Fasting serum triglyceride and high-density lipoprotein cholesterol levels in patients intended to be treated for dyslipidemia

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Objective: The aim of the present investigation was to evaluate the influence of serum triglycerides (TG) on other plasma lipids in patients to be treated for dyslipidemia.
Methodology: Lipid profiles of a cohort of 801 patients (487 males and 314 females) aged 57 ± 9 years (mean ± SD) were evaluated. Patients were stratified according to their plasma lipid levels. They were divided into various groups on the basis of serum TG (≥ 150 or < 150 mg/dL) and high-density lipoprotein cholesterol (HDL-C) (≥ 40 or < 40 mg/dL).
Results: Patients with TG ≥ 150 mg/dL had a higher total cholesterol and lower HDL-C levels compared with those with TG < 150 mg/dL, ($p < 0.001$). Patients with HDL-C < 40 mg/dL had a lower serum total cholesterol and higher TG compared with those with HDL-C ≥ 40 mg/dL ($p = 0.011$ and $p < 0.0001$, respectively). In all patients as well as in the subgroups, an inverse correlation between TG and HDL-C was found ($r = -0.377$, $p < 0.001$).
Conclusions: Although, the metabolic pathway for TG and HDL-C is closely linked, an inverse correlation between TG and HDL-C levels seems to exist in the entire sampled population. This correlation also appears to persist in fasting patients with low levels of TG.
Keywords: triglycerides, high-density lipoprotein cholesterol, dyslipidemia

Introduction

Increased levels of low-density lipoprotein cholesterol (LDL-C) are a well established risk factor for coronary artery disease (CAD) (Stamler et al 1986; The Scandinavian Simvastatin Survival Study Group 1994). The Prospective Cardiovascular Münster Study first unambiguously demonstrated that increased triglyceride (TG) concentration is an independent risk factor for major coronary artery events, even after adjustment for other positive CAD risk factors such as LDL-C and negative risk factors such as high-density lipoprotein cholesterol (HDL-C) levels (Assmann et al 1996). Although, it has taken many years to establish HDL-C as a risk factor for premature cardiovascular disease, it is now considered as an additional recognized target for the prevention and treatment of atherosclerosis (Kolovou and Cokkinos 2002). Certainly, Foody and colleagues (2000) have reported that HDL-C was the single most important predictor of survival after coronary artery bypass grafting in men.

Epidemiological evidence, based on data from Western countries, seems to support the concept of an inverse relationship between plasma TG levels to HDL-C cholesterol levels (Anonymous 1993). In a pathologic state such as the metabolic syndrome, the tandem high TG–low HDL-C occurs in a higher frequency, which cannot readily be considered as coincidental. Moreover, the report from the Expert Group on HDL-C points to the fact that many individuals with low plasma levels of HDL-C also have

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high levels of TG (Sacks 2002). Taken together, this may imply the existence of a specific metabolic relationship between the two molecules (ie, TG and HDL-C). In the present investigation, our aim was to evaluate the relationship between serum TG and HDL-C levels in patients with lipidemic disorders intended to be treated with lipid-lowering agents.

Materials and methods

Study design and population

Subjects for this investigation were selected from patients who were not being treated with lipid-lowering agents prior to referral to our Lipid Clinic. All patients were advised of lifestyle changes to be followed for at least 3 months. After this interval, fasting plasma samples for routine lipid analysis were obtained in a cohort of 801 patients aged 57 ± 9 years (mean ± SD). The gender composition of the group under the investigation was 487 (61%) males and 314 (39%) females. None of the females in this investigation were on hormone replacement therapy. All subjects fulfilled one or more of the following criteria: (1) total cholesterol (TC) > 240 mg/dL, or > 170 mg/dL in patients with CAD; (2) TG values > 150 mg/dL; and/or (3) HDL-C < 40 mg/dL.

In addition, based on TG and HDL-C levels, patients were subdivided into the following groups: (a) TG levels < 150 mg/dL or ≥ 150 mg/dL; (b) HDL-C levels, < 40 mg/dL or ≥ 40 mg/dL; (c) TG ≥ 150 mg/dL and HDL-C ≥ 40 mg/dL; (d) TG ≥ 150 mg/dL and HDL-C < 40 mg/dL; (e) TG < 150 mg/dL and HDL-C ≥ 40 mg/dL; and (f) TG < 150 mg/dL and HDL-C < 40 mg/dL.

