Doctoral School in Medical Sciences

Manuscript title:
U.D.C.: 616-056.52-06:616.12-053.2(043.2)

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CARDIOVASCULAR REMODELING IN PEDIATRIC METABOLIC SYNDROME

322.01 - PEDIATRICS AND NEONATOLOGY

Summary of Ph.D. Thesis in Medical Sciences

Chișinău, 2020

The PhD thesis has been elaborated within the Department of Pediatrics at "Nicolae Testemitanu State University of Medicine and Pharmacy " of the founding Consortium of the Doctoral School in the field of Medical Sciences.

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Ph.D. thesis defense will take place on 24.06.2020, 12:00 pm, online through the Google Meet application by accessing the link: https://meet.google.com/iiy-hcsz-rtx,, in the meeing of the Commission for the public defense of the PhD thesis, approved by the decision of the Scientific Council of the Consortium from 04.02.2020, (report No.8).

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THE RESEARCH CONCEPTUAL FRAMEWORK

The research actuality. Metabolic syndrome (MS) is considered a recent major health problem, although scientific advances and therapeutic strategies has provided lots of opportunities for its management. It gets even more important if it occurs in children, since the therapeutic possibilities in pediatric patients are quite limited due to the considerable side effects and/or no sufficient studies so far.

Metabolic syndrome is considered a pediatric pathology, leading to a number of early disorders, including cardiovascular disease (CVD) [12], showing an increased risk due to its early onset and duration. The incidence rate varies between 10 % and 84 %, depending on the geographical region, environment, individual demographic characteristics (gender, age, race and ethnic origin), as well as other criteria used for its defining [7]. In terms of gender, most studies show a higher frequency in males [8,10], whereas the differences also vary depending on the age gaps, being higher in males than adolescent females (10.9 % vs. 6.29 %), subsequently being reversed in adulthood (18 % vs. 20 % at the age of 20 - 39 years and 42 % vs. 51 % at the age ≤ 60 years) [4].

Pediatric metabolic syndrome correlates with cardiac structural and geometrical changes, leading to a cardiac pathological remodeling, which is considered a substrate for developing heart failure, being also a strong predictor of arrhythmia, characterized by an impaired heart function (systolic and diastolic) and an early risk of sudden death [13]. It also correlates with asymptomatic coronary atherosclerosis [3]. Actually, subclinical atherosclerosis might develop long before the clinical manifestations of CVD, whereas the CIMT is an established surrogate marker, found in children with MS [1]. Epicardial adipose tissue (EAT) is considered a predictor of this syndrome and a risk marker of cardiovascular disorders, being associated with subclinical coronary disease among pediatric population [2].

While considering the aforementioned arguments and the impact of childhood health on further adult health, we considered to choose the following research on "Cardiovascular remodeling in pediatric metabolic syndrome" that will contribute to the opening of new perspectives for identifying a single and effective approach, as well as for preventing cardiovascular complications of this syndrome, based on IDF criteria adapted for children, in order to reduce the morbidity and mortality rates at young age.

Within this framework, **the purpose** of this scientific work is to assess the clinical and paraclinical parameters in metabolic syndrome, as well as to establish the role of MS as a determinant for cardiac remodeling onset in children aged 10 - 18 years.

In order to achieve this purpose, the following **objectives** have been outlined:

1. To identify the incidence of metabolic syndrome in obese children, according to the International Diabetes Federation criteria.

2. To study the anthropometric patterns and identify their relationship with cardiovascular remodeling indicators.

3. To study the echocardiographic parameters of epicardial adipose tissue thickness and its correlative analysis with the anthropometric, hemodynamic, metabolic, and cardiovascular remodeling parameters.

4. To study the left ventricular remodeling patterns in children with metabolic syndrome.

5. To assess the subclinical atherosclerotic process by ultrasound measurement of the carotid intima-media thickness.

The scientific novelty and originality. The study was conducted on a group of children with metabolic syndrome from the Republic of Moldova via a complex assessment of clinical and paraclinical features, changes of the left ventricular myocardial structure and geometry, as well as evaluating the imaging status of the vascular endothelium and of the epicardial adipose tissue thickness. The relationship between cardiovascular remodeling and cardiovascular risk factors (anthropometric, metabolic, ultrasound, etc.) was analyzed, based on the relevant findings. Children with metabolic syndrome have been found to exhibit pathological cardiovascular remodeling patterns, as well as greater cardiac and adipose tissue measurements, but still with a preserved left ventricular function.

Theoretical significance of the study. The results of the study proved the importance of evaluating the indices of left ventricular remodeling, of the carotid intima-media thickness (index of subclinical atherosclerosis) and the epicardial adipose tissue thickness via echocardiography, thus validating the usefulness of an assessment algorithm among children with metabolic syndrome.

The applicative value of the PhD thesis. The applicative value of the thesis is described within the scientific activity of a number of concerned researchers either from the country or abroad, as well as the assumptions and the problematizations which have been carried out so far, the knowledge that we have gained during the doctoral research activity that will broaden the horizon upon the clinical features, changes of the left ventricular structure and geometry, the status of the vascular endothelium and the size of epicardial adipose tissue in children with metabolic syndrome. The didactic activity refers to conclusions and recommendations used within this study, which might be further used in training of students/residents.Practical activity will include the knowledge acquired and the proposed recommendations that might improve the activity of the profile clinics.

Implementation of research findings. The study results were used within the activity of the Pediatric Cardiology Clinic of the IMPH Mother and Child Institute, Chisinau, Republic of Moldova.

Research findings approval. A number of the research results were presented and discussed at various national and international scientific events: the annual scientific conferences at "Nicolae Testemitanu" SUMPh (Chisinau, 2015, 2016, 2017, 2018); National Conference with international participation "News in Pediatrics", dedicated to the 70th anniversary of the "Nicolae Testemitanu" SUMPh (Chisinau, 2015); National Conference with International Participation "Children's health problems and ways to solve them" (Chisinau, 2016); International Pediatrics Conference, dedicated to the Year of Nicolae Testemitanu. (Chisinau, 2017); The National Congress of Pediatrics, the 7th edition, "Pediatric emergencies and management of the medical act", organized by the Pediatric Society of the Republic of Moldova, jointly held with the Pediatric Society of Romania (Chisinau, 2018); The 7th International Medical Congress for Students and Young Doctors, MedEspera (Chisinau, 2018); Chisinau-Sibiu Biennial National Conference, 3rd edition, "Interdisciplinarity in pediatric infectious diseases" (Chisinau, 2019); Pediatrics National Conference organized by the Pediatrics Society of the Republic of Moldova, jointly held with the Pediatric Society of Romania(Chisinau, 2019); The 21st IAAH European Conference 2018 and the 3rd National Conference on Adolescent Health, "Equal opportunities for healthy development for all adolescents" (Chisinau, 2018); Pediatrics National Conference, Progress in Pediatrics (Romania, Bucharest, 2016, 2017, 2018, 2019); 57th National Congress of Cardiology (Romania, Sinaya, 2018, 2019); Congress of Pediatric Cardiology (Romania, Iasi, 2018); the 27th National

Congress of Endocrinology (Romania, Sibiu, 2018); the 45th National Congress of the Romanian Society for Diabetes, Nutrition and Metabolic Diseases, with international participation (Romania, Sibiu, 2019); the 27th National Congress of Endocrinology (Romania, Bucharest, 2019); National Conference within the Days of Pediatrics in Iasi "N. N. Trifan "XXXII edition (Romania, Iași, 2019); IDF 2017 Congress (UAE, Abu Dhabi, 2017); 1st International Congress of Hypertension in Children and Adolescents (ICHCA) (Spain, Valencia, 2018); The 3rd World Congress on Nutrition and Obesity Prevention Source (Germany, Frankfurt, 2018).

The thesis was discussed, approved and recommended for defense at the meeting of the Department of Pediatrics (report No. 13 dated from 11.06.2019), Profile scientific seminar (report No. 2 dated from 06.11.2019), and approved by the decision of the Scientific Council of the Consortium, (report no.8 from 04.02.2020) of "Nicolae Testemitanu" State University of Medicine and Pharmacy of the Republic of Moldova.

Publications related to PhD thesis. The obtained scientific findings were reflected in 28 scientific papers (13 national, 15 international, 1 with no co-authorship), including 8 articles (2 articles published in international scientific journals and 6 articles in accredited national scientific journals, of B category) and 20 theses.

Keywords: metabolic syndrome, epicardial adipose tissue, subclinical atherosclerosis, cardiac remodeling, International Diabetes Federation, children.

The research received a favorable opinion of the Research Ethics Committee (report no. 59 from 03.06.2016; Viorel Nacu – Professor, chairman of the Research Ethics Committee) of the "Nicolae Testemitanu" SUMPh PI.

Thesis structure and content. The thesis was performed according to the traditional criteria and included 156 pages, which comprised introduction, 5 chapters, discussions, general conclusions, recommendations, and reference list, citing 298 sources. Iconography includes 11 tables and 26 figures (25% of the total thesis amount).

1. RESEARCH METHODOLOGY

General characteristics of the research and sample size design. The study project was carried out within the IMPH IMC, at the Department of Pediatrics of the Pediatric Cardiology Clinic, to which 161 children were admitted, aged from 10 to 17 years 11 months and 29 days, from both urban and rural areas, the patients being selected electively during the 2016 – 2019 period. A observational analytical cohort study was planned to achieve the research purpose and objective

The research comprised several stages (the work steps were followed, graphically systematized in the diagram, which reflects the research design from Figure 1).

The 1st stage included 145 children (out of 161 participants, 16 ineligible), who were selected based on the inclusion/exclusion criteria, and made up the research group in accordance with **the following criteria**: the age of 10 - 17 years 11 months and 29 days (inclusive); with abdominal obesity (waist circumference (WC) ≥ 90 percentile); the child's parent or guardian consent, as well as children's assent (age ≥ 14 years) on research participation; being a citizen of the Republic of Moldova; ability to effectively communicate with the researcher; ability to understand and follow the study requirements; sufficient understanding in signing the informed agreement and written assent.

