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PREDICTORS OF ECHOCARDIOGRAPHIC CHANGES CONSIDERING CARDIOMETABOLIC RISK IN YOUNG ADULTS. DIFFERENTIATED APPROACH TO MANAGEMENT

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Abstract. Introduction. Cardiometabolic diseases represent a significant burden on global health. To ensure prevention of chronic heart failure, coronary artery disease and atrial fibrillation, it is crucial to understand changes in echocardiographic parameters with increase in cardiometabolic and residual risk in young adults. **Aim**. This study aims to identify predictors of cardiac structural and functional changes in young adults with cardiometabolic risk factors and propose an algorithm for differentiated management considering the cardiometabolic disease staging. **Materials and Methods**. This case-control study included 191 patients with a median age 35 [30.0-39.0] years. Patients were grouped according to the cardiometabolic disease staging. We performed in-depth clinical and laboratory examination, and echocardiography. Statistical analyses were performed in IBM SPSS Statistics 23. **Results and Discussion.** With progression of cardiometabolic disease stage, there is a rise in the cardiometabolic and residual risk and changes in cardiac structure and function (p_{K-W} = 0.001–0.028). Visceral fat level strongly correlated with end-systolic volume (r_s = 0.568; p = 0.000), end-diastolic volume (r_s = 0.563; p = 0.000), left atrial volume (r_s = 0.471; p = 0.000), stroke volume (r_s = 0.464; p = 0.000), and ejection fraction (r_s = -0.351; p = 0.000). We observed a weak inverse relationship between the N-terminal pro-brain natriuretic peptide and waist circumference (r_s = -0.257; p = 0.001), waist-to-hip ratio (r_s = -0.332; p = 0.000), and visceral fat level (r_s = -0.205; p = 0.011). Various statistical analyses showed independent role of visceral fat level in increasing the cardiac pre- and afterload. This allowed us to identify a subgroup CMDS 3-overly high, within CMDS 3. We proposed an algorithm suggesting a differentiated approach for the management of young adults with cardiometabolic risk factors that helps in stratifying individuals possessing higher risk of developing chronic heart failure, coronary artery disease, and atrial fibrillation. **Conclusions**. An increase in the burden of cardiometabolic and residual risk factors is associated with an increase in cardiac pre- and afterload. Excess visceral fat level most significantly contributed to cardiac structural and functional changes. Per our proposed algorithm, individuals with CMDS 3-overly high group are advised to consult a cardiologist and undergo echocardiography to detect early cardiac changes.
Keywords: cardiometabolic risk, cardiometabolic disease staging, echocardiographic changes, heart failure, visceral adiposity, algorithm.

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ПРЕДИКТОРЫ ЭХОКАРДИОГРАФИЧЕСКИХ ИЗМЕНЕНИЙ С УЧЕТОМ КАРДИОМЕТАБОЛИЧЕСКОГО РИСКА В МОЛОДОМ ВОЗРАСТЕ. ДИФФЕРЕНЦИРОВАННЫЙ ПОДХОД К ВЕДЕНИЮ

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Реферат. Введение. Кардиометаболические заболевания представляют собой значительное бремя для глобального здравоохранения. С позиций профилактики хронической сердечной недостаточности, ишемической болезни сердца и фибрилляции предсердий важно понимание изменений эхокардиографических показателей с учетом нарастания кардиометаболического и резидуального риска у лиц молодого возраста. **Целью** данного исследования было выявление предикторов структурных и функциональных изменений сердца у лиц молодого возраста с факторами кардиометаболического риска и предложение алгоритма дифференцированного ведения с учетом стадирования по cardiometabolic disease staging (CMDS). **Материал и методы**. В исследование по типу «случай-контроль» был включен 191 пациент в возрасте 35 [30,0–39,0] лет. Обследованные лица были классифицированы в соответствии с системой стадирования CMDS. Проведены детальное клинико-лабораторное обследование и эхокардиография. Статистические данные обработаны в программе IBM SPSS Statistics 23. **Результаты и их обсуждение.** При прогрессировании CMDS наблюдается нарастание факторов кардиометаболического и остаточного риска, а также изменений структуры и функции сердца (p_{K-W} = 0.001–0.028). Выявлена сильная корреляционная связь уровня висцерального жира с конечно-систолическим объемом (r_s =

