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Lipid profile peculiarities and matrix Gla protein concentration in Ukrainian pediatric patients with heterozygous familial hypercholesterolemia

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Atherosclerotic changes in the vascular walls begin early in childhood, especially in association with familial hypercholesterolemia (FH). The process may be subclinical, which nevertheless requires therapeutic and preventive measures.

Purpose — to evaluate baseline lipid profiles, the thickness of carotid intima-media complexes, blood pressure indices and the association with concentration changes of dephosphorylated-uncarboxylated matrix Gla protein (dp-uc MGP) as a marker of subclinical arterial lesions in different age groups of pediatric patients with FH.

Materials and methods. Children with heterozygous FH (n=15), stratified by age and sex, were included in the study. The control group consisted of healthy peers (n=21). Blood samples were analyzed to determine levels of total (TC), low-density (LDL-C), very-low-density (VLDL-C), high-density (HDL-C), remnant (rC) and non-high-density (non-HDL-C) cholesterol, triglycerides (TG), apolipoproteins A1 (apoA1) and B (apoB), lipoprotein (a), and dp-uc MGP. The intima-media complex thickness of the common carotid artery and blood pressure were measured in all study subjects. The obtained data were processed using the accepted methods of medical statistics and SAS® OnDemand for Academics.

Results. Lipid profile changes in pediatric patients with FH were characterized by high levels of LDL-C, non-HDL-C and lipoprotein (a) in the 5–9 years age group; in the 10–14 years age group — high levels of LDL-C, TG, rC, non-HDL-C and lipoprotein (a); in the 15–18 years age group — high levels of LDL-C, TG, non-HDL-C and lipoprotein (a). At the same time, the most marked dyslipidemia changes were evident in children aged 10–14 years in the FH group. apoA1 levels were significantly decreased in all FH children. Elevated levels of lipoprotein (a) (>30 mg/dL) in FH children were found in all age groups, suggesting that elevated lipoprotein (a) levels can be used as a factor for cardiovascular risk stratification. Dp-uc MGP levels were significantly elevated in all age groups of FH children compared to healthy peers.

Conclusions. A lipid profile examination is necessary to diagnose FH in children, along with family health history and cascade screening. As atherosclerotic changes at 5–18 years of age remain subclinical, and the instrumental tests available in routine medical practice are not sensitive enough to detect them, therefore, preventive or therapeutic measures cannot be initiated promptly. The evaluation of circulating matrix Gla protein in pediatric patients with FH can be used as a marker of vascular wall calcification, which may allow early preventive measures against microcalcification to be developed.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: children, familial hypercholesterolemia, lipid profile, lipoprotein (a), dp-uc matrix Gla protein, intima-media complex thickness, apolipoprotein A1, apolipoprotein B.

Особливості ліпідного профілю та концентрації матриксного Gla білка в українських педіатричних пацієнтів із гетерозиготною сімейною гіперхолестеринемією

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Атеросклеротичні зміни стінок судин починаються ще в дитячому віці, особливо за наявності такого фактора ризику, як сімейної гіперхолестеринемії (СГ), але можуть перебігати субклінічно, що потребує лікувально-профілактичних заходів.

Мета — вивчити ліпідний профіль, товщину комплексу інтима-медіа сонної артерії, показників артеріального тиску та їхньої кореляції зі змінами концентрації дефосфорильованого-некарбоксильованого матриксного Gla білка (dp-uc MGP), як маркера субклінічного ураження артерій, у різних вікових групах педіатричних пацієнтів із СГ.

Матеріали та методи. До дослідження залучено дітей з гетерозиготною СГ (n=15), стратифікованих за віком і статтю. Групу контролю становили здорові однолітки (n=21). Проаналізовано зразки крові з визначенням рівнів загального холестерину, ліпопротеїнів низької (ЛПНЩ), дуже низької (ЛДНЩ), високої щільності (ЛПВЩ), залишкового холестерину, не-ліпопротеїнів високої щільності (не-ЛПВЩ), тригліцеридів (ТГ), аполіпопротеїнів А1 і В, ліпопротеїну (а) та dp-uc MGP. Усім пацієнтам виміряно товщину комплексу інтима-медіа загальної сонної артерії та артеріальний тиск. Отримані дані опрацьовано прийнятими методами медичної статистики за допомогою «SAS® OnDemand for Academics».

