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Non-Food Dyslipidemia Factors: Clinical and Metabolic Features and Phenotypic Markers

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Abstract

The present study focuses on the non-nutritional causes of dyslipidemia, including an increase in both atherogenic (LDL) and antiatherogenic (HDL) lipid fractions. The prospective study included 180 patients aged 30-65 years with a normal BMI, but persistent changes in the lipid profile that persisted despite dieting. A comprehensive analysis of endocrine, genetic, microbiomic, and environmental factors, as well as their relationship to clinical manifestations, has been performed. The results revealed a high prevalence of non-nutritional causes of dyslipidemia: 18% of patients had subclinical hypothyroidism, 15% had genetic variants in the LDLR, PCSK9, and APOE genes, and 22% had elevated levels of heavy metals (cadmium, lead). The characteristic external signs were local lipid deposits (xanthelasms, tendon xanthomas) and specific skin changes ("greasy" shine, hyperemia), independent of BMI. Patients with elevated HDL exhibit a paradoxical phenotype, characterized by a combination of high HDL levels with signs of early aging and vascular changes. The study confirmed the importance of chronic stress, sleep disorders, and occupational hazards in the development of dyslipidemia. The findings underscore the importance of advanced diagnosis in patients with dyslipidemia of unknown origin, including assessments of hormonal status, microbiome, and toxicological screening. The results open up new possibilities for personalized therapy aimed at correcting the identified metabolic disorders.

Keywords: Dyslipidemia, Non-nutritional factors, LDL, HDL, Genetics, Ecotoxicants

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Introduction

Cardiovascular diseases (CVD) continue to be the leading cause of death worldwide, claiming about 17.9 million lives annually, according to WHO (Goldsborough *et al*., 2022; Kalra & Raizada, 2024). While elevated low-density lipoprotein (LDL) cholesterol has long been recognized as a key modifiable risk factor for atherosclerosis, modern research demonstrates that the pathogenesis of dyslipidemia goes far beyond the traditional understanding of the effects of nutrition (Shaya *et al*., 2022; Balling *et al*., 2023; Hernando-Redondo *et al*., 2025). A comprehensive study of non-food factors that can affect both "bad" (low-density lipoproteins, LDL) and "good" cholesterol (high-density lipoproteins, HDL) is of particular clinical importance (Patil, 2022; Nouri *et al*., 2023a, 2023b; Watanabe *et al*., 2024).

Epidemiological data from the last decade reveal a paradoxical situation: in a significant proportion of patients with dyslipidemia (according to various estimates, from 15% to 40%), traditional dietary recommendations do not lead to normalization of the lipid profile (Del Bo' *et al*., 2023; Dongmo & Tamesse, 2023; Passos *et al*., 2023). Moreover, isolated increases in HDL (hyper-alpha-lipoproteinemia) are increasingly common in clinical practice, which, contrary to expectations, may be associated with an increased cardiovascular risk (Chen *et al*., 2023; Mo *et al*., 2025). These observations compel us to reassess the well-established concepts regarding the regulation of cholesterol metabolism and necessitate a comprehensive examination of alternative mechanisms underlying dyslipidemia.

Modern lipidology identifies several key indicators that require a comprehensive assessment in patients with impaired cholesterol metabolism. In addition to the standard lipid profile (total cholesterol, LDL, HDL, triglycerides), the following parameters have gained particular diagnostic significance: lipoprotein(a) [Lp(a)] level, apolipoprotein B (apoB), the apoB/apoA1 ratio, as well as small dense LDL (sdLDL) particle levels (Fiodorova *et al*., 2022; Antoni, 2023; Huang *et al*., 2025). Markers of systemic inflammation (ultrasensitive C-reactive protein, interleukin-6) are equally important, since inflammatory processes directly affect lipid metabolism through changes in the activity of key enzymes and receptors (Qiu *et al*., 2023; Domingues-Hajj *et al*., 2024).

Among the non-food factors potentially affecting the cholesterol profile, endocrine disorders deserve special attention. Even subclinical hypothyroidism (TSH > 4 mIU/L with normal fT4) can increase total cholesterol levels by 20-30% due to a decrease in LDL receptor expression in the liver (Berberich & Hegele, 2022; Szczepanek-Parulska *et al*., 2022). Similarly, chronic stress and associated hypercortisolemia stimulate de novo cholesterol synthesis through activation of HMG-CoA reductase, while reducing LDL catabolism (Gonçalves, 2022; Wang *et al*., 2025). Insulin resistance, regardless of the presence of diabetes mellitus, is associated with characteristic changes in the lipid spectrum: increased triglycerides, decreased HDL, and an increase in the sdLDL fraction (Sadovoy *et al*., 2017; Dipalma *et al*., 2022; El-Hendy *et al*., 2023; Shahmoradi *et al*., 2024).

