



## Lipid Variables Related to the Extent and Severity of Coronary Artery Disease in Non-Diabetic Turkish Cypriots

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### Abstract

**Background:** We aimed to analyze the association between lipid variables and the extent and severity of coronary artery disease (CAD) in non-diabetic Turkish Cypriots.

**Methods:** Overall, 412 patients (mean (SD) age: 58.8 (10.5) yr, 50.1% male) who underwent diagnostic coronary angiography were included in this single-center, cross-sectional study. The Friesinger index (FI) was used to assess the extent and severity of CAD. The lipid variables [total cholesterol, LDL-c, HDL-c, triglyceride (TG) levels and the TG/HDL-C ratio] were categorized into quartiles and evaluated regarding extensive/severe CAD. Potential risk factors in the Turkish Cypriot cohort were evaluated as predictors of CAD in univariate and multivariate logistic regression models. The population of this study are non-diabetic Turkish Cypriots which are administrated North Cyprus.

**Results:** The mean (SD) Friesinger index was 6.9 (4.4), and 59.0% of the patients exhibited a Friesinger index category of  $\geq 5$ . In the univariate analysis, extensive/severe CAD was directly related to total triglycerides ( $P=0.01$ ) and TG/HDL-c quartiles ( $P=0.001$ ) and inversely related to HDL-c quartiles ( $P=0.001$ ). In the multivariate model, diabetes (OR: 4.9; 95% CI: 1.3 - 19.2;  $P=0.02$ ), male gender (OR: 3.1; 95% CI: 0.95 - 10.3;  $P=0.06$ ) and high TG/HDL-c ratio (OR: 2.2; 95% CI: 1.3 - 3.8;  $P=0.004$  in the overall population and OR: 1.9; 95% CI: 1.4 - 2.3;  $P=0.003$  except diabetics) were the significant predictors of CAD.

**Conclusion:** We found a significant relationship between the lipid quartiles and the extent and severity of CAD based on the Friesinger index. Male gender, co-morbid diabetes and the TG/HDL-C ratio also played significant roles in predicting CAD risk in non-diabetic Turkish Cypriots.

**Keywords:** Coronary artery disease, Extension, Non-invasive predictors, TG/HDL-c ratio, Dyslipidemia, Cyprus

### Introduction

Because of the significant reduction that has been documented in the progression of atherosclerosis and cardiovascular events through the treatment of dyslipidemia by statins, the non-invasive documentation of atherosclerotic lesions has become an increasingly important target for early treatment and preventive measures (1-3). Techniques such as density gradient ultracentrifugation, non-denaturing gradient gel electrophoresis, and nuclear magnetic resonance spectroscopy are available to measure lipid particles to predict the risk of coronary artery disease (CAD); however, these techniques are labor-intensive, technically demanding, expensive, and slow to produce results (4-6). Thus, although these techniques are precise and accurate, they are not widely used in clinical settings, and developing surrogate markers of lipid particle profiles is of

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considerable clinical and economic importance (3). The association between the serum levels of total cholesterol and low-density lipoprotein cholesterol (LDL-c) in the development of CAD has been well established, whereas low serum levels of HDL-c have been considered a major risk factor for CHD (7).

Lipid particle subfractions play an important role in the atherogenic process. Small, dense LDL particles are more atherogenic than larger particles. Larger, less dense HDL<sub>2</sub> particles are considered protective, whereas the smaller, denser HDL<sub>3</sub> particles are considered atherogenic (8, 9). The former particles correlate inversely with serum TG levels and small, dense LDL levels (10).

The TG/HDL-C ratio, which is a relatively novel lipoprotein index indicating the presence of small, dense LDL particles, serves as a potentially significant predictor of CAD (11, 12). Moreover, it was shown to be one of the non-invasive parameters that are most strongly associated with the extent of coronary disease, as assessed by the Friesinger index from conventional coronary angiography (13).

