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Associations of adipokines and metabolic hormones with low-density lipoprotein hypercholesterolemia in men and women under 45 years of age

Aim	To study the adipokine profile in young people with hypercholesterolemia and low-density lipoproteins (LDL) and to evaluate the relationship between concentrations of LDL cholesterol (LDL–C) and metabolic hormones in men and women younger than 45 years.
Material and Methods	This study included 304 subjects (group 1, 56 men with LDL–C concentration <2.1 mmol/l; group 2, 87 men with LDL–C concentration ≥4.2 mmol/l; group 3, 90 women with LDL–C concentration <2.1 mmol/l; and group 4, 71 women with LDL–C concentration ≥4.2 mmol/l). Serum concentrations of total cholesterol (C), triglycerides (TG), high-density lipoprotein C, and glucose were measured by an enzymatic assay with ThermoFisher Scientific kits and a KonelabPrime 30i biochemical analyzer. LDL–C was calculated using the Friedewald's formula. Concentrations of amylin, C-peptide, ghrelin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1 (GLP-1), glucagon, interleukin 6, insulin, leptin, monocyte chemotactic protein 1 (MCP-1), pancreatic polypeptide (PP), peptide YY (PYY), tumor necrosis factor alpha (TNF-α), adiponectin, adipsin, lipocalin-2, plasminogen activator inhibitor 1 (PAI-1), and resistin were measured by multiplex analysis (Human Metabolic Hormone V3 and Human Adipokine Panel 1 panels).
Results	The groups differed in traditional cardiometabolic risk factors. In the male and female patient groups with LDL–C ≥4.2 mmol/l, the prevalence of impaired fasting glucose, incidence of insulin resistance, TG, and TC were higher than in subjects with LDL–C <2.1 mmol/l. The odds for the presence of LDL hypercholesterolemia (LDL–C ≥4.2 mmol/l) were significantly associated with increased concentrations of C-peptide and lipocalin-2 in men and with increased concentrations of lipocalin-2 and decreased concentrations of GLP-1 in women ($p<0.05$).
Conclusion	Increased concentrations of LDL–C in young people were associated with changes in the adipokine profile and with the presence of metabolic syndrome components. These results were confirmed by changes in blood concentrations of metabolic markers that characterize disorders of metabolic processes.

Keywords	Low-density lipoproteins cholesterol; glucagon-like peptide-1; lipid metabolism; carbohydrate metabolism; lipocalin-2; adipokines
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Introduction

Until recently, cardiovascular risk factors were considered to mainly affect morbidity and mortality in elderly, and young patients were considered to have low risk of cardiovascular diseases (CVDs). However, recent findings of several studies show that the cardiovascular risk factors of CVDs at a young age [1–3]. Low-density lipoprotein (LDL) cholesterol is one of the most important modifiable CVD risk factors [4, 5]. The accumulation of lipid molecules and their metabolites, such as low-density lipoprotein cholesterol, triglycerides (TG), and free fatty acids, can cause pancreatic β-cell dysfunction and induce peripheral insulin resistance (IR) [6]. At the same time, blood insulin levels tend to increase in patients with IR, which can also contribute to lipid metabolism disorders, such as decreased high-density lipoprotein (HDL) cholesterol, increased TG and LDL cholesterol. These disorders play a key role in the pathophysiology of metabolic syndrome, which is characterized by increased visceral fat mass. Metabolic disorders in adipose tissue lead to changes in the secretory profile of adipokines, an imbalance between the formation of pro- and anti-inflammatory adipokines, which contributes

to the development of cardiometabolic syndrome and the risk of CVDs.

Therefore, researches aimed at studying biochemical molecules, which reflect various metabolic disorders in young people associated with elevated levels of LDL cholesterol are relevant and can be used to organize primary prevention of detected disorders. Our objective is to study the adipokine profile in young people with LDL hypercholesterolemia and to evaluate the correlation between LDL and metabolic hormones in male and female patients under the age of 45 years.

Material and methods

The study was conducted in a population sample of Novosibirsk residents of 25–44 years old, formed in Research Institute of Internal and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences in 2013–2016. During the study period, 1,512 people were examined in the cross-sectional population screening, biological material was collected, and a database was created. All patients signed the informed consent for the examination and processing of personal data. The study was approved by the local ethics committee (protocol no. 167 dated 26/11/2019).