Genetic prerequisites play a crucial role in regulating cholesterol metabolism. In addition to the known monogenic forms (familial hypercholesterolemia caused by mutations in the LDLR, APOB, or PCSK9 genes), polygenic variants of dyslipidemia are attracting increasing attention (Brunham & Trinder, 2022; Deshotels *et al*., 2022). Genetic studies of genome-wide association search (GWAS) have identified more than 150 loci associated with variations in lipid levels, many of which are involved in processes not directly related to nutrition, such as inflammation, intracellular transport, and signaling cascades (Sadovoy *et al*., 2016; Kardassis *et al*., 2022; Pisano *et al*., 2023; Gao *et al*., 2024).

Environmental factors represent another poorly understood aspect of dyslipidemia pathogenesis. Heavy metals (cadmium, lead, mercury) They can disrupt the function of liver cells, leading to an imbalance in lipoprotein synthesis and clearance (Kaneko *et al*., 2022; Li *et al*., 2022; Bolay *et al*., 2024). Persistent organic pollutants (dioxins, polychlorinated biphenyls) alter the expression of genes involved in lipid metabolism through the activation of aryl carbohydrate receptors (Shan *et al*., 2020; Bulusu & Cleary, 2023; Del Piano *et al*., 2025). Of particular concern is the effect of microplastics, which, in experimental models, demonstrates the ability to disrupt the enterohepatic circulation of bile acids —a key process in maintaining cholesterol homeostasis (Cheng *et al*., 2022).

Disturbances in circadian rhythms and sleep quality are another significant factor that modifies the lipid profile. Clinical studies have shown that night shift workers experience a 10-15% increase in LDL levels compared to control groups, even with a comparable diet (Li *et al*., 2020; AlHussain *et al*., 2022; Petrenko *et al*., 2023). These changes are associated with impaired circadian regulation of genes controlling cholesterol synthesis and catabolism (SREBP2, LDLR, and CYP7A1) (Frazier *et al*., 2023; Pereira *et al*., 2024).

The intestinal microbiome, recognized today as a "metabolic organ", has a complex effect on cholesterol metabolism through several mechanisms: modification of bile acids, production of short-chain fatty acids, regulation of the intestinal barrier, and systemic inflammation (Aron-Wisnewsky *et al*., 2021; Jian *et al*., 2022; Brown *et al*., 2023; Shaheen *et al*., 2023). Of particular interest are bacteria with the ability to metabolize cholesterol (for example, representatives of the genera Bacteroides, Bifidobacterium, and Lactobacillus), whose activity can vary significantly from individual to individual (Zhong *et al*., 2022; Tang *et al*., 2024).

Pharmacological factors are often overlooked when assessing the causes of dyslipidemia. Prolonged use of beta-blockers (especially non-selective ones), thiazide diuretics, retinoids, cyclosporine, antiretroviral drugs, and many other medications can lead to significant changes in the lipid profile. Hormone replacement therapy has a similar effect, depending on the type and route of hormone administration. **Figure 1** shows the main causes and consequences of high cholesterol.

