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Gender differences in LDL and HDL subfractions in atherogenic and nonatherogenic phenotypes

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ABSTRACT

Objectives: The aim of our study was to examine the role of low density lipoprotein (LDL)-subfractions in individuals with the atherogenic and non-atherogenic phenotype and the gender differences in lipoprotein subfractions including small dense LDL (sdLDL) and small high density lipoprotein (sHDL) subfractions representing the most atherogenic lipoprotein subfractions.

Design & methods: 35 persons in the atherogenic group (AG) (with $sdLDL_{3-7}$ subfractions ≥6 mg/dl) and 104 individuals in the non-atherogenic group (NAG) ($sdLDL_{3-7}$ subfractions < 6 mg/dl) were included in our study. To analyze plasma lipoprotein subfractions, a polyacrylamide gel electrophoresis–the Lipoprint system was used.

Results: Males compared to females in the AG had significantly higher levels of atherogenic lipoprotein subfractions such as HDL_8, HDL_9 and HDL_{10}. All participants in AG had significantly lower levels of intermediate density lipoprotein IDL-A than those in NAG but significantly higher levels of IDL-B and IDL-C. Males in the AG compared to NAG had significantly lower levels of LDL_1 and higher levels of LDL_2 and LDL_{3-7} subfractions. In the NAG LDL_2 positively correlated with sHDL subfractions while in the AG with the large HDL subfraction.

Conclusion: Results of our study demonstrate more atherogenic profile in males compared to females and a double role of LDL2 subfraction in the atherogenic process depending on the phenotype (atherogenic/non-atherogenic) of individuals.

1. Introduction

It is well described that atherosclerosis is an inflammation in the intima of large arteries which is triggered by high cholesterol levels in serum [1]. In the last few decades, lipoprotein research has focused on the phenomenon of atherogenic and non-atherogenic lipoprotein profile characterization [2]. Atherosclerosis has been considered the principal cause of myocardial and cerebral infarction [3]. Individuals with atherogenic lipoprotein profile are characterized by increased levels of atherogenic lipoproteins: very low density VLDL, intermediate density IDL_1 and IDL_2, small dense low density lipoproteins (sdLDL) and small high density lipoproteins (sHDL) [4]. In the past, hypercholesterolemia was considered a strong atherogenic risk factor for the development of cardiovascular disease until Castelli et al. published the evidence that > 75 percent of patients with an acute coronary syndrome or a myocardial infarction had normal plasma values of total cholesterol, LDL cholesterol and/or HDL cholesterol [5–7]. These results lead to a search for new risk factors of coronary events. Atherogenic lipoprotein subpopulations in plasma might be other risk factors. In spite of the fact that atherogenic lipoprotein subfractions appear in blood at very low concentrations, they can lead to the impairment of the vessel wall integrity and endothelial dysfunction [8]. To identify and quantify atherogenic and non-atherogenic lipoprotein subfractions in plasma, including sdLDL and sHDL, a polyacrylamide gel electrophoresis (Lipoprint system) was used [9]. Based on the particle size the Lipoprint LDL system identifies 7 LDL cholesterol subclasses: LDL_1 and LDL_2 (large subfractions) and LDL_{3-7} (small atherogenic subfractions). LDL_{3-7} fractions are smaller subfractions with a higher density than LDL_1 and LDL_2 [10]. Lipoprint HDL system identifies 10 HDL cholesterol subclasses: large HDL_{1-3} subfractions; intermediate HDL_{4-7}