Blood chemistry

The plasma levels of TC, TG, and HDL-C were measured using enzymatic colorimetric methods on Roche Integra Biochemical analyzer with commercially available kits (Roche Diagnostics GmbH, Mannheim, Germany). The serum LDL-C levels were calculated in patients with fasting TG concentrations < 4.5 mmol/l (400 mg/dL) using the Friedewald formula (Friedewald et al 1972).

Statistical analysis

Categorical variables are presented as percentages and numerical characteristics as mean values with one SD. Chi-square test was used for the comparison of categorical variables and t-test for independent samples or Mann Whitney U test for the comparison of numerical values following testing for normality. Correlation between HDL-C and TG was performed using Spearman correlation coefficient. A p-value of < 0.05 was taken to be significant.

Results

Characteristics of patients

Concentration of lipids in men, women, and the combined cohort are shown in Table 1. A small percentage of the population under investigation had only one abnormal lipid parameter; ie, 24.5% had increased TC levels (≥ 240 mg/dL), 2.7% had increased TG levels (≥ 150 mg/dL), while 4.2% of the cohort had low HDL-C levels (< 40 mg/dL).

Additionally, the percentages of the patients' anthropometric characteristics were estimated in a sample of 286 subjects, of which 47% were smokers, 19% had arterial hypertension, 7% had diabetes mellitus, 40% had CAD, and 20% had experienced one myocardial infarction.

Composition of cohort based on TG levels (≥ 150 or < 150 mg/dL)

Of the 801 subjects, 6.7% had normal TC levels with TG levels ≥ 150mg/dL–HDL-C < 40 mg/dL, while 22.7%, 8.4%, and 23.3% had abnormal TC levels with: TG ≥ 150 mg/dL–HDL-C ≥ 40 mg/dL, TG < 150 mg/dL–HDL-C < 40 mg/dL, and TG ≥ 150 mg/dL–HDL-C < 40 mg/dL, respectively.

Table 1 Concentration of various lipids in men, women, and the combined cohort

	All patients		Men		Women		
	Mean	SD	Mean	SD	Mean	SD	p[a]
N	801		487		314		
Age (years)	57	9	56	9	59	8	< 0.001
TC (mg/dL)	288	64	286	63	291	64	0.136
LDL-C (mg/dL)	207	62	207	61	207	64	0.994
TG (mg/dL)	182	101	187	100	174	102	0.009
HDL-C (mg/dL)	44	15	41	13	49	15	< 0.001
TC/HDL-C	7.1	2.7	7.4	2.7	6.5	2.6	< 0.001

[a] p-values refer to correlations between men and women.

Abbreviations for Tables 1–5: N, number of patients; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. NOTE: To convert TC, HDL-C, and LDL-C from mg/dL to mmol/L divide by 38.7. To convert TG from mg/dL to mmol/L divide by 88.6.

Table 2 Concentration of various lipids in subgroups with triglycerides ≥150 or <150 mg/dL

	TG ≥150 mg/dL		TG <150 mg/dL		
	Mean	SD	Mean	SD	p
N	444		357		
Age (years)	57	9	57	9	0.210
TC (mg/dL)	296	64	278	61	<0.001
LDL-C (mg/dL)	207	65	208	59	0.517
TG (mg/dL)	242	98	105	27	<0.001
HDL-C (mg/dL)	41	14	49	14	<0.001
TC/HDL-C	7.8	2.7	6.1	2.4	<0.001

Table 3 Concentration of various lipids in subgroups with HDL-C ≥40 or <40 mg/dL

	HDL-C ≥40 mg/dL		HDL-C <40 mg/dL		
	Mean	SD	Mean	SD	p
N	460		341		
Age (years)	57	9	56	9	0.167
TC (mg/dL)	292	61	282	67	0.011
LDL-C (mg/dL)	207	60	206	65	0.641
TG (mg/dL)	156	83	216	112	<0.0001
HDL-C (mg/dL)	53	13	32	5	<0.0001
TC/HDL-C	5.7	1.5	9.0	2.7	<0.0001

Patients with serum TG levels ≥150 mg/dL had lower HDL-C levels ($p < 0.001$), higher TC levels ($p < 0.001$), and higher TC/HDL-C ratio ($p < 0.001$) compared with those with serum TG levels <150 mg/dL. However, the two groups had similar LDL-C levels (Table 2).

