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The relationship between triglyceride/high-density lipoprotein cholesterol ratio and the functional significance of coronary lesions

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ABSTRACT

Aims: Have shown that triglycerides (TG) are an independent risk factor for cardiovascular disease (CVD). Dyslipidemia characterized by low high-density lipoprotein cholesterol (HDL-C) has been shown to be associated with symptoms of coronary artery disease (CAD). In studies, the TG/HDL-C ratio has been found to be strongly associated with parameters indicative of the severity of coronary disease. In this study, we aimed to investigate whether the TG/HDL-C ratio is associated with the functional significance of moderate coronary artery lesions.

Methods: A total of 102 consecutive patients, 72 male and 30 female, who underwent measurement of fractional flow reserve (FFR) due to moderate coronary stenosis (quantitative coronary analysis 40-70%) on angiography were included in the study. An FFR value ≤0.80 was accepted for hemodynamic significance.

Results: Among the 102 patients included in the study, it was determined that 52 (50.9%) had significant functional stenosis. Left ventricular ejection fraction of Group II was lower than Group I (60 (55-62.5) vs. 55(50-60), p=0.006). The male patient ratio was higher in Group II, but the difference between the two groups was not significant (68% and 77%, respectively, p=0.072). Univariate and multivariate logistic regression analysis showed that TG/HDL-C (OR=1.278, 95% CI=1.078-1.514, p=0.005) was an independent determinant of significant functional stenosis. ROC analysis revealed that the TG/HDL-C value was 3.89 and provided 64% specificity and 61.5% sensitivity in predicting hemodynamically significant coronary artery stenosis.

Conclusion: Elevated TG/HDL-C values are associated with the functional significance of angiographically moderate coronary artery stenosis.

Keywords: Coronary artery disease, triglyceride, fractional flow reserve, HDL-C

INTRODUCTION

Qualitative assessment of coronary artery stenosis with coronary angiography (CA) may not always be reliable. Measurement of fractional flow reserve (FFR) with a coronary pressure wire is a reliable method used for the functional assessment of coronary artery lesions, particularly when stenosis ranges between 40% and 70%, to measure the hemodynamic significance of coronary artery lesions and objectively quantify the severity of ischemia caused by coronary stenosis.[1-3] Fractional flow reserve is employed to directly assess the pressure decrease across epicardial coronary narrowings. It is acknowledged as the gold standard for identifying myocardial ischemia and is endorsed for use by the ESC 2018 myocardial revascularization guidelines. FFR-guided percutaneous coronary intervention (PCI) has demonstrated superiority over angiographic-guided PCI.[4] FFR-guided PCI results in better short-term and long-term outcomes than does angiographyguided PCI or medical therapy alone.[3] Studies have shown that an increase in plasma triglyceride (TG) levels is associated with an increased risk of coronary artery disease (CAD) even after adjustment for high-density lipoprotein cholesterol (HDL-C) levels.[5] Studies indicate that TGs are an independent risk factor for cardiovascular disease (CVD). High serum TGs are associated with the presence of atherogenic lipoproteins and are linked to important CVD risk factors such as metabolic syndrome. Patients with high TG levels have been reported to experience a greater increase in plaque volume.[6] Gianturco and colleagues illustrated that elevated triglyceride levels amplify macrophage phagocytosis and foster the transformation of macrophages into foam cells.[7] It has been shown that TGs increase the risk independently of these risk factors.[8] HDL-C is a class of lipoproteins responsible for reverse cholesterol transport. Low HDL-C has been shown to be associated with signs of CAD.[9] HDL-C reduction is common in CAD and is used as an indicator in assessing CVD risk. Evidence has emerged indicating that HDL-C is directly involved in the

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inflammatory process of atherosclerosis and that its predictive value can be enhanced by integrating it with inflammatory parameters.[10] Studies have reported that due to the limitations of FFR in identifying unstable plaques and its susceptibility to other factors, the close association between TG/HDL-C and coronary artery disease suggests that TG/HDL-C may play a significant role in identifying high-risk patients.[11]

The aim of this study is to examine the relationship between the TG/HDL-C ratio, which combines two accessible laboratory parameters with prognostic and predictive efficacy, and the functional significance of intermediate coronary artery stenosis assessed by FFR measurement.

