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Table 2

Variables	Control (n: 64)	1 vessel-plugged (n: 33)	2 vessel-plugged (n: 48)	3 vessel-plugged (n: 20)
TC (mg/dL)	197±23	178±40	190±40	180±44
TG (mg/dL)	119 (114-144)	104 (93-151)	137 (120-164)	113 (69-169)
LDL-C (mg/dL)	124±21	117±34	125±36	117±33
HDL-C (mg/dL)	48 (45-53)*	40 (37-45)a,‡	36 (35-42)	33 (29-36)
VLDL-C (mg/dL)	35 (30-70)	51 (47-58)	48 (40-52)	44 (30-55)
Apo B (mg/dL)	102±21	102±38	105±28	103±31
Apo AI (mg/dL)	153±29	149±26	147±21	138±24
Lp (a) (g/L)	12 (18-37)‡	13 (11-25)‡	25 (23-46)	28 (10-47)
Apo E (mg/dL)	4.5 (4.1-4.7)	4.5 (4.1-5.3)	4.3 (4.2-5.2)	3.4 (2.9-4.8)
LHDL-C (mg/dL)	13 (15-19)	14 (13-17)	12 (12-16)	11 (10-15)
IMHDL-C (mg/dL)	24 (22-25)	22 (20-24)	21 (19-22)	19 (16-20)
SHDL-C (mg/dL)	8.0 (6.9-8.8)*	3.0 (3.0-5.5)	4.0 (3.3-4.8)	4.4 (2.4-4.4)
HDL-LpPL A2 (ng/mL)	118 (75-143)*	36 (27-60)	34 (31-47)	34 (24-67)
PON1 activity (EU/L)	138 (61-191)	63 (40-177)	72 (57-161)	87 (72-141)
hs-CRP (mg/dL)	0.18 (0.21-0.38)	0.19 (0.8-0.79)	0.39 (0.21-1.63)	0.32 (0.18-1.12)

Lipidic profiles of the individuals with and without angiographic findings.

Table 3

	LHDL-C (r, p)	IMHDL-C (r, p)	SHDL-C (r, p)	HDL-Lp PL A2 (r, p)	PON1 (r, p)
LHDL-C	-	NS	NS	NS	NS
IMHDL-C	-	-	0.589, 0.006	NS	NS
SHDL-C	-	-	-	-0.596, 0.006	-0.551, 0.012
HDL-Lp PL A2	-	-	-	-	NS

Spearman rank correlations between HDL subfractions and HDL-associated with enzymes in patients with 3 vessel-plugged

OP-089

The Association Between Peri-aortic Fat and Long-term Incidence of Major Adverse Cardiovascular Events

Zeynettin Kaya[1], Seref Ulucan[1], Hüseyin Katlandur[1], Ahmet Keser[1], Abdullah Tuncez[3], Yusuf İzzettin Alihanoğlu[4], Duran Efe[5], Mehmet Kayrak[2], Mehmet Sıddık Ülgen[1]

[1]Department of Cardiology, Mevlana University, Konya, [2]Department of Cardiology, Necmettin Erbakan University, Konya, [3]Konya Numune State Hospital, Konya, [4]Department of Cardiology, Pamukkale University, Denizli, [5]Department of Radiology, Mevlana University, Konya

Background: Peri-aortic fat tissue is one of the visceral adipose deposits. Visceral adipose tissue is metabolically active and it is suggested that has proatherogenic effects induced by oxidative stress. Previous studies have shown that the relationship between peri-aortic adipose tissue and metabolic risk factors, coronary artery disease, and systemic inflammation. In this study, the association between peri-aortic adipose tissue and long-term incidence of major adverse cardiovascular events (MACE) was investigated.
Methods: 372 men, 61 women, a total of 433 consecutive patients between the ages 40- 75 were enrolled to the retrospective cohort study. Peri-aortic fat volumes were measured by electrocardiogram-gated 64-multi-detector computed tomography. In terms of the long-term incidence of MACE the three-year follow-up results of patients were evaluated. Patients were divided into two groups (group 1 that MACE was detected and group 2 those followed without any problem) according to results.
Results: MACE (4 death, 22 nonfatal myocardial infarction (7 patients with STEMI and 15 non-STEMI), 4 ischemic stroke, 9 new onset atrial fibrillation, 5 newly diagnosed heart failure development) was detected in 44 (10.2%) patients during follow-up. Demographic and clinical characteristics were similar in both groups. Peri-aortic fat volumes were found statistically significantly high in group 1 (35.4±26.1 vs. 24.1±14.9, p=0.000). A multiple logistic regression analysis showed that peri-aortic fat volume (hazard ratio: 1.03 (95%CI 1.01-1.05), p=0.001), glomerular filtration rate (hazard ratio: 0.98 (95%CI 0.96-0.99), p=0.028), and male gender (hazard ratio: 4.76 (95%CI 1.08-20.90), p=0.039) were independent predictors of development of MACE. ROC analysis demonstrated that peri-aortic fat volumes above 29.6 was predict to development of MACE at sensitivity of 45.45% and at specificity of 76.55% (AUC: 0.61 (95% CI 0.567 to 0.661) p=0.015). In addition, CRP failed to predict MACE.
Conclusion: Peri-aortic fat volume can predict the development of long-term MACE independent of other clinical variables.