The entire population sample was distributed by deciles based on the levels of LDL cholesterol. This study included 304 subjects from the first decile (146 subjects with LDL<2.1 mmol/L) and the last decile (158 subjects with LDL≥4.2 mmol/L). All subjects were divided to 4 groups:

- Group 1–56 male patients
- LDL<2.1 mmol/L;
- Group 2–87 male patients
- LDL≥4.2 mmol/L;
- Group 3–90 female patients
- LDL<2.1 mmol/L;
- Group 4–71 female patients
- LDL≥4.2 mmol/L.

Clinical examination of patients was carried out in Research Institute of Internal and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences. The examination protocol included the collection of demographic and social data, a survey of smoking habits, history of chronic diseases and use of medicines, nutrition survey, two measurements of blood pressure (BP), spirometry, anthropometry (height, body mass, waist circumference (WC), hip circumference (HC)), functional examinations, ultrasound examination, etc. Hypertension was defined as systolic blood pressure (SBP) above 140 mm Hg and diastolic blood pressure (DBP) above 90 mm Hg. Abdominal obesity was defined as WC >80 cm in female patients and >94 cm in male patients. Elevated plasma levels of glucose of more than 6.1 mmol/L was considered hyperglycemia. HOMA-IR index was determined to evaluate insulin resistance. It was calculated using the formula:

$$\text{HOMA-IR} = \text{glucose level (mmol/L)} \times \text{insulin level (μU/mL)} / 22.5.$$

HOMA-IR 0–2.7 were considered normal.

Table 1. Clinical and anamnestic characteristics and blood biochemical indicators in male patients

Parameters	Group 1, n=56	Group 2, n=87	p
Age, years	35.8±6.6	38±5.47	0.052
SBP, mm Hg	125.9±13.4	129.4±16.1	0.189
DBP, mm Hg	83.2±9.6	85.8±11.0	0.127
Waist circumference, cm	88.4±13.2	95.9±10.7	<0.0001
Arterial hypertension, %	25	35.6	0.181
Hyperglycemia, %	25	44.8	0.017
Glucose, mmol/L	5.86±0.89	6.32±2.12	0.008
HOMA IR >2.7, %	64	92.7	0.003
Abdominal obesity, %	28.6	54	0.003
TC, mmol/L	3.56±0.45	6.76±0.73	<0.0001
LDL, mmol/L	1.8±0.28	4.79±0.53	<0.0001
HDL, mmol/L	1.32±0.31	1.16±0.27	0.001
TG, mmol/L	0.97±0.71	1.78±1.1	<0.0001

The data are expressed as the means and standard deviations (M ± SD) and the absolute values and percentages (n (%)).
SBP, systolic blood pressure, DBP, diastolic blood pressure, TC, total cholesterol; LDL low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides.

Table 2. Clinical and anamnestic characteristics and blood biochemical indicators in female patients

Parameters	Group 3, n=90	Group 4, n=71	p
Age, years	35.6±5.2	38.0±5.6	0.005
SBP, mm Hg	111.8±12.7	118.0±15.0	0.004
DBP, mm Hg	71.9±9.5	78.6±9.9	<0.0001
Waist circumference, cm	77.1±12.1	83.0±15.6	0.10
Arterial hypertension, %	3.3	11.4	0.045
Hyperglycemia, %	11.1	28.2	0.006
Glucose, mmol/L	5.38±0.59	5.78±0.51	<0.0001
HOMA IR >2.7, %	47.4	71.9	0.025
Abdominal obesity, %	31.5	45.1	0.077
TC, mmol/L	3.66±0.49	6.63±0.62	<0.0001
LDL, mmol/L	1.76±0.27	4.61±0.49	<0.0001
HDL, mmol/L	1.51±0.36	1.41±0.32	0.063
TG, mmol/L	0.86±1.13	1.33±0.71	<0.0001

The data are expressed as the means and standard deviations (M ± SD) and the absolute values and percentages (n (%)).
SBP, systolic blood pressure, DBP, diastolic blood pressure, TC, total cholesterol; LDL low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides.