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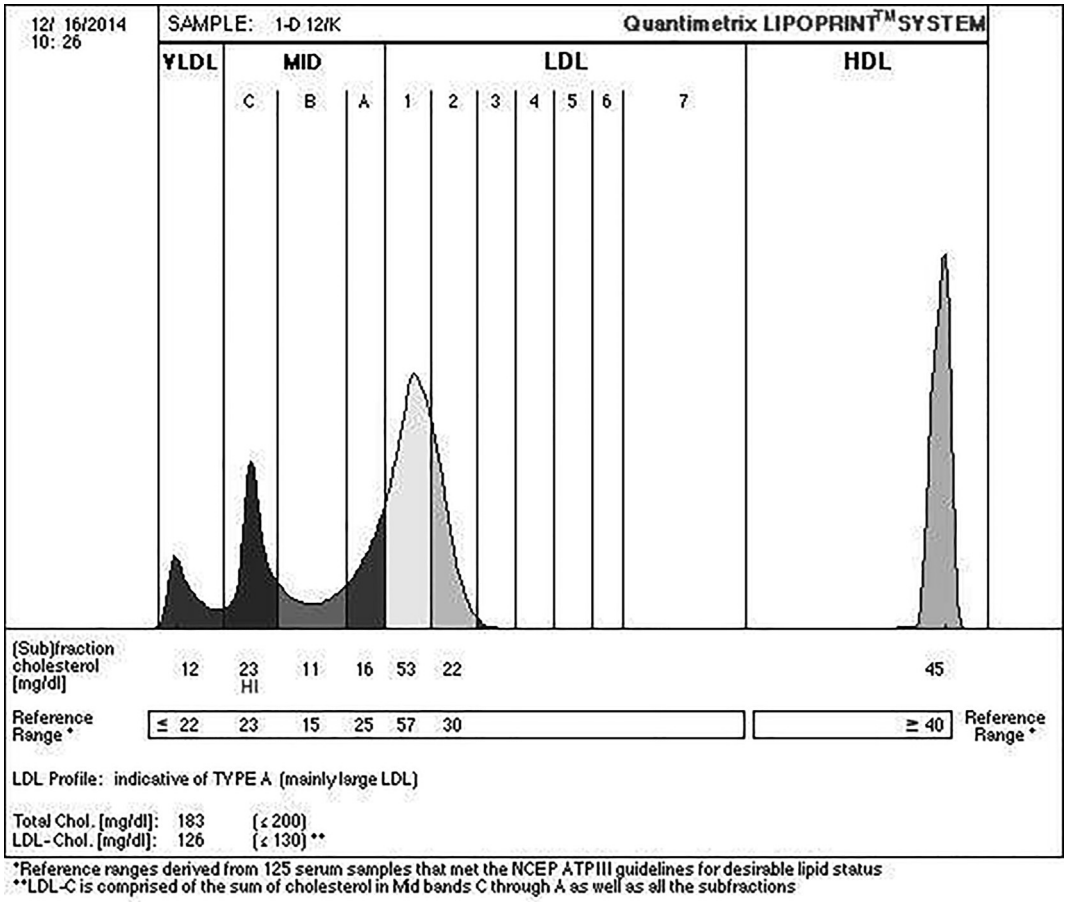

Fig. 1. Control group – a non atherogenic lipoprotein profile with no small dense LDL_{3-7} subfractions.

subfractions and small HDL_{8-10} subfractions (atherogenic) [11,12]. Small dense LDL and HDL are atherogenic due to the low recognition by receptors, enhanced aptitude for oxidation and acetylation, easier penetration into the subendothelial space and formation of cholesterol deposits [13]. The HDL family is generally considered a protective antiatherogenic part of the plasma lipoproteins and LDL family an atherogenic lipoprotein part. The Lipoprint system can identify individuals with atherogenic (small, dense LDL_{3-7} subfractions ≥6 mg/dl) and non-atherogenic phenotypes based on the levels of atherogenic lipoproteins in plasma. The aim of our study was to examine the role of LDL-subfractions in individuals with the atherogenic (AG) and non-atherogenic phenotype (NAG). In addition, we have examined the gender differences in LDL and HDL subclasses including small dense LDL (sdLDL) and small HDL (sHDL) subfractions representing the most atherogenic lipoprotein subfractions.