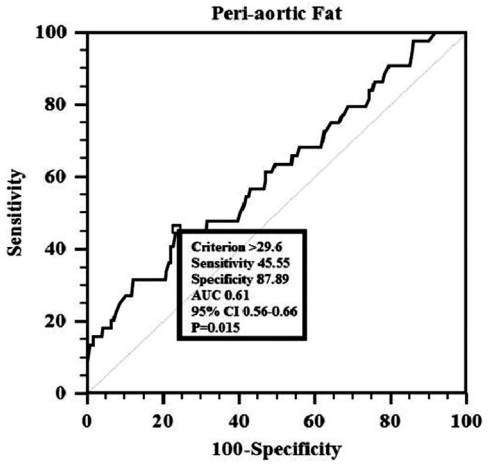


Table 1

		Hazard Ratio	95%CI for Hazard Ratio	P
Step 8	Peri-aortic fat	1.03	1.01-1.05	0.001
	Male gender	4.76	1.08-20.90	0.039
	GFR	0.98	0.96-0.99	0.028

Logistics regression analysis for independent predictors of long term major adverse cardiovascular events (GFR: Glomerular filtration rate) (R2:0.59, P=0.000)

Lipid

OP-090

High-density Lipoprotein Subfractions and Influence of Endothelial Lipase in Healthy Turkish Population: A Study in a Land of Low High-density Lipoprotein Cholesterol

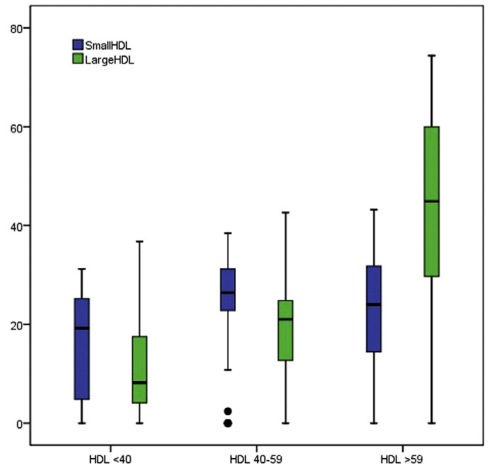
Harun Kılıç[1], Enver Atalar[2], İncilay Lay[2], Nuray Yazihan[3], Uğur Saygısunar[4], Fatih Büyükçam[4], Ramazan Akdemir[1]

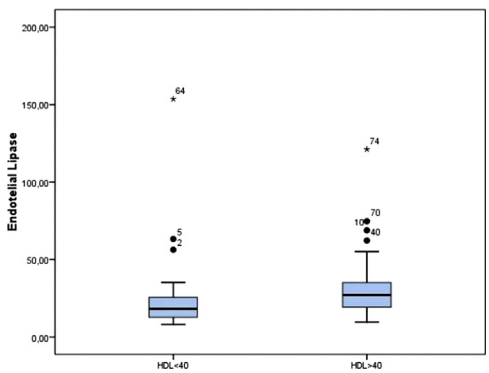
[1]Sakarya University, Sakarya, [2]Hacettepe University, Ankara, [3]Ankara University, Ankara, [4]Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara

Purpose: Low high-density lipoprotein (HDL) is prevalent in Turkey. HDL levels in Turkish population are 10-15 mg/dL lower than those of adults in the United States and Western Europa. Endothelial lipase (EL) regulates lipoprotein metabolism, mainly HDL metabolism. Decrease in the lipid content of HDL is thought to increase its capacity to remove cellular cholesterol; small, lipid-poor HDL particles thus represent more-efficient cholesterol acceptors than their large, lipid-rich counterparts. Aim of this study is to investigate HDL subfractions and effect of EL on HDL levels in healthy Turkish population.
Methods: A hundred two healthy subjects included to the study (Mean age 29,1+22 years, 42 female). Subjects who have secondary factors that can affect HDL metabolism excluded. HDL subfractions were assayed by combining a single precipitation method by heparin/Mn/Ds with a direct HDL assay. EL concentrations measured by competitive enzyme immunoassay (EIA) technique.
Results: Mean HDL levels were 56,2+14,4 mg/dL in women, 42,5+11,7mg/dL in men. Small HDL concentrations did not differ statistically between <40 mg/dL, >40 and <60 mg/dL, and >60 mg/dL total HDL groups (Table 1). High HDL levels were

mostly consisting of large HDL(Figure 1). Small HDL was not correlated with EL, total cholesterol, low density lipoprotein cholesterol (LDL), triglyceride (TG), age. Large HDL was positively correlated with EL (r=0.2, p=0.01), negatively correlated with age, LDL, TG (r=0.02, p=0.007, r=0.22, p=0.025, r=0.42, p<0.001) respectively. If subjects divided into 2 groups as HDL< 40 mg/dL and HDL> 40 mg/dL. EL levels are 25,79ng/mL and 30,77ng/mL respectively (p=0.004) (Figure 2).