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Blood samples for biochemical analysis were collected from all patients after an overnight fast, from the median cubital vein, not earlier than 12 hours after the last meal. Total cholesterol (TS), TG, HDL cholesterol, and serum glucose were determined by enzyme test using the Thermo Fisher Scientific Reagent Kits (ref. nos. 981812, 981301, 981823, 981304, Thermo Fisher Scientific, Finland) in the Konelab Prime 30i biochemistry system (Finland). LDL cholesterol levels were calculated using the Friedewald formula. The levels of amylin, C-peptide, ghrelin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1 (GLP-1), glucagon, interleukin 6, insulin, leptin, monocyte chemoattractant protein 1 (MCP-1), pancreatic polypeptide (PP), peptide YY (PYY), tumor necrosis factor alpha (TNF-α), adiponectin, adipsin, lipocalin-2, plasminogen activator inhibitor 1 (PAI-1), and resistin were determined by multiplex analysis using the Human Metabolic Hormone V3 Reagent Kit (HMH3-34K, MerckMillipore, USA) and Human Adipokine Panel 1 (HADK1MAG-61K, MerckMillipore, USA) in the Luminex MAGPIX system (USA).

Statistical processing of the results was carried out in SPSS Statistics 13.0. Normality of the distribution of continuous attributes was tested using the Kolmogorov-Smirnov method. Non-normally distributed quantitative attributes were presented as the medians (Me) and the 25th and 75th percentiles (Q25%; Q75%) (Table 3 and 4), normally distributed quantitative attributes as M ± SD, where M is the arithmetic mean and SD is the standard deviation (Table 1 and Table 2). Categorical variables were expressed as the percentages (%). The statistical significance of the differences in the quantitative indicators between the two groups was assessed using the non-parametric Mann-Whitney test. Pearson's (χ^2) test was used to determine the statistical significance of the differences in the qualitative attributes. Associations were studied using a multivariate logistic regression model. The results are presented as odds ratio (OR) and 95% confidence interval (CI) for OR. Differences were considered statistically significant with p less than 0.05

Results

The clinical and anamnestic characteristics and lipid profile of patients in the study groups are presented in Table 1 and Table 2.

Differences in some traditional cardiometabolic risk factors were found in the study groups (Table 1 and Table 2). More male patients with LDL≥4.2 mmol/L had abnormal glucose levels after an overnight fast, hyperglycemia (p=0.017) and abdominal obesity (p=0.003) were 1.8 times more common than in Group 1. Plasma TG and TC levels were higher and HDL cholesterol was lower in Group 2 (p<0.0001). In the group of patients with LDL≥4.2 mmol/L, HOMA-IR values and the prevalence of IR according to the HOMA-IR index were higher compared to male patients with LDL<2.1 mmol/L (p=0.003).

Female patients with LDL≥4.2 mmol/L had higher prevalence of abnormal fasting glucose (p<0.0001) and

Table 3. Levels of biochemical parameters in male patients of the study groups

Parameters	Group 1, n=56	Group 2, n=87	p
Amylin, pg/mL	12.95 [7.83; 18.52]	13.78 [8.59; 19.94]	0.344
C-peptide, ng/mL	0.71 [0.45; 1.03]	0.91 [0.61; 1.56]	0.013
Ghrelin, pg/mL	54.65 [29.24; 138.08]	66.83 [29.24; 125.12]	0.768
GIP, pg/mL	37.34 [19.23; 54.81]	28.84 [19.27; 48.54]	0.354
GLP-1, pg/mL	244.78 [138.9; 375.11]	186.43 [119.74; 270.46]	0.121
Glucagon, pg/mL	26.48 [15.57; 37.64]	26.47 [16.38; 41.97]	0.703
IL-6, pg/mL	1.09 [0.61; 3.6]	1.5 [0.67; 3.97]	0.558
Insulin, pg/mL	584.55 [305.17; 1291.56]	719.05 [584.55; 931.03]	0.402
Leptin, pg/mL	1323.25 [358.24; 2592.31]	2994.09 [1169.01; 4445.7]	0.001
MCP-1, pg/mL	157.07 [110.62; 233.65]	143.69 [114.96; 208.96]	0.338
PP, pg/mL	39.65 [22.07; 65.14]	36.67 [22.54; 54.82]	0.355
PYY, pg/mL	60.27 [33.45; 86.65]	54.14 [40.76; 84.0]	0.678
Secretin, pg/mL	14.12 [3.97; 34.53]	12.73 [5.55; 29.73]	0.930
TNFα, pg/mL	3.8 [2.66; 4.84]	2.95 [2.06; 4.98]	0.225
Adiponectin, μg/mL	29.55 [13.99; 41.65]	32.09 [14.97; 48.2]	0.499
Adipsin, μg/mL	7.8 [4.84;15.33]	8.46 [5.69; 22.86]	0.187
Lipocalin-2, ng/mL	160.5 [53.85; 232.03]	311.15 [167.38; 592.2]	<0.0001
PAI-1, ng/mL	14.01 [9.46; 24.68]	21.94 [13.79; 31.71]	0.004
Resistin, ng/mL	22.09 [0.47; 54.03]	123.62 [67.48; 177.2]	<0.0001