Результати. Зміни ліпідного профілю в педіатричних пацієнтів із СГ характеризувалися високими рівнями ЛПНЩ, не-ЛПВЩ і ліпопротеїну (а) у віковій групі 5–9 років; у віковій групі 10–14 років — високі рівні ЛПНЩ, ТГ, залишкового холестерину, не-ЛПВЩ і ліпопротеїну (а); у віковій групі 15–18 років — високі рівні ЛПНЩ, ТГ, не-ЛПВЩ і ліпопротеїну (а). При цьому пацієнти з СГ вікової групи 10–14 років показали найбільш виражені дисліпідемічні зміни. У всіх пацієнтів із СГ відмічався значно знижений рівень білка апоА1. У всіх вікових групах пацієнтів спостерігався значно підвищений рівень ліпопротеїну (а) (>30 мг/дл), що дає змогу рекомендувати

його для стратифікації кардіоваскулярного ризику для пацієнтів із СГ. У всіх вікових групах був значно підвищений рівень матриксного Gla білка порівняно з групою контролю.

Висновки. Для встановлення діагнозу СГ у дітей поряд з анамнезом і каскадним скринінгом слід проводити дослідження ліпідного профілю, оскільки судинні зміни у віці 5–18 років все ще перебігають субклінічно, та інструментальні дослідження, доступні в рутинній медичній практиці, не дають змоги виявити їх і своєчасно розпочати профілактичні або лікувальні заходи. Визначення циркулюючого матриксного Gla білка в педіатричних пацієнтів із СГ можна використати як маркер кальцифікації судинної стінки, що допомагає розробити ранні профілактичні заходи для запобігання мікрокальцифікації стінок судин.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду батьків дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: діти, сімейна гіперхолестеринемія, ліпідний профіль, ліпопротеїн (а), матриксний Gla-білок, комплекс інтима-медіа, аполіпопротеїн А1, аполіпопротеїн В.

Introduction

Atherosclerosis manifests clinically in middle and late adulthood, but it is well known to have a long asymptomatic phase of development. New research supports the concept that atherosclerosis as the main cause of cardiovascular disease in adults, originates in childhood. In most children, vascular atherosclerotic changes are minor and can be minimized or prevented with a healthy lifestyle [4]. However, in some groups of children this process is accelerated by risk factors or the presence of specific diseases [1]. Therefore, clinicians are faced with the question of finding markers-predictors of subclinical atherosclerotic lesions, especially in patients who have familial hypercholesterolemia (FH), since these patients are at high risk of developing cardiovascular events.

The relationship between dyslipidemia and vascular calcification has been known for a long time [23]. The accumulation of lipoproteins in the vascular intima leads to the formation of mildly oxidized phospholipids, which are bioactive stimulators of vascular cell calcification. To prevent excessive soft tissue calcification, there are a number of vitamin K-dependent calcification inhibitors, one of the most important among which is the matrix Gla protein (MGP) encoded by the MGP gene on the short arm of chromosome 12 [21]. To prevent vascular calcification, it is critical that MGP must be fully active — that is, fully carboxylated. MGP is significantly undercarboxylated in healthy adults [24], and even more pronounced undercarboxylation has been found in cardiovascular diseases and diseases associated with high cardiovascular risk: diabetes mellitus and chronic kidney disease [14]. Based on these observations, a concept was formulated that the plasma concentration of circulating non-carboxylated MGP fractions can be used as a marker of cardiovascular diseases, risk factor for their development and mortality.

According to R.E.W. Kavey [11], the earliest stages of atherosclerosis can be blocked by lowering apolipoprotein B (apoB) lipid levels. The interval between a person's exposure to a risk factor and the development of clinical manifestations provides an opportunity for prevention. Universal screening is recommended by the study authors at the age of 8–11 years and repeatedly at the age of 17–18 years.

As stated by the European Atherosclerosis Society report (2022) [12], high lipoprotein (a) concentrations are associated with ectopic cardiovascular microcalcification and macrocalcification of the aortic valve. It is recommended that lipoprotein (a) concentrations should be tested at least once in adults, and in patients with FH cascade testing is particularly useful.

Purpose of the study — to evaluate baseline lipid profiles, the thickness of carotid intima-media complexes, blood pressure indices and the association with concentration changes of dephosphorylated-uncarboxylated matrix Gla protein (dp-uc MGP) as a marker of subclinical arterial lesions in different age groups of pediatric patients with FH.