2. Methods

2.1. Study population

35 patients with atherogenic lipoprotein profile with small dense LDL_{3-7} subfractions (age 52.91 ± 13.71 years) (17 males/18 females) and 104 individuals with non-atherogenic lipoprotein profile without small dense LDL_{3-7} subfractions (age 54.41 ± 15.40 years) (33 males/71 females) were included in our study. Participants in the atherogenic group suffered from no ischemic heart disease, renal disease, diabetes mellitus, they were without any anti-lipid or anti-platelet therapy. Individuals in the non-atherogenic group were healthy individuals without any signs of acute or chronic diseases.

2.2. Plasma collection

Fasting venous blood with EDTA was collected after overnignt fasting at the 1st Department of Internal Medicine, University Hospital in Bratislava. Blood was centrifuged at 1200 × *g* for 15 min at 4 °C and plasma samples were stored in aliquots at −70 °C for the lipid profile determination. All individuals participating in our study signed an informed consent. This study was approved by the Ethics Committee of the Faculty of Medicine, Comenius University and the University Hospital in Bratislava (12/09/2016) and was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.3. Lipoprotein subfractions determination

To analyze plasma lipoprotein subfractions, a polyacrylamide gel electrophoresis – the Lipoprint system (Lipoprint LDL System and Lipoprint HDL System, respectively; Quantimetrix corp., Redondo Beach, CA, USA) was used according to the manufacturer's instructions. Participants were divided into two groups based on the results obtained by the Lipoprint system: individuals with LDL_{3-7} subfractions ≥6 mg/dl were included into the atherogenic experimental group (AG) and individuals with LDL_{3-7} subfractions below 6 mg/dl were included into the non-atherogenic group (NAG) (Figs. 1 and 2) [2,14].

2.4. Statistics

The statistical analysis was performed using SPSS ver. 18 (SPSS Inc., Chicago, IL, USA). Significance level was set at $P < 0.05$. Our results are expressed as means ± standard deviation (SD) for normally