The data are expressed as the medians and interquartile ranges (25th and 75th percentiles; Me (25–75 %)).
GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; IL-6, interleukin 6; MCP-1, monocyte chemotactic factor 1; PP, pancreatic polypeptide; PYY, peptide YY; TNFα, tumor necrosis factor alpha; PAI-1, plasminogen activator inhibitor 1.

Table 4. Levels of biochemical parameters in female patients of the study groups

Parameters	Group 3, n=90	Group 4, n=71	p
Amylin, pg/mL	8.88 [7.28; 14.47]	8.88 [7.04; 13.89]	0.968
C-peptide, ng/mL	0.69 [0.48; 0.98]	0.79 [0.51; 1.09]	0.126
Ghrelin, pg/mL	62.49 [23.62; 135.6]	84.47 [39.39; 155.28]	0.361
GIP, pg/mL	24.78 [16.58; 39.63]	23.52 [15.86; 34.34]	0.555
GLP-1, pg/mL	251.92 [154.76; 348.88]	157.68 [110.38; 201.45]	<0.0001
Glucagon, pg/mL	15.9 [8.62; 33.06]	17.45 [9.59; 31.72]	0.765
IL-6, pg/mL	0.84 [0.67; 1.27]	2.0 [0.38; 3.53]	0.518
Insulin, pg/mL	406.89 [272.95; 719.05]	651.8 [406.89; 998.17]	0.008
Leptin, pg/mL	4 360.55 [1 881.54; 10 362.75]	6 240.97 [3 098.36; 11 456.21]	0.028
MCP-1, pg/mL	139.75 [111.37; 200.71]	124.67 [96.4; 159.56]	0.032
PP, pg/mL	39.3 [18.62;63.8]	31.63 [18.78; 46.53]	0.448
PYY, pg/mL	46.49 [29.55; 66.71]	48.23 [35.99; 66.97]	0.809
Secretin, pg/mL	14.33 [4.88; 48.29]	21.22 [6.5; 61.56]	0.567
TNFα, pg/mL	3.25 [2.01; 4.66]	3.15 [1.83; 4.27]	0.397
Adiponectin, μg/mL	35.37 [29.73; 42.88]	32.54 [23.98; 41.18]	0.397
Adipsin, μg/mL	6.84 [4.7; 10.12]	7.59 [5.59; 15.16]	0.105
Lipocalin-2, ng/mL	157.65 [84.05; 243.71]	368.32 [157.68; 639.24]	<0.0001
PAI-1, ng/mL	13.10 [7.61; 20.92]	20.76 [12.87; 29.91]	<0.0001
Resistin, ng/mL	18.4 [11.89; 52.02]	113.45 [67.74; 144.76]	<0.0001

The data are expressed as the medians and interquartile ranges (25th and 75th percentiles; Me (25–75 %)).
GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; IL-6, interleukin 6; MCP-1, monocyte chemotactic factor 1; PP, pancreatic polypeptide; PYY, peptide YY; TNFα, tumor necrosis factor alpha; PAI-1, plasminogen activator inhibitor 1.

hyperglycemia (p=0.006) compared to female patients with LDL<2.1 mmol/L. In the groups of female patients, among the lipid profile indicators, statistically significant differences in the levels of TG and TC was found (p<0.0001). In the group of female patients with LDL≥4.2 mmol/L, the prevalence of IR, according to the HOMA-IR index, and AH was 1.5 and 3.5 times higher, respectively, compared to female patients with LDL<2.1 mmol/L (p=0.025).