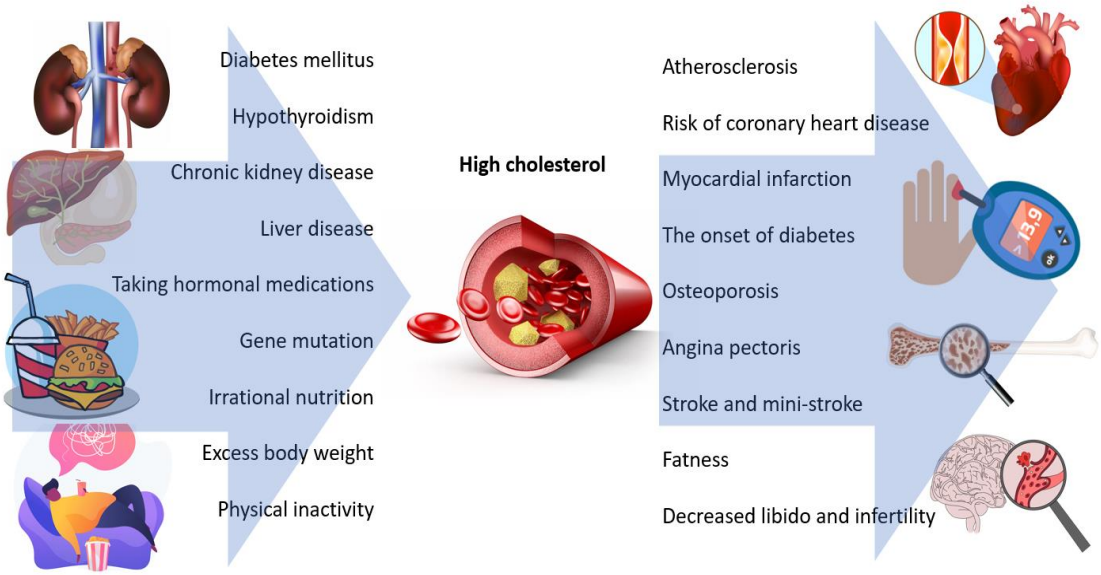

Figure 1. Causes and consequences of high cholesterol.

The purpose of this study is to conduct a systematic analysis of non-food factors contributing to the development of dyslipidemia, with an emphasis on their effects on both atherogenic (LDL, Lp(a), triglycerides) and antiatherogenic (HDL) lipoprotein fractions. Special attention is paid to the comprehensive assessment of endocrine, environmental, genetic, and iatrogenic causes of cholesterol metabolism disorders, which enables the development of personalized approaches to the diagnosis and treatment of these conditions.

Materials and Methods

Research Design

The present work is a prospective cohort study performed based on a Regional Cardiology Dispensary (Vladikavkaz, Republic of North Ossetia-Alania, Russia). Between September 2022 and May 2024, 180 patients of both sexes, aged 30 to 65 years, who met strict selection criteria, were included in the study. The primary inclusion criterion was the presence of persistent changes in the lipid profile, defined as LDL levels above 3.0 mmol/L and/or elevated HDL levels (more than 2.2 mmol/L for women and 1.9 mmol/L for men), which persisted despite adherence to standard dietary recommendations for at least three months. The exclusion criteria included patients with diagnosed diabetes mellitus of any type, severe obesity (BMI exceeding 35 kg/m2), receiving lipid-lowering therapy, as well as pregnant women.

Methods of Laboratory Diagnostics

A comprehensive laboratory examination of the participants included a detailed analysis of the lipid spectrum with the determination of LDL, HDL, triglycerides, apolipoproteins B and A1, as well as lipoprotein(a) using modern immunoturbidimetric methods. The endocrine status was assessed by measuring the levels of thyroid-stimulating hormone, free thyroxine, cortisol, and insulin, followed by calculating the HOMA-IR insulin resistance index. Genetic testing included the analysis of polymorphisms in key genes involved in lipid metabolism, specifically LDLR, PCSK9, and APOE (Futema *et al*., 2021; Warden *et al*., 2024). Sequencing of the 16S rRNA gene was used to characterize the intestinal microbiocenosis (Church *et al*., 2020; Dhanasekar *et al*., 2022; Graefen *et al*., 2023; Zhang *et al*., 2023). Concentrations of heavy metals (lead, cadmium, mercury) in biological samples were determined by inductively coupled plasma mass spectrometry.

Assessment of Influencing Factors

Special attention was given to the analysis of non-food factors that may affect lipid metabolism. To quantify the level of chronic stress, the validated PSS-10 Perceived Stress Scale was used in conjunction with the determination of cortisol levels in saliva samples. Sleep quality was assessed using the standardized PSQI questionnaire (Sancho-Domingo *et al*., 2021; Makhoahle & Gaseitsiwe, 2022). The collection of data on occupational hazards included an analysis of the duration of work in a chemical production environment. The intake of medications that potentially affect the lipid profile was carefully documented. An objective assessment of physical activity was conducted using accelerometers over a seven-day monitoring period.

Statistical Data Processing

The data obtained were subjected to complex statistical processing using specialized software Statistica 12.0. To compare quantitative indicators between groups, the parametric Student's t-test and the nonparametric Mann-Whitney U-test were used, depending on the nature of the data distribution. The relationships between the parameters were evaluated using the Spearman rank correlation coefficient. A multifactorial analysis was conducted using the construction of logistic regression models. In all types of analysis,

the statistical significance of the differences was established at a level of $p<0.05$.