METHODS

The study protocol was approved by the Bursa City Hospital Clinical Researches Ethics Committee (Date: 20.12.2023, Decision No: 2023-21/15) and conducted according to the principles of the Helsinki Declaration. Due to the retrospective design of the study, written informed consent could not be obtained from the patients.

This retrospective study was conducted with a total of 102 consecutive patients diagnosed with single intermediate coronary stenosis (quantitatively defined as 40-70%) between January 2020 and December 2023, who were evaluated with FFR measurement, including 30 women and 72 men. Patients who underwent coronary angiography for stable angina pectoris indication were included in this study. Patients with acute coronary syndrome; moderate or severe valvular heart disease; significant arrhythmia; hemodynamic instability; second lesion in the index coronary artery; another coronary artery with ≥40% lumen narrowing (determined by coronary angiography); history of previous surgical or PCI; acute or chronic inflammatory or infectious diseases; conditions such as anemia, chronic kidney failure, malignancy, and alcohol use were excluded from the study. Hospital records and charts were reviewed to determine patients' demographic, clinical, and angiographic data. Patients presented to the hospital electively, and blood parameters were calculated from blood samples obtained from the antecubital region after an 8-hour fasting period. Measurements included lipid profile, serum creatinine, and complete blood count. Baseline TG/HDL-C values of patients were determined by dividing triglyceride levels by HDL cholesterol levels. The institutional local ethics committee approved the study protocol.

FFR measurements for intermediate lesions in the coronary artery (40-70% stenosis rate) were performed at the discretion of cardiologists. After intracoronary administration of a bolus of 5000 units of heparin following calibration, the lesion was examined using a guide catheter without coronary artery side holes. After calibration, a 0.014-inch pressure monitoring guide wire (Abbott, PressureWire X) was placed distal to the stenosis. Before FFR measurements, a 200 μg bolus of nitroglycerin was administered intracoronarily. The distal intracoronary pressure of patients was recorded by gradually increasing doses of intracoronary adenosine until hyperemia was induced. FFR was determined as the ratio between the mean distal intracoronary pressure at the peak of hyperemia and the mean aortic pressure.

An FFR value of ≤0.80 was defined as functionally significant. Patients with an FFR value >0.80 constituted Group I, and patients with an FFR value ≤0.80 constituted Group II.

Statistical Analysis

The necessary statistical analyses were performed using SPSS software version 20.0 for Windows (SPSS Inc., Chicago, IL, USA), and the distribution shapes of variables were analyzed using the Kolmogorov-Smirnov test. While categorical determinants were given as percentages and numbers, continuous variables were presented as mean±standard deviation or median with interquartile range, depending on the distribution model of the variables. The Mann-Whitney U-test was preferred to calculate differences between non-parametric continuous variables, and categorical variables were compared using the Pearson chi-square test. Possible confounding factors for the severity of coronary artery lesions were determined using univariate and multiple logistic regression analysis. The multiple regression model was used to test variables with p values <0.10 in univariate regression analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal TG/HDL-C cutoff value to predict hemodynamically significant coronary artery stenosis. The level of statistical significance was set at<0.05.