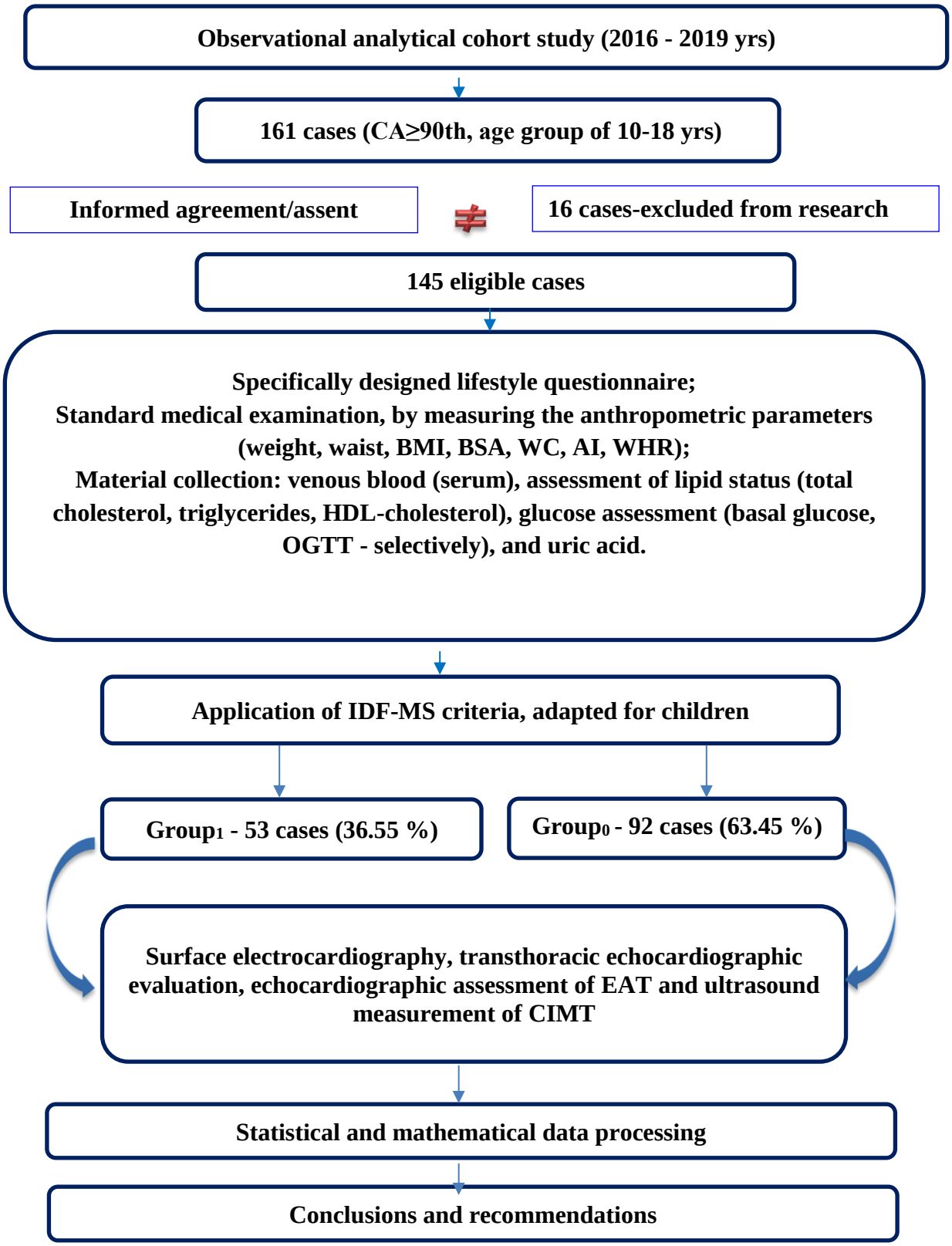

Figure 1. **Study design**

Note: *WC* – waist circumference*; BMI – body mass index; BSA -body surface area; AI – abdominal index; WHR – waist-to-hip ratio; HDLc – high density cholesterol; OGTT – oral glucose tolerance test; MS – metabolic syndrome; IDF – International Diabetes Federation*

The **study exclusion criteria** for the patients were the following: secondary obesity: endocrine, genetic and neurological type, having a suggestive clinical examination, confirmed by specialized examinations; secondary high blood pressure (HBP): renal, endocrine, neurogenic, drug induced, etc., patients having a suggestive clinical examination, confirmed by specialized examinations; acute conditions, whether or not accompanied by fever, whether or not undergoing treatment; chronic respiratory, cardiovascular, gastrointestinal, renal, neurological, endocrine disease etc., disorders, whether or not undergoing treatment; the child's parents or legal representative disagreement, child's refusal to participate in the research, with a difficult ultrasound window, low compliance, patient's refusal to be included in the study.

The selected participants underwent a complex examination, which included: filling in a specific questionnaire (food and physical activity survey), clinical examination on systems, laboratory testing for lipid status (total cholesterol, triglycerides, HDL-cholesterol), the glucose spectrum (basal glucose, OGTT (oral glucose tolerance test - selectively)) and level of uric acid. Following the clinical and paraclinical findings, *the 2nd stage* included the respondent's self-division into 2 groups, by using the criteria of metabolic syndrome (MS) according to the Consensus of the International Diabetes Federation, adapted for children, namely: the research group **(L_1)** - 53 de children with metabolic syndrome (3-5 criteria) and control group **(L_0)** - 92 children without metabolic syndrome (1-2 criteria). The ratio of the study groups was 1:2.

Subsequently, subjects from both groups were subjected to the following instrumental investigations: surface electrocardiography, transthoracic echocardiographic evaluation, echocardiographic assessment of epicardial adipose tissue (EAT) and ultrasound measurement of carotid intima-media thickness (CIMT).

The 3rd stage included a comparative study of the two groups, in terms of lifestyle, symptoms, demographic, anamnestic and biochemical profile, cardiac function and morphology; values of the CIMT, EAT, the severity MS score etc., as well as a statistical analysis of the obtained results. Practical conclusions and recommendations, based on the obtained results, were traced out at *the 4th stage* of study.

All the participants were selected and informed about the research stages, being enrolled only by personal agreement, following a detailed explanation on the requirements and procedures of necessary investigations by discussing with each subject individually. All the procedures were performed, based on children's parent and legal representative consent, as well as on written assent of children $\geq$ 14 years old. They were not paid and have not suffered any financial costs for participation.

Ethical considerations. The study complied with the international standards of medical ethics, developed by the Declaration of Helsinki, regarding confidentiality and personal data protection of the participants. The research was approved by the Research Ethics Committee of "Nicolae Testemitanu" State University of Medicine and Pharmacy (report no. 59 of 03.06.2016).

The resulting data were revealed only to the concerned participant, the personal data of each subject were not used and will not be used for any other purpose.

The study applied the following research methods: historical, comparative, biostatistic ones, and other [5].

The data collected from the primary material were introduced in the electronic database, whereas the statistical processing was performed using the SPSS (Statistical Package for the Social Sciences) version 20.

2. CHAPTER SUMMARY

2.1. The study of clinical-paraclinical parameters.

According to the inclusion and exclusion criteria, there were formed two groups viz. a general group, including 145 participants, of which 53 children with metabolic syndrome (research group) and 92 children with no metabolic syndrome (non-MS control group). **Gender groups** were divided into 55.9 % boys (81 patients) and 44.1 % girls (64 patients) of the total number of enrolled children. **The age groups** included in the research ranged from 10 to 17 years 11 months and 29 days, with the total mean age of 13.71 ± 2.33 years. **The overall urban-rural** distribution revealed an average of 63 children (43.4 %) from urban areas and 82 (56.6 %) from rural ones. According to **the regional distribution** of participants from the Republic of Moldova, the share was higher in those from the center and south areas (north - 34 (23.4 %), center - 57 (37.2 %) and south - 54 (37.2 %).

According to **metabolic syndrome criteria** and based on the International Diabetes Federation agreement, 24.9 % subjects presented 3 criteria, 11 % - 4 criteria, and 0.7 % - 5 positive criteria, whereas 25.5 % of the participants presented 1 criterion, and 37.9 % - 2 of the mentioned criteria (see Figure 2). **Gender distribution** revealed that 24.7% (20 pts) boys and 25% (16 pts) girls had 3 positive criteria, and 14.8 % (12 pts) boys and 7.8 % (5 pts) girls – 4 -5 positive criteria for metabolic syndrome ($\chi 2 = 1.77$; $p > 0.05$).

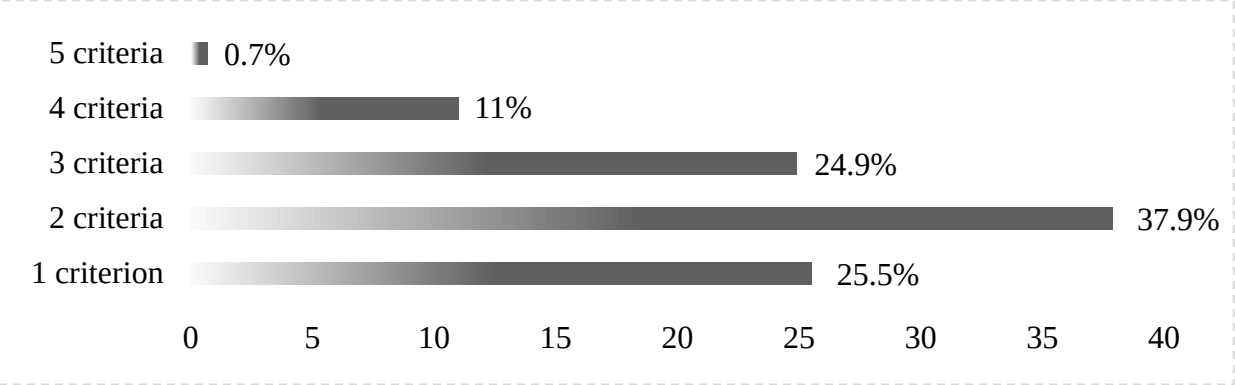

Figure 2. **The participant distribution based on the number of criteria and IDF consensus for children (%) (n = 145; p > 0,05)**

Note: *Data expressed in relative values (%)*

There were selected **5 factors of MS** (according to the IDF consensus, adapted for children).The first factor (F1) - obesity, was recorded in 100 % (145 pts) of cases in order of prevalence (it might be due to the fact that children included in the study exhibited WC ≥ 90 percentile), the second factor (F2), found in 47.6 % (69 pts) of cases, showed low values of high-density cholesterol and the third factor (F3), found in 25.5 % (37 pts) of cases, which were defined by triglycerides was named the lipidic factor. The fourth factor (F4), recorded in 42.8 % (62 pts) of cases with high blood pressure values, was called the blood pressure factor, and the fifth factor (F5), reported in 7.6 % (11 pts) of cases with higher than normal blood glucose levels, was related to carbohydrate metabolism, being less prevalent.

The frequency and significance assessment of MS components depending on gender distribution revealed the following: F1 was recorded in all participants in both sexes, F2 was recorded in 31 (38.3 %) male subjects and 38 (59.4 %) females, F3 was present in 27 (33.0 %) boys and 10 (15.6 %) girls, F4 was registered in 41 (50.6 %) males and 21 (32.8 %) females, and F5 was found in 6 (7.4 %) boys and 5 (7.8 %) girls.

The assessment of pediatric metabolic syndrome was also performed by detecting the components and their association. The prevalence of cases with defined MS was assessed by means

of **clustering patterns**, being estimated according to the number of criteria. Cluster WC - HDLc - HBP was found in 10.3 % of cases, WC - TG - HDLc was registered in 8.3 %, WC - TG - HDLc - HBP - 7.6 %, WC - TG - HBP - 5,5 % of cases. The clusters WC - HDLc - Glu - HBP and WC - TG – HDLc- Glu were found to exhibit the same frequency of 1.4 %, whereas WC - Glu - HBP, WC - TG - Glu - HBP and WC - TG - HDL - Glu - HBP in 0.7 % of cases. **Gender** – based clustering showed higher rate of WC - HDL - HBP in females vs male (10 (15.6 %) vs 5 (6.2 %)) ($p < 0.01$); higher WC - TG - HDL cluster rate in males vs females (8 (9.9 %) vs 4 (6.3 %)) ($p <0.01$); high rate of WC - TG - HDLc - HBP cluster in males vs females (8 (9.9 %) vs 3 (4.7 %)) ($p < 0.01$); WC - TG - HBP cluster prevailing in males vs females (7 (8.6 %) vs 1 (1.6 %)) ($p < 0.01$); WC - HDLc - Glu - HBP cluster was recorded in 1 case, both in females and males; WC - TG - HDLc - Glu cluster in 2 male cases. Clusters WC - Glu - HBP, WC - TG - Glu - HBP and WC - TG - HDLc - Glu - HBP were found in 1 case per each. Obesity cases were found to be associated with dyslipidemia, high blood pressure and glycoregulation disorders (similar data was found in specialized literature among adult population, whereas no data were recorded for pediatric population).