Conclusion: There were no differences between small HDL concentrations in the HDL low and high groups. Low HDL concentrations may be functionally effective as high HDL concentrations. EL concentrations were positively correlated with HDL levels but EL primarily affects large HDL. Our results in healthy population may serve as a reference for clinical studies on HDL subfractions.





HDL Subfractions According to the HDL Levels

HDL Concentrations mg/dL	Small HDL(HDL3)	Large HDL(HDL2)	Small/Large HDL Ratio
HDL <39	19,2+11,0	8,2+10,3	2,2
HDL 40-59	26,4+9,8	21,0+9,6	1,2
HDL >60	24,0+12,4	44,9+20,2	0,6
p=0.074 for small HDL between HDL<39 and HDL > 60 groups p<0.0001 for large HDL between HDL<39 and HDL > 60 groups			

OP-091

The Gap between the Current Dyslipidemia Guidelines and the Physicians' Treatment Targets in Patients with Type 2 Diabetes

Nihan Kahya Eren[1], Ece Harman[2], Devrim Dolek[2], Sadık Volkan Emren[1], Aliye Pelin Tütüncüoğlu[2], Cem Nazlı[1], Oktay Ergene[3]
[1]Izmir Katip Celebi University Ataturk Education and Research Hospital, Cardiology Department, İzmir, [2]Izmir Katip Celebi University Ataturk Education and Research Hospital, Endocrinology Department, İzmir, [3]Dokuz Eylül University, Faculty of Medicine, Cardiology Department, İzmir

Introduction: Lipid-lowering therapy (LLT) is a key factor in the prevention of cardiovascular mortality and morbidity in diabetic patients. Current guidelines have expanded the population of patients with diabetes for whom aggressive low-density lipoprotein cholesterol (LDL-C) lowering therapy should be considered. This study evaluated the management of dyslipidemia in patients with type 2 diabetes in real life.

Methods: Secondary care physicians in a tertiary center recruited 707 patients. The prevalence of statin use along with the achievement of cholesterol targets, predictors for receiving statin, and possible reasons for lack of therapy were investigated.

Results: The mean age of the patients was 58±11.04, and 40% were male. Cardiovascular disease (CVD) was present in 32% (n=225) of the patients. There were 499 patients (71%) who had hypertension (HT), 19% (n=134) had nephropathy, and 23% (n=162) had diabetic retinopathy. Only 33% of the patients were on statin therapy, and this was significantly higher in those with cardiovascular disease (47% versus 27%; p<0.001). Most of the patients had LDL-C levels of > 100 mg/dl (77%), with only 5% having LDL-C levels of < 70 mg/dl. Among patients with CVD, only 7% achieved the target LDL-C levels of < 70 mg/dl. At multivariate analysis the presence of CVD, HT, retinopathy, doing regular physical exercise and being at fifth decade of life were predictors for statin usage (Table 1). Among the patients who were not on statin therapy, 288 (61%) had never been prescribed LLT previously, and 183 patients (39%) had used statins in the past but had stopped using it. The most frequent reason for discontinuation of the statin therapy was a physician's advice to stop the medication. The patients taking statins had similar LDL-C levels as those who had never been prescribed statins and those who had discontinued their use of statins on the advice of a physician (123.0±41.4 vs. 125.1±33.2, p=0.333; 123.0±41.4 vs. 129.0±33.1 mg/dl; p=0.116, respectively).

Conclusion: The majority of diabetic patients are undertreated with statins and minority of them achieve LDL-C target levels. Our findings suggest that there is a large discrepency between evidence-based recommendations and physicians' treatment attitudes.

Table 1

	Odds ratio	95% Confidence interval	p value
Hypertension	2.54	1.63-3.95	<0.001
Coronary artery disease	1.51	1.02-2.26	0.039
Peripheral artery disease	2.63	1.19-5.84	0.017
Diabetic retinopathy	1.8	1.20-2.70	0.004
Physical activity	1.69	1.11-2.57	0.013
Age (years)			
<40	0.50	0.15-1.65	0.260
40-50	1.13	0.59-2.16	0.707
51-60	1.70	1.01-2.85	0.043
61-70	1.10	0.64-1.90	0.712
Predictors of statin therapy at multivariate logistic regression analysis			

OP-092

Plasma Lipoprotein (a) Levels in Patients with Slow Coronary Flow

Habil Yücel[1], Abdullah Doğan[2], Ahmet Altınbaş[2], Salaheddin Akçay[3], Atilla İçli[4], Hasan Aydın Baş[2], Betül Mermi Ceyhan[5], Akif Arslan[2]
[1]Department of Cardiology, Isparta State Hospital, Isparta, [2]Department of Cardiology, Suleyman Demirel University, Isparta, [3]Department of Cardiology, Celal Bayar University, Manisa, [4]Department of Cardiology, Ahi Evran University Training and Research Hospital, Trabzon, [5]Department of Biochemistry, Suleyman Demirel University, Isparta

Objective: Slow coronary flow (SCF) is a microvascular disorder characterized by delayed opacification of coronary vessels with normal coronary angiogram. It may be due to endothelial dysfunction and diffuse atherosclerosis. Lipoprotein (a) [Lp(a)] is related to cardiovascular events. Although various cardiovascular biomarkers have been studied in patients with SCF, plasma Lp (a) levels have not been studied previously. We investigated the plasma Lp (a) and fibrinogen levels and the relationship between plasma Lp (a) and coronary flow rate in patients with SCF.