Composition of cohort based on HDL-C levels (≥40 or <40 mg/dL)

Patients with HDL-C <40 mg/dL had a significantly lower TC and higher TG levels compared with those with HDL-C ≥40 mg/dL and similar LDL-C levels. The patients with higher HDL-C levels demonstrated significantly lower TC/HDL-C ratio (Table 3).

Composition of cohort based on HDL-C (≥40 or <40 mg/dL) and TG (≥150 or <150 mg/dL) levels

To examine the distribution of patients with two or more risk factors and to compare their lipid profile, we divided the population according to their HDL-C and TG levels.

Patients with TG levels <150 mg/dL and HDL-C levels ≥40 mg/dL were the largest group (32% of the study population), and those with TG levels <150 mg/dL and HDL-C levels <40 mg/dL were the smallest group (13% of the study population). The group with TG levels ≥150 mg/dL and HDL-C levels ≥40 mg/dL and the group with TG levels ≥150 mg/dL and HDL-C <40 mg/dL were 25% and 30% of all study patients, respectively (Table 4).

Patients with TG levels ≥150 mg/dL and HDL ≥40 mg/dL had higher TC, lower TG levels, and lower TC/HDL-C ratio compared with those with TG levels ≥150 mg/dL and HDL-C levels <40 mg/dL. Similar results were found in patients with TG levels <150 mg/dL. Those with HDL-C levels ≥40 mg/dL demonstrated higher TC and lower TG and TC/HDL-C ratio. In patients with TG ≥150 mg/dL and HDL-C ≥40 mg/dL, the highest TC levels were observed. Patients with TG ≥150 mg/dL and HDL <40 mg/dL had the highest TG levels, the highest TC/HDL-C ratio, and the lowest HDL-C levels. Patients with TG <150 mg/dL and HDL ≥40 mg/dL had the highest HDL-C levels and the lowest TG levels and TC/HDL-C ratio (Table 4).

Composition of cohort based on gender and TG levels (≥150 or <150 mg/dL)

Women were found to have higher HDL and lower TG levels as well as a lower TC/HDL-C ratio than men (Table 1). When both genders were selected according to TG levels, they followed the same lipid profile pattern (Table 5).

Table 4 Concentration of various lipids in subgroups with triglycerides ≥150 or <150 mg/dL and HDL-C ≥40 or <40 mg/dL

	TG ≥150 mg/dL and HDL-C ≥40 mg/dL		TG ≥150 mg/dL and HDL-C <40 mg/dL			TG <150 mg/dL and HDL-C ≥40 mg/dL		TG <150 mg/dL and HDL-C <40 mg/dL		
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
N	204		240			256		101		
Age (years)	57	8	56	9	0.141	57	9	57	9	0.907
TC (mg/dL)	303	59	290	68	0.007	284	61	263	59	0.01
LDL-C (mg/dL)	207	61	206	68	0.486	208	60	208	58	0.764
TG (mg/dL)	224	80	259	105	<0.0001	103	28	111	23	0.018
HDL-C (mg/dL)	51	14	32	5	<0.0001	55	12	33	5	<0.0001
TC/HDL-C	6.2	1.5	9.2	2.6	<0.0001	5.3	1.4	8.3	2.9	<0.0001

Table 5 Concentration of various lipids in subgroups with triglycerides ≥ 150 or < 150 mg/dL in men and women