The results obtained from **the analysis on the correlation matrix** showed that only two components (WC and BP) have greater values than 1, making up 59 % (respectively, over 50 % of data) from the total variance, and becoming independent vectors obtained on the basis of their own values, on which the main components will be found. The two variables that describe MS indicators were found to explain only 25 % of the total amount of variance (the most useful structure for interpretation being, however, the one obtained after rotating the factors, which provides a better "vision"). The typical graphical representation of PCA, respectively the obtained

Scree plot, confirms the two main components resulting from the application of this method. Analyzing the graphical presentation of our own values, while complying with the Evrard criterion for obtaining the number of principal components, we can decide upon choosing 2 components. Moreover, we consider the fact that only the first 2 components add more information to a variable in the initial form, thus we will keep only the latter ones. Additionally, we observe that 59% of the initial information for MS is extracted from the new ones. Furthermore, WC, sBP, were found to be strongly related, HDLc was poor-related and Glu and TG are not related to the first principal component, whereas the second main component is not related to Glu, TG and HDLc.

MS score was calculated based on the reference values and by using the following formula = (2xWC/h) + (Glu (mmol/l)/5.6) + (TG (mmol/l)/1.7) + (sBP/130) - (HDLc (mmol/l)/1.02). Thus the following scores were found (participants aged 16-18 years were not included in the study, considering their small number, thus requiring application of other formulas): L_0 – 2,20 ± 0,05, L_1– 2,58 ± 0,11 ($p > 0,05$), by gender: 2.94 ± 0.1 – for females, 2,97 ± 0.05 ($p > 0.05$) – for males. The correlation coefficient of the pediatric MS score with the clinical and paraclinical parameters was assessed, showing a strong positive association with TG (+ 0.9**, $p < 0.001$), waist, age, weight, BMI, BSA, AI, SBP, DBP, LDLc (+ 0.3**, $p < 0.001$), HG (+ 0.24**, $p < 0.001$), Glu (+ 0.2**, $p < 0,05$), OD (+ 0.2*, $p > 0.05$), LVPWd (+ 0.23**, $p < 0.001$), LVMM (+ 0.2*, $p > 0.05$), and strong negative association with HDLc (- 0.6**, $p < 0.001$), WHR (- 0.21*, $p > 0.05$). There are no similar data recorded in specialized literature, thus comparative studies were not performed.

The results of the study of the spectrum of clinical manifestations. Examining the specificity of the clinical manifestations of children included in the study, 38 (71.7 %) patients with MS vs 51 (55.4 %) with non-MS complained of precordial pains ($\chi 2 = 3.73$; $p > 0.05$). Heart palpitations were present in 38 (71.7 %) of participants from the study group and in 51 (55.4 %)

cases from MS control group ($\chi2 = 0.53$; $p > 0.05$). 30 (56.6 %) and 61 (66.3 %) with non-MS complained of dyspnoea ($\chi2 = 1.35$; $p > 0.05$). Epistaxis was present in 7 (13.2 %) participants from the study group and 12 (13.0 %) children from the control group ($\chi2 = 0.001$; $p > 0.05$). Headaches were reported in 44 (84.6 %) children with MS vs 66 (71.7 %) children with non-MS ($\chi2 = 3.05$; $p > 0.05$). Vertigo was present in 11 (20.8 %) MS children and 16 (17.4 %) non-MS children ($\chi2 = 0.25$; $p > 0.05$); hot flushes were registered in 3 (5.7 %) children from the study group and 9 (9.8 %) from the control group ($\chi2 = 0.75$; $p > 0.05$). 15 (28.8 %) children with MS and 21 (22.8 %) with non-MS ($\chi2 = 0.64$; $p > 0.05$) felt fatigued. Lipotemia was found in one child (1.9 %) from the MS group and in four (4.3 %) children from the non-MS group ($\chi2 = 0.61$; $p > 0.05$). There were no statistically significant differences regarding the assessment of clinical manifestations in the two groups. All subjects included in the research were overweight.

The results of the analysis of pre-, peri- and postnatal risk factors.

Pregnancy evolution. It was found that mothers of children with both MS and non-MS were exposed to psycho-emotional stress (20.8 % vs 17.4 %, $\chi2 = 0.25$; $p > 0.05$), poor nutrition (22.6 % vs. 25.0 %, $\chi2 = 0.10$; $p > 0.05$), had bacterial/viral infections (9.4 % vs. 9.4 %, $\chi2 = 2.46$; $p > 0.05$) and used drugs (9.4% vs. 3.3%, $\chi2 = 2.46$; $p > 0.05$) during pregnancy. Unique cases of toxic exposure and active smoking were registered.

The gestational age at the time of birth. Premature birth was considered when the child was born with a gestational age of less than 37 weeks, term birth at 37 - 42 weeks, post-term birth, when more than 42 weeks. The term birth occurred in 82 (89.1 %) children with non-MS and 49 (92.5 %) with MS, premature births were registered in 10 (10.9 %) cases from the control group and 4 (7.5 %) cases from study group, post-term births were not recorded ($\chi2 = 0.43$; $p > 0.05$).

Birth route. Caesarean section births were recorded in 6 (11.3 %) cases with MS vs. 8 (8.7 %) with non-MS, and natural births were registered in 47 (88.7 %) subjects from the research group and 84 (91.3%) children from the control group ($\chi2 = 0.83$; $p > 0.05$).

Low-weight births were considered when a full-term child weighed less than 2500 g (according to WHO), being registered in 4 (4.3 %) children with non-MS and 2 (3.8 %) with MS; children weighing between 2500-3500 g were found in 62 (67.4 %) cases from the control group and 26 (49.1 %) from the research group; children's weight of 3500 - 4000g was present in 20 (21.7 %) cases with non-MS and 20 (37.7 %) with MS; children weighing > 4000 g was found in 6 (6.5 %) cases with non-MS and 5 (9.4 %) with MS ($\chi2 = 5.39$; $p > 0.05$).

Duration of natural breast-feeding. 31 (33.7 %) children with non-MS and 10 (18.9 %) with MS were breastfed less than 6 months, 10 (10.9 %) children from the control group and 5 (9.4 %) children from the research group were breastfed for a period of 6 months, and 51 (55.4 %) non-MS children and 38 (71.7 %). MS children were naturally fed for more than 6 months ($\chi2 = 4.13$; $p > 0.05$).

Age of dietary diversification. The dietary diversification was introduced in 16 (17.4%) children with non-MS vs. 7 (13.5%) with MS by the age of 6 months, 73 (79.3%) children from the control group and 43 (82.7%) from the study group- at 6 months, and 3 (3.3%) non-MS children and 2 (3.8%) MS children started diversification after 6 months ($\chi2 = 0.40$; $p>0.05$).

Immunization. The preventive measures were performed in 52 (98.1 %) children from the research group vs 90 (97.8 %) from the control group, one child with non-MS got a partial vaccination and 2 children with MS and one with non-SM were not immunized ($\chi2 = 0.73$; $p > 0.05$).

The results of the study of heredocolateral antecedents. DM (type 1/2) showed a higher percentage among 1st and 2nd degree relatives in children with non-MS vs MS (43.5 % vs 32.1 % and 9.8 % vs 5.7 %; $\chi 2 = 6.84$; $p > 0.05$). Cerebrovascular pathology occurrence was higher in MS group, among first-degree relatives (39.6 % vs. 30.4 %) and in non-MS group in second-degree relatives (17.4 % vs 13.2 %) and in third-degree ones (1.1 % vs 0) ($\chi 2 = 5.07$; $p > 0.05$), respectively. Higher HBP incidence was found among 1st and 2nd degree relatives in those with non-MS vs MS (8.7 % vs 7.5 % and 2.2 % vs 0) ($\chi 2 = 1.25$; $p > 0.05$), whereas AMI showed a higher incidence among second-degree relatives, in children with MS (9.4 % vs. 6.5 %), and in those with non-MS among first-degree relatives (6.5 % vs. 3.8 %) ($\chi 2 = 2.77$; $p > 0.05$). Obesity and thyroid gland disease had a higher frequency among 1st, 2nd and 3rd degree relatives in both study and control lots (13.2 % vs. 17.4 %; 7.5 % vs 3.3 %; 1.9 % vs 3.3 % $\chi 2 = 1.89$; $p > 0.05$) (7.5 % vs 2.2 %; 0 vs 3.3 %; 3.8 % vs. 2.2 %; $\chi 2 = 1.89$; $p > 0.05$). Dyslipidemia was found in unique cases from both groups, due to the lack of data regarding both participants, parents/legal representatives, and health condition.

The results of the selective analysis of some anthropometric parameters. The studied groups were characterized by the following values: 80.5 ± 2.05 kg in the study group vs. 73.4 ± 2.3 kg in the control group, with the statistical difference ($p < 0.01$) for weight, the waist values were 168.4 ± 1.7 cm in MS group, and 161.4 ± 1.5 cm in non-MS group, with a true statistical difference ($p < 0.01$), the mean BMI index showed absolute values in the study group - 28.2 ± 0.4 kg/m^2, and in the control group 27.1 ± 0.5 kg/m^2 ($p > 0.05$), according to the percentiles - 94.7 ± 0.6 vs. 93.9 ± 0.4 ($p > 0.05$), and according to the Z score both groups had the same mean value of 1.7 ± 0.05 ($p > 0.05$); the mean values of WC were 94.5 ± 1.2 cm in the MS group and 90.5 ± 1.07 cm in the control group (according to the percentiles, in 100% of WC cases ≥ 90th), with a statistically significant difference ($p > 0.05$); hip circumference (HC) was 103.5 ± 1.3 cm in children with MS and 98.7 ± 1.3 cm in those with non-MS, with a statistically significant difference ($p > 0.05$); AI = 0.9 ± 0.01 and IAF = 0.6 ± 0.01 showed the same values in both groups, and the WHR was higher in the study vs control group 1.88 ± 0.03 m^2 vs. 1,76 ± 0.03 m^2, but with no true statistical difference ($p > 0.05$).

The correlational study between the main anthropometric parameters (weight, waist circumference, hip circumference) and hemodynamic parameters, lipid and glycemic profile, ultrasound parameters of epicardial fat type and CIMT in children with metabolic syndrome (see Figure 3) revealed a statistically significant positive correlation coefficient between weight and BMI ($r = 0.7^{**}$, $p < 0.001$), WC ($r = 0.7^{**}$, $p < 0.001$), HC ($r = 0.6^{*})^{*}$, $p < 0.001$), SBP values ($r = 0.5^{**}$, $p < 0.001$), DBP ($r = 0.4^{**}$, $p < 0.001$), LA ($r = 0.4^{**}$, $p < 0.001$), IVS ($r = 0.5^{**}$, $p < 0.001$), LVPWd ($r = 0.6^{**}$, $p < 0.001$), LV Mass ($r = 0.6^{**}$, $p < 0.001$), LVED ($r = 0.5^{**}$, $p < 0.001$), LVEDV ($r = 0.5^{**}$, $p < 0.001$), EAT ($r = 0.4^{*}$, $p > 0.05$). Waist circumference showed a positive correlation coefficient with the mean weight ($r = 0.7^{**}$, $p < 0.001$), BMI ($r = 0.6^{**}$, $p < 0.001$), HC ($r = 0.8^{**}$), $p < 0.001$, strong correlation coefficient), SBP values ($r = 0.4^{**}$, $p < 0.001$), DBP ($r = 0.4^{**}$, $p < 0.001$), uric acid ($r = 0{,}4^{**}$, $p < 0.001$), LA ($r = 0.4^{**}$, $p < 0.001$), IVS ($r = 0.4^{**}$, $p < 0.001$), LVPWd ($r = 0.5^{**}$, $p < 0.001$), LV Mass ($r = 0.5^{**}$, $p < 0.001$), LVEDD ($r = 0.4^{**}$, $p < 0.001$), LVEDV ($r = 0.4^{**}$, $p < 0.001$), EAT ($r = 0.4^{*}$, $p < 0.05$). The hip circumference was positively correlated with weight ($r = 0.6^{**}$, $p < 0.001$), BMI ($r = 0.6^{**}$, $p < 0.001$), WC ($r = 0.8^{**}$, $p < 0.001$), SBP values ($r = 0.4^{**}$, $p < 0.001$), DBP ($r = 0.4^{**}$, $p < 0.001$), LA ($r = 0.4^{**}$, $p < 0.001$), IVS ($r = 0.4^{**}$, $p < 0.001$), LVPWd ($r = 0.4^{**}$, $p < 0.001$), LVM ($r = 0.5^{**}$, $p < 0.001$), LVED ($r = 0.4^{**}$, $p < 0.001$), LVEDV ($r = 0.4^{**}$, $p < 0.001$).

