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Original article

Running title: THR in type 2 DM with chronic complications

Triglyceride to High Density Lipoprotein Cholesterol Ratio is Elevated in Patients with Complicated Type 2 Diabetes Mellitus

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SUMMARY

Introduction/Aims: Microvascular and macrovascular complications lead to recurrent hospital admissions, hospitalizations, disability, and death in the course of type 2 diabetes mellitus (T2DM). Triglyceride to HDL cholesterol ratio (THR) is associated with insulin resistance. We aimed to find out whether there is a relationship between THR and diabetic complications in patients with T2DM.
Methods: Patients with T2DM were enrolled in the study. The study population was divided into two groups according to the presence or absence of diabetic complications. Characteristics and laboratory data of the patients with (group A) and without (group B) diabetic complications were compared.
Results: Median THR values of the groups A and B were 3.86 (0.33 - 53.38) and 2.86 (0.63 - 17.88), respectively (p = 0.006). THR level was significantly and positively correlated with glycated hemoglobin (HbA1c) (r = 0.12, p = 0.04) and fasting glucose levels (r = 0.14, p = 0.02).
Conclusion: We suggest that THR should be monitored in patients with type 2 diabetes mellitus in order to detect diabetic microvascular complications earlier. Increased THR levels should prompt further investigation of diabetic complications in this population.

Keywords: **type 2 diabetes mellitus, HbA1c, triglyceride to HDL cholesterol ratio, diabetic complications**

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INTRODUCTION

The frequency and complications of type 2 diabetes mellitus (T2DM) are increasing all over the world. While coronary artery disease, peripheral artery disease and stroke are macrovascular complications, diabetic retinopathy, neuropathy, and nephropathy are considered as microvascular complications of T2DM (1, 2). Microvascular and macrovascular complications lead to recurrent hospital admissions, hospitalizations, disability and death in the course of the disease (3 - 5).

The incidence of atherosclerotic heart disease is also increasing in T2DM. Dyslipidemia, as well as hypertension, has a pivotal role in this increase. Especially high plasma triglyceride (TG), high low density lipoprotein (LDL) and low high density lipoprotein (HDL) levels have been reported (6, 7). In the lipid arm of The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, it was mentioned that cardiovascular deaths can be prevented by intensive use of statins and/or fibrates in patients with T2DM. The aim of that study was to reduce LDL and TG levels as much as possible by administering large amounts of lipid-lowering drugs in diabetic patients with impaired lipid profile and it was determined that cardiovascular complications and mortality decreased by decreasing those lipid parameters in following years after the reduction of lipid parameters (8). There are studies in the literature showing that high TG levels and TG/HDL ratio (THR) indicate insulin resistance (9, 10). There is also a study in the literature showing that THR may be an indicator of T2DM (11).

In this study, we aimed to find out whether there is a relationship between THR and diabetic microvascular complications in subjects with T2DM by comparing THR levels of the patients with and without diabetic complications.

PARTICIPANTS AND METHODS

Patients

Patients with type 2 diabetes mellitus who visited internal medicine outpatient clinics of Abant Izzet Baysal University hospital between 2020 January and December 2020 were enrolled to the present retrospective study. Patients younger than 18 years of age, pregnancy, thyroid diseases, and duration of diabetes less than 5 years were excluded. The study population was divided into two groups. After getting approval from the ethics committee (approval number: 2021/92), age, gender, anthropometric measurements (height, weight, waist and hip circumference) of the subjects with T2DM patients, the drugs they use (oral antidiabetics, insulins, lipid-lowering drugs and other drugs, if any), complications (if any: neuropathy, nephropathy, retinopathy, coronary artery disease, peripheral artery disease, stroke) were recorded from the institutional database and patients' files. Group A consisted of diabetic patients with any diabetic chronic complications, such as retinopathy, neuropathy, nephropathy, coronary artery disease, peripheral artery disease and stroke. Patients with either microvascular or macrovascular complications were enrolled into this group. Group B was type 2 diabetic subjects without chronic complications. Moreover, diabetics with an HbA1c level lower than 7% are classified as well-controlled diabetics and the remaining subjects were assigned as poorly controlled diabetics. Characteristics of the group A and B were compared.