RESULTS

The initial characteristics of patients are shown in. Significant functional stenosis was detected in 52 (50.9%) of the 102 patients included in the study. The left ventricular ejection fraction (EF) of Group II was lower than that of Group I (60 (55-62.5) vs. 55 (50-60), p=0.006). Although the proportion of male patients was higher in Group II, the difference between the two groups was not statistically significant (68% vs. 77%, p=0.072). There was no statistically significant difference between the two groups in terms of coronary risk factors, hyperlipidemia, hypertension, and diabetes mellitus. There was no statistically significant difference detected between the two groups in terms of coronary arteries undergoing FFR. The laboratory parameters of the two groups are reported in. Triglyceride levels were higher in Group II (129 (101-195) vs. 178 (122-269) mg/dl, p=0.010). The total cholesterol level was also higher in Group II, but the difference was not statistically significant. White blood cell (WBC) count (7.8 (6.5-9.2) vs. 9.5 (7.6-11.1) x103/μL, p=0.003), neutrophil count [4.6 (3.4-6.1) vs. 5.7 (4.2-7.3)x103/μL, p<0.026], and TG/HDL-C (3.74±2.13 vs. 6.14±4.37, p=0.003) were higher in Group II. Other laboratory data did not show significant differences between the two groups (Table 1). Univariate and multiple logistic regression analysis showed that TG/HDL-C (OR=1.278, 95% CI=1.078-1.514, p=0.005) was an independent determinant of significant functional stenosis (Table 2). ROC analysis revealed that a TG/HDL-C value of 3.89 had 64% specificity and 61.5% sensitivity in predicting hemodynamically significant coronary artery stenosis (Figure).

Table 1. Baseline characteristics and laboratory parameters of the study groups

Variables	Insignificant FFR (Group 1) (n= 50)	Significant FFR (Group 2) (n=52)	p value
	Total study population (n=102)		
Baseline characteristics			
Age, years	59.4±9.5	56.1±7.3	0.058
Male gender, n (%)	32 (64)	40 (76.9)	0.152
Diabetes mellitus, n (%)	16 (32)	20 (38.5)	0.495
Hypertension, n (%)	31 (62)	31 (59.6)	0.805
Dyslipidemia, n (%)	16 (32)	21 (40.4)	0.379
Current smokers, n (%)	21 (42)	28 (53.8)	0.231
Left ventricle EF, %	60 (55-62.5)	55 (50-60)	**0.006**
After adenosin FFR	0.86±0.03	0.74±0.03	**<0.001**
Body-mass index, kg/m^2	28.2(25.7-29.9)	28.4(26.4-29.9)	0.458
Laboratory parameters			
Glucose, mg/dl	105 (93-148)	110 (96-154)	0.364
Urea, mg/dl	14.1 (12.5-17)	13.7 (11-16.8)	0.286
Serum Creatinine, mg/dl	0.87 (0.74-1.00)	0.85 (0.75-0.99)	0.658
Total cholesterol, mg/dl	177.2±35	184.6±49.7	0.388
HDL cholesterol, mg/dl	42 (37-51)	38 (32-44)	**0.013**
LDL cholesterol, mg/dl	100.2±29.6	104.6±43.1	0.547
Triglycerides, mg/dl	129 (101-195)	178 (122-269)	**0.010**
WBC count, x10^3/µL	7.8 (6.5-9.2)	9.5 (7.6-11.1)	**0.003**
Neutrophil count, x10^3/µL	4.6 (3.4-6.1)	5.7 (4.2-7.3)	**<0.026**
Lymphocyte count, x10^3/µL	2.1 (1.6-2.6)	2.4 (1.9-2.9)	0.162
Hemoglobin, g/dl	13.8±1.8	13.7±2.1	0.639
RDW, fL	13.1 (12.4-14)	13.3 (12.5-14.1)	0.393
MPV, fL	10.4 (10-11.1)	10.1 (9.8-10.7)	0.026
Platelet count, x10^3/µL	244 (207-289)	268 (233-313)	0.072
TG/HDL-C	3.74±2.13	6.14±4.37	0.003
Coronary Arteries			
LAD	23	21	0.424
CX	14	15	0.568
RCA	13	16	0.385

All values are expressed as mean±standard deviation, median (25th and 75th interquartile range), and number (%). Abbreviations; CX: Circumflex, EF: Ejection fraction, FFR: Fractional flow reserve, HDL: High-density lipoprotein, LAD: Left anterior descending, LDL: Low-density lipoprotein, MPV: Mean platelet volume, RCA: Right coronary artery, RDW: Red cell distribution width, TG/HDL-C: Triglyceride/high-density lipoprotein cholesterol ratio, WBC: White blood cell. p values in bold signify statistically significant differences

Table 2. Univariate and multivariate logistic regression analysis showing the independent predictors for hemodynamically significant coronary artery stenosis