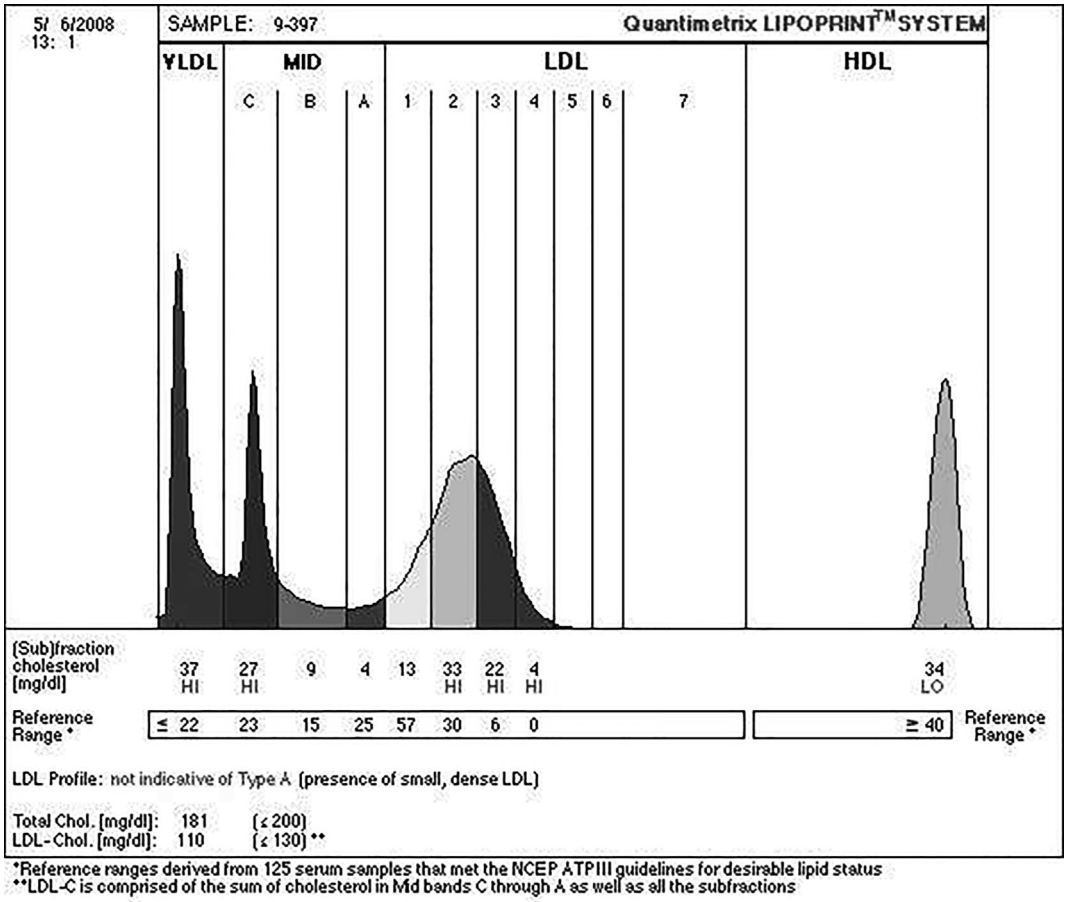

Fig. 2. Atherogenic group – a lipoprotein profile with small dense LDL_{3-7} subfractions ≥6 mg/dl.

Table 1
Age (years) and lipid paramaters (mg/dl) of individuals in nonatherogenic (NAG) and atherogenic groups (AG).

	NAG (n = 104)	AG (n = 35)	P
Age	54.13 ± 15.65	52.91 ± 13.17	0.609
total chol	214.69 ± 48.84	242.74 ± 66.83	**0.010**
VLDL	25.61 ± 8.47	35.5(27–44)	**0.000**
IDL-A	21(15.5–29.0)	14.34 ± 5.36	**0.034**
IDL-B	12.51 ± 5.13	15.34 ± 7.47	**0.016**
IDL-C	19.91 ± 6.07	26.51 ± 8.06	**0.000**
total LDL	134.39 ± 39.66	157.97 ± 36.85	**0.003**
LDL_1	57.29 ± 17.86	39.89 ± 15.28	**0.000**
LDL_2	20(13–28)	42.03 ± 14.82	**0.000**

Results are expressed as the mean ± SD or the median (upper quartile – lower quartile). P < 0.05 is considered statistically significant; bold values indicate statistical significance. total chol – total cholesterol, HDL – high density lipoproteins, VLDL – very low density lipoproteins, IDL – intermediate density lipoproteins, LDL – low-density lipoproteins, n – number of participants in a particular group.

distributed data, or medians (upper quartile–lower quartile) for data not normally distributed. The Studenťs unpaired *t* test or non-parametric Mann-Whitney test was used for the comparison between groups of continuous parameters as appropriate. To quantify association between two variables, Pearson or Spearman correlations were used.

3. Results

In the non-atherogenic group (NAG) there were significantly lower levels of all atherogenic lipoprotein parameters such as total cholesterol, VLDL, IDL-B, IDL-C, LDL, LDL_2 (Table 1) as well as atherogenic HDL subfractions such as $HDL_{8–10}$ (Table 2). However, atheroprotective lipoproteins IDL-A and LDL_1 (Table 1) as well as total HDL and large HDL subfractions (Table 2) in NAG were significantly higher than in the atherogenic group (AG). When analyzing gender differences in NAG we found no significant changes in all measured parameters but a few HDL subfractions (total, large and imHDL) that were higher in females compared to males (Table 3).