Materials and methods of the study

A retrospective study was conducted of pediatric patients from all regions of Ukraine who were seen in the Department of Cardiology at Kyiv City Children's Clinical Hospital No.1.

Inclusion criteria for the study were: a confirmed diagnosis of FH for at least 6 months, age between 5 and 18 years old, adherence to prescribed antilipid therapy and an appropriate diet (CHILD-1), signed informed consent by a child and parent(s) (or legal guardian(s)).

Exclusion criteria were withdrawal of informed consent, age less than 5 years old, interruption of antilipid therapy >1 month, presence of an confirmed disease or condition other than FH that causes lipid metabolism disorders (diabetes mellitus, hypothyroidism, nephrotic syndrome, chronic

kidney disease, primary cholangitis, obstructive jaundice, obesity, Cushing's syndrome, pheochromocytoma and etc.); intake of medications that cause lipid metabolism disorders (amiodarone, thiazide diuretics, beta-blockers, glucocorticoids, estrogens, androgens, immunosuppressants, anticancer agents, antipsychotics, HIV-1 protease inhibitors, anticonvulsants, retinoids, growth hormones and others).

118 children were assessed between January and December 2021. 15 of these met the inclusion criteria and agreed to participate in the study, with informed consent given by both the children and their parent(s) (or legal guardian(s)). The following age groups were identified according to WHO guidelines: 5 to 9 years old, 10 to 14 years old, and 15 to 18 years old.

Pediatric patients with FH were included in the FH group (hereinafter referred to as «FH children»), (n=15). The Dutch Lipid Clinic Network criteria were used to establish the diagnosis of FH [5]. FH children were mostly in the age range 5–17 years old (53.4% girls and 46.6% boys). Each age group consisted of 5 children.

The control group consisted of healthy peers in the age range 6–17 years old (hereinafter referred to as «Controls»), (n=21, 47.7% girls and 52.3% boys). Each age group consisted of 7 children. The groups were representative of age and sex.

Blood samples for measurement of biochemical parameters including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) obtained by Friedewald's formula [7], high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoprotein A1 (apoA1), apoB and lipoprotein (a) were taken after at least 8 hours fasting. Non-high-density (non-HDL-C) cholesterol was calculated TC minus HDL-C. Remnant cholesterol (rC) calculated from the standard lipid profile as TC minus LDL-C minus HDL-C. Subjects' blood plasma was also used to quantify the inactive dp-uc isoform of MGP (IDS-iSYS InaKtif MGP® UK) on the IDS-iSYS Multi-Discipline Automated System.

The resting blood pressure was measured in each child in both FH and control groups.

The intima-media complex thickness (cIMT) of the common carotid arteries on the right and left was measured by B-mode ultrasound using the 12 MHz linear transducer L12-5 (Philips, USA). cIMT was calculated as the distance between the leading edge of the lumen — intima interface and the media — adventitia interface on the far wall of the common carotid artery on the longitudinal section, freezed on the R-wave of the electrocardiogram.

The study was conducted in accordance with the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, and Ukrainian laws governing research on human subjects.

Statistical analysis. Extended lipid profile data (TC, LDL-C, HDL-C, VLDL-C, TG, rC, non-LDL-C, apoA1, apoB, lipoprotein (a)), MGP were analyzed with SAS® OnDemand for Academics (SAS Institute Inc, North Carolina, USA). Data were assumed to be normally distributed (verified analytically by Shapiro–Wilk, Kolmogorov–Smirnov, and graphically by Q-Q plot). Continuous variables with a normal distribution were reported as mean with standard deviation, and a t-test was used to compare the data from the FH and control groups. Intragroup comparisons in FH children were made using one-way analysis of variance (ANOVA). Chi-square (χ^2) test was used to compare categorical variables. Pearson correlation was performed to test whether there was a correlation between age and MGP in the FH group. Statistical significance was set at $p \leqslant 0.05$.

Results and discussion of the study

Pearson's chi-squared value was 1.818 with 1 degree of freedom. The corresponding p-value was 0.177, which means there was no significant evidence of an association between sex and the presence of the disease. For Fisher's exact test, the two-tailed p-value was 0.369, which also confirmed the absence of the association.