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.956 (0.911-1.002)	0.062	0.956 (0.906-1.008)	0.094
Neutrophil	1.235 (1.022-1.492)	0.029	0.995 (0.576-1.719)	0.986
TG/HDL-C	1.269 (1.090-1.477)	0.002	1.278 (1.078-1.514)	0.005
WBC	1.242 (1.053-1.465)	0.010	1.187 (0.739-1.906)	0.478

Abbreviations; CI: Confidence interval, TG/HDL-C: Triglyceride/high-density lipoprotein cholesterol ratio, OR: Odds ratio, WBC: White blood cell

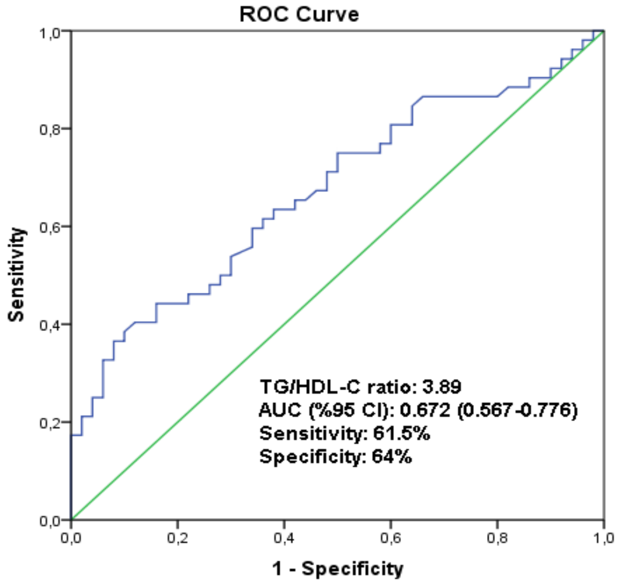

Figure. ROC curve analysis

DISCUSSION

In this study, we demonstrated that TG/HDL-C levels were significantly higher in patients with functionally significant coronary artery stenosis assessed by FFR measurement. We also found that TG/HDL-C was an independent determinant of hemodynamically significant coronary artery stenosis.

Qualitative assessment of stenosis seen with coronary angiography may not always be possible, and visible anatomical stenosis may not necessarily result in hemodynamic disturbance in the myocardial tissue.[12] Therefore, FFR measurement is a well-established method for the functional assessment of lesion severity. FFR measures the pressure drop across the stenosis by measuring pressure distal and proximal to the stenosis after achieving maximal hyperemia. This technique is linearly correlated with maximum myocardial blood flow provided by the respective coronary artery. Hemodynamically significant coronary artery stenosis reduces distal coronary artery pressure, thus reducing the ratio of distal coronary artery pressure to proximal coronary artery pressure and impairing myocardial tissue perfusion.[13] Pressure-derived FFR is an effective procedure for determining the hemodynamic significance of coronary artery stenosis and is superior to angiography when used to guide revascularization strategies.[14] In a study, patients with moderate coronary artery stenosis demonstrated similar outcomes regarding mortality, myocardial infarction, or any revascularization within 24 months following the index procedure, regardless of whether they were guided by FFR or IVUS.[15] In addition to determining hemodynamic significance, FFR also has prognostic predictive value. Tonino et al.[16] showed that routine FFR measurement in patients with multivessel CAD planning to undergo percutaneous coronary intervention reduced the rate of major adverse cardiac events in a 1-year follow-up. Earlier research indicated that in patients with acute MI and multivessel disease, both FFR-guided PCI and angiography-guided PCI targeting non-IRA lesions to achieve complete revascularization markedly decrease adverse clinical outcomes compared to performing PCI solely on the IRA.[17] Therefore, in this study, FFR measurement was used to determine the functional significance of coronary lesion severity and its relationship with TG/HDL-C levels. We found that TG/HDL-C levels were significantly higher in patients with functionally significant lesions (FFR≤0.80) assessed by FFR measurement.