	Men with TG ≥ 150 mg/dL		Men with TG < 150 mg/dL			Women with TG ≥ 150 mg/dL		Women with TG < 150 mg/dL		
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
N	286		199			155		155		
Age (years)	56	9	56	10	0.442	59	8	59	8	0.827
TC (mg/dL)	293	60	275	66	0.001	301	71	281	55	0.018
LDL-C (mg/dL)	205	61	209	62	0.697	209	72	206	55	0.555
TG (mg/dL)	242	95	108	27	< 0.0001	246	99	102	27	< 0.0001
HDL-C (mg/dL)	39	14	45	12	< 0.0001	43	13	54	16	< 0.0001
TC/HDL-C	8.0	2.6	6.5	2.4	< 0.0001	7.4	2.6	5.6	2.3	< 0.0001

Correlations

A correlation between HDL-C and TG was found to exist in the entire population that was studied ($r = -0.377$, $p < 0.001$) (Figure 1). HDL-C levels were correlated to the TG concentration in patients with HDL-C < 40 mg/dL ($r = -0.139$, $p < 0.010$) and with HDL-C ≥ 40 mg/dL ($r = -0.284$, $p < 0.001$). Additionally, HDL-C levels were correlated to the TG concentration in patients with TG ≥150 mg/dL ($r = -0.224$, $p < 0.0001$), and with TG < 150 mg/dL ($r = -0.223$, $p < 0.0001$) (Figure 2). After segregating the population according to HDL-C cut-off point of 40 or TG cut-off point of 150, an inverse correlation was found ([$r = -0.139$, $p = 0.01$] and [$r = -0,284$, $p < 0.0001$], respectively). When examined the correlations between TG and HDL-C in terms of quartile of TG, significant inverse correlations were observed in the 3rd quartile in women ($r = -0.275$, $p = 0.015$) and in the 1st, 2nd, and 3rd quartiles in the combined cohort ([$r = -0.222$, $p = 0.002$] [$r = -0.214$, $p = 0.003$] and [$r = -0.147$, $p = 0.036$], respectively). There was no significant correlation found in any quartile in men.

Discussion

The data in the present study support the view that in untreated dyslipidemic patients, the fasting TG levels correlated inversely with HDL-C levels. This correlation not only exists in the condition where TG levels are high but also when TG levels are low.

Over 25 years ago, data from the Framingham Heart Study demonstrated that TG levels can influence the CAD risk only in patients with low HDL-C concentration (Castelli 1986). Now, after numerous reports, the association of high TG concentration with low HDL-C levels is well established among patients with CAD (Jeppesen et al 2003), diabetes mellitus (Wilson et al 1985; Teno et al 2000), metabolic syndrome (Reaven 1988; Jeppesen et al 1997), familial combined dyslipidemia (Soro et al 2003), and Tangier disease (Kolovou et al 2003). Our current study confirmed that patients with HDL-C < 40 mg/dL, which is considered as low levels according to the last ATP III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001), have higher serum TG levels

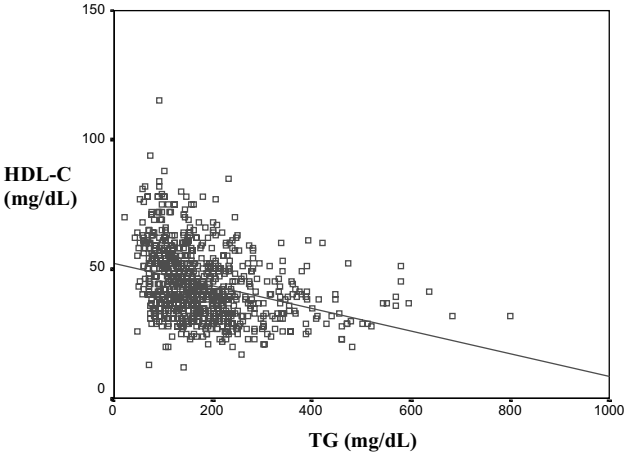

Figure 1 The correlation of high-density lipoprotein cholesterol (HDL-C) with triglyceride (TG) levels in the entire population.