To the best of our knowledge, despite the growing number of patients diagnosed with CAD, no study has reported an association between the lipid parameters, particularly the TG/HDL-C ratio, and extensive CAD in Mediterranean populations, particularly in Cypriots. Therefore, the present study was designed to investigate the association between lipid variables, particularly the TG/HDL-C ratio, and the extent and severity of CAD in Turkish Cypriots with suspected CAD.

## Materials and Methods

### Study population

A total of 412 consecutive non-diabetic patients with suspected CAD (mean (SD) age: 58.8 (10.5) years, 50.1% male) who admitted to the hospital between January 2009 and January 2012 who underwent diagnostic coronary angiography upon referral to our cardiovascular laboratory were included in this single-center, cross-sectional study.

Non-diabetic patients aged 18-70 years were included in the study, whereas we excluded patients with co-morbid chronic diseases, concomitant medications affecting carbohydrate metabolism, pregnant patients and Turkish patients who were born outside Cyprus.

Cyprus is the third largest island in the Mediterranean Sea. There are two major ethnic groups in the island, namely the Turkish Cypriots who speak Turkish and are Muslims and the Greek Cypriots who speak Greek and are mostly Orthodox Christians. In addition, other ethnic groups include Maronites, Armenians and Latins. Study population included non-diabetic Turkish Cypriots living in North Cyprus since 1974.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki"; this study was approved by the institutional ethics committee.

### Study parameters

The clinical variables included patient demographics (age, gender), traditional risk factors for atherosclerosis (such as hypertension, diabetes, smoking, hyperlipidemia, and positive family history) and the blood biochemistry of the lipid parameters, including total cholesterol, LDL-c, HDL-c, triglycerides and the TG/HDL-c ratio; these variables were categorized into quartiles. The potential risk factors in the Turkish Cypriot cohort were also evaluated as predictors of CAD in the univariate and multivariate logistic regression models.

### Coronary angiography and the Friesinger index

Coronary angiography was performed for the patients with suspected CAD, unstable angina pectoris, a positive cardiac stress test, or a history of myocardial infarction. Selective coronary cineangiography was performed through the radial or femoral approach using the Judkins technique and a General Electric angiographic system. Multiple views were recorded for all the patients; the left

anterior descending and left circumflex coronary arteries were visualized in at least four views, whereas the right coronary artery was visualized in at least two views. The coronary angiograms were recorded on compact discs in the Digital Imaging and Communications in Medicine format.

Coronary disease severity was assessed by the number of vessels involved (vessel score) and by a severity score. "Target" vessels were those that included target lesions; all other vessels were designated "non-target" vessels. Significant stenosis was determined visually and was defined as a reduction in the lumen diameter by  $\geq 70\%$  in any view compared to the nearest normal segment. The vessel score ranged from 0 to 3, depending on the vessels that were involved. CAD severity was assessed using the Friesinger index (14). The Friesinger index is an overall score that ranges from 0 to 15 and is based on the individual scores of each of the three main coronary arteries from 0 to 5 using the following criteria for categorization: 0, no arteriographic abnormalities; 1, trivial irregularities (lesions with stenosis severity of 1–29%); 2, lesions with stenosis severity of 30–68%; 3, multiple narrowing in the same vessel, with the stenosed segment having either one lesion with a morphology defined as multiple, diffuse, or tubular or two segments having lesions with a stenosis severity of 30–68%; 4, at least one lesion with a stenosis severity of 69–100%, except in the proximal segment in which the severity should be  $< 100\%$ ; and 5, the occlusion of the proximal segment of a vessel. Patients with scores higher than the cut-off value of 5 were considered to have severe CAD (3). Lesions in the left main cardiac artery were counted as proximal lesions for both the left descending and circumflex arteries. Coronary lesions were scored by experts blinded to the patient lipid profiles. Angiographic scoring was performed by two observers who were blinded to the results and clinical data.