The lipid profile of the examined children was analyzed and revealed some peculiarities with regard to such parameters as LDC-C, HDL-C, non-HDL-C, VLDL-C, rC, TG, apoB, apoA1 and lipoprotein (a) (Table 1).

Thus, LDL-C levels in all age groups in FH children exceeded the recommended [25] level of <1.8 mmol/L for the high-risk group before 70 years of age to reduce their cardiovascular risk.

None of our subjects had HDL-C below the acceptable [6] range (<1.0 mmol/L).

There were no elevated levels of VLDL-C in the FH and control groups.

Non-HDL levels were elevated in the 10–14 years old age group in FH children and in the 15–18 years old age group in controls. Dyslipidemia — non-HDL levels ⩾3.8 mmol/L —

Table 1

Data on the lipid profile of children in the patient and control groups

Assessed data	FH children		Controls		p-value
	Mean	±SD	Mean	±SD	
The 5–9 years old age group					
TC (mmol/L)	6.72	1.34	4.03	2.04	0.22
LDL-C (mmol/L)	5.33	1.25	2.43	1.14	0.18
HDL-C (mmol/L)	1.21	0.30	1.03	0.67	0.64
VLDL-C (mmol/L)	0.33	0.09	0.12	0.08	0.16
TG (mmol/L)	0.97	0.47	0.74	0.33	0.71
rC (mmol/L)	0.17	0.38	0.57	0.12	0.45
Non-HDL-C (mmol/L)	5.66	1.30	2.55	1.86	0.17
apoA1 (g/L)	1.23	0.21	1.07	0.64	0.57
apoB (g/L)	2.13	0.04	0.48	0.07	**0.0008**
Lipoprotein (a) (mg/dL)	58.33	35.80	8.00	3.68	0.34
MGP (pmol/L)	894.00	132.68	170.00	65.47	**0.04**
The 10–14 years old age group					
TC (mmol/L)	6.94	2.25	3.86	1.07	0.06
LDL-C (mmol/L)	3.02	1.21	2.24	0.74	0.33
HDL-C (mmol/L)	1.40	0.63	1.20	0.28	0.58
VLDL-C (mmol/L)	0.27	0.29	0.38	0.33	0.68
TG (mmol/L)	1.47	0.86	1.05	0.59	0.29
rC (mmol/L)	2.53	4.04	0.43	0.31	0.33
Non-HDL-C (mmol/L)	3.29	1.46	2.62	0.78	0.46
apoA1 (g/L)	1.17	0.31	1.23	0.17	0.77
apoB (g/L)	1.43	0.81	0.73	0.22	0.15
Lipoprotein (a) (mg/dL)	47.00	42.88	14.25	3.30	0.17
MGP (pmol/L)	921.67	83.76	419.25	151.35	**0.0037**
The 15–18 years old age group					
TC (mmol/L)	4.88	1.83	4.21	1.63	0.82
LDL-C (mmol/L)	3.44	1.66	2.92	1.52	0.63
HDL-C (mmol/L)	1.29	0.23	1.2	0.26	0.70
VLDL-C (mmol/L)	0.52	0.21	0.54	0.30	0.92
TG (mmol/L)	1.14	0.46	1.29	0.49	0.65
rC (mmol/L)	0.14	0.06	0.47	0.21	**0.02**
Non-HDL-C (mmol/L)	3.96	1.68	3.45	1.69	0.66
apoA1 (g/L)	1.07	0.04	1.57	0.45	0.06
apoB (g/L)	2.21	0.09	1.02	0.25	**<0.0001**
Lipoprotein (a) (mg/dL)	76.75	27.38	18.80	3.83	**0.0056**
MGP (pmol/L)	1166.75	92.35	624.00	87.72	**<0.0001**

Note: values outside the age-specific reference range are highlighted in grey. Statistically significant p-values are shown in bold.

was detected in the 5–9 years old age group and the 15–18 years old age group in FH children. The high-degree correlation was found between non-HDL levels and body weight in controls (r=0.70; p=0.024), while no such correlation existed among those in the FH group.

Remnant cholesterol (rC) levels were significantly elevated (⩾0.75 mmol/L) only in FH children in the 10–14 years old age group. Also, levels of rC in FH children aged 15–18 years old were statistically significantly different from those in the control group (t=-2,99; p=0.002; 95% CI [-0,06; –0,58]).

All age groups in FH children and controls were found to have apoA1 levels below the acceptable [6] level.