Methods: The study group consisted of 50 patients with SCF and an age and gender matched 30 controls who had normal coronary arteries and normal coronary flow. Coronary flow rates of all patients and control subjects were documented by Thrombolysis in Myocardial Infarction (TIMI) frame count. We measured plasma Lp (a), fibrinogen and routine biochemical parameters at the same time in patients with SCF and control subjects in this cross-sectional observational study.

Results: There were no statistically significant differences between the two groups with respect to body mass index, systolic and diastolic blood pressures, heart rate and the risk factors for coronary artery disease such as hyperlipidemia, cigarette smoking, family history and obesity (All p>0.05). The use of aspirin was significantly higher in the SCF group than control group (50% vs 17%, p=0.004) but there were no significant differences between the two groups with respect to the use of other medications (All p>0.05). Fasting glucose was significantly higher in SCF than controls (p=0.01). Inversely, high density lipoprotein (HDL) cholesterol was significantly lower in SCF (p=0.03). There were no significant differences between the two groups with respect to plasma Lp (a) (21 mg/dL vs 14 mg/dL, p=0.11) and fibrinogen (278 mg/dL vs 291 mg/dL, p=0.48) levels. The mean TIMI frame count was not correlated with plasma Lp(a) (r=0.13, p=0.25) and fibrinogen (r=-0.14, p=0.28) levels. Similarly, plasma Lp (a) levels were not corralated with fibrinogen (r=0.31, p=0.053) in SCF group.

Conclusion: Our results suggest that Lp (a) appears not to be associated with SCF.

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Scandinavian Journal of Clinical & Laboratory Investigation, 2014; Early Online: 1–7

ORIGINAL ARTICLE

High-density lipoprotein subfractions and influence of endothelial lipase in a healthy Turkish population: A study in a land of low high-density lipoprotein cholesterol

HARUN KILIC[1], ENVER ATALAR[2], INCILAY LAY[3], NURAY YAZIHAN[4], FATIH BUYUKCAM[5], UGUR SAYGISUNAR[5], MURAT AKSOY[1], HUSEYIN GUNDUZ[1] & RAMAZAN AKDEMIR[1]

[1]*Department of Cardiology, Faculty of Medicine, Sakarya University, Sakarya, Departments of* [2]*Cardiology and* [3]*Biochemistry, Faculty of Medicine, Hacettepe University, Ankara,* [4]*Pathophysiology Department, Internal Medicine, Faculty of Medicine, Ankara University, Ankara, and* [5]*Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey*

Abstract

Purpose. Low concentration of high-density lipoprotein (HDL) is prevalent in Turkey. Endothelial lipase (EL) regulates lipoprotein metabolism. Small, lipid-poor HDL particles represent more-efficient cholesterol acceptors than their large, lipid-rich counterparts. The aim of this study was to investigate HDL subfractions and the effect of EL on HDL concentrations in healthy Turkish population. ***Methods.*** 102 healthy subjects were included in the study (mean age 33.6 ± 10.3 years, 42 female). HDL subfractions were assayed by single precipitation method and EL concentrations were measured by competitive enzyme immunoassay. ***Results.*** Mean HDL concentrations were 1.45 ± 0.37 mmol/L in women, 1.10 ± 0.30 mmol/L in men. Small HDL subfraction levels did not differ statistically between <1 mmol/L and ≥ 1.6 mmol/L total HDL groups. Small HDL was not correlated with EL, low density lipoprotein cholesterol (LDL), triglyceride (TG) and age but positively correlated with total cholesterol and HDL ($r = 0.2$, $p = 0.017$; $r = 0.2$, $p = 0.028$, respectively). Large HDL was not correlated with age, EL and total cholesterol, and negatively correlated with HDL, LDL, TG ($r = -0.7$, $p < 0.001$; $r = -0.2$, $p = 0.045$; $r = -0.3$, $p < 0.001$, respectively). If subjects were divided into two groups as HDL$<$ 1 mmol/L and HDL $>$ 1.6 mmol/L, mean EL concentrations were 475.83 ± 521.77 nmol/L and 529.71 ± 276.92 nmol/L, respectively ($p = 0.086$). ***Conclusion.*** There were no differences between small HDL concentrations in the HDL low and high groups. Our data did not support EL to be the reason for low HDL in a healthy Turkish population. Our results in a healthy population may serve as a reference for clinical studies on HDL subfractions.