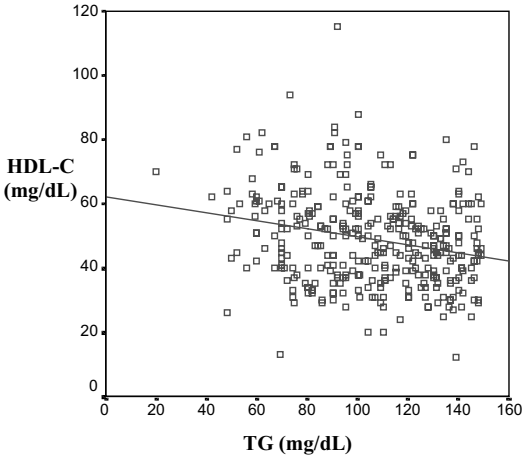

Figure 2 The correlation between high-density lipoprotein cholesterol (HDL-C) with triglyceride (TG) levels in patients with TG levels < 150 mg/dL.

($p < 0.0001$) compared with patients with HDL-C levels ≥ 40 mg/dL. This relationship between low HDL and high TG levels appears to be independent of other plasma lipids. In addition, in these patients an inverse correlation between TG and HDL-C levels was found. Moreover, such correlation was found in the entire population presently studied (even in those with low TG levels) independently of HDL-C. The suggestion that the correlation between TG and HDL-C levels in the group with HDL-C level < 40 mg/dL was strong enough to influence the correlation in the whole study population is plausible. However, we have also found the same correlation among patients with normal or low TG levels and among patients with normal or high HDL-C levels. Up to now, it was not clearly established if the serum levels of TG correlated in any fashion with the HDL-C levels. Evidence published in the current literature seems to indicate that the correlation between TG and HDL-C levels is not a simple one. For example, Le and Ginsberg (1988) have demonstrated heterogeneity in apolipoprotein A-I turnover in patients with different TG and HDL-C levels. While it has been suggested that TGs could influence HDL and apolipoprotein A-I turnover and clearance (Lamarche et al 1999). Our present results show that even in patients with HDL-C ≥ 40 mg/dL, TG concentration inversely correlates with the HDL-C levels.

Evidence from the Québec Cardiovascular Study demonstrated a correlation between fasting TG and HDL-C levels (Lamarche et al 1996). In the latter study, whilst a significant inverse relationship ($r = -0.49$, $p < 0.0001$) between TG and HDL-C levels was reported, the correlation was not linear as most of the variance in HDL-C levels was found within TG concentration below 2.5 mmol/L (221.5 mg/dL) (Lamarche et al 1996). In addition, in patients with TG levels above 3.0 mmol/L (265.8 mg/dL), a further increase of TG did not provoke additional reduction in HDL-C levels. The difference between our present findings and the Québec Cardiovascular Study (Lamarche et al 1996) may be attributed to the fact that some of the patients in the latter study were being treated with lipid-lowering agents. Moreover, the entire cohort of the patient pool consisted of men, and grouping was made according to the cut-off point as set by the Canadian Consensus Conference on Cholesterol (1988).

A number of epidemiological studies have demonstrated a negative correlation between HDL-C levels and CAD. It seems that no relationship between fasting TG concentration and atherosclerosis could be found if the TG concentrations were examined alone without HDL-C. Thus, it has been suggested that the negative correlation between serum TG and HDL-C concentrations is a good marker, which may be used to tie the state of hypertriglyceridemia with CAD (Hulley et al 1980; Austin 1991; Lamarche et al 1996).

One hypothesis, which has been proposed by Patsch and colleagues (1987; Gotto et al 1991) to explain the correlation between HDL-C and TG levels, suggests that a low concentration of HDL-C is the consequence of non efficient postprandial clearance of TG-rich lipoproteins and that it is a marker of postprandial hypertriglyceridemia. This latter phenomenon can, at least, in part, explain the correlation between low TG and high HDL-C levels found in our study. However, it is likely that the relation between HDL-C–TG is bidirectional and that it encompasses more than one metabolic route. For example, in a hypertriglyceridemic state, the coupling low HDL-C–high TG may be related to one of the following states:

1. The HDL particles are TG-enriched via cholesteryl ester transfer protein mediated exchange with TG-rich lipoproteins. The HDL-TG enriched particles are cleared more rapidly from the circulation (Lamarche et al 1999), leading to low HDL-C levels.
2. The TG-enriched HDL particles are a better substrate for intravascular lipolysis, resulting in smaller HDL particle size, which leads to faster HDL clearance (Brunzell et al 1983; Santamarina-Fojo et al 1994).
3. The decreased lipoprotein lipase activity reduces the availability of surface constituents of TG-rich lipoproteins, which are important to the nascent HDL particle forming (Eisenberg 1984; Brewer et al 1991).