The results of biochemical tests reflecting metabolic disorders are presented in Table 3 and Table 4.

There were statistically significant differences in the indicators of interest between the Group 1 and Group 2 for C-peptide, leptin, lipocalin-2, PAI-1, and resistin. Male patients with LDL≥4.2 mmol/L had higher levels of C-peptide and insulin to patients with LDL<2.1 mmol/L. Among adipokines, the levels of leptin, resistin, and lipocalin-2 were elevated in male patients in Group 2. Among the inflammation markers of interest, a significant difference was found only for PAI-1. Its levels were higher in male patients with LDL≥4.2 mmol/L.

Statistically significant differences in the levels of GLP-1, insulin, leptin, MCP-1, lipocalin-2, PAI-1 and resistin were found in female patients. Thus, female patients with LDL≥4.2 mmol/L had higher levels of insulin and lower levels of GLP-1 and MSP-1 compared to patients with LDL<2.1 mmol/L. Among adipokines, the levels of leptin, resistin, and lipocalin-2 were elevated in female patients in Group 4.

All the biochemical parameters of interest were included in the logistic regression analysis model at the next stage of statistical processing. The presence of extremely high and extremely low levels of LDL cholesterol was used as a dependent variable. All the biochemical parameters of interest, age, WC, the presence of AH and hyperglycemia were used as independent variables.

The multivariate analysis showed that the odds of having elevated levels of LDL in male patients are most associated with elevated levels of C-peptide (OR=3.290, 95% CI: 1.219–8.883, p=0.019) and less associated with lipocalin-2 (OR=1.005, 95% CI: 1.001–1.008; p=0.006). The odds of having elevated LDL are associated in female patients with elevated levels of lipocalin-2 (OR=1.003, 95% CI: 1.001–1.005, p=0.013) and decreased GLP-1 (OR=0.991, 95% CI: 0.986–0.996; p=0.001).

Discussion

Studies conducted over the past decade have demonstrated the important role of adipokines in the regulation of various physiological processes, including insulin sensitivity, glucose and lipid metabolism, and endothelial function, inflammatory reactions, cytokine signaling [7] and, thus, can be significant predictors of cardiometabolic and other chronic diseases.

Although the main biological effect of leptin in the central nervous system is the control of food consumption and energy expenditure, there is a significant correlation between the levels of leptin and chronic subinflammatory condition in obesity, which suggests other possible peripheral biological effects associated with cytokines [8]. There is an increased

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pro-inflammatory response in hyperleptinemia [9], which may be related to the fact that leptin controls the production of tumor necrosis factor and macrophage activation [8]. Leptin can trigger the synthesis of endothelin-1 and nitric oxide (NO) synthase, and the expression of MCP-1 [10] and the proliferation of endothelial cells [11]. Moreover, leptin promotes platelet aggregation and cholesterol accumulation in macrophages in hyperglycemia [12, 13] and angiogenesis. These observations point to a potentially damaging effect of leptin on arterial walls. On the other hand, leptin improves insulin sensitivity by activating adenosine monophosphate-activated protein kinase [14], which results in a decrease in intracellular malonyl-CoA and reduced lipogenesis associated with increased beta-oxidation of fatty acids. However, high levels of circulating leptin are observed in common obesity, which is indicative of resistance to leptin. We observed elevated levels of leptin in patients with LDL≥4.2 mmol/L in this study.

