

Clinical Research

Influence of Triglycerides on Other Plasma Lipids in Middle-Aged Men Intended for Hypolipidaemic Treatment

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Introduction: The present investigation aimed to evaluate the influence of serum triglycerides (TG) on other plasma lipids in male patients less than 65 years of age intended for hypolipidaemic treatment.

Methods: Lipid profiles of a cohort of 412 dyslipidaemic male patients aged 53.4 ± 7.7 years (mean \pm standard deviation) were evaluated. Patients were stratified in accordance with their fasting plasma lipid levels. They were divided into multiple 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 higher total cholesterol and lower HDL-C levels compared with those with TG < 150 mg/dl ($p=0.005$ and $p<0.001$, respectively). Patients with HDL-C < 40 mg/dl had similar total cholesterol levels and higher TG levels compared to those with HDL-C ≥ 40 mg/dl ($p<0.001$). In all patients, an inverse correlation between TG and HDL-C was found ($r= -0.286$, $p<0.001$). Additionally, HDL-C levels were inversely correlated with the TG concentration in patients with TG < 150 mg/dl ($r= -0.135$, $p=0.042$) and TG ≥ 150 mg/dl ($r= -0.188$, $p=0.002$).

Conclusions: An inverse correlation between TG and HDL-C levels seems to exist in the sampled population, revealing a close link between the metabolic pathways for TG and HDL-C. This inverse correlation appears to persist even in patients with low fasting TG levels.

Increased levels of low-density lipoprotein cholesterol (LDL-C) are a widely recognised risk factor for coronary artery disease.^{1,2} The Prospective Cardiovascular Münster Study first unambiguously demonstrated that increased triglyceride (TG) concentration is also an independent risk factor for major coronary artery events. Moreover, low HDL-C levels are a well established risk factor for premature cardiovascular disease, being considered as an additional recognized target for the prevention and treatment of atherosclerosis,³ and are now reported as the single most important

predictor of survival after coronary artery bypass grafting in men.⁴

Epidemiological evidence based on data from western countries seems to support the concept of an inverse relationship between plasma TG and HDL-C levels.⁵ In a pathological state such as the metabolic syndrome, the tandem high TG - low HDL-C occurs in a higher frequency that cannot readily be considered as coincidental. Also 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 high levels of TG.⁶ Taken together, these

may imply the existence of a specific metabolic relationship between the two molecules (i.e. TG and HDL-C). In the present investigation, our aim was to evaluate the relationship between serum TG and HDL-C levels in middle-aged male patients with lipidemic disorders about to be treated with lipid lowering agents.

Methods

Study design and population

Subjects for this investigation were selected from male patients less than 65 years of age, 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 412 patients aged 53.4 ± 7.7 years (mean \pm standard deviation: SD). All subjects fulfilled one or more of the following criteria as defined by the NCEP ATP III report:⁷ 1) total cholesterol (TC) >240 mg/dl, or >170 mg/dl in patients with coronary artery disease; 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 according to: 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 by enzymatic colorimetric methods using a Roche Integra Biochemical analyser 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.⁸

Statistical analysis

Categorical variables are presented as percentages and numerical characteristics as mean values \pm one SD. The chi-square test was used for the comparison of categorical variables, and the t-test for independent samples or the Mann Whitney U test for the comparison of numerical values following testing for normality. Correlation between HDL-C and TG was one-tailed

and performed using Pearson's coefficient; a p value of <0.05 was taken to be significant.

Results

Characteristics of patients

The mean values and respective SD of the various plasma lipids in the studied population were: TC = 288 ± 63 mg/dl, LDL-C = 209 ± 62 mg/dl, TG = 187 ± 99 mg/dl, HDL-C = 41 ± 11 mg/dl and the ratio TC/HDL-C = 7.5 ± 2.7 . A small percentage of the study cohort had only one abnormal lipid parameter, i.e. 20.9% had elevated TC levels (≥ 240 mg/dl), 3.2% had elevated TG levels (≥ 150 mg/dl) and 4.4% of the cohorts had low HDL-C levels (<40 mg/dl). In 29.1% of the study cohort all three of the lipid parameters were abnormal.

Of the 412 subjects, 6.6% had normal TC levels with TG levels ≥ 150 mg/dl + HDL-C <40 mg/dl, while 20.4% and 9% had abnormal TC levels with TG ≥ 150 mg/dl + HDL-C ≥ 40 mg/dl and TG <150 mg/dl + HDL-C <40 mg/dl, respectively.

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

Patients with serum TG levels ≥ 150 mg/dl had lower HDL-C levels, higher TC levels and a higher TC/HDL-C ratio compared to those with serum TG levels <150 mg/dl. However, the two groups had similar LDL-C levels (Table 1).

Table 1. Concentration of various lipids in subgroups according to triglyceride levels.