Laboratory analyses

Blood glucose, urea, creatinine, glomerular filtration rate (GFR), total cholesterol, LDL cholesterol, HDL cholesterol, TG values, aspartate transaminase (AST), alanine transaminase (ALT), glycated hemoglobin (HbA1c), leukocyte (WBC), hemoglobin (HGB), hematocrit (HCT), platelet (PLT), protein and creatinine in spot urine values were recorded retrospectively. THR was calculated by division of triglyceride with HDL. Variables of the groups A and B were compared.

Statistical analyses

Statistical analyses were held with SPSS software (SPSS for Windows 20.0, IBM Co, Chicago, IL, USA). Kolmogorov-Smirnov test was used to analyze whether study parameters were distributed normally or not between the study groups. While variables with normal distribution were expressed as mean ± standard deviation and compared with independent samples t test, variables without normal distribution were expressed as median (min-max) and compared with Mann-Whitney U test. Categorical variables were analyzed with Chi-square test

and expressed as numbers and percentage. Correlation analysis was held with either Pearson's correlation analysis test (for parametric variables) or Spearman's correlation analysis test (for non-parametric variables). ROC analysis was done to determine sensitivity and specificity of THR in detecting diabetic complications. The p value lower than 0.05 was considered as statistically significant.

RESULTS

The study population consisted of 261 subjects (149 men and 112 women) - 162 in group A and 99 in group B. Ages of group A and B were 64 (42 - 89) years and 60 (33 - 93) years, respectively (p = 0003). There were 98 (60.5%) men and 64 (39.5%) women in group A and 51 (51.5%) men and 48 (48.5%) women in group B. Gender was not statistically different in both groups (p = 0.15).

General characteristics and laboratory data of group A and group B are summarized in Table 1. Body weight (p = 0.22), waist circumference (p = 0.37) and body mass index (p = 0.64) were not significantly different between the groups.

Serum levels of LDL (p = 0.1), HDL (p = 0.28), total cholesterol (p = 0.48) and uric acid (p = 0.6) were similar between the groups.

Median glucose levels of groups A and B was 173 mg/dl (50 - 800 mg/dl) and 141 mg/dl (68 - 326 mg/dl) (p < 0.001), respectively. Median HbA1c levels of groups A and B was 8.75% (5.7% - 17.6%) and 7.5% (5.4% - 16.5%), respectively. The difference between groups was statistically significant (p < 0.001). The duration of T2DM was significantly longer in group A (10 (1 - 40) years) compared with group B (5 (1 - 30) years) (p = 0.002).

Median serum urea level was significantly higher in group A compared with group B - 36 (13 - 334) mg/dl and 30 (17 - 83) mg/dl, respectively (p < 0.001). Median serum creatinine levels was signif-