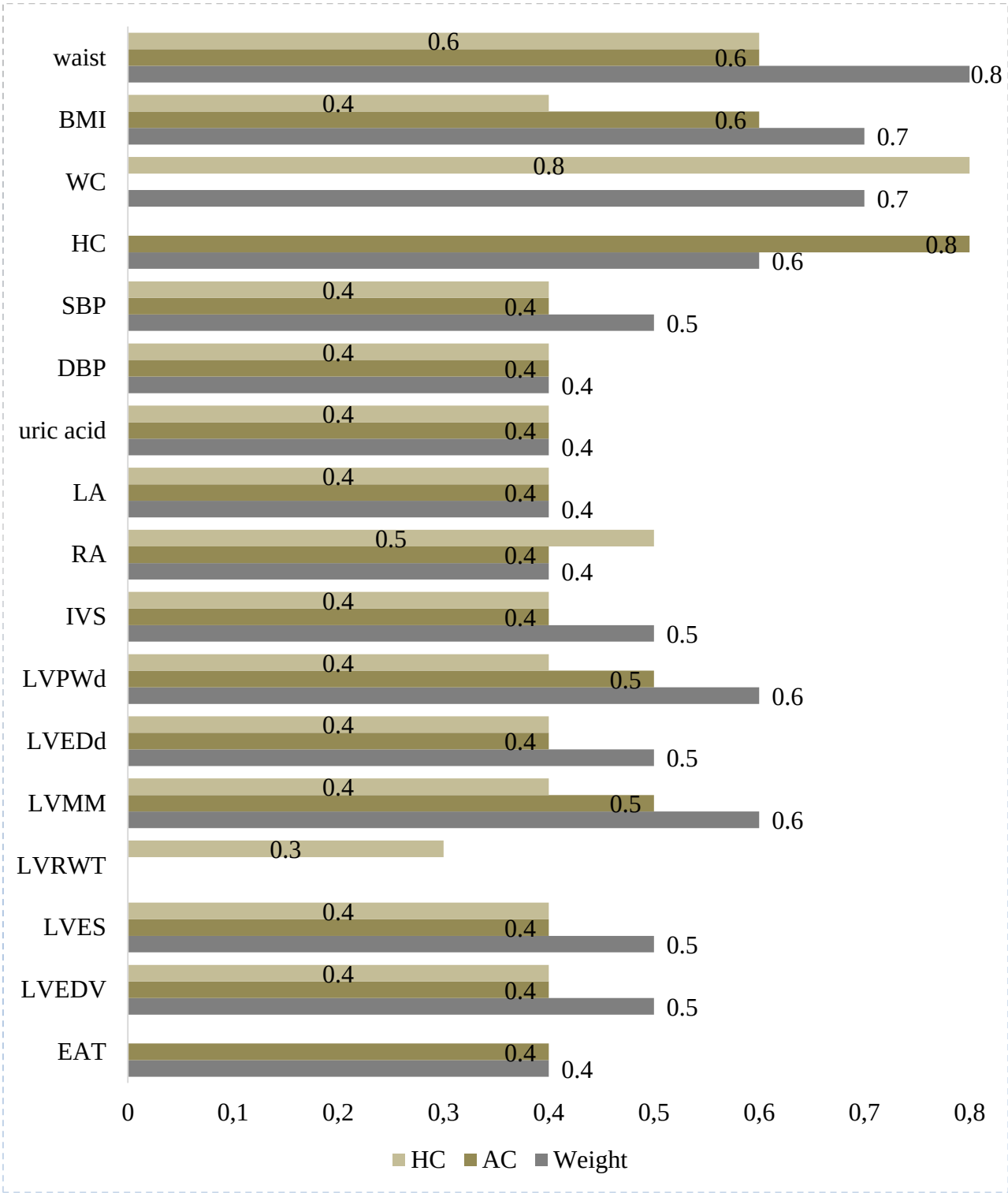

Figure 3. **Statistical correlations of weight, WC, and HC with other variables**

Note:* *p<0.001;* p>0.05; r – Pearson correlation coefficient; BMI – body mass index; WC - waist circumference; HC – hip circumference; SBP – systolic blood pressure; DBP – diastolic blood pressure; LA – left atrium; RA – right atrium; IVS – interventricular septum; LVPWd – left ventricular posterior wall; LVEDD – left ventricular end-diastolic diameter; LVRWT – left ventricular relative wall thickness; LVEDV – left ventricular end-diastolic volume; LV Mass – left ventricular mass; EAT – epicardial adipose tissue*

Despite the literature data described by other researchers, no statistically significant correlations between the anthropometric characteristics and lipid-carbohydrate metabolism parameters were recorded in the present study. On the one hand, this might be due to a small

number of subjects included within the research groups and short duration of MS pathology, on the other hand, the results confirm the impact of obesity factor on the risk of LV remodeling patterns (similar to data from the other studies).

The results of the evaluation of some biochemical parameters. A comparative study between the biochemical indices in children with MS vs non-MS revealed the following mean values: TG – 1.97 ± 0.2 mmol/l, compared to 1.16 ± 0.03 mmol/l ($p < 0.001$); TC – 4.09 ± 0.14 mmol/l, compared to 4.06 ± 0.09 mmol/l ($p > 0.05$); HDLc – 1.03 ± 0.03 mmol/l vs. 1.33 ± 0.03 mmol/l ($p < 0.001$); LDLc – 2.11 ± 0.12 mmol/l vs. 2.05 ± 0.17 mmol/l ($p < 0.001$); LDLc/HDLc – 2.04 ± 0.04 mmol vs. 1.54 ± 0.05 mmol/l ($p < 0.001$); TC/HDLc – 3.97 ± 0.01 mmol/l vs. 3.05 ± 0.01 mmol/l ($p > 0.05$); ß-lipoproteins – 45.15 ± 1.78 mmol/l, compared to 46.74 ± 1.21 mmol/l ($p>0.05$); and uric acid – 315.41 ± 10.65 mmol/l, compared with 292.88 ± 8.56 mmol/l ($p > 0.05$).

The results of eating behavior analysis. 15.2 % of children with non-MS and 15.1 % of those with MS were recorded to have less than 4 meals per day ($p > 0.05$), 81.5 % vs. 83 % had 4 - 5 meals a day ($p > 0.05$) and 3.3 % vs 1.9 % stated a consumption greater than 5 meals a day (according to WHO recommendations a healthy diet should consist of 4 - 5 meals a day); 14.1 % of subjects with non - MS and 13.2 % of those with MS do not have breakfast ($p > 0.05$); 3.8 % of respondents with MS do not have lunch ($p > 0.05$); all the participants have dinner.

Improper food intake, in terms of consuming more food in the second part of the day, was recorded in both groups, in more than 50 % of cases (75 % vs. 77.4 %; $p > 0.05$), whereas a higher percentage of children with MS, compared with those with non - MS (28.3 % vs. 9.8 % and 18.9 % vs. 14.1 %; $p > 0.05$) stated an absence of snacks in the first and the second half of the day, that is without a true statistical significance. After - dinner snacking was recorded in both groups, thus, 1 - 2 times a week in 26.4 % of cases from the study group and 25.0 % from the control group, 3 - 4 times a week in 17.0 % of cases among children with MS and 4.0 % for those with non - MS, and daily intake was identified in 25 % vs. 20.8 %, respectively There was no true statistical difference between groups ($p > 0.05$).

The nutrition survey included the 6 major categories of nutrients included in the food pyramid framework.

Fruit and vegetable consumption. 40.2 % of children with non - MS and 47.2 % of those with MS eat fruits and vegetables on a daily basis; 53.5 % of patients with non - MS and 39.6 % with MS consume them 3 - 4 times/week; 5.4 % of participants with non - MS and 3.8 % with MS – 1 - 2 times/week; 10.9 % of children from the control group and 9.4 % from the study group eat fruits and vegetables occasionally ($\chi 2 = 0.76$; $p > 0.05$) .

Meat and meat products consumption. 5.4 % of children with non - MS and 11.3 % with MS eat meat 3 - 4 times/week; 16.3 % of participants with non - MS and 20.8 % with MS – 1 - 2 times/week; 71.7 % of children with non - MS and 54.7 % with MS eat them occasionally ($\chi 2 = 5.07$; $p > 0.05$).

Dairy intake. 3.8 % of children with MS (0 – non - MS) have dairy products on a daily basis; 30.3 % of children with non - MS and 31.5 % with MS consume them 3 - 4 times/week; 15.2 % of participants with non - MS and 15.1 % of those with MS – 1 - 2 times/week; 28.3 % from the control group and 26.1 % from the study group - occasionally ($\chi 2 = 4.57$; $p > 0.05$).

Fish consumption. 7.6 % of children with non - MS and 3.8 % with MS eat fish 3 - 4 times/week; 24.8 % of participants with non - MS and 30.2 % of those with MS – 1 - 2 times/week; 70.7 % of children from the control group and 66.0 % from the study group use it occasionally ($\chi 2 = 1.87$; $p > 0.05$).

Consumption of sweets. 15.2 % of children with non - MS vs. 15.1 % with MS eat sweets daily; 57.6 % of children with non - MS and 52.8 % with MS – 3 - 4 times/week; 22.8 % of participants with non - MS and 28.3 % of those with MS – 1 - 2 times/week; 4.4 % of children from the control group and 3.8 % from the study group eat sweets occasionally ($\chi 2 = 2.01$; $p > 0.05$).

Soft drink and juice consumption. 13.0 % of children with non - MS and 17.0 % with MS drink them 3 - 4 times/week; 42.4 % of participants with non - MS and 28.3 % with MS – 1 - 2 times/week; 38.5 % of children from the control group and 41.4 % from the study group – occasionally ($\chi 2 = 3.93$; $p > 0.05$).

Fast food consumption. 6.5 % of children with non - MS and 9.4 % with MS eat fast - food 3 - 4 times/week; 5.4 % of participants with non - MS and 13.2 % with MS – 1 - 2 times/week; 67.4 % of children from the control group and 60.4 % from the study group eat fast food occasionally ($\chi 2 = 3.32$; $p > 0.05$).

Cereal grain consumption. 5.4 % of children with non - MS and 7.5 % with MS eat grains daily; 48.9 % of respondents with non - MS and 37.7 % with MS - 3 - 4 times/week; 26.1 % of participants with non - MS and 37.7 % with MS - 1 - 2 times/week; 19.6 % of children in the control group and 17.0 % in the study group eat them occasionally ($\chi 2 = 2.8$; $p > 0.05$).

The results of physical activity analysis.

Morning exercises. No respondents (0 % of cases) from both groups do morning exercises and 3 - 4 times/week; 11 (12.0 %) participants with non - MS and 9 (17.0 %) with MS – 1 - 2 times/week; 70 (76.1 %) of subjects from the control group and 39 (73.6 %) from the study group – occasionally; and 5 (9.4 %) children with MS and 11 (12.0 %) in the control group do not do morning exercises ($\chi 2 = 0.84$; $p > 0.05$).

Physical training and sports class attendance. 38 (71.7 %) children with MS (15 (28.3 %) – absent) and 69 (75.0 %) with non - MS (23 (12.0 %) – are absent) go in for sport classes ($\chi 2 = 0.58$; $p > 0.05$).

