Idiopathic Thrombocytopenic Purpura and Cardiovascular Disease: Is Elevated Triglycerides to High-density Lipoprotein Cholesterol Ratio a Marker?

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ABSTRACT

Introduction: Triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) ratio is used as a cardiovascular risk marker. We aimed to investigate the relationship between TG/HDL ratio and eltrombopag use, current platelet values and whether or not splenectomy was performed in patients with chronic idiopathic thrombocytopenic purpura (ITP), and to emphasize its prognostic importance in terms of cardiovascular markers.

Methods: One hundred and thirty-nine chronic ITP patients followed in the hematology outpatient clinic were evaluated retrospectively. We investigated the negative effect of splenectomy, eltrombopag use and current platelet values on cardiovascular diseases. Patients were stratified into two groups according to their baseline TG/HDL-C ratio, using a TG/HDL-C ratio cut-off value of 2.5.

Results: A total number of 139 chronic ITP patients aged between 18-76 years, followed-up in the hematology outpatient clinic, were included in the study; and 102 of the patients were female (75%). The mean platelet value was 2913.24±103353.64/mm³, and the mean TG/HDL-C ratio was 2.91±2.09. There were 46 (33.8%) patients who had splenectomy. When patients were evaluated in terms of treatment modalities; 127 patients (93.4%), 60 patients (44.1%), and 19 (13.9%) patients were using methyl prednisolone, intravenous immunoglobulin, and eltrombopag, respectively. It was observed that the parameters were similar in patients using and not using eltrombopag (p>0.05). There was a weak and statistically significant correlation between TG/HDL-C values and age (r=0.275; p=0.001). There was a significant correlation between the presence of DM and hyperlipidemia and the TG/HDL-C ratio (p<0.05). In risk assessment, the TG/HDL-C ratio of individuals without coronary artery disease was 2.29 (1.47 3.38) and it was found to be statistically significantly low (p=0.025).

Conclusion: TG/HDL-C ratio can be used as an independent risk marker that can be diagnostic in predicting cardiovascular disease risk in ITP patients with advanced age and additional comorbid diseases (DM and hyperlipidemia).

Keywords: Triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-C), ITP, cardiovascular disease, splenectomy

Introduction

Worldwide, cardiovascular disease (CVD) is a major factor in both death and morbidity. Hypertriglyceridemia is clinically useful for estimating CVD risk independently. Low levels of high-density lipoprotein cholesterol (HDL) are significantly linked to the development and death from CVD (1). Additionally, the biomarker Triglycerides (TG)/HDL-C, which measures the relationship between high plasma TG and good cholesterol, was studied to help people with high cardiometabolic risk (2). High TG levels and rapidly catabolized HDL particles result in lower HDL concentrations and smaller, and dense TG-enriched HDL particlesreduce the cardio-protective, antioxidant and anti-inflammatory effects. As a result, the risk of atherosclerotic disease is increased by higher TG levels and lower HDL-C concentrations (3).

In patients who are unresponsive to first-line treatments, including corticosteroids, intravenous immunoglobulin (IVIG), and RhoGA, thrombopoietin receptor analogs used recently are among the treatment options in addition to splenectomy, rituximab, and immunosuppressive treatments. Rompilostim and eltrombopag are agents with proven efficacy in this group. In our country, only eltrombopag is used among this group of drugs.

An autoimmune condition called idiopathic thrombocytopenic purpura (ITP) is characterized by a low platelet count and a higher risk of

bleeding. Patients receiving continuous steroid therapy with hemostatic agents are at risk of atherosclerosis and thrombosis at the same time (4). Our main objective was to investigate the association between chronic patients with ITP' risk status and coronary artery disease (CAD); however, but we also wanted to determine how splenectomy, eltrombopag use, and current platelet values affected CAD.