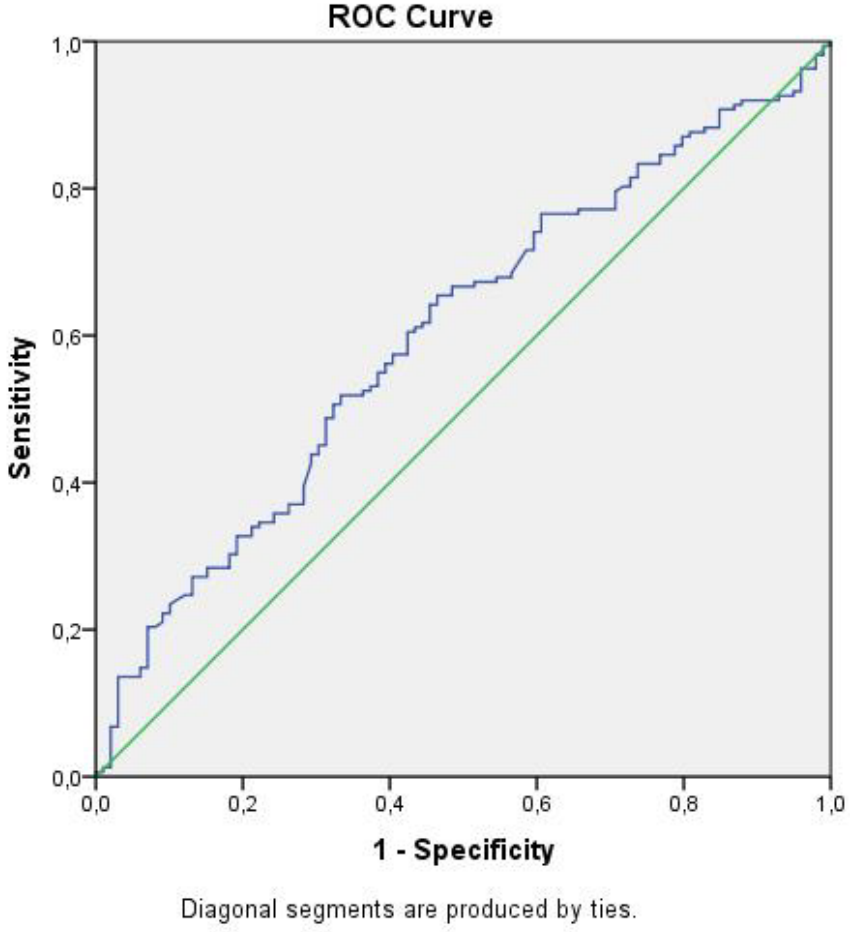

Figure 1. *The ROC curve of THR in complicated type 2 diabetes mellitus patients*

Table 1. *General characteristics and laboratory data of the study population*

	Group A	Group B	p value
Men (n %)	98 (60,5%)	51 (51,5%)	0.15
Women (n %)	64 (39,5%)	48 (48,5%)	0.15
Mean ± SD			
Age (years)	64,7 ± 9,6	60,9 ± 10,6	**0.003**
Weight (kg)	83,6 ± 14,6	80,4 ± 11,7	0.08
LDL (mg/dL)	100,8 ± 34,8	108 ± 33,3	0.10
Median (Min. – Max.)			
BMI (kg/m²)	30,3 (19,6 - 55,6)	29,8 (22 - 41,3)	0.64
Waist circumference (cm)	105 (72 - 149)	103 (82 - 128)	0.37
Duration of T2DM (years)	10 (1 - 40)	5 (1 - 30)	**0.002**
HbA1c (%)	8,8 (5,7 - 17,6)	7,5 (5,4 - 16,5)	**< 0.001**
Glucose (mg/dL)	173,5 (50 - 800)	141 (68 - 326)	**< 0.001**
Urea (mg/dL)	36 (13 - 334)	30 (17 - 83)	**< 0.001**
Creatinine (mg/dL)	0.94 (0,4 - 6,2)	0.82 (0,6 - 2)	**< 0.001**
GFR (%)	76,8 (8,2 - 120)	89 (62 - 122)	**< 0.001**
HDL (mg/dL)	43,55 (7,4 - 110,4)	45,3 (21,2 - 71,9)	0.28
THR (%)	3,86 (0,3 - 53,4)	2,86 (0,6 - 17,9)	**0.006**
Total Cholesterol (mg/dL)	175 (83 - 293)	179 (112 - 342)	0.48
Albumin (g/dL)	4,3 (2,4 - 5,2)	4,4 (2, 33, 4, 9)	**0.001**

Group A: diabetic subjects with chronic complications; group B: diabetic subjects without chronic complications

icantly higher in group A compared to group B - 0.94 (0.39 - 6.2) mg/dl and 0.82 (0.56 - 2) mg/dl, respectively ($p < 0.001$). Median GFR levels were significantly lower in group A compared to group B - 76.75 (8.2 - 120 mg/dl and 89 (62 - 122) mg/dl, respectively ($p < 0.001$).