Mechanisms of the biological effect of resistin on human body are only partially understood. The main physiological role of resistin may be the modulation of inflammatory, immune, and autoimmune reactions. Resistin is involved in a wide range of physiological and pathological processes, such as atherosclerosis and cardiovascular diseases [15, 16]. In our study, the levels of resistin were significantly higher in the groups of patients with LDL≥4.2, which may be associated with the early stage of metabolic syndrome characterized by a burst of inflammation detected in the early stages of metabolic disorders [17–19]. Malo et al. showed that resistin contributed significantly to the onset of type 2 diabetes mellitus, which is an additional risk factor for higher morbidity and mortality in obese individuals due to metabolic disorders [20]. Zakovryashina et al. consider resistin as an unfavorable marker of metabolic disorders [21].

Studies of the role of resistin in dyslipidemia are controversial. Resistin appears to activate de novo hepatic lipogenesis and control peripheral lipid metabolism [22, 23]. Some studies showed that plasma levels of resistin are positively correlated with levels of the levels of TG, TC, and VLDL cholesterol, and inversely correlated with the levels of HDL cholesterol [24, 25]. Owecki et al. showed positive correlation of resistin and HDL cholesterol and inverse correlation of LDL cholesterol with resistin [26].

Wang et al. (2007) showed that serum levels of lipocalin-2 were closely associated with obesity and related chronic inflammation and metabolic complications [27]. In some studies, a significant correlation was found between lipocalin-2 and atherosclerosis in patients with diabetes mellitus, obesity, and metabolic syndrome [28, 29]. Other studies correlated it with uncontrolled type 2 diabetes mellitus [30] and diabetic kidney disease [31–33]. We detected a statistically significant increase in the levels of lipocalin-2 in the groups of male and female patients with LDL≥4.2 mmol/L, which may point to their predisposition to the development of complications associated with lipocalin-2, such as metabolic syndrome, insulin resistance, coronary artery disease, and diabetic nephropathy. The multivariate analysis showed that the odds ratio of having LDL≥4.2 mmol/L is associated in both male and female patients with elevated levels of lipocalin-2. Further research should determine whether elevated lipocalin-2 is a causal factor or only a minor link in the pathogenesis of obesity-related metabolic disorders.

Our study showed that young people with LDL≥4.2 mmol/L have lipid and carbohydrate metabolism disorders, which is characterized by elevated levels of C-peptide, glucose, and HOMA-IR in male patients, and elevated insulin, glucose, HOMA-IR, and reduced GLP-1 in female patients. Our findings are consistent with several studies. Seino et al., Holst et al. indicate that a decrease in the incretin effect is an early and characteristic feature of the pathogenesis of type 2 diabetes mellitus [34, 35]. Wang et al. showed a decrease in GLP in patients with type 2 diabetes mellitus [36]. Reduced secretion of GLP-1 may contribute to the development of obesity [37]. Although the main physiological function of GLP-1 is related to glycemic control, there is increasing evidence that it can also play an important role in the cardiovascular system [34, 35].

We detected changes in the indicators reflecting abnormalities in the blood coagulation system, as well as lipid and carbohydrate metabolic disorders. For example, patients with LDL≥4.2 had elevated levels pf PAI-1. It should be noted that patients with metabolic syndrome and/or type 2 diabetes mellitus have elevated plasma concentration of PAI-1, which contributes to the hypofibrinolytic state [38, 39]. Elevated levels of PAI-1, as well as influence clot lysis, directly accelerate the atherothrombotic process, thus contributing to the formation of neointima. [40]. This points to the fact that coagulation disorders not only influence the potential for clotting, but can contribute to the progression of atherosclerosis.

Limitations

The study is limited by the fact that only the population sample of 25–44-year old male and female patients was studied.

Conclusion

The findings of this study show that elevated levels of LDL cholesterol in young people is associated with changes in the adipokine profile and the presence of metabolic syndrome components. These data are supported by changes in blood biochemical markers characterizing metabolic disorders in the human body. Accordingly, young people with LDL≥4.2

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have increased levels of C-peptide, insulin, leptin, lipocalin-2, PAI-1, resistin and reduced GLP-1. The most significant biomolecules associated with the presence of elevated LDL cholesterol are lipocalin-2 (direct correlation), C-peptide (direct correlation), GLP-1 (inverse correlation). Our findings showed a clear association of biomolecules secreted by visceral adipocytes with elevated levels of LDL cholesterol. This highlights the need for primary prevention of obesity in young people, as well as lipid disorders.

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