Statistically significant differences in apoB levels were found in FH children in the 5–9 years old age group (t=-35,97; p=0.0008; 95% CI [-1,85; -1,45]) and the 15–18 years old age group (t=-8,88; p<0.0001; 95% CI [-1,50; -0,87]).

Lipoprotein (a) levels in the 10–14 years old age group in FH children were 31 to 50 mg/dL, which according to the recommendation [12] is classified as a high risk of cardiovascular disease. Very high-risk lipoprotein (a) levels (⩾51 mg/dL) were found in children 5–9 years old and 15–18 years old in the FH group. Lipoprotein (a) levels in the 15–18 years old age group in FH children significantly differ from those of

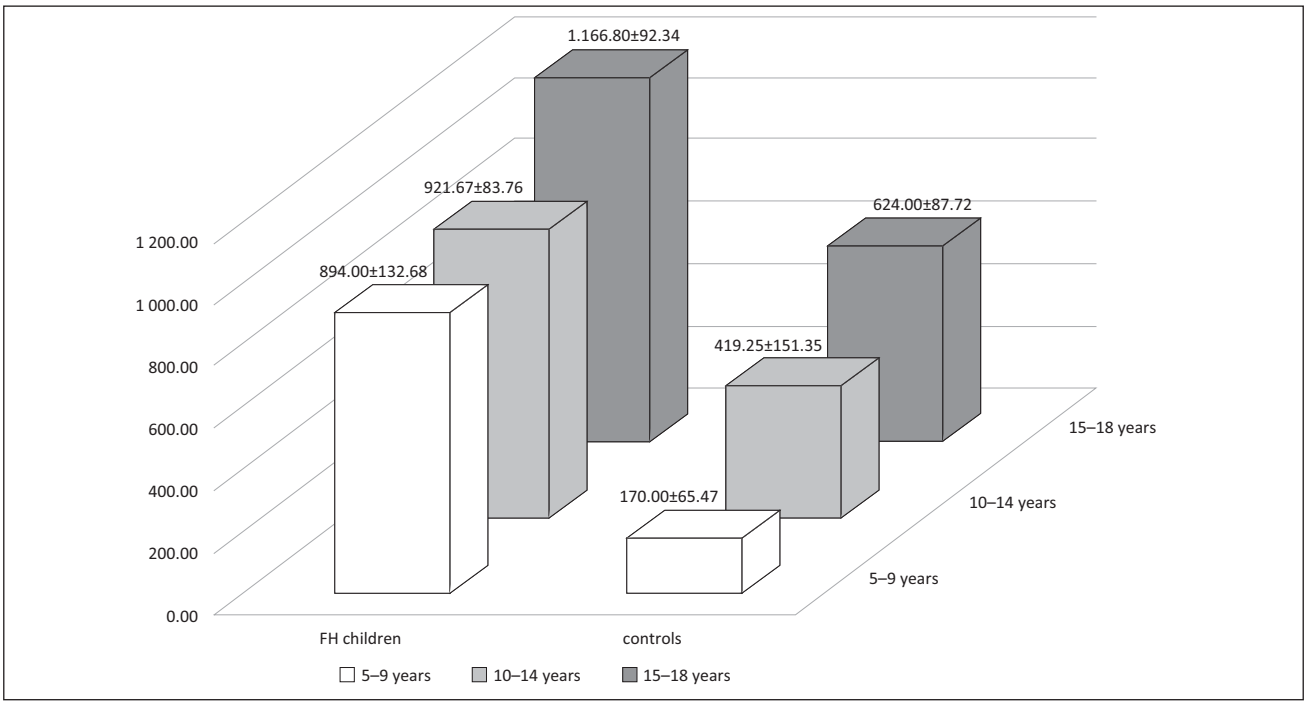

Fig. 1. Mean concentration values of dp-uc matrix Gla protein levels in FH children and controls, by age group

the control group (t=-3,94; p=0.0056; 95% CI [-76,75; -19,14]).

The analysis of the descriptive statistics showed that the 5–9 years old age group in FH children had higher mean values for dp-uc MGP (M=894.00, SD=132.68) than their healthy peers (M=170.00, SD=65.47), (Fig. 1). The FH group aged 10–14 years old also had higher mean values (M=921.67, SD=83.76) than the 10–14 years old age group of controls (M=419.25, SD=151.35). The FH children in the 15–18 years old age group had higher values for dp-uc MGP (M=1166.8, SD=92.34) than the control group (M=624.0, SD=87.72).