Serum albumin level was significantly lower in group A compared to group B - 4,29 (2,36 - 5,2) g/dL and 4,4 (2, 33, 4, 9) g/dL, respectively ($p = 0.001$).

Median THR of groups A and B was 3.86 (0.33 - 53.38) and 2.86 (0.63 - 17.88), respectively. The difference between groups was statistically significant ($p = 0.006$).

HbA1c level was significantly and positively correlated with the duration of T2DM ($r = 0.39$, $p < 0.001$), glucose ($r = 059$, $p < 0.001$) and THR ($r = 0.12$, $p = 0.04$) levels. THR level was significantly and positively correlated with glucose ($r = 0.14$, $p = 0.02$) levels. The duration of T2DM, urea, creatinine, GFR and albumin was not correlated with THR levels.

The rates of statin use was more common in group A compared to group B ($p = 0.04$). The rates of fibrate use ($p = 0.48$), cigarette use ($p = 0.11$), exercise ($p = 0.21$) were similar in study groups ($p = 0.48$). The presence of additional disease was significantly higher in group A than in group B ($p = 0.02$). In terms of dietary compliance, diet noncompliance patients were significantly higher in group A than in group B ($p < 0.01$).

More patients in group A were using insulin alone or combined with insulin and oral antidiabetic drugs compared to group B ($p < 0.01$). The number of patients with poorly controlled diabetics in group A was statistically significantly higher than in group B ($p = 0.04$). One hundred twenty-six of 162 patients in group A were poorly controlled diabetics, while 36 were well controlled diabetics.

A ROC analysis revealed that THR values greater than 2.92 were 67% sensitive and 51% specific for determining T2DM patients with diabetic complications (AUC: 0.60, $p = 0.006$, 85% CI: 0.53 - 0.67). Figure 1 shows the ROC curve of the THR.

DISCUSSION

The main finding of the present study is that THR of the type 2 diabetic subjects with diabetic complications was significantly elevated compared to the THR of the subjects without diabetic complications. Interestingly, THR levels of the diabetic patients were correlated both with HbA1c and fasting blood glucose levels. Considerably high sensitivity and specificity of the THR in selecting diabetic subjects with diabetic complications were also noted as an important result of the present study.

Type 2 diabetes mellitus is characterized with inflammatory burden and this degree of inflammation is even higher in diabetic subjects with microvascular complications. The MADKID study showed that inflammatory markers were increased in patients with diabetic kidney injury compared to the diabetics without diabetic kidney damage (12). Another inflammatory predictor that has shown to be elevated in diabetic subjects with complications is platelet distribution width. Data in literature suggest that platelet distribution width of the diabetic patients with diabetic nephropathy and diabetic neuropathy was significantly higher than the platelet distribution width of the diabetic subjects without nephropathy and neuropathy (13).

Diabetic microvascular complications may also promote alteration in metabolism. Kocak et al. found that diabetic nephropathy was associated with increased serum uric acid levels (14). The ratio of uric acid and HDL cholesterol is also related with diabetic complications. Authors reported that uric acid/HLD ratio was positively correlated with serum creatinine and negatively correlated with glomerular filtration rate in patients with type 2 diabetes mellitus (15).

Inflammatory cytokines have also been suggested to be related with diabetic microvascular complications in recent studies. For instance, neuregulin-4 levels of the diabetic patients without microvascular complications was significantly increased compared to the neuregulin-4 levels of the diabetic subjects with microvascular complications (16). Authors found that urinary kidney injury molecule-1 levels were significantly increased in diabetic patients with nephropathy compared to those in healthy controls (17). Serum omentin levels of the patients with diabetic nephropathy and healthy volunteers were compared and significantly decreased omentin levels were reported in diabetic nephropathy group (18). THR is also considered as an inflammatory predictor similar to the novel hemogram derived inflammatory indices, uric acid, uric acid/HDL ratio, neuregulin-4, omentin and urinary kidney injury molecule-1. Therefore, the association between THR and diabetic complications in patients with type 2 diabetes mellitus is a finding which is consistent with literature sources.