Key Words: *HDL subfractions, endothelial lipase, lipoprotein metabolism*

Introduction

It has been shown that plasma high-density lipoprotein cholesterol (HDL) concentrations are inversely correlated with coronary heart disease [1]. Low concentration of HDL is prevalent in Turkey. The Turkish Adults Risk Factor study showed mean values of 0.95 ± 0.31 mmol/L in men and 1.16 ± 0.33 mmol/L among women [2]. According to a previous study, HDL concentrations in Turkish population were 0.26–0.38 mmol/L lower than those of adults in Western Europe and in the United States [3].

HDL can be divided into subfractions; different subfractions play different roles in reverse cholesterol transport and represent different stages in the overall metabolism of HDL [4]. HDL consists of two major subfractions: Large buoyant HDL_2 (d = 1.063–1.125 g/mL) and small dense HDL_3 (d = 1.125–1.210 g/mL). Small, dense HDL (HDL_3) particles display higher cholesterol efflux capacity [5], potent protection for low-density lipoprotein (LDL) and oxidation [6,7]. They also exert greater inhibition of adhesion protein expression in endothelial cells [8] and possess stronger anti-inflammatory properties than large HDL particles (HDL_2) [8]. It was soon reported that small to medium-sized HDL, not large HDL, cholesterol concentrations were inversely

Correspondence: Harun Kilic, Sakarya University Hospital, Cardiology Department, Sakarya, Turkey. Tel: +90 05053 595852. E-mail: hkilic@superposta.com

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associated with total stroke risk [9]. Several lines of evidence suggest that the protective effect of HDL may be better reflected in the concentrations of HDL_3 than in those of total-HDL or HDL_2 [10–12]. Other studies, however, provide no support for this [13–15].

Little is known about the pathophysiology of low HDL [16–19]. The complex interactions among genetic and behavioral factors that influence HDL concentrations partially account for this lack of knowledge. Triglyceride (TG) concentrations of Turks with low HDL were not significantly elevated. Thus, the low HDL concentrations in our population may represent an example of isolated low HDL [3]. Previously elevated hepatic lipase (HL) activity was observed in a normotriglyceridemic, non-obese Turkish population with low concentrations of HDL [20].

Endothelial lipase (EL) is a phospholipase that belongs to the lipoprotein lipase (LPL) family [21]. Similar to LPL and HL, EL regulates lipoprotein metabolism, mainly HDL metabolism and HD concentrations in humans [22].

The aim of this study was to investigate levels of HDL subfractions and the effect of EL on HDL concentrations in a healthy Turkish population.

Materials and methods

Subjects

The study protocol was approved by the ethics committee of Hacettepe University's Faculty of Medicine. Each patient was informed about the scope of the study and gave approval for participation. Individuals recruited for the study were all aged above 18 years old. We recruited healthy Turkish subjects who were employees of the Diskapi Yildirim Beyazit Hospital, Ankara. The participants were screened to exclude those with TG $>$ 200 mg/dL and those with chronic medical problems including diabetes mellitus, coronary heart disease, or hypertension, thyroid disorder, and familial hyperlipidemias. Patients using hypolipidemic drugs, hormone replacement, oral contraceptives, b-blockers, thiazide diuretics, body mass index $>$25, and smokers were also excluded. All subjects fasted for 12 hours before their blood was drawn to measure the plasma lipids and lipoproteins. Healthy subjects who had low ($<$1 mmol/L), medium (1–1.5 mmol/L), high HDL ($<$1.6 mmol/L) concentrations were included in the study.

Blood samples

Blood samples were collected into EDTA-containing glass tubes, which were placed immediately on ice. Plasma was separated by a 10-min centrifugation at 3000 *g* and aliquots were kept at − 80°C until analysis.

Laboratory procedures

The plasma cholesterol, TG, HDL and LDL concentrations were measured by standard enzymatic methods using commercially available test kits on Chemistry Auto analyzer, Modular P-800 by Roche, Cobas (Germany). HDL_3 and HDL_2 concentrations were determined by single precipitation method with heparin/manganese (Mn)/dextran sulfate (DS). Apo-B containing lipoproteins (VLDL, IDL, LDL and chylomicrons) and HDL_2 were simultaneously precipitated with heparin/Mn/DS. HDL_3 was determined in the supernatants by using HDL plus kit (Roche Diagnostics, Manheim, Germany). HDL_2 was calculated as the difference between total HDL and HDL_3. In the single precipitation method the reagent was consisted of heparin (1071 U/mL), $MnCl_2$ (98.7 mg/mL) and DS (12 mg/mL). The precipitation reagent (0.006 mL) was added to 0.3 mL of plasma and mixed. The precipitation reaction left at room temperature for 30 min and centrifuged at 10,000 rpm for 10 min at 4°C. The final concentrations of heparin, $MnCl_2$ and DS in single precipitation method were 180 U/mL, 83 mmol/L and 2 mg/mL, respectively. Measured value of HDL_3 was multiplied by 1.2 to correct the dilution with reagents. The HDL_3 and HDL_2 values determined by the precipitation method were identical to those determined by ultracentrifugation, and there were excellent correlations between the methods in the measurements of HDL_3 and HDL_2 [23].

Measurement of endothelial lipase (EL)

EL plasma protein concentrations were analyzed in samples by a competitive enzyme immunoassay technique (EIA). Measurement was performed by a commercial kit (Aviscera Bioscience, CA, USA) according to kit procedure.