Physical activity and sports outside the school hours. 16 (30.2 %) subjects from the study group (37 (69.8 %) participants – absent) and 30 (32.6 %) from the control group (62 (67.4 %) participants – absent) practice physical activity ($\chi 2 = 3.93$; $p > 0.05$).

Regular leisure - time physical activity. 13 (24.5 %) participants with MS (40 (75.5 %) subjects – absent) and 29 (31.5 %) children (63 (68.5 %) subjects – absent) practice sports ($\chi 2 = 0,80$; $p > 0.05$).

The last leisure - time physical activity. 29 (31.5 %) children from the control group vs 0 from the study group practiced sports yesterday/today; 27 (29.3 %) subjects with MS and 14 (26.4 %) with non - MS – a few days ago; 2 (3.8 %) participants from the study group vs 0 from the control group – a few months ago (> 3 months); 4 (4.3 %) children with non - MS and 7 (13.2 %) with MS and a few years ago ($\chi 2 = 9.01$; $p > 0.05$).

Time spent on TV/computer/phone/tablet (hours). 41 (77.4 %) children with MS and 80 (87.0 %) with non - MS spend > 4 hours, 5 (9.4 %) subjects in the study group and 7 (7.6 %) children in the control group spend 2 - 4 hours, and 7 (13.2 %) participants with MS and 5 (5.4 %) with non - MS spend <2 hours ($\chi 2 = 2.96$; $p > 0.05$).

Computer/tablet/mobile games. 28 (52.8 %) children from the study group and 39 (42.4 %) from the control group were registered to play computer games daily; 18 (34.0 %) children from the study basic group and 42 (45.7 %) from the control group – 1 - 2 times/week; 5 (9.4 %) subjects

with MS and 10 (10.9 %) with non - MS – 3 - 5 times a week ($\chi 2 = 6.02$; $p > 0.05$). There is no true statistical difference between the study findings ($p > 0.05$).

2.2. Study of echocardiographic parameters of epicardial fat type and carotid intima-media thickness

The results of the echocardiographic evaluation of the epicardial adipose tissue thickness. The study was conducted on 118 pediatric subjects (63 boys and 55 girls), 45 with MS, and 73 with non - MS. Depending on the **presence/absence of the metabolic syndrome,** the mean value of the epicardial adipose tissue thickness was beyond the accepted cut - off points both in the main study and control group (5.39 ± 0.22 mm vs. 4.97 ± 0.17 mm; $p > 0.05$; see Figure 4), with no true statistical difference. The findings are similar to those reported in other studies [6, 10], depending on heterogeneous clinical and paraclinical characteristics and incidence data [6], whereas the age, gender, body weight and ethnicity are the key determinants considered in prognostic value assessment [11].

Figure 4. **The echocardiographic imaging assessment of epicardial adipose tissue thickness in children ($p > 0.05$)**

Note: *MS + – confirmed metabolic syndrome, MS - – non - confirmed metabolic syndrome, n – number of participants*

In terms of gender, the mean value of EAT thickness was higher in males vs females, without any statistically significant difference (5.27 ± 0.2 mm vs. 4.97 ± 0.19 mm; $p > 0.05$). Currently, there is no consensus regarding the impact of gender, though, some research findings state that females would exhibit higher values, other researchers do not prove any associations.

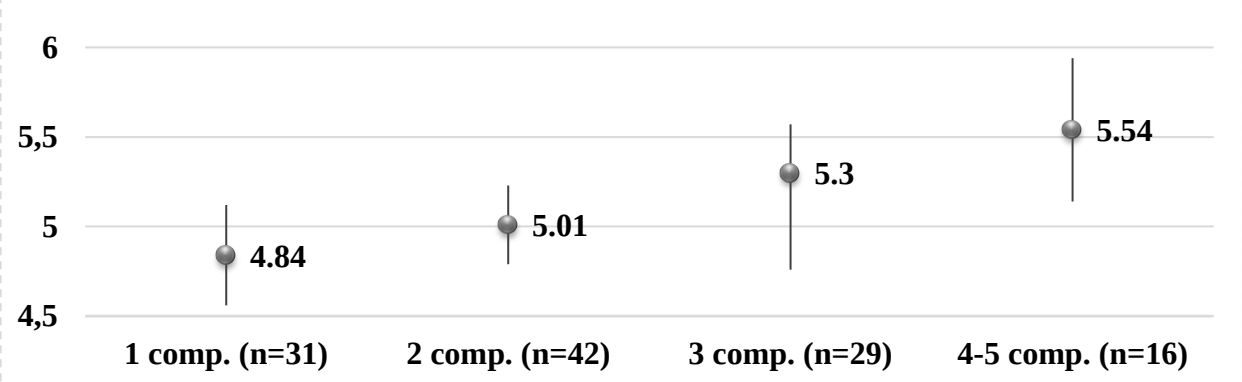

Figure 5. **Epicardial adipose tissue thickness in children, according to the number of metabolic syndrome components ($p > 0.05$)**

Note*: n – number of participants*

According to **the number of MS components**, the study participants showed an increasing tendency in EAT thickness value depending upon the number of MS components, thus being higher in subjects with three, four or five components, compared to those with a single component,

but not for two components (5.30 ± 0.27 mm vs. 5.54 ± 0.4 mm, vs. 4.84 ± 0.28 mm vs. 5.01 ± 0.22 mm; F = 0.96; p > 0.05; see Figure 5), with no true statistical significance. Therefore, we can conclude that higher values of high blood pressure and waist circumference, dyslipidemia and hyperglycemia have synergistic effects on the increase of EAT thickness among children with MS.

MS clustering. As regarding the distribution of the EAT thickness mean values among the MS clusters, it was found to be higher in subjects with four and five positive criteria, respectively (WC - HDLc - HBP = 5.47 ± 0.44 mm, vs. WC - TG - HBP = 5.6 ± 0.84 mm, vs. WC - TG - HDLc = 4.65 ± 0.38 mm and WC - TG - HDLc - HBP = 5.77 ± 0.52 mm; F = 0.82; p > 0.05). However, the number of participants with MS, who presented three criteria, also showed values above the admitted threshold, the difference being the combinations of risk factors (except for the basic WC criterion ≥ 90^{th}), thus the following components were predominant: obesity, dyslipidemia and high blood pressure values. No comparative review of specialized literature was carried out, since no similar data are available among adults and children, particularly.

Statistical correlations of epicardial adipose tissue thickness. The study on children from the MS group, regarding the relationship between the epicardial adipose tissue thickness, the anthropometric parameters, hemodynamics, the lipid profile and the glucose level, via the ultrasound parameters of cardiovascular remodeling, found a positive and moderate association with the body weight (r = 0.41*; p < 0.001), body mass index (kg/m^2/Z score) (r = + 0.33*/ r = + 0.31*; p > 0.05), waist circumference (r = + 0.4*; p > 0.05, which suggests that EAT is a good indicator of visceral fat), hip - to - waist ratio (r = + 0.35*; p > 0.05), interventricular septum (r = + 0.3*; p > 0.05), left ventricular posterior wall (r = + 0.34*; p > 0.05) and left ventricular mass (r = + 0.3*; p < 0.05), which suggests that the increase of EAT thickness is associated with a consensual and proportional increase of the LV Mass), showing a true statistical significance; no correlations or weak correlation coefficient being recorded, not statistically significant with hemodynamic, lipid metabolism, carbohydrate and vascular remodeling parameters (similar data are present in the literature [6]).

The results of the ultrasound evaluation of the CIMT. 117 participants (62 boys and 55 girls) were included within the study, 44 children with MS, and 73 with non - MS.

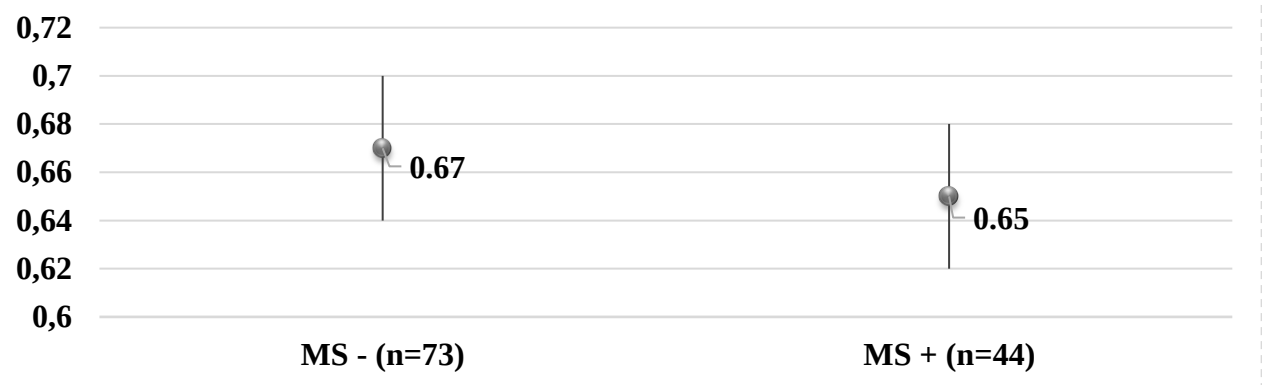

Figure 6. **CIMT (ultrasound parameter of subclinical atherosclerosis) in children (p>0.05)**
Note: *MS + – confirmed metabolic syndrome, MS - – non - confirmed metabolic syndrome, n – number of participants*

In terms of **presence/absence of the metabolic syndrome**, and according to the research findings (see Figure 6), the average value of CIMT exceeded the admitted threshold in both groups with MS (0.65 ± 0.03 mm) and with non - MS (0.67 ± 0.03 mm), not showing significant statistical differences (p>0.05). Similar to epicardial adipose tissue, the age, gender, ethnicity are considered

the key factors in estimating the prognostic value and CIMT, being higher in male (gender - related), in African - American population (rather than in Caucasians), and increasing with age [12].

Gender - based distribution revealed no statistically significant changes in the mean values of CIMT (boys 0.66 ± 0.03 mm vs. girls 0.67 ± 0.03 mm; p>0.05).

Depending on the **number of MS components** (see Figure 7), the study participants presented the following CIMT values: 0.67 ± 0.02 mm for one component, 0.69 ± 0.04 mm for 2 components, 0,68 ± 0.04 mm for 3 components and 0.6 ± 0.04 mm for 4 - 5 components, thus the study results were found partially similar to those described in other studies, tending to increase, probably due to a small number of participants with "4 - 5 components", with no significant statistical difference (F = 0.96; p > 0.05).

The tendency to increase along with an increase in the number of MS components, might be explained by the presence of obesity, a mandatory component and an important cardiovascular risk factor that strongly affects the endothelial functioning, a fact confirmed in a series of studies, whereas the subclinical atherosclerosis measures for cardiovascular prediction might require probably considering the number of MS components, rather than establishing its presence.