A two-sided t-test for independent samples (assumed equal variance, p=0.88) showed that circulating dp-uc MGP levels in the 5–9 years old age group in FH children were statistically significantly different from control group levels at the same age (t=-4.73; p=0.004; 95% CI [-1383.2; -64.80]). There was also a significant difference in MGP levels in the 10–14 years old age group between the FH children and controls (t=-5.11; p=0.0037; 95% CI [-755.0; -249.8]), as well as among research subjects in the 15–18 years old age group (t=-9.02; p<0.0001; 95% CI [-685.1; -400.4]).

A Pearson correlation was performed to test if there is a relationship between age and MGP. The results of the Pearson correlation indicated that there was a significant correlation between age and MGP level in group FH children, r=0.81, p=0.0039. A similar relationship of the same strength was also present in the control group (r=0.89, p=0.0005).

There was sufficient evidence to conclude that there were statistically significant differences in mean MGP levels between age groups in FH children (F=7.58, p=0.0177).

The blood pressure indices were within the normal range (50–75th percentiles) in both FH children and controls (Table 2).

cIMT on both sides did not exceed 0.9 mm both in the FH children and control groups, while statistically significant difference of left cIMT was found in the 15–18 years old age group (t=-3,08; p=0.001; 95% CI [-6,44; -0,84]).

Discussion

The pattern of lipid profile changes in our pediatric patients with heterozygous FH includes significantly elevated LDL-C levels, despite the maximum-tolerated statin therapy and adherence to a specific diet (CHILD-1) for at least 6 months. S. Béliard [2] notes that about 20% of patients with heterozygous FH fail to achieve LDL-C goal levels <2.6 mmol/L when using statins and/or other lipid-lowering drugs such as ezetimibe and/or bile acid sequestrants, a finding that is interpreted as the treatment's lack of efficacy in these patients.

FH children had no HDL-C levels below the acceptable value (1.0 mmol/L), which is generally consistent with the literature [17]. Attention should be drawn to current trends regarding the question of HDL-C dysfunctionality [18], where its level within the reference values did not guarantee effective reverse cholesterol transport. Accord-

Table 2

Data on arterial blood pressure and carotid intima-media thickness in the FH and control groups

Assessed data	FH children		Controls		p-value
	Mean	± SD	Mean	±SD	
The 5–9 years old age group					
Systolic blood pressure (mmHg)	119.00	9.64	124.00	8.13	0.69
Diastolic blood pressure (mmHg)	73.33	10.06	61.00	5.80	0.39
Right cIMT* (mm)	0.460	0.252	0.178	0.205	0.43
Left cIMT (mm)	0.484	0.308	0.176	0.401	0.47
The 10–14 years old age group					
Systolic blood pressure (mmHg)	112.00	6.00	119.25	6.39	0.18
Diastolic blood pressure (mmHg)	64.00	10.00	73.25	8.99	0.25
Right cIMT (mm)	0.326	0.230	0.175	0.220	0.37
Left cIMT (mm)	0.322	0.219	0.199	0.370	0.40
The 15–18 years old age group					
Systolic blood pressure (mmHg)	117.75	6.89	126.80	5.71	0.06
Diastolic blood pressure (mmHg)	68.75	8.95	69.60	9.76	0.89
Right cIMT (mm)	0.662	0.183	0.371	0.263	0.10
Left cIMT (mm)	0.696	0.114	0.331	0.211	**0.001**

Note: Statistically significant p-values are shown in bold. *cIMT — intima-media complex thickness.

ing to S.T. Chiesa (2019) [3], an inverse correlation of HDL-C with cardiovascular risk has been confirmed, but a lack of causality in reducing this cardiovascular risk has also been established.

The elevated levels of VLDL-C, which are considered to be a biomarker for major adverse cardiovascular events in the general population [8], were not observed in our sample. Despite the fact that TG levels were slightly elevated in the 10–14 years old and 15–18 years old age group in FH children, as well as in the 10–14 years old age group in controls, the critical level [16] for cardiovascular risk of 2 to 10 mmol/L was not exceeded.

