-cause mortality and poor outcomes in patients with acute ischemic stroke (19-20). TyG index, an indicator of insulin resistance in many atherogenic diseases such as stroke, has been accepted as a helpful marker. Insulin resistance contributes to mortality by causing apoptosis in macrophages of vascular smooth muscle cells by causing muscle loss with increased proinflammatory cytokines and prothrombotic effect, increased sympathetic activity in muscles and catabolism, and increased platelet adhesion in CVD (21-23).

CONCLUSIONS

In our study, the TyG index was higher in hemodialysis patients with CVD than in those without. It is known in the literature that the TyG index is high in both CVD and CKD patients, but data on patients with CVD undergoing dialysis are scarce. Quiroga et al. (15) compared to his study, the median value of the TyG index was found to be higher in our study (respectively,8.63-9.07). This was thought to be because our study included stroke and CKD patients. Again, as in the study mentioned above, the stroke rate was higher in the group with a TyG index above the median value. In addition, the determination of the TyG index as an independent predictor for stroke in the regression analysis in our study proves that the TyG index is a helpful indicator for stroke in patients undergoing hemodialysis (15).

Etik Kurul: This retrospective studywas approved from the Medical Ethics Committee of our hospital (Date and Ethics Committee Number2022-4084).

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