Similarly, in the AG there were no significant gender differences in the total cholesterol levels, VLDL and all LDL subfractions (Table 3), but atherogenic $HDL_{8–10}$ subfractions were significantly higher in males than in females (Table 3). However, total HDL and imHDL were significantly lower in males of AG than in females (Table 3). When comparing males in NAG and AG we found significantly higher levels of atherogenic lipids such as total cholesterol, VLDL, IDL-C, LDL, LDL_2, as well as small HDL subfractions 8–10 in AG (Table 3). Atheroprotective fractions (IDL-A, LDL_1 and imHDL) were however, significantly lower in male AG (Table 3). When comparing females in NAG and AG, the situation was similar to males (Table 3), however, there were no significant differences in the levels of atherogenic $HDL_{8–10}$ subfractions. IDL-A significantly positively correlated with large HDL in the NAG. In the AG the correlation was nonsignificant (Table 4). IDL-B and IDL-C positively correlated with small HDL subfractions only in the NAG, however, in the AG these correlations were nonsignificant. LDL_1 subfraction significantly positively correlated with large HDL in the AG, while in the NAG this correlation was nonsignificantly positive. LDL_2 subfraction significantly positively correlated with the large HDL in the AG. In the NAG this correlation was nonsignificantly negative. LDL_2 subfraction significantly positively correlated with the small HDL subfractions in the NAG. In the AG this correlation was nonsiginificantly positive (Table 4).

Table 2
HDL subfractions (mg/dl) of individuals in nonatherogenic (NAG) and atherogenic groups (AG).

	NAG (n = 66)	AG (n = 19)	P
total HDL	55.11 ± 13.91	42.58 ± 11.81	**0.0007**
large HDL	21.89 ± 10.21	11.74 ± 6.54	**0.0001**
imHDL	25.89 ± 5.65	23.37 ± 8.99	0.1469
small HDL	6(5–9)	8(5–9)	0.5354
HDL_8 (area%)	5(4–6)	5(5–8)	**0.0429**
HDL_9 (area%)	4.00 ± 1.85	5.68 ± 2.43	**0.0019**
HDL_{10} (area%)	3(2–7)	6(4–9)	**0.0297**

Results are expressed as the mean ± SD or median (upper quartile – lower quartile). P < 0.05 – statistically significant; bold values indicate statistical significance. HDL – high density lipoproteins.

4. Discussion

To separate LDL subfractions several laboratory techniques have been developed, and the results obtained by different methods cannot be compared in most cases [15]. In most studies LDL particles are classified into 3 or 4 subclasses, including large (LDL I), intermediate (LDL II), small (LDL III), and, in some studies, very small (LDL IV) LDLs. LDL III and LDL IV are referred to as sdLDL. In the Lipoprint system which we used, LDL particles are classified into 7 subclasses with LDL3–7 classified as small dense subfractions. Therefore, care should be taken while comparing the results of clinical studies employing different methods. The results of recent studies demonstrate that HDL and LDL subfractions have different atherogenity [13]. While large HDL and LDL_1 subfractions are known anti-atherogenic fractions, small dense $LDL_{3–7}$ subfractions have atherogenic properties [16]. Based on the concentration of small, dense LDL_{3-7} subfractions ($sdLDL_{3–7}$), we have divided our volunteers into two experimental groups: atherogenic (AG) ($sdLDL_{3–7}$ subfractions ≥6 mg/dl) and nonatherogenic (NAG) ($sdLDL_{3–7}$ subfractions < 6 mg/dl). We found that individuals in the AG had significantly higher levels of parameters such as total cholesterol, VLDL, IDL-B, IDL-C, total LDL cholesterol and LDL_2 fraction and lower levels of IDL-A and LDL_1 compared to NAG. Similarly, Austin et al [14] also found that different phenotypes were closely associated with variations in plasma levels of other lipids, lipoproteins, and apolipoproteins.