Methods

One hundred and thirty-nine chronic patients with ITP followed in the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Hematology Outpatient Clinic were included in the study. The patients who were included were split into two groups: those who had splenectomy surgery and those who did not. The use of methylprednisolone, IVIG, rituximab, and eltrombopag was evaluated in terms of treatment. Newly diagnosed solid organs or untreated malignancies, advanced neuropsychiatric disease, pregnancy, emergencies, and acute or chronic infections were excluded. Age, gender, splenectomy surgery, presence of CAD, and additional disease [hypertension (HT), diabetes mellitus (DM), hypothyroidism, hyperlipidemia], use of eltrombopag, TG and HDL levels, and platelet counts were recorded. Previous myocardial infarction and cardiac surgery, presence of a cardiac pace-maker and arrhythmia, and heart failure with stent were accepted for the diagnosis of CAD. Patients diagnosed with DM, HT, hypercholesterolemia, and hypothyroidism under medical treatment were included.

After 8 h of fasting, venous blood was drawn in a lab setting to examine the basic blood sample. Low levels of HDL (mmol/L) and TG (mmol/L) were tested and recorded. By dividing the TG level (mmol/L) by the HDL-C level (mmol/L) for each patient, the baseline TG/HDL-C ratio was calculated. Two groups of patients were categorized based on a cut point of 2.5.

Ethics committee approval was obtained from University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital for the study (approval number: 2022/514/228/26, date: 30.06.2022). Informed consent papers were collected after inviting patients to participate in the study.

Statistical Analysis

The Shapiro-Wilk test was used to determine whether numerical variables were normal. Student's t-test was used to compare differences between two groups whose data were regularly distributed, whereas the Mann-Whitney U test was used to compare differences between groups whose data were not normally distributed. To determine the linear association between the TG/HDL and PLT variables, Spearman's rank correlation coefficient was used. For numerical variables, the descriptive statistics were mean ± SD, median (25%, 75%), and numbers and percentages (%) for categorical variables. P-values less than 0.05 were statistically significant when doing statistical analyses using the SPSS Windows version 21.0 program (SSPSS Inc, Chicago, IL, USA).

Results

A total number of 139 chronic patients with ITP aged between 18 and 76 years, followed up in the hematology outpatient clinic, were included in the study; and 102 of the patients were female (75%) and 34 were male (25%). The average age was 46.24±14.14 years and the median age was 44. The average platelet count was 92913.24±103353.64/mm³, and the median platelet count was 66,500/mm³; maximum platelet count was determined as 588,000/mm³. Average TG level was 128.12±74.73 mg/dL and median TG level was 114 mg/dL. The average HDL level was 50.02±22.86 mg/dL, and the median HDL level was 48 mg/dL. The average TG/HDL-Cratio was 2.91±2.09 and median TG/HDL-C ratio was 2.45. There were 46 (33.8%) patients who had splenectomy and comparison of age, platelet count, HDL, TG, TG/HDL-C parameters were found to be similar with those without splenectomy (p>0.05) (Table 1).

When patients were evaluated in terms of treatment modalities: 127 patients (93.4%), 60 patients (44.1%), and 19 (13.9%) patients were

Table 1. Descriptive statistics of demographic characteristics			
	Median	Mean ± SD	Min.-max.
Age	44	46.24±14.14	18-76
Female, n (%)	102 (75)	-	-
Male, n (%)	34 (25)	-	-
Methylprednisolone, n (%)	127 (93.4)	-	-
IVIG, n (%)	60 (44.1)	-	-
Hypothyroidism, n (%)	22 (16.2)	-	-
Splenectomy, n (%)	46 (33.8)	-	-
Coronary artery disease, n (%)	12 (8.8)	-	-
Hyperlipidemia, n (%)	7 (5.1)	-	-
Diabetes mellitus, n (%)	24 (17.6)	-	-
Hypertension, n (%)	27 (19.9)	-	-
Platelet	66,500	92913.24±103353.64	0-588000
HDL	48	50.02±22.86	0-188
Triglyceride	114	128.12±74.73	0-581
TG/HDL	2.45	2.91±2.09	0.48-15.70

SD: Standard deviation, IVIG: Intravenous immunoglobulin, Min.: Minimum, max.: Maximum, TG/HDL: Triglycerides to high-density lipoprotein cholesterol

using methyl prednisolone, IVIG, and eltrombopag, respectively. We observed that the parameters were similar in patients using and not using eltrombopag (p>0.05). The distribution of additional diseases is as follows: CAD in 12 patients (8.8%), hyperlipidemia in 7 patients (5.1%), DM in 24 patients (17.6%), HT in 27 patients (19.9%), and hypothyroidism in 22 patients (16.2%) (Table 1).