Statistical analysis

SPSS (Statistical Package for Social Science) 17.0 for Windows was used in to analyze the data. The continuous variables are presented as mean, median and standard deviations; nominal variables were expressed as numbers and percentages. Histogram and the one-sample Kolmogorov-Smirnov test were used to evaluate whether the continuous variables were distributed normally. The significance of the difference between the independent variables and values that were not normally distributed was evaluated by Mann-Whitney U-test and Kruskall-Wallis test; for normally distributed variables independent samples, the *t*-test was used. The relationship between nominal variables was evaluated by Pearson Chi-square test and Fisher's Exact test. Pearson correlation coefficient was used for continuous variables; $p < 0.05$ was considered to be significant.

Results

The American Association of Clinical Endocrinologists [24] recommends measurement of HDL as a screening test for dyslipidemia. Low HDL (< 1 mmol/L) can act synergistically with other lipid risk factors to increase coronary artery disease risk. An HDL concentration greater than 1.6 mmol/L is an independent negative risk factor. HDL concentrations between 1–1.5 mmol/L were considered borderline [24].

Some 102 healthy subjects were included in the study (mean age 33.6 ± 10.3 years, 42 female). Mean HDL concentrations were 1.45 ± 0.37 mmol/L in women, 1.10 ± 0.30 mmol/L in men. We divided the subjects into three categories according to their HDL concentrations (< 1, 1–1.5, > 1.6 mmol/L). Results of the subjects are given in Table I.

Small HDL (HDL_3) concentrations did not differ statistically between < 1 mmol/L and ≥ 1.6 mmol/L total HDL groups. High HDL levels were mostly consisting of large HDL subfractions (HDL_2). There was a decreasing small HDL/large HDL ratio with increasing total HDL. HDL subfractions according to the HDL concentrations are given in Figure 1. Small HDL (HDL_3) was not correlated with EL, LDL and TG concentrations and age but positively correlated with total cholesterol and HDL concentrations ($r = 0.2$, $p = 0.017$; $r = 0.2$, $p = 0.028$, respectively). Large HDL (HDL_2) was not correlated with age, EL and total cholesterol; and negatively correlated with HDL LDL, TG ($r = -0.7$, $p < 0.001$; $r = -0.2, p = 0.045$; $r = -0.3, p < 0.001$, respectively). If subjects were divided into two groups as HDL< 1 mmol/L and HDL ≥ 1.6 mmol/L, mean EL concentrations were 475.83 ± 521.77 nmol/L and 529.71 ± 276,92 nmol/L, respectively ($p = 0.086$) (Figure 2). EL was non-significantly high in total high HDL levels.

Discussion

There has been increasing evidence that the quality and not the quantity of HDL are important [4–10]. Decrease in the lipid content of HDL is thought to increase its capacity to remove cellular cholesterol; small, lipid-poor HDL particles thus represent more-efficient cholesterol acceptors than their large, lipid-rich counterparts [4].

In the Physician's Health Study, total HDL cholesterol and both HDL_2 and HDL_3 were inversely related to risk of myocardial infarction. The stronger association was with HDL_3 [25]. Yu et al. [26] found that HDL_3 was strongly and inversely associated with the risk of incident coronary artery disease, whereas HDL_2 was not significantly associated with risk of subsequent coronary artery disease. It was soon recently reported that small to medium-sized HDL, not large HDL, cholesterol concentrations were inversely associated with total stroke risk [9]. The Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT) demonstrated that the fibric acid derivative gemfibrozil reduced the new coronary heart disease events. Overall HDL was raised 6% and triglycerides lowered 31% by gemfibrozil [27]. In this trial, gemfibrozil significantly increased small HDL concentrations but not large HDL [28].

The HDL accumulating in cholesterol ester transfer protein (CETP)-deficient subjects was predominantly a larger HDL particle, reflecting the decreased removal of HDL [29]. The existence of coronary disease in some CETP-deficient individuals was documented [30]. The direct CETP inhibitor torcetrapib was evaluated in a large-scale trial called ILLUMINATE (Investigation of lipid level management to understand its impact in atherosclerotic events) [31]. Patients receiving torcetrapib experienced a 72.1% increase in HDL. The ILLUMINATE trial was prematurely terminated because of an increase in

Table I. Mean characteristics of subjects according to the high-density lipoprotein (HDL) concentrations.