When examining *gender differences* in measured parameters we found that males in the *atherogenic group* (AG) have more atherogenic lipoprotein profile than females due to significantly higher levels of small, atherogenic $HDL_{8–10}$ subfractions and significantly lower levels of athero-protective imHDL subfractions. Anagnostis et al (2015) came to the same conlusion when they examined effects of menopause, gender and age on serum lipid risk markers for vascular disease [17]. In the *non-atherogenic group* (NAG) there were no significant gender differences in all measured parameters but HDL subfractions. Females, generally, have higher total HDL cholesterol levels compared to males, which is in accord with our results. From HDL subfractions females had higher levels of large HDL and imHDL subfractions, while small HDL subfractions were not significantly different from males. Large HDL subfraction is considered an atheroprotective fraction. We have found its positive correlations with IDL-A in the non-atherogenic group indicating a protective role of IDL-A in the atherogenic process. Moreover, IDL-A was significantly higher in the NAG compared to the AG. However, in the AG large HDL subfraction did not significantly correlate with IDL lipoproteins. In the AG large HDL subfraction positively correlated only with LDL_1 and LDL_2 subfractions. Athero-protective role of LDL_1 subfraction has been demonstrated in several studies [18], but the role of LDL_2 subfraction has not been determined yet. Particularly strong association between the large HDL subfraction and LDL_2 subfraction found in the AG (P = 0.0004) might indicate an atheroprotective role of LDL_2 in individuals with atherogenic phenotype. In our previous study [19] involving pacients 24 h after ischaemic stroke vs healthy controls, we found a possitive association of LDL_2 subfraction with the antioxidant enzyme catalase in males of the patients group which might confirm our conclusion on positive effect of LDL_2 subfraction in the atherogenesis. However, in the group of healthy controls the previous study [19] have reported a positive correlation between LDL_2 subfraction and lipoperoxides which confirms our conclusion on atherogenic property of this LDL subclass in the non-atherogenic group. Lipoperoxides are markers of oxidative damage to lipids produced during an oxidative stress which can play a role in the process of

Table 3
Gender differences in age and lipoprotein profile (mg/dl) (total cholesterol, VLDL, IDL and LDL) in individuals with non-atherogenic and atherogenic lipoprotein profile.

	Females		Males		P	P	P	P
	NAG (n = 71)	AG (n = 18)	NAG (n = 33)	AG (n = 17)	M/F NAG	M/F AG	M/M NAG/AG	F/F NAG/AG
Age	54.14 ± 15.41	52.06 ± 13.25	53.41 ± 16.07	53.82 ± 13.83	0.9354	0.7018	0.9285	0.5999
total chol	219.59 ± 47.48	245.22 ± 80.61	206.03 ± 50.67	240.12 ± 50.73	0.1051	0.8252	**0.0280**	0.0819
VLDL	24.87 ± 8.62	34(25–44)	27.29 ± 8.12	38.00 ± 13.97	0.2319	0.8638	**0.0011**	**0.0003**
IDL-A	22(17–30)	13.44 ± 4.54	21.00 ± 9.64	15.29 ± 6.10	0.1680	0.3144	**0.0249**	**0.0001**
IDL-B	12.58 ± 5.11	15(11–18)	12.47 ± 5.29	14.71 ± 5.37	0.7496	0.6313	0.1631	0.1498
IDL-C	20.26 ± 6.23	26.89 ± 9.26	19.18 ± 5.81	26.12 ± 6.82	0.2829	0.7818	**0.0004**	**0.0005**
LDL total	136.09 ± 39.04	154.72 ± 26.15	131.79 ± 41.52	161.41 ± 46.20	0.4469	0.5989	**0.0249**	0.0585
LDL_1	59.11 ± 17.71	41.56 ± 16.91	53.91 ± 17.90	38.12 ± 13.62	0.1243	0.5140	**0.0024**	**0.0003**
LDL_2	20.79 ± 11.55	42.00 ± 14.21	20(13–31)	42.06 ± 15.88	0.5564	0.9908	**0.0001**	**0.0000**
LDL_{3-7}	0(0–2)	12.5(8–16)	1(0–4)	18(10–37)	0.0886	0.0531	**0.0001**	**0.0001**
total HDL	58.53 ± 13.27	48.00 ± 12.53	45.24 ± 10.61	36.56 ± 8.78	**0.0005**	**0.0358**	0.0513	**0.0259**
large HDL	24.16 ± 10.23	14.20 ± 6.66	15.35 ± 6.34	9.00 ± 5.96	**0.002**	0.0922	**0.0231**	**0.0054**
imHDL	26.76 ± 5.43	27.30 ± 11.06	23.53 ± 5.61	19.00 ± 3.71	**0.046**	**0.0471**	**0.0444**	0.8014
small HDL	7(2–9)	5.5(4–9)	6.24 ± 2.34	8.11 ± 1.54	0.1967	0.0564	**0.0457**	0.4132
HDL_8 (area%)	5(4–6)	5(5–6)	5.47 ± 1.97	7.89 ± 2.93	0.6547	**0.0156**	**0.0209**	0.5845
HDL_9 (area%)	3.86 ± 1.70	4.50 ± 1.35	4.41 ± 2.17	7.00 ± 2.87	0.2942	**0.0244**	**0.0178**	0.2712
HDL_{10} (area%)	3(2–7)	4.5(2–7)	4(3–5)	8.33 ± 3.00	0.3754	**0.0046**	**0.0071**	0.7284

