ORIGINAL ARTICLE

SMALL LDL: A HELPFUL PARTICLE IN MONITORING PATIENTS WITH METABOLIC SYNDROME

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Abstract

Patients with metabolic syndrome have a higher risk of cardiovascular events than healthy subjects. Many studies proved that plasma lipoprotein levels represent predictive factors for coronary disease. Among lipoproteins, small low density lipoproteins (sLDL) particles have the highest atherogenic potential. For patients with metabolic syndrome, levels of plasma sLDL, as compared to other lipid markers that constitute cardiovascular risk factors, and correlated with carotid artery intima-media thickness (IMT) measured by ultrasound imaging, may represent useful markers for medical and pharmaceutical practice.

Rezumat

Subiecţii care prezintă sindrom metabolic sunt mult mai expuşi la dezvoltarea de accidente şi evenimente cardiovasculare decât subiecţii care nu prezintă acest sindrom. Numeroase studii au arătat că nivelurile lipoproteinelor plasmatice sunt factori predictivi importanţi pentru riscul de boală coronariană, dar dintre aceste fracţiuni particulele de sLDL (lipoproteine cu densitate joasă, de dimensiuni mici) prezintă cel mai înalt grad de aterogenitate. Evaluarea nivelurilor serice ale sLDL comparativ cu ceilalţi markeri lipidici favorizanţi ai bolii cardiovasculare, alături de modificările de la nivel cardiac evaluate prin ecocardiografie, pot constitui markeri utili, atât pentru practica medicală, dar şi farmaceutică, în cazul pacienţilor cu sindrom cardiometabolic.

Keywords: metabolic syndrome, small low density lipoproteins (sLDL), coronary disease

Introduction

Metabolic syndrome is represented by a cluster of cardiovascular risk factors that can cause the onset and development of atherosclerotic plaque, leading to an increased morbidity and mortality due to cardiovascular events [2]. Atherosclerosis is a degenerative process of the arterial wall, which results into alterations of elastic fibres and replacement with collagen fibres (sclerosis), along with cholesterol deposit and calcification, leading to formation of plaques. The process is asymptomatic for a long time, most patients being diagnosed in the late stages, when clinical symptoms set in [11]. The hypothesis that subjects with metabolic syndrome have a higher risk of cardiovascular disease has been confirmed by many analyses. Dyslipidaemia represents the main atherogenic factor; patients with metabolic syndrome develop an association of high levels of low density lipoproteins (LDL) and triglycerides, combined with low levels of high density lipoproteins (HDL) [6, 7, 12]. Although all LDL particles are considered to have atherogenic potential, sLDL is associated with the highest cardiovascular risk [13]. The aim of our study was to evaluate the sLDL levels among the other lipoprotein subclasses, and correlate them with carotid intima-media thickness, in order to assess the risk of coronary heart disease in patients with metabolic syndrome.

Materials and Methods

The study was conducted between 01.04.2014 and 01.03.2015 on 102 patients (72 men and 30 women) with metabolic syndrome, diagnosed according to National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) criteria. The patients that were included in the study presented changes only for the lipid parameters values, the

glycemia levels being in the normal range. The test panel included biochemical markers of lipid profile: triglycerides (TG), total cholesterol, HDL-cholesterol, LDL-cholesterol, sLDL. Blood samples were collected; serum was separated after blood centrifugation at 4000 g for 15 minutes. Triglycerides and total cholesterol concentrations were assessed using spectrophotometric enzymatic methods [3, 15]. HDL-cholesterol was assessed after the precipitation of chylomicrons, VLDL (very low density lipoproteins) and LDL with phosphotungstic acid and $MgCl_2$, followed by determination of HDL-cholesterol in the supernatant. LDL-cholesterol concentration was measured using a direct colorimetric enzymatic method, which implied micellar solubilisation of LDL-cholesterol by a non-ionic detergent and interaction between lipoproteins (VLDL and chylomicrons) and a polysaccharide compound. The method fulfils the NCEP (National Cholesterol Education Program) requirement of total analytical error ≤ 12% [10]. sLDL fraction concentration was measured using a "two step" method, with surfactant and specific enzymes. The determinations were performed on a RX-Imola automatic analyser, using RANDOX kits with calibrators and control sera included. The carotid ultrasound examination was performed by a sonographer, using an ESAOTE MyLab50 with 2.5/3.5 MHz probe. The quantification of the atherosclerotic process was made measuring the ejection fraction (LVEF), of the left ventricle mass (LVM) and aortic atheroma. Statistical analyses were performed using SPSS/ v. 20, (t-Student test, Mann-Whitney U test).