There are several reports pointing out the correlation between THR and various clinical inflammatory states. Elevated THR levels were associated with all-cause mortality in patients with renal transplant recipients (19). Furthermore, chronic graft failure after renal transplantation was suggested to be predicted by increased THR levels (20). In addition, high THR was correlated with the risk of mortality in peritoneal dialysis patients (21). Similarly, we reported an elevated THR in diabetic subjects with microvascular complication, including diabetic nephropathy.

Development of arterial stiffness and other types of coronary arterial diseases were associated with elevated THR levels (22). Authors found that increased levels of THR were independent risk factor for peripheral and carotid arterial diseases (23). In a recent study, the author concluded that intracranial atherosclerosis was associated with high THR values (24). These data claimed that THR could be a predictor of vascular conditions in various diseases. Our data also suggested previous findings by reporting higher THR levels in diabetic subjects with microvascular complications.

Recent studies found that THR was associated with other metabolic disorders, including hepatic steatosis (25). Hepatic steatosis is also associated with metabolic disturbance and increased insulin resistance as seen in type 2 diabetes mellitus. Similarly, we found elevated THR levels in diabetic subjects in the present study.

The limitations of the present study are relatively small study population and single- center nature of the work. A retrospective design could also be another limitation. However, to the best of our knowledge, this is the first study in literature that reported higher THR levels in diabetic subjects with diabetic microvascular complications.

CONCLUSION

We suggest that THR should be monitored in patients with type 2 diabetes mellitus in order to detect diabetic chronic complications earlier. Increased THR levels should prompt further investigation of diabetic complications in this population.

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Article info

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Odnos triglicerida i lipoproteinskog holesterola visoke gustine povišen je kod bolesnika sa iskomplikovanim dijabetesom melitusom tipa 2

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S A Ž E T A K

Uvod/Ciljevi. Mikrovaskularne i makrovaskularne komplikacije dovode do rekurentnih prijema u bolnicu, invaliditeta i smrtnog ishoda tokom dijabetesa melitusa tipa 2 (T2DM-eng). Odnos trigicerida i lipoproteinskog holesterola visoke gustine (THR-eng.) povezan je sa insulinskom rezistetncijom. Cilj ove studije bilo je ispitivanje veze između odnosa triglicerida i lipoproteinskog holesterola i dijabetičkih komplikacija kod bolesnika sa dijabetesom melitusom tipa 2.

Metode. Studija je uključila bolesnike sa dijabetesom melitusom tipa 2 koji su bili podeljeni u dve grupe u zavisnosti od prisustva ili odsustva dijabetičkih komplikacija. Upoređivane su karakteristike i laboratorijski podaci bolesnika sa (grupa A) i bez (grupa B) dijabetičkih komplikacija.

Rezultati. Medijana THR vrednosti iznosila je 3,86 (0,33 - 53,38) u grupi A i 2,86 (0,63 - 17,88) u grupi B, (p = 0,006). Nivo odnosa trigicerida i lipoproteinskog holesterola visoke gustine bio je u značajnoj i pozitivnoj korelaciji sa glikoziliranim hemoglobinom (HbA1c) (r = 0,12, p = 0,04) i vrednostima šećera u krvi pre jela i pića (r = 0,14, p = 0,02).

Zaključak. Smatramo da odnos trigicerida i lipoproteinskog holesterola visoke gustine kod bolesnika sa dijabetesom melitusom tipa 2 treba pratiti kako bi se na vreme otkrile dijabetičke mikrovaskularne komplikacije. Povišene THR vrednosti bi trebalo da budu znak za dalje ispitivanje dijabetičkih komplikacija kod ove populacije.

Ključne reči: **dijabetes melitus tipa 2, HbA1c, odnos trigicerida i lipoproteinskog holesterola visoke gustine, dijabetičke komplikacije**