	TG ≥ 150 mg/dl	TG <150 mg/dl	p
N	246	166	
Age (years)	53.4 ± 7.5	53.4 ± 8.1	0.923
TC (mg/dl)	294.6 ± 60.7	276.9 ± 65	0.005
LDL-C (mg/dl)	207.7 ± 61.5	210.5 ± 62	0.656
TG (mg/dl)	240.4 ± 94.7	107.9 ± 27	<0.001
HDL-C (mg/dl)	38.8 ± 10.4	44.8 ± 11.5	<0.001
TC/HDL-C	8.1 ± 2.7	6.6 ± 2.5	<0.001

All values are given as mean \pm SD.

HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; N – number of patients; TC – total cholesterol; TG – triglycerides.

For TC, HDL-C and LDL-C; to convert from mg/dl to mmol/L divide by 38.7.

For TG, to convert from mg/dl to mmol/L divide by 88.6.

Table 2. Concentration of various lipids in subgroups according to HDL cholesterol levels.

	HDL-C \geq 40 mg/dl	HDL-C <40 mg/dl	p
N	208	204	
Age (years)	53.8 \pm 7.6	53 \pm 7.8	0.315
TC (mg/dl)	290.5 \pm 62	284.3 \pm 64	0.323
LDL-C (mg/dl)	209.2 \pm 61.5	208.4 \pm 61.9	0.892
TG (mg/dl)	158.4 \pm 71.8	216.8 \pm 114.2	<0.001
HDL-C (mg/dl)	50 \pm 8.5	32.3 \pm 4.9	<0.001
TC/HDL-C	5.9 \pm 1.4	9.0 \pm 2.8	<0.001

Notes as in table 1.

Composition of cohort based on HDL-C levels (\geq 40 or <40 mg/dl)

Patients with HDL-C <40 mg/dl had significantly higher TG levels and similar LDL-C and TC levels compared to those with HDL-C \geq 40 mg/dl. The patients with higher HDL-C levels demonstrated a significantly lower TC/HDL-C ratio (Table 2).

Composition of cohort based on HDL-C (\geq 40 or <40 mg/dl) and TG (\geq 150 or <150 mg/dl)

Patients with TG levels \geq 150 mg/dl and HDL-C levels <40 mg/dl were the largest group (35.7% of the study population) and those with TG levels <150 mg/dl and HDL-C levels <40 mg/dl were the smallest group (13.6% of the study population).

Patients with TG levels \geq 150 mg/dl and HDL \geq 40 mg/dl had lower TG levels and a lower TC/HDL-C ratio compared to those with TG levels \geq 150 mg/dl and HDL-C levels <40 mg/dl. On the other hand, patients with TG levels <150 mg/dl and HDL-C levels \geq 40 mg/dl demonstrated higher TC and a lower TC/HDL-C

ratio compared to those with TG levels <150 mg/dl and HDL-C levels <40 mg/dl (Table 3).

Correlations

An inverse correlation between HDL-C and TG was found to exist in the entire population studied ($r = -0.286$, $p < 0.001$). Additionally, HDL-C levels were inversely correlated with TG concentration in patients with TG <150 mg/dl ($r = -0.135$, $p = 0.042$) and TG \geq 150 mg/dl ($r = -0.188$, $p = 0.002$). When examining the correlations between TG and HDL-C in terms of quartiles of TG, a significant inverse correlation was observed only in the fourth quartile ($r = -0.171$, $p = 0.042$).

Discussion

The data collected in the present study support the view that, in untreated, dyslipidaemic, middle-aged men, fasting TG levels correlate inversely with HDL-C levels. This inverse correlation exists not only when TG levels are high, but also when they are low.

Data collected over 25 years ago from the Framingham Heart Study demonstrated that TG levels could influence the coronary artery disease risk only in patients with a low HDL-C concentration.⁹ After numerous reports, the association of high TG concentration with low HDL-C levels is now well established among patients with coronary artery disease,¹⁰ diabetes mellitus,^{11,12} metabolic syndrome,^{13,14} familial combined dyslipidaemia,¹⁵ and Tangier disease.¹⁶

Our current study confirmed that patients with HDL-C <40 mg/dl, a low concentration according to the last NCEP ATP III,⁶ have higher serum TG levels than do patients with HDL-C levels \geq 40 mg/dl. The relationship between low HDL and high TG levels appears

Table 3. Concentration of various lipids in subgroups according to levels of triglycerides and HDL cholesterol.

	TG \geq 150 mg/dl + HDL-C \geq 40 mg/dl	TG \geq 150 mg/dl + HDL-C <40 mg/dl	p	TG <150 mg/dl + HDL-C \geq 40 mg/dl	TG <150 mg/dl + HDL-C \geq 40 mg/dl	p
N	99	147		109	57	
Age (years)	54.2 \pm 6.9	52.9 \pm 7.8	0.190	53.4 \pm 8.3	53.3 \pm 7.7	0.916
TC (mg/dl)	294.7 \pm 58.7	294.5 \pm 62.1	0.980	286.8 \pm 64.8	257.2 \pm 61.4	0.006
LDL-C (mg/dl)	203 \pm 59.9	210.8 \pm 62.5	0.331	214.8 \pm 62.7	202 \pm 60.2	0.212
TG (mg/dl)	215.8 \pm 60.4	257 \pm 109	<0.001	106.3 \pm 28.3	111.1 \pm 24.3	0.276
HDL-C (mg/dl)	48.8 \pm 8.2	32.1 \pm 4.9	<0.001	51.1 \pm 8.6	32.7 \pm 4.9	<0.001
TC/HDL-C	6.2 \pm 1.3	9.4 \pm 2.5	<0.001	5.7 \pm 1.4	8.2 \pm 3.2	<0.001