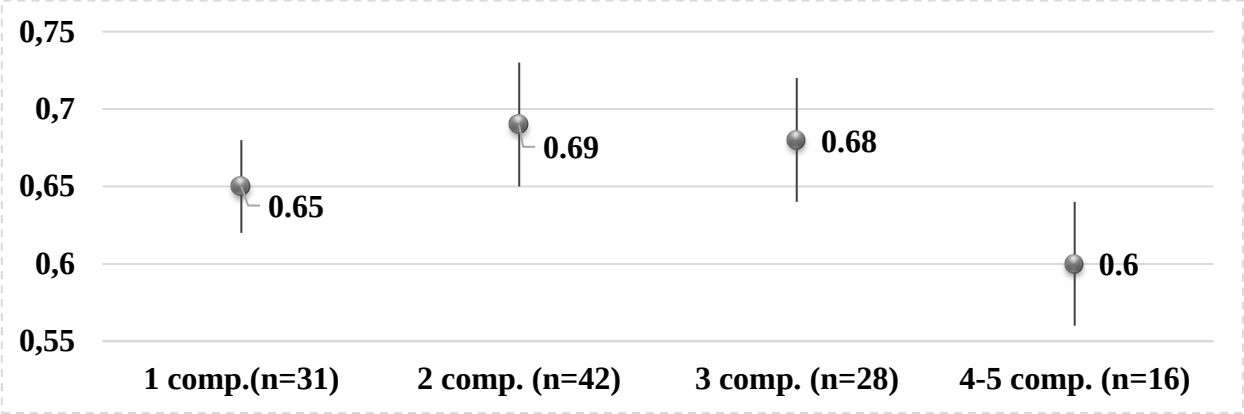

Figure 7**. CIMT (ultrasound parameter of subclinical atherosclerosis) according to the number of components (p > 0.05)**

Note: *n – number of participants*

Clustering revealed the following CIMT values: 0.62 ± 0.04 mm for WC - TG - HDLc - HBP; 0.63 ± 0.05 mm – WC - TG - HDLc; 0.65 ± 0.03 mm – WC - HDLc - HBP and 0.8 ± 0.16 mm – WC - TG - HBP, being not statistically significant (F = 1.35; p > 0.05). Obesity, atherogenic dyslipidemia, and HBP, exhibiting a higher frequency in descending order of clusters, directly contribute to vascular endothelium changes (likely to have synergistic effect) and underlines the crucial role of hypertensive component and obesity in the pathogenesis of subclinical atherosclerosis associated with this syndrome.

The CIMT value was also studied in accordance with the Mannheim consensus (2004 - 2006), which cites *"the 75th percentile is considered as a cut - off point for CIMT, in a reference population"* [12]. Depending on the **presence/absence of the metabolic syndrome**, 68 (93.2 %) participants from non - MS group showed CIMT values > 75^{th} vs 5 (6.8 %) with CIMT ≤ 75^{th}, whereas 43 (97.7 %) subjects from MS group had CIMT values > 75^{th} vs 1 (2.3 %) subject with CIMT ≤ 75^{th} (p > 0.05). In terms of **gender,** a CIMT value > 75^{th} was registered in 58 (93.5 %) males vs 53 (96.4 %) females and a CIMT value ≤ 75^{th} in 4 (6.5 %) males vs 2 (3.6 %) females (p > 0.05). Depending on **the number of components**, a CIMT value > 75^{th} was recorded in 27 (87.1 %) children vs 4 (12.9 %) with CIMT ≤75^{th} with 1 component, in 41 (97.6 %) participants vs 1

(2.4 %) with 2 components, in 28 (100 %) of subjects vs 0 with 3 components and in 15 (93.8 %) children vs 1 (6.3 %) with 4 - 5 components ($\chi 2 = 6.06$; $p > 0.05$).

Clustering revealed the following CIMT values: CIMT > 75th was found in 90 % of cases within the WC - TG - HDLc - HBP cluster, and in 100 % of cases: WC - TG - HDLc, WC - HDLc - HBP and WC - TG - HBP, being not statistically significant ($\chi 2 = 7.23$; $p > 0.05$).

Statistical correlations of the CIMT. The relationship between CIMT and the anthropometric, hemodynamic, complete blood count (CBC), lipid and carbohydrate metabolism, echocardiographic parameters of epicardial fat and cardiac remodeling in children with metabolic syndrome was studied. Therefore, there existed no/or weak correlation coefficient with the anthropometric, haemodynamic, carbohydrate metabolism and echocardiographic parameters such as epicardial fat and cardiac remodeling, though a moderate positive correlation with one of the lipid metabolism constants was found, namely HDLc ($r = + 0.4^*$; $p > 0.05$), LDLc ($r = + 0.3^*$; $p > 0.05$), SBP ($r=+0,3^{**}$; $p < 0,001$), DBP ($r=+0,2^*$; $p < 0,05$), AI ($r=+0,3^{**}$; $p < 0,001$), hip - to - waist ratio ($r=+0,4^{**}$; $p < 0,001$), WC ($r=+0,2^*$; $p < 0,05$), BSA ($r=+0,2^*$; $p < 0,05$), BMI ($r=+0,2^*$; $p < 0,05$), as well as with CBC parameters, such as hemoglobin ($r = + 0,4^*$; $p > 0.05$), RBC ($r = + 0.3^*$; $p > 0.05$), thus proving their potential role in the installation, progression and acceleration of vascular remodeling in children with MS (there were found no similar results in specialized literature; the researchers described this correlation only in patients undergoing kidney transplantation [3]).

2.3. Study of geometry parameters and left ventricular function

The results of the analysis of some echocardiographic parameters. Echocardiographic assessment of left atriul (LA), right atrium (RA), left ventricle (LV), right ventricle (RV) both groups revealed no true statistical difference for LA parametres (MS group - 32.14 ± 0.52 mm vs. non - MS group - 30.18 ± 0.53 mm; $p > 0.05$), RA (RA_1 :MS group - 32.78 ± 0.55 mm vs non - MS group - 31.38 ± 0.72 mm; $p > 0.05$, RA_2: MS group - 32.24 ± 0.76 mm vs non - MS group - 31.1 ± 0.60 mm; $p > 0.05$), RV (MS group - 17.48 ± 0.47 mm vs. non - MS group - 17.33 ± 0.36 mm; $p > 0.05$), LVESD (MS - 29.23 ± 0.6 mm vs non - MS group - 17.33 ± 0.36 mm; $p > 0.05$), however a true statistical difference of the LVEDD values was recorded (MS - 47.13 ± 0.63 mm vs. non - MS group - 45.67 ± 0.55 mm; $p < 0.01$). Left ventricular systolic function did not show any alterations in the studied groups (LVEF: MS group - 67.72 ± 1.1 % vs. non - MS group - 68.46 ± 0.57 %; $p > 0.05$, LVSF: group MS - 39.77 ± 0.91 % vs non - MS group - 38.37 ± 0.44 % ($p > 0.05$), and LVDF has not been studied, being considered a research limitation. The data are presented in Table 1.

The results of the study of echocardiographic parameters for left ventricular myocardial remodeling. The analysis revealed the following major parameteres: the interventricular septum (9.55 ± 0.18 mm vs. 8.88 ± 0.14 mm), the left ventricular posterior wall thickness (9.55 ± 0.18 mm vs. 8.64 ± 0.14 mm), the left ventricular end-diastolic diameter (47.13 ± 0.63 mm vs. 45.67 ± 0.55 mm), the left ventricular relative wall thickness (0.40 ± 0.006 mm vs. 0.38 ± 0.005 mm), showing a statistically significant difference between the two groups $p < 0.01$; see Table 1).

The distribution of the Z - score for the echocardiographic parameters of the left - side heart from the research vs. control group, was as follows : LA = 0.29 ± 0.12 vs. 0.18 ± 0.9, IVS = 1.05 ± 0.07 vs. 0.72 ± 0.2, LVPWd = 1.09 ± 0.09 vs. 0.81 ± 0.1, LVEDD = - 0.33 ± 0.01 vs. - 0.32 ± 0.12, LVESD = - 0.55 ± 0.10 vs. - 0.54 ± 0.13, showing no statistically significant difference between the research groups ($p > 0.05$).

Table 1. **Echocardiographic parameters of cardiac geometry and function in children**

Variables	Total (n=145)	MS - (n=92)	MS + (n=53)	P
LA (mm)	30.89±0.39	30.18±0.53	32.14±0.52	SI
LA (Z score)	0.16±0.8	0.18±0.9	0.29±0.12	SI
RA_1 (mm)	31.92±0.49	31.38±0.72	32.78±0.55	SI
RA_2 (mm)	31.53±0.47	31.1±0.60	32.24±0.76	SI
RV (mm)	17.38±0.29	17.33±0.36	17.48±0.47	SI
IVS (mm)	9.11±0.11	8.88±0.14	9.55±0.18	**<0.01**
IVS (Z - score)	0.82±0.68	0.72±0.2	1.05±0.07	SI
LVPWd (mm)	8.98±0.12	8.64±0.14	9.55±0.18	**<0.01**
LVPWd (Z score)	0.79±0.69	0.81±0.1	1.09±0.09	SI
LVEDD (mm)	46.21±0.42	45.67±0.55	47.13±0.63	**<0.01**
LVEDD (Z score)	- 0.33±0.14	- 0.32±0.12	- 0.33±0.01	SI
LVM_1 (g)	145.72±4.14	137.05±5.22	159.80±6.38	SI
LVM_2 (p)	82.33±1.67	80.63±2.30	85.09±2.26	SI
$LVMI_1$ (g/m^2)	37.83±0.76	37.02±0.92	39.14±1.29	SI
$LVMI_2$ (p)	80.58±1.71	78.72±2.32	83.59±2.39	SI
LVMI (Z score)	0.24±0.1	0.15±0.13	0.4±0.15	SI
LV RPWT (mm)	0.39±0.004	0.38±0.005	0.40±0.006	**<0.01**
LVESD (mm)	29.73±0.59	30.03±0.86	29.23±0.6	SI
LVESD (Z score)	- 0.54±0.08	- 0.54±0.13	- 0.55±0.10	SI
LVEDV (ml)	100.06±2.02	97.44±2.55	104.49±3.25	SI
LVESV (ml)	31.79±0.89	30.86±1.0	33.37±1.7	SI
LVEF (%)	68.18±0.54	68.46±0.57	67.72±1.1	SI
LVFS (%)	38.89±0.44	38.37±0.44	39.77±0.91	SI

Note: *Values are presented as mean ± standard deviation for numerical data; SI – statistically insignificant (p>0.05); value of p<0.001; p<0.01 – considered as statistically significant; LA – left atrium; RA – right atrium; IVS – interventricular septum; LVPW – left ventricular posterior wall thickness; LVEDD – left ventricular end - diastolic diameter; LV Mass – left ventricular mass; LV RPWT – left ventricular relative posterior wall thickness; LVESD – left ventricular end - systolic diameter; LVEDV – left ventricular end - diastolic volume; LVESV – left ventricular end - systolic volume; LVMI – LV myocardial mass index; LVEF – left ventricular ejection fraction; LVFS – LV fractional shortening*

The results of the evaluation of some electrocardiographic parameters. A sinus rhythm was recorded in 100 % of cases (ventricular pacing pulse: MS - 75.2 ± 1.60 bpm, non - MS - 76.96 ± 1.38 bpm; p > 0.05). The rhythm disorders included the supraventricular arrhythmias: sinus bradycardia - in 24 subjects (17.4 %) of which 13 cases (26.0 %) were from the MS group and 11

(12.5 %) from non - MS group ($\chi 2 = 4.05$; $p > 0.05$), sinus tachycardia in 5 (3.6 %) children, of which 3 (3.4 %) with non - MS and 2 (4 %) with MS ($\chi 2 = 0, 03$; $p > 0.05$), extrasystoles were found in 1 (1.1 %) participant with non - MS ($\chi 2 = 0.57$; $p > 0.05$). Ventricular arrhythmias were not recorded. Conduction disorders: right bundle branch block was found in 15 participants (10.9 %), of which 12 (13.8 %) were from the control group and 3 (6.0 %) from the main group ($\chi 2 = 1.98$; $p > 0.05$). Left ventricular repolarization processes were registered in 9 (6.5 %) children, of which 6 (12.0 %) with MS and 3 (3.4 %) with non - MS ($\chi 2 = 3.86$; $p > 0.05$).