Elevated non-HDL-C levels in the 10–14 years old age group in FH children and the 15–18 years old age group in controls, and dyslipidemia in the 5–9 years old and 15–18 years old age group in FH children, indicate an increased risk of cardiovascular disease in the FH group as well as in the control group, where non-HDL-C levels and weight are also correlated. According to the M. Juonala (2020) study [10], elevated levels of non-HDL-C, especially among 15–19 year-olds, strongly predicted increased thickness of the intima-media complex in adulthood. No thickening of carotid intima-media complex in all age groups of FH children was observed, which may suggest subclinical nature of atherosclerotic changes.

Remnant cholesterol, which is also referred to as the sum of non-LDL-C and non-HDL-C, was significantly elevated in FH children aged 10–14 years old. rC levels are significantly associated [13] with residual cardiovascular risk after LDL-C lowering, but how high this residual risk is in patients with FH remains unclear.

ApoB levels did not exceed the recommended level [6] among the FH group.

The reduced apoA1 protein levels found in all age groups in both FH children and controls suggest a possible lack of protection from LDL oxidation and its pro-inflammatory properties [15].

Lipoprotein (a), which like apoB-containing lipids is known to be atherogenic, was critically elevated in adolescents (10–14 years old) and young adults (15–18 years old) within our FH sample. According to a study by R. Rikhi (2022) [20], a group of patients with LDL-C levels >2.6 mmol/L and lipoprotein (a) >50 mg/dL showed a significantly higher risk of acute coronary syndrome in the next 13.4 years of follow-up compared with patient groups whose LDL-C and lipoprotein (a) levels were significantly lower. In addition to determining lipoprotein (a) levels, FH children may also need to be screened for apoE genotype.

According to the Roadmap for Cholesterol 2022 [19], issued by the World Heart Federation (WHF), the evaluation of an extended lipid profile, including a one-time determination of apoA1, apoB and lipoprotein (a), for children with FH as high-risk patients is of fundamental importance. In accordance with the WHF Roadmap principle of «the earlier — the better» and «the lower — the better», physicians should be aiming at early identification of patients with elevated LDL-C, and in the case of FH, timely diagnosis and appropriate treatment aimed at reducing LDL-C below