Sex (*n*, %)	HDL < 1 mmol/L	HDL 1–1.5 mmol/L	HDL ≥ 1.6 mmol/L
Male	27 (90.0%)	29 (51.8%)	4 (25.0%)
Female	3 (10.0%)	27 (48.2%)	12 (75.0%)
	mean ± SD	mean ± SD	mean ± SD
Age (years)	35.43 ± 12.39	32.71 ± 8.90	33.62 ± 11.14
Endothelial lipase (nmol/L)	475.83 ± 521.77	564.50 ± 354.73	529.71 ± 276.92
Glucose (mmol/L)	2.23 ± 0.42	2.05 ± 0.29	2.11 ± 0.27
Total cholesterol (mmol/L)	4.34 ± 0.95	4.63 ± 0.83	4.73 ± 1.59
LDL (mmol/L)	2.60 ± 0.86	2.67 ± 0.68	2.66 ± 0.77
TG (mmol/L)	4.09 ± 2.44	3.02 ± 2.41	1.70 ± 0.63
HDL (mmol/L)	0.86 ± 0.86	1.26 ± 0.17	1.89 ± 0.28
Total HDL (mmol/L)	0.86 ± 0.14	1.25 ± 0.21	1.91 ± 0.31
Small HDL (mmol/L)	0.49 ± 0.23	0.69 ± 0.17	0.62 ± 0.31
Large HDL (mmol/L)	0.36 ± 0.25	0.55 ± 0.22	1.29 ± 0.41
Small HDL/Large HDL	2.63 ± 2.22	1.59 ± 1.02	0.59 ± 0.44

$p = 0.001$ for small HDL between HDL < 1 mmol/L and HDL ≥ 1.6 mmol/L groups; $p < 0.001$ for large HDL between HDL < 1 mmol/L and HDL ≥ 1.6 mmol/L groups.

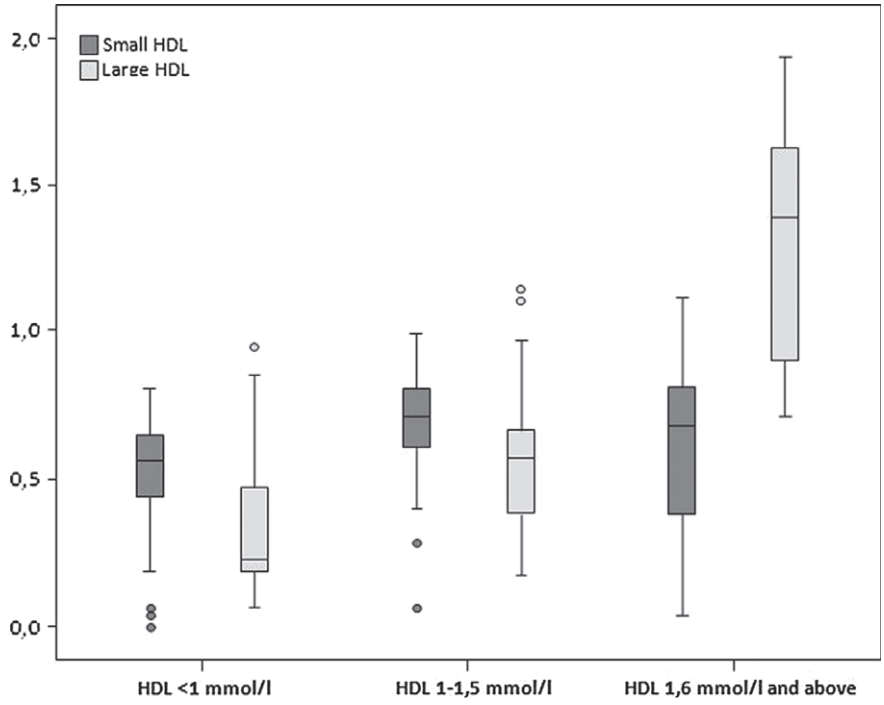

Figure 1. High-density lipoprotein (HDL) subfraction concentrations according to the total HDL concentrations.

cardiovascular events. Torcetrapib increases large HDL [32]. Among patients with atherosclerotic cardiovascular disease, there was no incremental clinical benefit from the addition of niacin to statin therapy [33]. There was a non-significant trend in stroke among patients assigned to niacin. Niacin therapy has had differential effects on HDL, increased large HDL, and either decreased or had no effect on small HDL [33,34]. According to the clinical and drug treatment trials, small HDL particles, and not large HDL particles, seemed to predict cardiovascular events. A shift in the distribution of HDL subfractions should have clinical results.

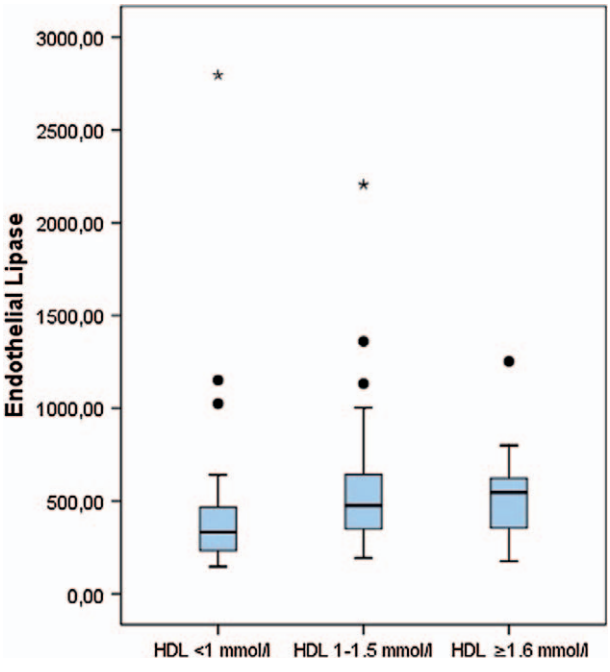

Figure 2. Endothelial lipase concentrations according to the total high-density lipoprotein (HDL) concentrations.