The results of the study of left ventricular hypertrophy (electrocardiographic vs. echocardiographic)

LVH electrocardiographic. The most common and simple criteria and recognized limits for defining LVH on ECG are as following: Sokolow - Lyon index > 35 mm, or R in aVL ≥ 11 mm; Cornell voltage product > 2440 mm.ms, or Cornell voltage > 28 mm in males and r > 20 mm in females. The study used the first two variants, namely the presence of LVH on ECG was low, thus attesting the low prevalence reported in specialized literature (3 cases, $\chi 2 = 1.23$; $p > 0.05$); similar data were recorded for RVH, only 2 cases ($\chi 2 = 1.15$; $p > 0.05$), LAH - 1 case ($\chi 2 = 0.57$; $p > 0.05$), RAH was not recorded (the ECG alterations show a low sensitivity that is below 35% for milder types of LVH and up to 50% for severe LVH, whereas sensitivity varies depending on the body weight).

LVH echocardiographic. The recommended values for defining echocardiographic LVH (AAP, 2017) are the following :(1) LV mass/height^{2,7} (formula) > 51 (g/m^{2,7}) (a cut - off point for for both genders and age > 8 years), or (2) LV mass/body surface > 115 (g/m^2) for males and > 95g for females. The LVH was evaluated according to the first LV Mass variant > 51 (g/m^2) (for both genders, age > 8 years), since the body surface index the can be applied in normal - weight subjects.

Depending on the **presence/absence of the metabolic syndrome**, LVH was predominantly registered in MS children (63.6 % (n = 7)), compared with non - MS subjects (36.4 % (n = 4)), showing no true statistical difference ($\chi 2 = 2.16$; $p > 0.05$; see Figure 8).

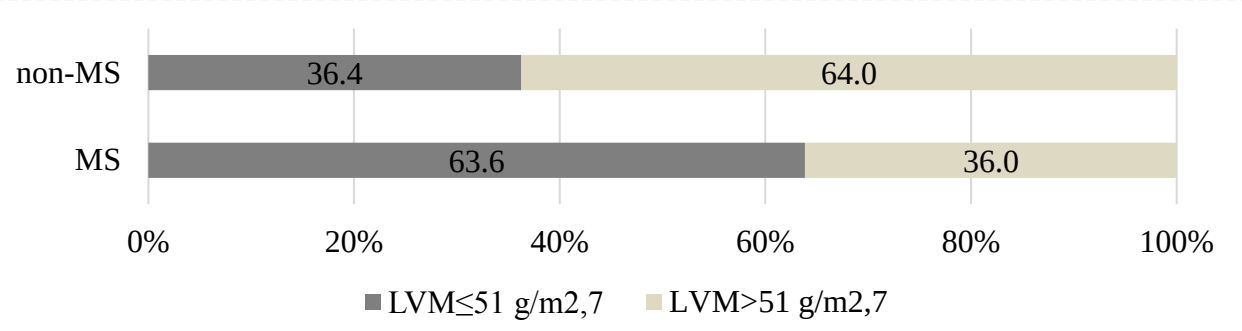

Figure 8. **Echocardiographyic study of left ventricular hypertrophy based on the presence/absence of the metabolic syndrome (p > 0.05)**

Note: *LV Mass – left ventricular mass*

Depending on **the number of MS criteria**, the children with 3 criteria exhibited a higher prevalence - 45.5 % (n = 5), children with 2 criteria - 36.4 % (n = 4) and 4 - 5 criteria - 18.2 % (n = 2), showing no statistically true difference ($\chi 2 = 5.12$; $p > 0.05$; see Figure 9).

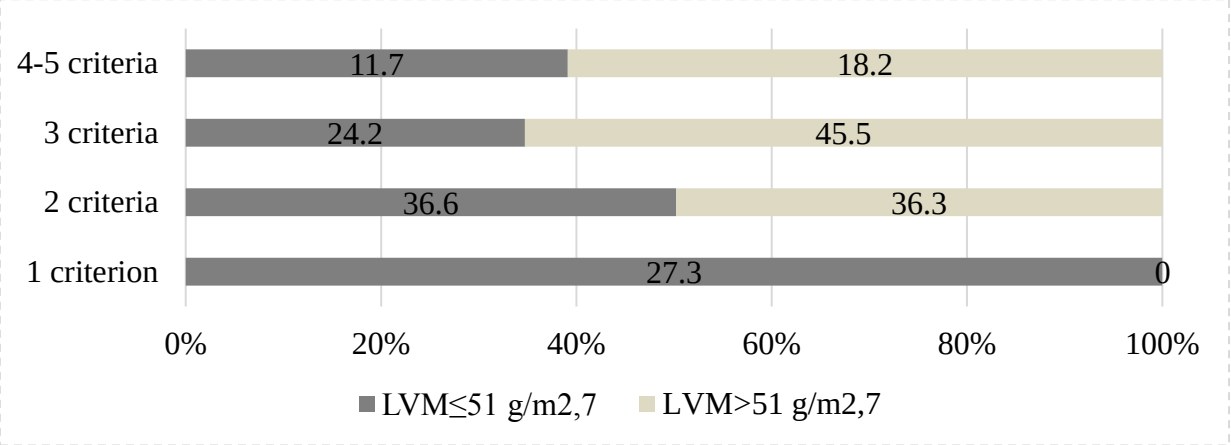

Figure 9. **The echocardiographic study of left ventricular hypertrophy according to the number of MS criteria (p > 0.05)**

Note: *LV Mass – left ventricular mass*

The results of the evaluation of the types of remodeling of the left ventricular myocardium. The distribution of left ventricular remodeling (LVR) types was carried out according to the recommendations of the American and European Society of Echocardiography, based on the measurements of left ventricular mass index (LVMI) and the left ventricular relative wall thickness (LV RWT) index. The **types of pathological remodeling** were distributed as follows: 62.1 % (n = 90) participants showed a normal geometry pattern, 27.6% (n = 40) - concentric hypertrophy (cLVH), 5.5 % (n = 8) - concentric remodeling (cLVR) and 4.8% (n = 7) - left ventricular eccentric hypertrophy (eLVH).

In terms of **presence/absence of MS**, 54.7 % (n = 29) participants from the research group showed a normal geometry pattern, 32.1 % (n = 17) - concentric hypertrophy, 5.7 % (n = 3)) - concentric remodeling, and 7.5 % (n = 4) – left ventricular eccentric hypertrophy, whereas 66.3 % (n = 61) participants from the control group presented normal geometric appearance, 25% (n = 23) - concentric hypertrophy, 5.4 % (n = 5) - concentric remodeling, and 3.3 % (n = 3) - LV eccentric hypertrophy ($\chi 2 = 0.52$; $p > 0.05$; see Figure 10).

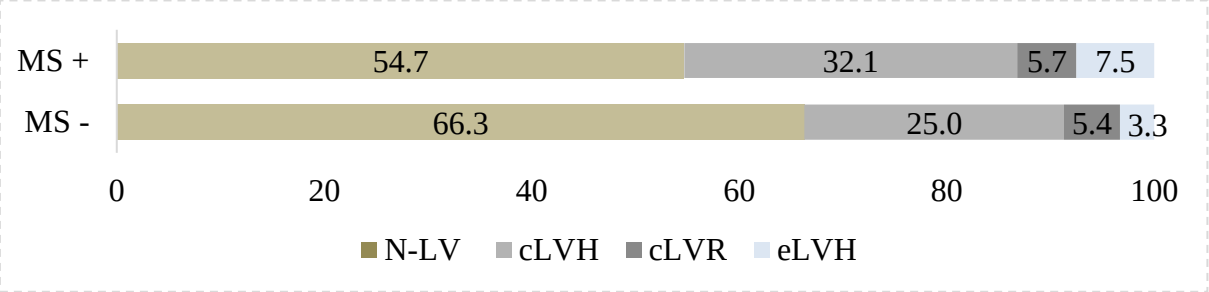

Figure 10. **Left ventricular remodeling patterns depending on the presence/absence of metabolic syndrome (p > 0.05)**

Note: *N - LV – Normal left ventricular appearance, cLVR – LV concentric remodeling; cLVH – LV concentric hypertrophy; eLVH – LV eccentric hypertrophy*

The gender - related distribution revealed the following results in boys: 63.4 % (n = 52) - normal geometric appearance, 24.4 % (n = 20) - concentric hypertrophy, 4.9 % (n = 4) - concentric remodeling, and 7.3 % (n = 6) - LV eccentric hypertrophy, and in girls: 60.3 % (n = 38) - normal geometric appearance, 31.7 % (n = 20) - concentric hypertrophy, 6,3 % (n = 4) - concentric remodeling, and 1.6 % (n = 1) showed LV eccentric hypertrophy ($\chi 2 = 0.34$; $p > 0.05$).

Depending on the **number of MS criteria**, a normal LV geometry appearance was found in 25.8 % (n = 24) of MS children with 1 positive criterion, 38.7 % (n = 37) - 2 criteria, 24.2 % (n = 21) - 3 criteria and in 11.3 % (n = 8) cases with 4 - 5 criteria. LV concentric remodeling was recorded in 10.0 % (n = 1) subjects with 4 - 5 MS criteria, and in 30.0 % (n = 2) of cases with 1, 2 and 3 criteria. LV concentric hypertrophy was recorded in 15.2 % (n = 8) of MS children with 1 positive criterion, 27.3 % (n = 15) - 2 criteria, 32.6 % (n = 11) - 3 criteria and 24.9 % (n = 6) - 4 - 5 criteria. LV eccentric hypertrophy was found in 11.7 % (n = 1) of MS children with 1 positive criterion, 19.1 % (n = 2) - 2 criteria, 27.9 % (n = 1) - 3 criteria and 41.3 % (n = 3) - 4 - 5 criteria ($\chi 2 = 3.58$; $p > 0.05$; see Figure 11).

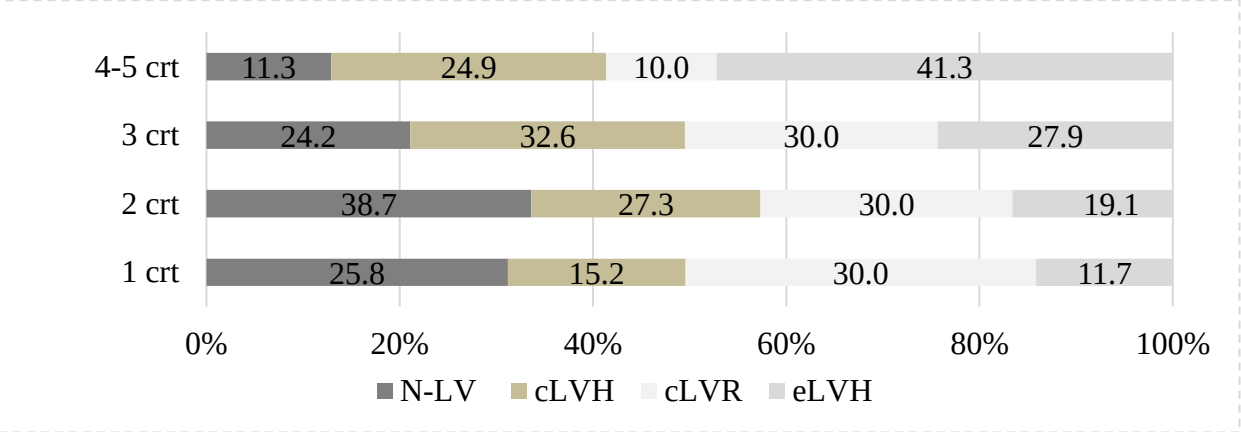

Figure 11. **Left ventricular remodeling patterns depending on number of MS criteria, and according to IFD Consensus for children (p>0.05)**

Note: *N - LV – Normal left ventricular appearance, cLVR – LV concentric remodeling; cLVH – LV concentric hypertrophy; eLVH – LV eccentric hypertrophy*

According to **MS clustering,** LV concentric remodeling was recorded in 15.0 % (n = 1) of subjects with WC - TG - HBP, WC - HDLc - HBP and WC - HDLc - TG - HBP clustering patterns, LV eccentric hypertrophy was recorded in 14.7 % (n = 1) of participants with WC - HDLc - HBP, WC - HDLc - TG - HBP - Glu and 27.9 % (n = 2) of subjects with WC - HDLc - TG - HBP cluster patterns, LV concentric hypertrophy was found in 18.7 % (n = 6) of participants with WC - HDLc - HBP clusters, 6.1 % (n = 4) of cases with WC - TG- HBP and WC - TG - HDLc - HBP, and in 1.6 % (n = 1) - WC - TG - HDLc, WC - TG - Glu - HBP, WC - TG - HDLc - Glu. The left ventricle with normal geometric appearance had a different overall distribution, being registered in all clinical patterns ($\chi 2 = 11.96$; $p > 0.05$).