Oxidative stress and inflammation are central mechanisms in the development and progression of atherosclerosis.[18,19] Unlike larger, low-density lipoprotein cholesterol (LDL-C) particles, small and dense LDL-C particles are more prone to oxidative damage.[20] These particles are rapidly taken up by arterial tissue and thus cause oxidative damage.[21-23] Hypertriglyceridemia is associated with the presence of small, dense LDL-C particles that are more easily oxidized, have higher affinity for extracellular matrix, migrate more easily from arterial walls, and are highly retained in the subendothelial space.[20-24] Hypertriglyceridemia is generally associated with a decrease in HDL-C.[25] Lipoproteins rich in triglycerides have various properties, such as increasing the expression of endothelial adhesion molecules and stimulating macrophage chemotaxis.[26] HDL-C molecules reduce macrophage accumulation and support the removal of oxidized cholesterol from the arterial wall.[27,28] Recent studies have also shown that HDL-C can inhibit monocyte activation, adhesion, and inflammation.[29,30] HDL-C increases nitric oxide synthase expression in endothelial tissues and supports vasorelaxation, in addition to its antioxidative and anti-inflammatory effects.[31] Higher HDL-C levels are known to provide protection against atherosclerosis and are associated with a better prognosis in patients with atherosclerosis.[32] Therefore, a high TG/HDL-C ratio may reflect an increased atherogenic risk and may play a role in explaining our findings as discussed above. The studies revealed that an elevated TG/HDL-C ratio, after adjusting for established CVD risk factors, was linked to an increased risk of CVD.[33] Plasma's atherogenic lipoprotein profile is an important risk factor for CAD. It is characterized by a high LDL-C to HDL-C ratio and elevated TG levels.[34] Studies have shown that the TG/HDL-C ratio is strongly associated with major adverse cardiovascular events (MACE) in patients with acute coronary syndrome undergoing percutaneous coronary intervention.[35] The high TG/HDL-C ratio has been shown to be an independent risk factor for recurrent percutaneous coronary intervention.[36] In a study by Kundi et al.,[37] it was suggested that a high TG/HDL-C ratio could increase the risk of in-stent restenosis through increased insulin resistance, endothelial dysfunction, atherosclerosis, oxidative stress, proinflammatory state, and proliferation of vascular smooth muscle cells. In another study by Luz et al.,[38] it was found that the TG/HDL-C ratio is a strong independent predictor of widespread coronary artery disease. In yet another study, the TG/HDL-C ratio was found to be strongly associated with noninvasive parameters of coronary disease severity.[39] Our study also found a significant association between TG/HDL-C levels and coronary artery stenosis evaluated after adenosine-induced hyperemia. All these literature data clearly demonstrate that patients with hemodynamically significant coronary lesions have a poor prognosis and are closely associated with increased TG/HDL-C.

Furthermore, white blood cell (WBC) and neutrophil counts were significantly higher in Group 2 patients. Studies have shown that total WBC counts are higher in patients with critical lumen narrowing compared to those with non-critical lumen narrowing.[40] However, in our study, WBC and neutrophil elevation were not identified as independent predictors in multivariate analysis.

It is noteworthy that coronary artery risk factors such as diabetes mellitus, hypertension, hyperlipidemia, smoking, and male gender were similar between Groups 1 and 2 in our study. It would be expected that one or more of these risk factors would be significantly higher in Group 2 patients. The reason for this may be the inadequacy of the sample size. Therefore, larger studies with larger sample sizes are needed.

Limitations

This study has some limitations. Firstly, the study has a retrospective design with a limited number of patients. Secondly, our study analyses are based on a single TG/HDL-C value, and we did not follow up on temporal changes and variations in TG/HDL-C. Lastly, our study does not provide a mechanistic explanation for the effect of specific TG and HDL-C subgroups on CAD severity and TG/HDL-C.

CONCLUSION

This study demonstrated that TG/HDL-C levels were independently associated with the functional significance of coronary artery stenosis assessed by FFR measurements. Lipid panels are widely used and cost-effective. Therefore, TG/HDL-C values can be easily determined in clinical settings to predict the likelihood of hemodynamically significant coronary artery stenosis. Larger sample sizes and prospective designs are needed in future studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Bursa City Hospital Clinical Researches Ethics Committee (Date: 20.12.2023, Decision No: 2023-21/15).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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