The traditional risk factors were defined as follow: hypercholesterolemia (TC  $> 200$  mg/dL), hypertriglyceridemia ( $> 150$  mg/dL), high LDL-C ( $> 130$  mg/dL), low HDL-C ( $< 40$  mg/dL for

males and  $< 50$  mg/dL for females), elevated TG/HDL-C ratio ( $> 4$ ), diabetes mellitus (fasting glucose  $\geq 126$  mg/dL), casual or 2-h OGTT  $> 200$  mg/dL, hypertension (cutoff points, 140/90 mmHg), and being a current smoker. For patients with serum triglyceride levels exceeding 400 mg/dL, a novel method used to estimate LDL-C using an adjustable factor for the TG/VLDL-C ratio provided a more accurate guideline for risk classification than the Friedewald equation (15).

### Statistical analysis

The statistical analyses were performed using computer software (SPSS version 13.0, SPSS Inc. Chicago, IL, USA). The statistical analyses involved a univariate analysis using the Chi-square  $\chi^2$  test and a non-parametric analysis of variance (ANOVA; Kruskal–Wallis test) followed by a multivariate analysis using stepwise forward logistic regression to assess the independent influence of lipid variables on the extent and severity of CAD (dichotomized by a Friesinger index of 5). The data were expressed as the mean (SD), minimum-maximum and percent (%) where appropriate.  $P < 0.05$  was considered statistically significant.

### Results

The study sample comprised 412 patients (mean (SD) age: 58.8 (10.5) years, 50.1% male). Of the total 412 patients, 44 patients had no coronary lesions, and the remaining 368 patients had CAD that ranged from irregularities to total occlusions. The mean (SD) Friesinger index was 6.9 (4.4), and 59.0% of the patients belonged to a Friesinger index category of  $\geq 5$ . Hypertension (75.8%), low HDL-C levels ( $< 40$  mg/dL, 63.6%) and hypercholesterolemia (62.6%) were the leading comorbidities (Table 1).

The mean (SD) serum levels of cholesterol, TG, HDL-C, and LDL-C were 224.9 (48.2) mg/dL, 177.9 (81.7) mg/dL, 37.5 (12.8) mg/dL, and 146.9 (35.0) mg/dL, respectively, and the mean (SD) TG/HDL-C ratio was 5.3 (4.2).

**Table 1:** Demographic and clinical characteristics of the study population (N = 412)

Variable	n(%)
<b>Gender</b>	
Male	210 (50.1)
Female	202 (49.9)
<b>Age (years)</b>	58.8 (10.5)
<b>Mean (SD)</b>	
<b>Coronary lesions</b>	368 (89.3)
<b>Frisenger index</b>	
Mean (SD)	6.9 (4.4)
0	88 (21.0)
1-4	81 (20.0)
5-10	142 (34.0)
11-15	101 (25.0)
<b>Co-morbidities (%)</b>	
Diabetes	33.3
Hypertension	75.8
Smoking	62.6
Hypercholesterolemia	62.6
Hypertriglyceridemia	49.2
Low HDL-c	63.6

Q1-4: lipid quartiles, HDL-c: high density lipoprotein cholesterol

**Frequency of CAD severity by lipid quartiles (univariate analysis)**

In the univariate analysis, extensive/severe CAD showed a direct relationship with the quartiles of total triglycerides (71% of patients with extensive CAD were in quartile Q4, whereas 52% were in Q1,  $P=0.01$ ), and TG/HDL-c (72% in Q4 vs. 44% in Q1,  $P=0.001$ ), and an inverse relationship was noted between extensive/severe CAD and the HDL-c quartiles (73% in Q1 vs. 41% in Q4,  $P=0.001$ ) (Table 2).