The assessment of 6 children with **present/absent metabolic syndrome and congenital heart malformations** (4 participants with MS, Ao stenosis and Ao coarctation, and 2 children with non - MS, one child with Ao stenosis and one child with Ebstein's anomaly) detected 2 MS subjects with congenital aortopathy (CoA and AoSt, showing the the highest pressure gradient on the aortic valve) and LV concentric remodeling (in males, with three criteria, WC - TG - HBP, WC - HDLc - HBP cluster patterns); 4 – LV with normal appearance, and unchanged systolic function (diastolic function was not assessed, $\chi 2 = 3.73$; $p > 0.05$). Early MS detection in children with congenital heart defects should not be underestimated, since the higher is the number of positive components, the higher is the severity score, whereas after intervention, the parameter regression, which affects the cardiac geometry is reduced in presence of MS, which definitely might have an impact in adulthood, leading to an increased morbidity and premature mortality rates [9].

The risk of installing left ventricular myocardial remodeling. During the research, it was also performed the estimation of the risk of installing the remodeling of the left ventricular myocardium in children with MS, initially being formed "Table 2x2", afterwards calculate the necessary indicators with the interpretation of the obtained results. Respectively, RR (relative risk) = 1.7 was obtained, being in the range 1.7 - 2.5, considered moderate risk, respectively the metabolic syndrome is a risk factor for the development of remodeling of the left ventricular myocardium, taking into account that HI does not include value 1 (CI is between 1.3 and 4.2) it can be concluded that there is a positive association between metabolic syndrome and remodeling of the left ventricular myocardium.

Limitations of the study. The current study included *a relatively small number of patients*, particularly of subjects aged between 16 - 18 years, although the metabolic syndrome is considered to have a high incidence rate. The main study limitation regarding the patients'enrollment was the fact that we aimed at identifying *pediatric subjects with MS from within the Cardiology Clinic.* Another reason for a relatively small number of participants was the careful selection of patients as to obtain an optimal ultrasound window, for an accurate analysis of the echocardiographic data: heart function and geometry, epicardial adipose tissue and intima - media complex. The *short - term MS installation* is another study limitation. Another limitation was *the lack of diastolic function assessment* due to insufficient relevant studies on this type of impairment among MS patients.

GENERAL CONCLUSIONS

1. The current PhD study assessed the metabolic syndrome criteria, which were proposed by the International Diabetes Federation and found that 24.9 % of the subjects presented 3 criteria, 11 % - 4 criteria and 0.7 % - 5 positive criteria (25.5 % - 1 criterion, 37.9 % - 2 criteria), whereas based in prevalence, the waist circumference ≥ 90 percentile was recorded in 100 % of cases, high density cholesterol value <1.03 mmol/l – in 47.6 %, triglyceride value ≥ 1, 7 mmol/l – in 25.5 %, systolic blood pressure value ≥ 130 mmHg /diastolic blood pressure ≥ 85 mmol/l – in 42.8 %, and glucose values ≥ 5.6 mmol/l – in 7.6 %. The factorial analysis established that abdominal obesity and blood pressure express 59 % (respectively take over 50 % of the information) and explain 25 % of the total variance.
2. The most common clustering patterns were the WC - HDLc - HBP – in 10.3 % of cases, WC - TG - HDLc - in 8.3 %, WC - TG- HDLc - HBP – in 7.6 %, WC - TG - HBP – in 5.5 %, WC - HDLc - Glu - HBP and WC - TG - HDLc - Glu clusters were found in 1.4 % of cases each, WC - Glu - HBP, WC - TG - Glu - HBP and WC - TG - HDLc - Glu - HBP in 0.7 % of cases, the incidence being higher in males versus females ($p < 0,01$).
3. The anthropometric parameters (weight, waist circumference, hip circumference), which were correlated with hemodynamic parameters (systolic and diastolic blood pressure, $r = 0.5^{**}$, $p < 0.001$), ultrasound parameters of cardiac remodeling (interventricular septum, LV posterior wall, LV mass, LV end-diastolic volume, LV end-diastolic diameter, $r = 0.5^{**}$, $p < 0.001$) and of the epicardial adipose tissue ($r = 0.4^{**}$, $p > 0.05$), revealed that the increase of the anthropometric parameters values is associated with the installation of cardiovascular remodeling and the increase of the adipose tissue thickness.
4. The ultrasound imaging of epicardial adipose tissue (5,39 ± 0,22 mm) and carotid intima - media thickness (0,65 ± 0,03 mm) exceeded the admitted cut - off point values in children with metabolic syndrome (4.0 mm and 0.4 to 0.6 mm, respectively), showing a tendency to increase depending on the number of risk factors, as wel as higher values were present in the clinical forms, which mainly contain obesity, low - density lipoprotein cholesterol and high blood pressure ($p > 0.05$).
5. The positive linear correlation of the epicardial adipose tissue thickness with the anthropometric parameters ((weight ($r = 0.4^{**}$, $p < 0.001$), body mass index($r = 0.3^{*}$, $p < 0.05$)), waist circumference and waist - to - hip index ($r = 0.5^{*}$, $p < 0.05$)) indicates that it is a good indicator of visceral fat, whereas the correlation with cardiac remodeling values (interventricular septum, left posterior wall and left ventricular mass ($r = 0.5^{*}$, $p < 0.05$)) suggested that an increased epicardial adipose tissue thickness is associated with a consensual and proportional progression of left ventricular structural changes.
6. The CIMT is correlated with the anthropometric (waist circumference, BSA, body mass index ($r = 0.2^{*}$, $p < 0.05$), abdominal index, waist-to-hip ratio ($r = 0.4^{**}$, $p < 0.001$)) and haemodynamic parameters (systolic blood pressure ($r = 0.4^{**}$, $p < 0.001$), diastolic blood pressure $r = 0.2^{*}$, ($p < 0.05$), with the lipid metabolism indices (high and low density cholesterol ($r = 0,2^{*}$, $p < 0.05$)) suggesting a potential role in the installation, progression and acceleration of vascular remodeling.
7. The analysis of cardiac remodeling types showed a higher incidence in pediatric subjects with normal geometric appearance - 62.1 %. The three pathological remodeling subtypes (eccentric hypertrophy, concentric hypertrophy and concentric remodeling) showed a higher rate for

concentric hypertrophy - 27.6 %, followed by concentric remodeling type - 5.5 % and eccentric hypertrophy - 4.8 %, which was predominantly found in males, for three positive criteria and within the following clusters WC - HDLc - HBP, WC - TG - HDLc, WC - TG - HDLc - Glu, WC - TG - HDLc - HBP, showing no statistically significant difference ($p > 0.05$).

8. In children aged 10-18 years, metabolic syndrome is a risk factor and has a positive association with the development of left ventricular myocardial remodeling (relative risk = 1.7, confidence interval = 1.3 - 4.2).

Practical recommendations

1. In children aged 10 to 18 years, with abdominal obesity, it is recommended to perform a screening of the metabolic syndrome, in order to detect children at risk of developing complications.
2. It is recommended to perform echocardiography as a method of assessing the presence of structural remodeling type of the left ventricular myocardium, it will promote the detection of children with metabolic syndrome with increased risk for cardiovascular complications.
3. Evaluation of the echocardiographic profile of the epicardial fat type, by measuring the thickness of the epicardial adipose tissue, as a predictor of associated cardiovascular risk.
4. In all children with confirmed metabolic syndrome, it is recommended to perform ultrasound of the common carotid artery with the measurement of the the carotid intima-media thickness, considered a surrogate imaging marker for screening for vascular changes.

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at which the PhD thesis - related research findings were presented on

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At the Department of Pediatrics, within PI "Nicolae Testemitanu" SUMPh,
Of the PhD candidate, Esanu Veronica

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- **Active participations at scientific forums:**

✓ **Internaţional events**

29. **Eșanu Veronica,** Palii I., Eșanu Valeriu. The severity score of metabolic syndrome and cardiac remodeling patterns in children with metabolic syndrome. *26th National Congress of Endocrinology*. Sibiu, România, 27 - 30 June, 2018.
30. **Eșanu V.** Anthropometric, metabolic, echocardiographic parameters in children with metabolic syndrome versus pre - metabolic syndrome. *Congress of Pediatric Cardiology* Iasi, România, 17 - 19 May, 2018.
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✓ **National events**

33. **Eşanu Veronica,** Eșanu Valeriu. Palii I. Metabolic syndrome in pediatrics: disease vs. syndrome vs. clinical entity. *Conference dedicated to the Days of the State University of Medicine and Pharmacy Nicolae Testemitanu.* Chisinau, 2016 (2nd degree diploma).
34. **Eșanu V.** Metabolic syndrome in pediatric practice: diagnosis and therapeutic management. *Pediatric National Conference with International Participation. "Children's health problems and solutions",* Chisinau, 2016.

- **Participations in poster sessions at scientific forums:**

✓ **International**

35. Eșanu Valeriu, **Eșanu Veronica,** Palii I., Vudu L. Different groups of risk factors in children with metabolic syndrome. *45th National Congress of the Romanian Society for Diabetes, Nutrition and Metabolic Diseases - with international participation*. Sibiu, România, 22 - 25 May 2019.
36. **Eșanu Veronica,** Palii I., Eșanu Valeriu, Gavriliuc N. Metabolic syndrome and congenital heart malformations in children: contribution to global cardiometabolic risk. *The 21st IAAH*

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37. **Esanu Veronica**, Esanu Valeriu, Gavriliuc N., Pîrțu., et.al. Association of metabolic syndrome and hypertension with left ventricular geometry in children. *MedEspera 2018. The 7th International Medical Congress for Students and Young Doctors*. Chisinau, 3 - 5 May 2018.
38. **Eșanu V.,** Palii I. Severity score of metabolic syndrome in children: intervals and associations with cardiovascular risk factors. *"Nicolae Testemitanu" SUMPh National Conference.* Chisinau, 15 - 19 October, 2018.
39. **Eșanu V**eronica, Palii I., Eșanu Valeriu, Gavriliuc N., et.al. Behaviors related to perinatal, sociodemographic and parental risk factors associated with metabolic syndrome in children aged 10 - 18 years. *Congress of Pediatric Cardiology.* Iasi, România, 17 - 19 May, 2018 (I prize).
40. **Eșanu V**. The Association of Metabolic Syndrome with Cardiac Remodeling in the Hypertensive Pediatric Population. 1st International Congress of Hypertension in Children and Adolescents (ICHCA).Valencia, Spain, February 9 - 11, 2018.
41. **Eșanu Veronica,** Eșanu Valeriu, Gavriliuc N., Pîrțu L., et.al. Severity score of metabolic syndrome in children with healthy metabolic versus with metabolic syndrome versus in metabolically healthy children. *57th National Congress of Cardiology.* Sinaia, România, 19 - 22 September, 2018
42. **Eșanu V**., Palii I. Metabolic syndrome and congenital aortopathies in children: contribution to global cardiometabolic risk. *7th National Congress of Pediatrics with international participation, "Pediatric emergencies and management of medical records"*. Chisinau, 14 - 15 September 2018.
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✓ **National**

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