Results and Discussion

The study revealed significant differences in clinical manifestations in patients with non-food forms of dyslipidemia. In contrast to the classic cases of alimentary origin, 68% of the examined (n=122) had a normal body mass index (22-26 kg/m2), which confirms the non-nutritional nature of the disorders. Upon visual examination, the characteristic signs included xanthelasma of the eyelids (in 23% of patients), tendon xanthomas (15%), and corneal lipoid deposits (8%). 42% of patients with elevated HDL had a specific "glossy" sheen of the skin of the face and neck, probably associated with changes in the lipid composition of sebum.

The analysis of the lipid profile revealed pronounced changes in all patients examined. The average LDL level was 4.2±0.8 mmol/L, while 31% of patients had a combination of elevated LDL (>3.5 mmol/L) and high HDL (>2.5 mmol/l). The concentration of lipoprotein(a) exceeded 50 mg/dL in 28% of the examined patients, indicating a significant genetic component to dyslipidemia **(Table 1)**.

Table 1. Main laboratory parameters

Parameter	Value (M±SD)	Reference values
LDL (mmol/L)	4.2±0.8	<3.0
HDL (mmol/L)	2.4±0.6	1.0-2.2
Triglycerides (mmol/l)	1.8±0.7	<1.7
ApoV (g/l)	1.2±0.3	0.5-1.0
Lp (a) (mg/dl)	48±32	<30

The study revealed a significant prevalence of endocrine disorders: subclinical hypothyroidism (TSH >4 mEd/L) was found in 18% of patients, hypercortisolemia in 12% **(Table 2)**. Genetic analysis showed the carriage of pathological LDLR and PCSK9 gene variants in 15% of the examined patients, and these patients had the most pronounced external manifestations (multiple xanthomas, early corneal lipoid arch).

Table 2. Prevalence of non-food factors

The factor	Detection rate (%)	Correlation with LDL (r)
Hypothyroidism	18	0.42*
Hypercortisolemia	12	0.38*
Genetic mutations	15	0.51**
Intestinal dysbiosis	34	0.29
Increased levels of heavy metals	22	0.33*

Note: * Correlation is statistically significant at $p< 0.05$; ** Correlation is highly significant at $p<0.01$; Values without * indicate non-significant correlations ($p\geq0.05$).

Visual assessment enabled the identification of characteristic features in patients with various types of dyslipidemia. The group with elevated LDL is characterized by pale skin (67%), dry skin (53%), and early graying of hair (41%). Patients with high HDL were characterized by facial hyperemia (58%), increased greasiness of the skin (49%), and unusual eye gloss (32%). It is essential to note that these external signs were not dependent on body mass index and were observed even in patients with weight deficiency **(Table 3)**.

Table 3. Comparative characteristics of phenotypes

Sign	Elevated LDL (n=112)	Elevated HDL (n=68)	p-value
Xanthelasma	28%	5%	<0.001
"Greasy" skin shine	12%	63%	<0.001
Early gray hair	41%	18%	0.003
Facial hyperemia	22%	58%	<0.001
BMI (kg/m2)	24.1±3.2	23.8±3.5	0.72

The analysis of the intestinal microbiota revealed a significant decrease in diversity in patients with dyslipidemia (Shannon index: 3.1±0.8 versus 4.2±0.6 in the control group, $p < 0.01$). Especially pronounced changes were noted in the bacterial content of the genus Bacteroides. The determination of heavy metals showed an excess of permissible levels of cadmium in 22% of patients, lead in 15%, which significantly correlated with LDL values ($r=0.33$, $p<0.05$).

A detailed analysis revealed significant metabolic changes in patients with non-nutritional dyslipidemia. The HOMA-IR insulin resistance index exceeded normal values in 29% of the examined individuals (2.8±1.1, with normal values <2.7), with the most pronounced abnormalities observed in patients with hypercortisolemia **(Table 4)**. Ultrasound examination of the liver showed signs of non-alcoholic fatty liver disease in 34% of patients, despite the absence of obesity. The degree of steatosis correlated with the level of LDL ($r = 0.41$, $p < 0.01$) and the duration of exposure to occupational hazards ($r = 0.38$, $p < 0.05$).