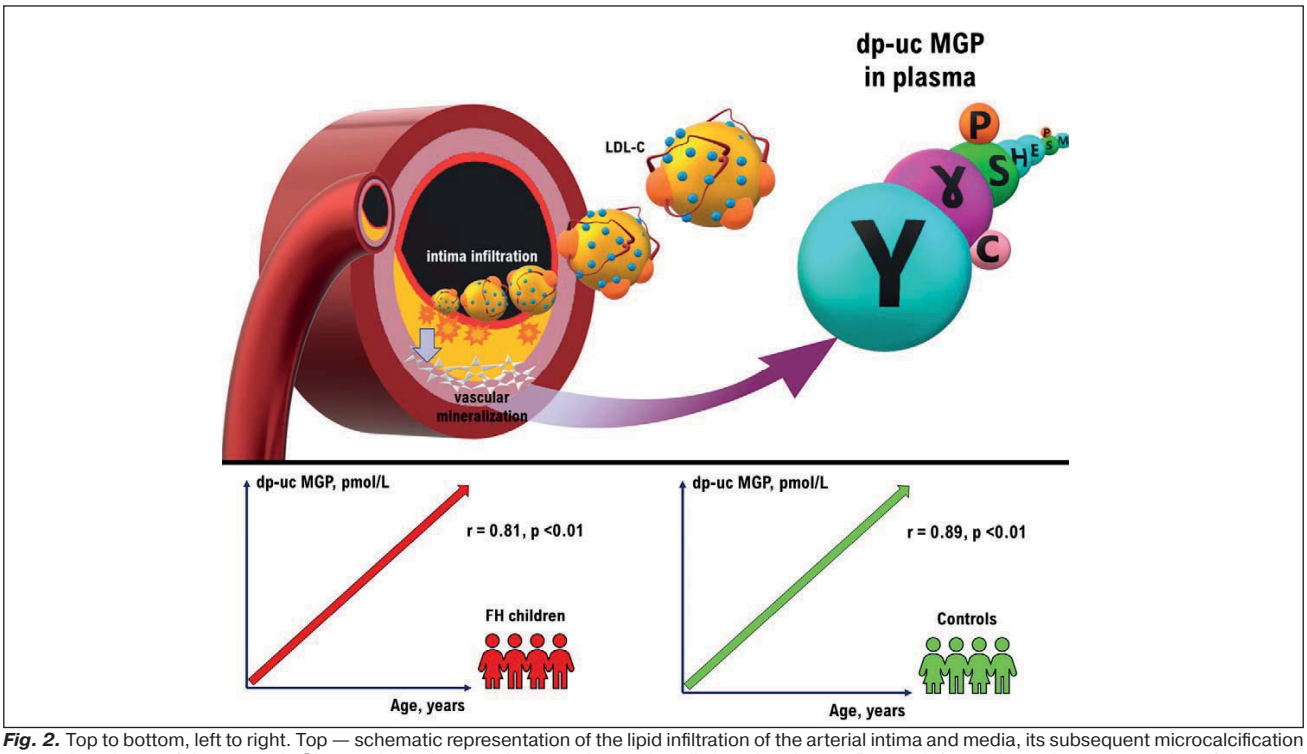

Fig. 2. Top to bottom, left to right. Top — schematic representation of the lipid infiltration of the arterial intima and media, its subsequent microcalcification and — the release of dp-uc matrix Gla protein by the vascular smooth muscle cells into the plasma. Bottom left — schematic representation of the direct high positive correlation between dp-uc MGP levels in plasma and age in the FH group. Bottom right — schematic representation of the direct high positive correlation between dp-uc MGP levels in plasma and age in controls

1.8 mmol/L, thus minimizing the cardiovascular risk for these pediatric patients in the future.

Our study showed a high correlation between dp-uc MGP levels and age in both FH children and controls (Fig. 2).

There is the correlation with FH diagnosis and dp-uc MGP elevation in blood plasma, as the arterial media calcification marker was significantly elevated in our pediatric patients with FH compared to the controls. In this regard, MGP could be used as a marker of vascular microcalcification [26] regardless of etiology. A. Jaminon (2020) [9] also confirmed MGP levels as an independent predictor of intimal and medial calcification and an influencing factor on arterial stiffness and cardiovascular morbidity and mortality. The possible use of vitamin K_2 (or menaquinone-7) as one of the prerequisites for MGP carboxylation, thereby preventing mineralization of the vascular intima and media, is considered one of the ways to prevent microcalcifications. However, there is a paucity of literature data regarding the possible effect of menaquinone on the microcalcification reversibility in the vascular walls in patients with FH. So far, such placebo-controlled studies have been conducted in adults with chronic kidney disease or other cardiovascular disease, but menaquinone supplements have had no or little effect on femoral artery cIMT or calcium-score screening heart test. The question of conducting similar research in the pediatric population is now being considered.

As in the R.C. Shroff study [22], no association was found between dp-uc MGP levels and carotid cIMT in our study. Our subjects' blood pressure indices were within reference range, further confirming the subclinical nature of vascular disease in FH children and the importance of laboratory diagnosis in identifying such patients.

Conclusions

Lipid profiling for FH should be performed in addition to family health history check and cascade screening, as vascular changes at 5–18 years old of age remain subclinical, and the instrumental tests available in routine medical practice are not sensitive enough to detect them, therefore, preventive or therapeutic measures cannot be initiated promptly.

Lipid profile changes in FH children were characterized by high levels of LDL-C, non-HDL-C and lipoprotein (a) in the 5–9 years old age group; in the 10–14 years age group — high levels of LDL-C, TG, rC, non-HDL-C and lipoprotein (a); in the 15–18 years old age group — high levels of LDL-C, TG, non-HDL-C and lipoprotein (a). At the same time, the most marked dyslipidemia changes were evident in children aged 10–14 years old

in the FH group. apoA1 levels were significantly decreased in all FH children. Elevated levels of lipoprotein (a) (>30 mg/dL) in FH children were found in all age groups, suggesting that elevated lipoprotein levels can be used as a factor for cardiovascular risk stratification.

Thus, from our perspective, the assessment of an extended lipid profile including apoA1, apoB and lipoprotein (a) at least once in a lifetime is crucial for pediatric patients with FH.

Dp-uc MGP levels were significantly elevated in all age groups of FH children compared to healthy peers. The evaluation of circulating MGP in pediatric patients with FH can be used as a marker of vascular wall calcification, which may allow early preventive measures against microcalcification to be developed. In patients with FH, the assessment of dp-uc MGP levels may provide a back-up screening method for reducing cardiovascular morbidity and mortality.

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