Results are expressed as the mean ± SD or the median (upper quartile – lower quartile). P < 0.05 – statistically significant; bold values indicate statistical significance.
NAG – nonatherogenic group, AG – atherogenic group, n – number of participants in a particular group, M – males, F – females, total chol – total cholesterol, VLDL – very low density lipoproteins, IDL – intermediate density lipoproteins, LDL – low-density lipoproteins, HDL – high density lipoproteins, imHDL – intermediate HDL subfractions, small HDL – small HDL subfractions, P < 0.05 – statistically significant.

Table 4
Statistical significance (P) of correlations between lipid parameters in non-atherogenic (NAG) and atherogenic groups (AG) using Spearman correlation test.

Parameters	NAG		AG	
	r	P	r	P
IDL-A/large HDL	0.2610	**0.0173**	0.3040	> 0.05
IDL-B/small HDL	0.3305	**0.0035**	−0.2500	> 0.05
IDL-C/small HDL	0.3223	**0.0043**	−0.3310	> 0.05
LDL_1/large HDL	0.2620	> 0.05	0.7685	< **0.0001**
LDL_2/large HDL	−0.1570	> 0.05	0.7149	**0.0004**
LDL_2/small HDL	0.3724	**0.0011**	0.2242	0.175

IDL – intermediate density lipoproteins, HDL – high density lipoproteins, r – correlation coeficient, P < 0.05 – statistically significant.

atherogenesis. However, this correlation between LDL_2 subfraction and lipoperoxides [19] was not as strong ($p = 0.02$) as in the present study ($P = 0.0004$) which may result from the fact that also persons with atherogenic profile (small dense $LDL_{3-7} \geq 6$ mg/dL) among the healthy controls might have been included in the control group. Taking into account also results of the present study (the positive association of LDL_2 subfraction with small HDL subfractions) we might assume a pro-atherogenic properties of LDL_2 subfraction in individuals with non-atherogenic phenotype.

Many studies have been studying metabolism of sdLDL subfractions, however, there is no study yet focusing on LDL_2 subfraction. We are the first to report the possible double role of LDL_2 subfraction in the atherogenic process depending on the phenotype of individuals.

Small HDL subfractions have been reported pro-atherogenic fractions [20]. We have found their positive correlation with IDL-B and IDL-C only in the NAG indicating pro-atherogenic function of intermediate density lipoproteins B and C in individuals with non-atherogenic phenotype.

We have not found any significant differences in small dense LDL_{3-7} subfractions between genders in the AG as well as in the NAG. However, small atherogenic fractions HDL_{8-10} were significantly higher in the male AG compared to the female AG. In the NAG those differences were nonsignificant.

In this study we have found the double role of LDL_2 subfraction in the atherogenic process depending on the phenotype of individuals. In addition, we have found that males in the atherogenic group have more atherogenic lipoprotein profile than females.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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