When the relationship between the demographic data, comorbidities, demographic characteristics of the patients, and an analysis of the TG/HDL-C ratio revealed a strong correlation between the levels of DM and hyperlipidemia and the ratio. In the presence of DM and hyperlipidemia, the TG/HDL-C value was determined to be statistically significant (p<0.05) (Table 2).

The relationship between the presence of CAD and demographic and biochemical parameters in the patients is shown in Table 3. It was determined that the age values of individuals with CAD, 59.5 (50 61.5), were found to be significantly higher the age values of individuals without CAD, 43 (34.5 57.5) (p=0.003). It was determined that the TG/HDL-C values of individuals with CAD, 3.50 (2.67 4.11), were found to be significantly lower than the TG/HDL-C values of individuals without CAD, 2,29 (1.47 3.38) (p=0.025) (Figure 1).

Discussion

We found that the TG/HDL-C ratios of the patients differed significantly among those without CAD, and the ratio suggests that it can be used as an independent predictor and biomarker. The coexistence of ITP and cardiovascular disease requires serious management by evaluating the thrombosis and hemorrhagic risk. In a meta-analysis of 207,515 participants, the TG/HDL-C ratio was independently associated with a higher risk of cardiovascular events (10). In the cohort study conducted between 2010 and 2020, 9,704 participants were followed for 6 years, and it was concluded that TG/HDL-C may be an important unique biomarker to predict CVD outcomes and progression when evaluating cardiovascular diseases (11).

"Early diagnosis, early treatment" has become critical to the prevention of coronary heart disease as the incidence of the condition has increased
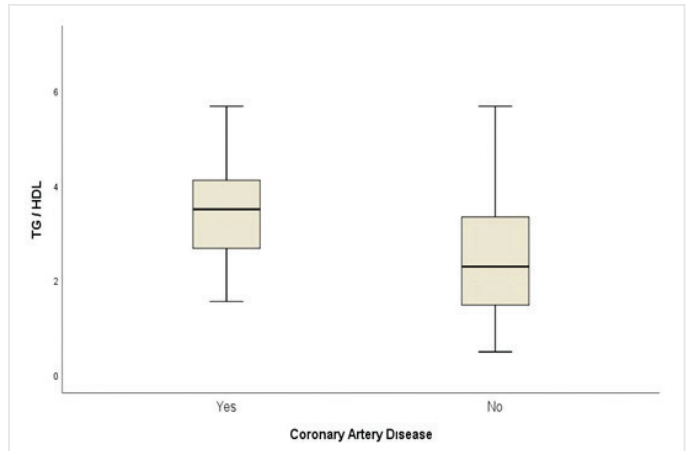

Figure 1. Coronary artery disease and healthy triglycerides to high-density lipoprotein cholesterol (box-plot)

TG/HDL: Triglycerides to high-density lipoprotein cholesterol

Table 2. The relation of triglyceride/HDL ratio of general features of the cases

		TG/HDL	p
Gender	Male Female	2.58 (1.76 3.53) 2.32 (1.47 3.40)	0.426
Methylprednisolone	Yes No	2.46 (1.55 3.39) 1.59 (1.19 7.97)	0.905
Diabetes mellitus	Yes No	2.92 (2.30 3.93) 2.28 (1.47 3.39)	**0.012**
Hypertension	Yes No	2.75 (2.20 4.25) 2.28 (1.47 3.34)	0.097
Hypothyroidism	Yes No	2.33 (1.48 4.54) 2.47 (1.57 3.38)	0.557
Hyperlipidemia	Yes No	4.54 (2.32 8.58) 2.31 (1.48 3.39)	**0.026**