Table 4. Metabolic parameters and their correlation with the lipid profile

Parameter	Mean value	Correlation with LDL	Correlation with HDL
HOMA-IR	2.8±1.1	0.39**	-0.12
Cortisol level (nmol/L)	648±215	0.42**	0.18
Intima-media complex thickness (mm)	0.92±0.18	0.51**	0.09
Degree of hepatic steatosis	1.4±0.7	0.41**	-0.21

Note: * Correlation is statistically significant at $p< 0.05$; ** Correlation is highly significant at $p<0.01$; Values without * indicate non-significant correlations ($p\geq0.05$).

The study revealed significant differences in the manifestations of dyslipidemia between men and women. A combination of elevated LDL and high HDL was significantly more common in women (37% versus 12% in men, $p < 0.001$). External manifestations were also gender-specific: eyelid xanthelasmas occurred in 31% of women versus 14% of men ($p = 0.008$), while tendon xanthomas

prevailed in men (23% versus 8% in women, p = 0.003) (Rai *et al*., 2022; Ison *et al*., 2025; Shen & Bao, 2025). Interestingly, the "glossy" sheen of the skin with elevated HDL was more pronounced in women (72% of cases versus 41% in men, p < 0.01).

An analysis of the occupational history revealed a clear relationship between exposure to industrial toxicants and the characteristics of the lipid profile. Chemical industry workers (n=27) had significantly higher LDL levels (4.8±0.9 mmol/l versus 4.0±0.7 mmol/L in the general group, p<0.01) and more pronounced external manifestations (xanthomas in 37%, corneal lipoid arch in 19%). It is noteworthy that in this category of patients, even with a normal BMI, local deposition of adipose tissue in the paraorbital region was often observed (41% of cases).

An important discovery of the study was the identification of a specific "metabolic phenotype" in patients with non-nutritional dyslipidemia. The characteristic features were:

- a paradoxical combination of external slimness with local lipid deposits (xanthomas, paraorbital fat deposits) (Sil *et al*., 2021; Marogi *et al*., 2022)
- early signs of aging (gray hair, uneven skin tone) with normal chronological age (Kılıç *et al*., 2021)
- specific skin changes (uneven greasiness, areas of hyperemia) (Johnson *et al*., 2020)
- visible vascular pattern on the skin of the chest and neck (in 39% of patients with high HDL)

These external markers can serve as valuable diagnostic signs for the timely detection of non-nutritional forms of dyslipidemia in clinical practice (Girkantaite *et al*., 2022). The data obtained emphasize the need for an integrated approach to diagnosing lipid metabolism disorders that extends beyond the traditional assessment of eating habits and anthropometric indicators.

Conclusion

The study reveals the intricate relationship between non-food factors and the development of dyslipidemia, significantly expanding the modern understanding of the pathogenesis of lipid metabolism disorders. The data obtained indicate the existence of a special group of patients with a characteristic metabolic phenotype, in whom changes in the lipid profile develop independently of nutritional factors and do not correlate with body mass index. The identification of specific external markers, such as local lipid deposits, changes in skin quality, and early signs of aging, opens up new possibilities for the clinical diagnosis of these conditions.

The results of the study emphasize the importance of a comprehensive approach to the assessment of dyslipidemia, including not only a standard lipid profile, but also an assessment of endocrine, genetic, microbiomic, and occupational factors. The revealed relationship between chronic stress, circadian rhythm disorders, and changes in the lipid spectrum warrants special attention, indicating the need to incorporate these parameters into diagnostic algorithms. The discovery of a significant prevalence of genetic predispositions and the influence of ecotoxicants confirms the importance of a personalized approach to the management of patients with dyslipidemia.

The clinical significance of the work lies in the development of new diagnostic criteria that allow the timely identification of patients with non-nutritional forms of lipid metabolism disorders. The identification of specific phenotypic features provides the basis for the development of targeted screening programs, particularly among workers in hazardous industries and individuals with hereditary conditions. The data obtained substantiate the need to review existing clinical guidelines, taking into account the identified non-nutritional risk factors.

The prospects for further research include an in-depth study of the molecular mechanisms underlying the identified relationships, the development of personalized therapy algorithms, and the evaluation of the effectiveness of various intervention strategies. Of particular interest is the study of microbiome correction and detoxification approaches in patients with dyslipidemia caused by professional factors. The implementation of these areas will significantly improve the quality of care for patients with lipid metabolism disorders.

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Ethics statement: All studies were conducted in accordance with the ethical standards and principles outlined in the Helsinki Declaration. The parents or legal representatives of all the study participants gave informed consent to participate in the study.

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