It seems that the content of serum in terms of lipids in the fasting state is a consequence of the postprandial state. There are some exceptions with positive correlation between TG and HDL-C levels such as in high alcohol intake (Rimm et al 1999) and estrogen replacement therapy (Mercuro et al 2003). Reportedly, males, generally, present worse lipid and lipoprotein profiles when compared with women (Godsland et al 1987). Similarly, in our study, men had higher TG and TC/HDL-C ratio and lower HDL-C levels than the women. However, when their lipid profile was examined according to TG levels (≥ 150 or < 150 mg/dL), men and women followed the same pattern when compared with the combined cohort. Nevertheless, the profile for males is characterized by an increased abdominal fat accumulation compared with women, despite having similar levels of total

body fat (in kilograms) (Couillard et al 1999). Also in men, the plasma TG levels peak later during the postprandial period suggesting impaired postprandial clearance. However, no differences have been found between men and women when visceral adipose tissue accumulation was assessed (Couillard et al 1999).

A number of genes are responsible for the synthesis, transport, and clearance of TG and HDL. The apolipoprotein CIII polymorphism (Ordovas et al 1991) and the lipoprotein lipase deficiency (Anonymous 1993) seem to lead to hypertriglyceridemia, but not to obligatory low HDL-C levels. However, apolipoprotein CIII gene is considered as the main candidate for the TG levels control, since apolipoprotein CIII inhibits the lipoprotein lipase. The apolipoprotein CIII gene is a member of a gene cluster on chromosome 11, including apolipoprotein AI and apolipoprotein AIV genes, which are related to the HDL synthesis and removal. Mutations in the ATP-binding cassette transporter A1 mutations result in the formation of a defective HDL (Clee et al 2000), frequently accompanied with high plasma TG levels. According to the contemporaneous knowledge, it is difficult to explain the correlations between TG and HDL-C levels with metabolic pathways, which are under a single-gene control.

In comparing our present data to other studies, some observations on the frequency of variable HDL-C levels in patients free of medication can be made. In the present population, the frequency of low HDL-C levels was 42.5%, while in the Israeli Ischemic Heart Disease Study it was 31% in male subjects without CAD and a HDL-C level of < 35 mg/dL (Goldbourt et al 1997). In contrast, the prevalence of low HDL-C in USA is only 15% among the general male population and 5% among the general female population (Maron 2000). The discrepancy between our study and the US study is probably due to the fact that the population we studied was dyslipidemic and did not represent the general Greek population. As well, the high use of hormone replacement therapy in the US may have an impact on the observed differences in the prevalence of low HDL. On the other hand, the Mediterranean diet of the Greek population differs in terms of a lower intake of saturated fatty acids when compared with the dietary habits in the US population; a fact that should benefit the lipid profile of the Greek population, but one that cannot be concluded based on the present data. The higher prevalence of low HDL observed in our patient population could also be attributed to differences in genetic background and to factors such as the higher tobacco smoking and lower alcohol consumption of the Greek population in contrast to other populations (Fumeron et al 1995; Kauma et al 1996). Our data are probably closer to those from the Québec Cardiovascular Study (Lamarche et al 1996). In the patient group without CAD, low HDL-C levels were observed in 30% (vs 42.5% in our study) and high TG levels in 20% (vs 75.3% in our study).

Certainly, information on height and weight of the patients could be valuable in estimating the prevalence of the metabolic syndrome in the present population. Unfortunately, such data were not systematically collected and this lack of information could be considered a limitation of the present study.

In conclusion, an inverse correlation between fasting TG and HDL-C levels was found among dyslipidemic untreated patients. The most interesting finding is that this correlation seems to exist also in subjects with low TG levels. The relationship between TG-HDL-C remains stable in all patients' phenotypes and indirectly implies that TG and HDL-C levels depend on common metabolic pathway(s). This correlation should be taken into consideration when the risk of atherosclerosis is evaluated.

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