P-value Mann-Whitney U or Student's t- obtained from the test. M: Median, Q1: Quarter 1 (p25), Q3: Quarter 3 (p75), HDL: High-density lipoprotein cholesterol

Table 3. Relationship between cardiovascular disease and biochemical parameters

	Yes (n=12) M (Q1-Q3)	No (n=124) M (Q1-Q3)	p
Age	59.5 (50-61.5)	43 (34.5-57.5)	**0.003**
Platelet	74,500 (15,000-141,500)	66,500 (23,000-112,000)	0.830
HDL	42 (38.5-47)	48.5 (39.5-55.5)	0.148
Triglyceride	138 (125-162)	111 (82-138.5)	0.055
TG/HDL	3.50 (2.67-4.11)	2.29 (1.47-3.38)	**0.025**

P-value Mann-Whitney U obtained from the test. M: Median, Q1: Quarter 1 (p25), Q3: Quarter3 (p75), TG/HDL: Triglycerides to high-density lipoprotein cholesterol

(7). Advanced age, male gender, diabetes, aberrant lipid metabolism, HT, smoking, impaired renal function, and inflammation are risk factors for vascular calcification (8-10). Although there has been improvement in the management of coronary heart disease, mortality rates are rising and the illness's prevalence and morbidity remain significant. In the study, which analyzed 106,653 patients with ITP and 79,636,090 members of the control group between 2002 and 2011, it was discovered that patients with ITP had a considerably greater incidence of non-ST segment elevation myocardial infarction than people without ITP (13).

While 17% of the patients in our study were diagnosed with DM and under treatment; 5% were under treatment for hyperlipidemia and had no additional cardiovascular outcome. The examination of the TG/HDL-C levels revealed a statistically significant connection (p=0.05). When other diseases are present in patients with ITP patients, cardiovascular risk evaluations are useful for making an early diagnosis. In a study that involved 3,131 patients and compared the rates of cataract, diabetes, renal failure, vascular events, lymphoma, and leukemia in those with and without chronic ITP, it was discovered that patients have a higher risk of developing many comorbidities, including hematological malignancies (15).

In a retrospective cohort research that included 6,591 patients with ITP and 24,275 control individuals, the CVD risk was assessed, and during a 6-year observation period, a diagnosis of CVD was reported in 392 (5.9%) patients with ITP and 1,114 (4.5%) control patients. It has been determined that people with ITP are more likely to acquire CVD, and that people with ITP who have splenectomy are considerably more likely to do so (12). In our study, we found no difference in the risk between patients who underwent splenectomy and those who did not.

A relative risk of 1.82 (95% CI: 0.78-4.24) was revealed by the meta-analysis in 2022. Our results show that patients with ITP who receive TPO-RA (eltrombopag) treatments have a non-significantly increased risk of thrombosis than patients with ITP who do not receive TPO-RA treatments (14). In our investigation, it was not discovered that using TPO-RA increased the frequency of cardiovascular events.

Study Limitations

Our study was designed as a retrospective-observational study. The fact that the cholesterol values of the patients were not checked before the treatment, the history of previous acute cardiac events is not known, the short follow-up period, the insufficiency of the number of patients, and the fact that it is a single-center study can be counted among the limitations of the study, and for this reason, this study may not reflect the general population. The strength of our study is that it consisted of hematology outpatients of a tertiary hospital with regular follow-up.

Conclusion

Limited use of steroid therapy in the future, and less frequent splenectomy with the widespread use of new generation therapies, may change the development of cardiovascular events in chronic patients with ITP. While the advanced age of the patients and additional comorbid diseases (DM, hyperlipidemia) pose a risk, the TG/HDL-C ratio

can be used as an independent risk marker in this sense with diagnostic efficacy in predicting cardiovascular disease.

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