Notes as in table 1.

to be independent of other plasma lipids. Additionally, an inverse correlation was found in the entire population being studied, independently of HDL-C. Such a correlation persists even in those patients with low TG levels. Up to now, it was not clearly established if the serum TG levels were correlated in any fashion with the HDL-C levels. Evidence published in the current literature indicates that the correlation between TG and HDL-C levels is not a simple one. For example, Le Na and Guinsberg¹⁷ 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 determine HDL catabolism rate.¹⁸

One hypothesis that has been proposed by Patsch and colleagues,^{19,20} to explain in part 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 comprises a marker of postprandial hypertriglyceridaemia. A plausible mechanism to explain this inverse correlation is that in the hypertriglyceridaemic state, the TG-rich lipoproteins being formed are more prone to cholesteryl ester transfer protein (CETP) action, exchanging TG for HDL-cholesteryl esters. This enhanced HDL-cholesteryl ester turnover causes a low state of plasma HDL-C levels (Figure 1).²¹ However, it is likely that this relationship is bidirectional and encompasses more than one metabolic route.²² Inhibition of CETP has been proposed as a strategy to raise HDL-C levels. CETP inhibitors such as JTT-705 and torcetrapid have been shown to increase plasma HDL levels in experimental animals as well as in humans.²³

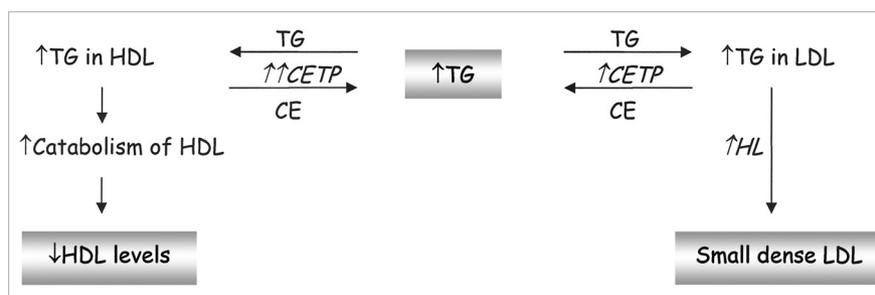
Other factors besides TG that have a further influence on HDL-C levels are body mass index, adipose tissue distribution, serum glucose and insulin levels, smoking and alcohol intake.^{24,25} However, De Oliveirae Silva

et al²⁶ showed that in a multiple regression analysis the next strongest HDL-C covariate after apo A-I levels is the log of TG concentration.

Certainly, information on the above factors could be valuable in estimating their supplementary effect on HDL-C and the prevalence of the metabolic syndrome in the population that we studied. Our initial aim was to evaluate the influence of TG on the baseline lipid profile, therefore such data were not systematically collected and that lack of information could be considered as a limitation of the present study.

A number of epidemiological studies have demonstrated an inverse correlation between HDL-C levels and coronary artery disease.²⁷ Thus, it has been suggested that the inverse correlation between serum TG and HDL-C concentrations is a good marker, which may be used to tie the state of hypertriglyceridaemia with coronary artery disease.^{28,29,30}

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 49.5%, while in the Israeli Ischemic Heart Disease Study³¹ 31% of the male civil servants without coronary artery disease had HDL-C <35mg/dl. In contrast, the prevalence of low HDL-C in the USA is only 15% among the general male population.³² The greater discrepancy between our study and the US is probably due to the fact that the population we studied was dyslipidaemic and did not represent the general Greek population. On the other hand, the Mediterranean diet of the Greek population differs in terms of a lower intake of saturated fatty acids when compared to the dietary habits in the US population, a fact that should benefit the lipid profile of the Greek population, even if that cannot be concluded based on the present data. The higher prevalence of low HDL observed in our patient popu-



TG: triglyceride, HDL: high-density lipoprotein cholesterol, CETP: cholesteryl ester transfer protein, CE: cholesteryl ester, LDL: low-density lipoprotein, HL: hepatic lipase.

Figure 1. Mechanism of the inverse relation between high triglyceride and low HDL cholesterol levels.

lation could also be attributed to differences in the genetic background and other factors, such as the higher tobacco smoking and lower alcohol consumption of the Greek population in contrast to other populations.^{33,34}

In conclusion, an inverse correlation between fasting TG and HDL-C levels was found among dyslipidaemic, untreated, middle-aged men. Of particular importance is that this inverse correlation also appears to exist in subjects with low TG levels. This correlation indirectly implies that TG and HDL-C levels depend on common metabolic pathway(s), a possibility that should be taken into consideration when the risk of atherosclerosis is evaluated.

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