**Logistic regression analysis of risk factors for CAD**

In the multivariate model, diabetes (OR, 4.9; 95% CI: 1.3 - 19.2;  $P=0.02$ ) and male gender (OR, 3.1; 95% CI: 0.95 - 10.3;  $P=0.06$ ) were significantly associated with a higher risk of CAD; likewise a higher triglyceride to HDL ratio was associated with a higher risk of CAD, both in the overall study population (OR, 2.2; 95% CI: 1.3 - 3.8;  $P=0.004$ ) and in the non-diabetic patients (OR, 1.9; 95% CI: 1.4 - 2.3;  $P=0.003$ ) (Table 3).

**Table 2:** Frequency of CAD severity according to lipid quartiles\* in Turkish Cypriots (univariate analysis) (CAD %)

	Extensive CAD (%)				Pvalue
	Q1	Q2	Q3	Q4	
Cholesterol	71	68	65	75	0.43
LDL-c	63	55	64	69	0.51
HDL-c	73	72	43	41	0.001
TG	52	46	77	71	0.01
TG/HDL-c	44	54	68	72	0.001

LDL-c: low density lipoprotein cholesterol; HDL-c: high density lipoprotein cholesterol; TG: triglycerides; Q1-4: lipid quartiles

\*Friesenger index: Q1, Q2, Q3, Q4 are lipid quartiles/Q1 : 0/Q2 : 1-4/Q3: 5-10/Q4: 11-15

**Table 3:** Multivariate logistic regression model of risk factors

Multivariate Baseline Predictors*	Odds Ratio (95% CI)	P-value
Triglyceride to HDL ratio (total)	2.2 (1.3, 3.8)	0.004
Diabetes	4.9 (1.3, 19.2)	0.02
Gender (Male)	3.1 (0.95, 10.3)	0.06
Triglyceride to HDL ratio (non-diabetics)	1.9 (1.4, 2.3)	0.003

\*Other significant factors from the univariate models: hyperlipidemia, total cholesterol, triglyceride, HDL, daily dietary fat (marginal) and age (marginal). Hyperlipidemia, total cholesterol, triglyceride, and HDL were not included in the multivariate model because of co-linearity with the triglyceride to HDL ratio. Other factors were not significant in the multivariate model.

† Continuous factor where <25: 1, 25-30: 2, 30-35: 3, 35-40: 4, ≥40: 5

## Discussion

Our findings in a cohort of non-diabetic Turkish Cypriots with suspected CAD revealed a diagnosis of CAD in 89.3% of patients and a Friesinger index category of ≥5 in 59.0% of patients. The lipid quartiles showed direct (TG/HDL-c and triglycerides) and inverse (HDL-c) relationships with extensive/severe CAD in the univariate analysis, whereas the presence of comorbid diabetes, male gender and a high TG/HDL-c ratio (in non-diabetics) were significant predictors of a higher CAD risk in Turkish Cypriots.

Our findings of direct (TG/HDL-c and triglycerides) and inverse (HDL-c) relationships between lipid quartiles and extensive/severe CAD are in agreement with the well-documented correlation between CAD and dyslipidemia-related risk factors, such as high triglyceride and LDL levels but low HDL-C levels (16,17).

The inverse relationship of the HDL-C quartiles with the extent and severity of CAD in Turkish Cypriots supports the data from the Lipid Research Center (18) and the Framingham studies (16) and emphasizes that lower levels of HDL-C are associated with a higher Friesinger index. Therefore, a low HDL-c level is an independent risk factor for CAD (13, 17, 18).