The research has been conducted with the approval of the Ethics Committee of the University of Medicine and Pharmacy "Grigore T. Popa" Iaşi and in accordance to the European Communities Council Directive 86/609/EEC, with the informed consent of the patients.

Results and Discussion

The descriptive statistics bring the following results: out of the 102 analysed patients, 72 (70.58%) were male, 30 (29.41%) were female and the mean age was 49.10 ± 12.45 years. The average values along with standard deviation for age, lipid profile (cholesterol, LDL, sLDL, HDL, TG, LDL/HDL ratio) and cardiac function parameters (left ventricular ejection fraction - LVEF and left ventricular mass - LVM) by sex are shown in Table I. The variation of lipid parameters is depicted in Figure 1. The evaluation of the lipid parameters was performed in relation to the reference ranges for the age groups that were included in the study.

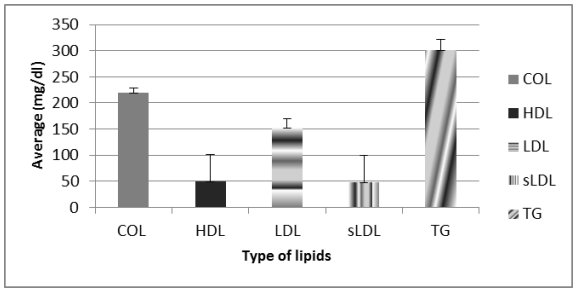

Figure 1.
The variation of the lipidic profile

Table I
Mean values of the studied parameters

Parameter	Groups	
	Men (mean ± standard deviation)	**Women** (mean ± standard deviation)
Age (years)	48.056 ± 15.615	52.115 ± 11.582
Cholesterol (mg/dL)	248.842 ± 67.894	251.963 ± 54.665
HDL (mg/dL)	50.505 ± 7.759	45.367 ± 12.896
LDL (mg/dL)	165.789 ± 55.090	156.913 ± 51.197
sLDL (mg/dL)	61.558 ± 26.805	65.856 ± 28.612
Triglycerides (mg/dL)	344.210 ± 239.970	426.993 ± 254.041
LDL/HDL ratio	3.239 ± 0.861	3.581 ± 1.1929
LVEF (%)	65.500 ± 6.833	60.230 ± 10.497
LVM (g)	216.333 ± 57.109	271.760 ± 80.684

The statistical analysis by *Student t-test* did not shown significant statistical differences between the up-mentioned parameters by sex groups, while a positive *Pearson* correlation was obtained by comparing male and female gender. The statistical analysis revealed that 68.4% of the patients presented left ventricular dysfunction assessed by cardiac echocardiography while the majority of subjects (94.7%) had aortic atheromatosis. The total cholesterol values had positive and significant correlations with HDL, LDL and sLDL, while LDL correlated with HDL, sLDL, respectively HDL/LDL ratio. The triglycerides levels presented positive associations with the left ventricular ejection fraction and high sLDL values. The following correlations have been obtained: HDL-cholesterol ($r = 0.587$, $p = 0.008$), LDL-cholesterol ($r = 0.782$, $p < 0.001$), sLDL-cholesterol ($r = 0.845$, $p < 0.001$),

LDL-HDL (r = 0.512, p = 0.025), LDL-sLDL (r = 0.711, p = 0.001), LDL - HDL/LDL ratio (r = 0.480, p = 0.038), sLDL-triglycerides (r = 0.28, p = 0.01), triglycerides-left ventricular ejection fraction (r = 0.490, p = 0.033). T-test statistical differences have been statistically significant (p < 0.001), considering sLDL values compared to LDL, cholesterol and triglycerides (Tabel II).