The present study was the first study showing that there are no differences between small HDL (HDL_3) concentrations in the HDL low and high quartiles in a healthy Turkish population sample. Our study is likely to be useful for determining the relative risk predictive powers of different HDL subfractions in clinical studies.

There are several methods to assess HDL subclasses. Researchers first used analytical ultracentrifugation and then density gradient ultracentrifugation to resolve HDL subclasses which can resolve up to five different subclasses of HDL. While tedious to perform, it is still considered the gold standard for separating HDL lipoprotein subclasses. A higher resolution method, two-dimensional agarose gel electrophoresis, can resolve up to 14 different subclasses of HDL. In the first dimension, HDL subclasses separate largely based on charge into pre-beta, alpha, and pre-alpha migrating forms. The second dimension separates the particles by size under non-denaturing conditions. There is also non-denaturing, gradient polyacrylamide gel separation for HDL subclass separation. After the HDL subclasses are separated on the gel and stained, the gel is analyzed by densitometric scanning to quantify the amount of each subclass. Another test for resolving HDL subclasses uses nuclear magnetic resonance (NMR).

However those methods are technically demanding, very tedious, and therefore impractical for clinical laboratories. Researchers have also developed immunoassays against specific subfractions of HDL.

There is another HPLC method which separates HDL particles into four size forms.

We determined HDL_3 and HDL_2 levels by a single precipitation method with heparin/manganese/dextran sulfate. Demacker et al. [35] compared the precipitation method by the procedure of Gidez et al. [36] with gold standard density gradient ultracentrifugation and obtained optimal accuracy. Hirano et al. [23] made a mixture of heparin/manganese/dextran sulfate for the precipitation of both HDL_2 and apoB-containing lipoproteins simultaneously while leaving the HDL_3 in the supernatant, as we used this method. They found accurate HDL_2 and HDL_3 results which were matched with the gold standard ultracentrifugation method. This supported the accuracy of the single precipitation method for the HDL subfractions.

In conclusion, the single precipitation method and direct HDL assay is very simple, precise, reliable even for chylomicronemic samples, and very convenient, practical and less time-consuming for clinical laboratories. Also, the running cost is cheaper than other methods and a homogenous HDL assay is applicable to an autoanalyzer for clinical laboratories. This method is useful and precise for determining different HDL fractions in clinical studies.

A major part of this atheroprotective potential of HDL conceivably consists of its key role in reverse cholesterol transport (RCT) [37]. Among the factors modulating HDL metabolism, lipases such as HL and EL are of prime importance. HL and EL both belong to the triacylglycerol lipase family, which also includes LPL, but members of this family differ in their respective hydrolytic activities. Whereas LPL is almost exclusively a triglyceridase, HL uses both phospholipids and triglycerides as substrates, and EL possesses predominantly phospholipase and very little triglyceridase activity [38]. By decreasing the triglyceride and phospholipid content of HDL, HL and EL are both significant negative regulators of plasma HDL concentrations [37]. The current data on the role of EL and HL in cholesterol efflux are not conclusive. Both enzymes increase hepatic selective cholesterol uptake; however, this does not translate into altered biliary cholesterol secretion, which is regarded as the final step of RCT. Also, the impact of HL and EL on atherosclerosis is not clear [39]. Previously Bersot et al. [22] have found an elevated hepatic lipase activity in a normotriglyceridemic, non-obese Turkish population with low concentrations of HDL.

In vitro, EL effectively hydrolyzes high-density lipoprotein HDL phospholipids. In mice, EL has a major influence on HDL metabolism. Adenovirally-mediated overexpression of human EL in mice dramatically reduced HDL cholesterol concentrations [40], shown to be due to rapid catabolism of HDL [41]. Similarly, studies have indicated that in humans the plasma EL mass inversely correlates with plasma HDL concentrations and positively correlates with features of atherosclerosis and metabolic syndrome [21].

As opposed to previous studies, in our study we found endothelial lipase concentrations non-significantly higher in subjects >1.6 mmol/L group than in the <1 mmol/L group. According to our findings, our data did not support EL to be the reason for low HDL concentrations in a healthy Turkish population.

Conclusion

There were no differences between small HDL (HDL_3) concentrations in the total HDL <1 mmol/L and ≥ 1.6 mmol/L groups. It remains to be determined whether a shift in the distribution of HDL particles confers a greater benefit than an increase in total HDL alone. Our results in a healthy population may serve as a reference for clinical studies on HDL subfractions. EL did not seem to be a factor for low HDL in Turks.

Study limitations

The present study evaluated basic data in healthy subjects. Subjects will be followed for their cardiovascular events in the future years. HL and LPL were not measured in our study. It would be better to measure HL and LPL concentrations in future research. This study was an observational and non-randomized study; the number of cases included in the study was low and the authors suggest confirmation of the findings in a larger number of subjects.

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