The TG/HDL-C ratio, which is a relatively novel lipoprotein index, has been considered to indicate the presence of small, dense LDL particles; thus, it can serve as a good predictor of CHD and shows promise as an attractive and powerful

surrogate index of the atherogenicity of the plasma lipid profile (11-13). Several studies have attempted to determine whether the TG/HDL-C ratio can function as an atherogenic index to be a highly significant independent predictor of myocardial infarction and whether it is even stronger than the TC/HDL-C and LDL-C/HDL-C levels (12). Accordingly, the identification of the TG/HDL-C ratio as a powerful independent indicator of extensive CAD in Turkish Cypriots with suspected CAD is consistent with the consideration of a high TG/HDL-C ratio to predict the extent of CAD better than any other lipid parameter, which has been reported in several similar studies conducted in Turkish, Brazilian and Iranian populations and in studies reported by the Asia-Pacific Cohort Studies Collaboration (2, 3, 7, 8, 11). Additionally, Da Luz et al. showed that a TG/HDL-C ratio of >4 is the most powerful independent predictor of CAD development (3). In another study, a TG/HDL-C ratio of ≥3.5 from a multivariate analysis was reported to be associated with an increased CAD burden (OR: 2.87; 95% CI: 1.03–7.96; *P* = 0.04) (19).

The TG/HDL-C ratio was shown to be one of the non-invasive parameters most strongly associated with the extent of coronary disease, as assessed by the Friesinger index from conventional coronary angiography (13).

Both insulin resistance and central obesity have been suggested as essential factors for the development of metabolic syndrome and are associated with high TG levels and low HDL



levels, which are characteristic features of this syndrome (20-22). The TG/HDL-C ratio is a good surrogate marker of insulin resistance in the general population worldwide (23), except in African Americans (24). Moreover, in premenopausal women, a TG/HDL-C ratio of  $>3$  is associated with a moderate risk of developing metabolic syndrome (25). Given the correlation of a low TG/HDL-C ratio primarily with large, non-atherogenic LDL particles and a high TG/HDL-C ratio with a larger population of small, dense, pro-atherogenic LDL particles (26), the measurement of the TG/HDL-C ratio should be considered in the risk assessment of CHD in individuals with a high prevalence of metabolic syndrome.

Given that the male gender and co-morbid diabetes were also associated with an increased risk of CAD in Turkish Cypriots, our findings are in agreement with data from previous studies in Turkey that demonstrated that in Turkish adult males with a high prevalence of metabolic syndrome, low HDL levels and high TG levels were predictive of cardiovascular events (27,28). In the Framingham study, the risk of CAD was reported to be 4.9 times higher in diabetic women and 2.1 times higher in men with diabetes (16). For a recent study, increased TG/HDL ratio has been shown association with increased arterial stiffness in apparently healthy individuals (29).

Notably, because 33% of our study population was composed of diabetic patients who have characteristically higher TG/HDL-C ratios, the identification of the TG/HDL-C ratio was one of the significant predictors of CAD risk in our study population, even after the exclusion of diabetic patients, indicates the direct association between the TG/HDL-C ratio and extensive CAD; thus, this relationship supports the use of the TG/HDL-C ratio as a surrogate marker in the non-invasive documentation of atherosclerotic lesions in non-diabetic patients.

### **Study limitations**

The present study has a number of limitations that should be considered when evaluating the results. First, given the relatively low sample size

because of the single-center design, our findings might not be generalizable to the entire Cypriot population. Second, the cross-sectional design made it impossible to establish any cause and effect relationships. Nevertheless, despite these limitations, given the paucity of solid information available on this area and the fact that Cyprus is an island nation and a substantial portion of its population are foreign residents, the inclusion of Cyprus-born patients with Cypriot parents in our cohort represents a valuable contribution to the literature and provides data on the extent and severity of CAD using lipid parameters in the Turkish Cypriot population for the first time.

### **Conclusion**

Our findings revealed a significant relationship between lipid quartiles and the extent and severity of CAD as assessed by the Friesinger index. This study also demonstrated significant roles of male gender, co-morbid diabetes and the TG/HDL-C ratio in predicting CAD risk among Turkish Cypriots for the first time in the literature. Therefore, in patients with suspected CAD, the TG/HDL-C ratio should be used to measure disease severity prior to coronary angiography because it is an easy, noninvasive, and economical method of discerning the extent of coronary atherosclerosis.

### **Ethical considerations**

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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