Table II

Pearson correlation

		age	COL	HDL	LDL	sLDL	TG	HDL/LDL ratio	LVEF (%)	LVM (g)
Age	Pearson Correlation	1	-0.547*	0.204	-0.185	-0.644**	-0.638**	-0.324	-0.579*	0.402
	Sig. (2-tailed)		**0.023**	0.433	0.477	**0.005**	**0.006**	0.204	**0.015**	0.110
COL	Pearson Correlation	-0.547*	1	0.587**	0.782**	0.845**	0.076	0.217	0.099	-0.128
	Sig. (2-tailed)	0.023		**0.008**	**0.000**	**0.000**	0.758	0.373	0.688	0.601
HDL	Pearson Correlation	0.204	0.587**	1	0.512*	0.333	-0.310	-0.418	-0.349	0.194
	Sig. (2-tailed)	0.433	0.008		**0.025**	0.163	0.196	0.075	0.143	0.425
LDL	Pearson Correlation	-0.185	0.782**	0.512*	1	0.711**	-0.040	0.480*	-0.199	0.066
	Sig. (2-tailed)	0.477	0.000	0.025		**0.001**	0.871	**0.038**	0.415	0.788
sLDL	Pearson Correlation	-0.644**	0.845**	0.333	0.711**	1	0.090	0.300	0.197	-0.118
	Sig. (2-tailed)	0.005	0.000	0.163	0.001		0.713	0.212	0.420	0.629
TG	Pearson Correlation	-0.638**	0.076	-0.310	-0.040	0.090	1	0.273	0.490*	-0.228
	Sig. (2-tailed)	0.006	0.758	0.196	0.871	0.713		0.258	**0.033**	0.349
HDL/LDL ratio	Pearson Correlation	-0.324	0.217	-0.418	0.480*	0.300	0.273	1	0.169	-0.244
	Sig. (2-tailed)	0.204	0.373	0.075	0.038	0.212	0.258		0.488	0.314
LVEF (%)	Pearson Correlation	-0.579*	0.099	-0.349	-0.199	0.197	0.490*	0.169	1	-0.386
	Sig. (2-tailed)	0.015	0.688	0.143	0.415	0.420	0.033	0.488		0.102
LVM (g)	Pearson Correlation	0.402	-0.128	0.194	0.066	-0.118	-0.228	-0.244	-0.386	1
	Sig. (2-tailed)	0.110	0.601	0.425	0.788	0.629	0.349	0.314	0.102	

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

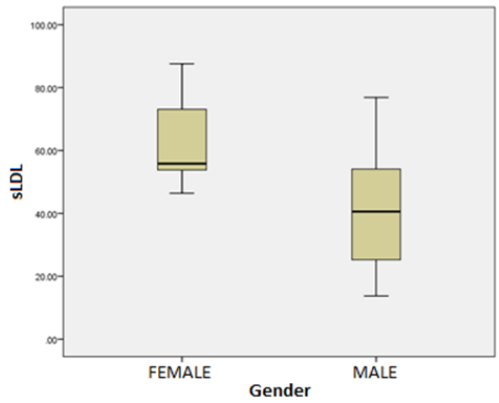

Figure 2.

sLDL variation according to gender

Mann-Whitney U test showed a significant correlation between age (57.41 ± 20 years) and left ventricular dysfunction (p = 0.027) as well as between sLDL (47.18 ± 10.16 mg/dL) and gender (p = 0.029) (Figure 2).

The correlations between age and ventricular dysfunction, as well as between ventricular dysfunction and sLDL levels [1], suggest that elevated levels of sLDL contribute to the onset of cardiac disease. Our data are consistent with the Hulthe J 2000 study [8], which stated that patients with risk factors for metabolic syndrome had a higher concentration of sLDL and a higher value for intima-media thickness of the carotid and femoral artery. sLDL levels increase in parallel with visceral adiposity and TG levels [14], but independent of age and other lipid parameters. The presence of atherosclerotic plaques in 94.7% patients, including some with normal HDL-cholesterol or LDL-cholesterol levels, but with increased sLDL fraction, proves the importance of sLDL evaluation in order to identify subclinical atherosclerosis [5]. Metabolic syndrome correlates

best with sLDL values, especially in female patients, our data being consistent with data reported in literature [4]. Among all measured lipid markers, the correlation of age with sLDL values in patients with metabolic syndrome, especially in young subjects, could be a useful predictive factor in monitoring patients with cardiovascular risk. The atherogenic potential of sLDL particles is due to their ability to penetrate the arterial wall [9], low affinity for LDL receptor, increased plasma half-life and high susceptibility to glycation and oxidative stress [16].

Conclusions

Our results show that sLDL could be a valuable marker for the risk of coronary heart disease, better than the LDL levels, in patients with metabolic syndrome. The value of this marker is increased and statistically correlated with age and triglycerides levels. sLDL can bring its contribution not only in the evaluation of atherosclerosis risks, but also in the therapy individualization and monitoring.

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