0,568; p = 0,000), конечно-диастолическим объемом (r_s = 0,563; p = 0,000), объемом левого предсердия (r_s = 0,471; p = 0,000), ударным объемом (r_s = 0,464; p = 0,000), фракцией выброса (r_s = -0,351; p = 0,000). Также выявлена обратная корреляция слабой силы натрийуретического пептида с окружностью талии (r_s = -0,257; p = 0,001), отношением окружности талии к окружности бедер (r_s = -0,332; p = 0,000) и уровнем висцерального жира (r_s = -0,205; p = 0,011). Разносторонняя статистическая обработка показала независимый вклад уровня висцерального жира в увеличение пред- и пост-нагрузки на сердце. На основании этого предложено выделение в группе пациентов молодого возраста с CMDS 3 подгруппы CMDS 3-overly high. Нами разработан алгоритм, предлагающий дифференцированный подход к ведению лиц молодого возраста с факторами кардиометаболического риска, который помогает стратифицировать пациентов с более высоким риском развития сердечной недостаточности, ишемической болезни сердца и фибрилляции предсердий. **Выводы**. Увеличение бремени факторов кардиометаболического и резидуального риска ассоциировано с нарастанием пред- и постнагрузки на сердце. Наиболее значимый вклад в изменение структурно-функциональных параметров вносит увеличение уровня висцерального жира. Согласно предложенному нами алгоритму лицам из группы CMDS 3-overly high рекомендована консультация кардиолога и прохождение эхокардиографии с целью выявлении ранних изменений сердца.
Ключевые слова: кардиометаболический риск, Cardiometabolic disease staging, эхокардиографические изменения, сердечная недостаточность, висцеральный жир, алгоритм.
Для ссылки. Парве С.Д., Синеглазова А.В. Предикторы эхокардиографических изменений с учетом кардиометаболического риска в молодом возрасте. Дифференцированный подход к ведению // Вестник современной клинической медицины. – 2024. – Т. 17, вып. 4. – С.73–81. **DOI:** 10.20969/VSKM.2024.17(4).73-81.

Introduction. Cardiometabolic diseases represent a significant burden on global health [1]. Despite recent advances in diagnosis and implementation of high-tech interventions, cardiovascular diseases continue to be the leading cause of morbidity and mortality in the Russian Federation and the world [1–3]. The presence of one or more cardiometabolic risk factors (CMRF), including elevated blood pressure, obesity, dysglycemia, dyslipidemia, as well as associated neurohumoral, dysmetabolic, and pro-inflammatory changes, contribute to this phenomenon [4].

According to the cardiometabolic-based chronic disease model [5], coronary artery disease (CAD), chronic heart failure (CHF), and atrial fibrillation (AF) are the primary endpoints of cardiometabolic abnormalities. Each metabolic driver and residual risk element influence genesis and progression of heart failure phenotypes. Albeit CHF is an end stage, subclinical left ventricular structural and functional deterioration starts much earlier [4]. Evidence suggests these individuals are prone to have heart failure with preserved ejection fraction [6]. While researchers are now widely discussing the cardiometabolic phenotype of heart failure [6, 7], there are limited data on changes in insulin resistance, leptinemia, visceral adiposity index and level, concentrations of C-reactive protein and natriuretic peptide, as well as cardiac changes at the early stages of the cardiometabolic cascade [8, 9]. Thus, from the perspective of assessing cardiometabolic risk, it is imperative to modify approaches on risk stratification and learn about their progression [5, 10–12].

To date, there is no universally accepted system for assessing cardiometabolic risk; barring a few position papers, consensus statements and recommendations [12–15]. In our view, utility of cardiometabolic disease staging (CMDS) in primary care cannot be overstated. This system categorizes patients into different stages of disease risk allowing for tailored interventions and improved management outcomes [16, 17]. A recent study on the CMDS model suggested that in comparison with other risk assessment tools, CMDS had a similar or superior ability to predict the 10-year risk of major adverse cardiovascular events (MACE) [18]. Thus, it is not surprising, that it has been widely recommended [14, 19, 20].

The current literature indicates a lack of comprehensive data on the effectiveness of various interventions across different populations and the need for more robust evidence to guide clinical decision-making. Thus, considering the increase in cardiometabolic risk there is a need to develop a differentiated approach to assess cardiometabolic and hemodynamic parameters to identify groups of people most susceptible to CHF.

In view of above, understanding the profile of CMRF and associated changes in cardiac structure and function among Russian young adults are critical for promoting health. Moreover, proposing an algorithm for early screening may result in preventing future disease and significant reductions in the incidence of CVDs and other related conditions [15].

Aim. The goal of this study was to identify predictors of cardiac structural and functional changes in young adults with cardiometabolic risk factors and propose an algorithm for early screening and prevention strategies.

Materials and Methods. This study was conducted at the Department of Primary Care and General Practice of the Kazan State Medical University centered at the Consultative Diagnostic Center of Aviastroytelniy District from 2019 to 2022. The study was approved by the Local Ethics Committee of Kazan State Medical University.

This was a case-control study in which participants were selected based on their body mass index (BMI) (1/3 normal weight, 1/3 overweight, and 1/3 obese). A total of 191 individuals were enrolled. We included a total of 97 females (50.8%) and 94 males (49.2%). The median patient age was 35 [30.0-39.0] years. Inclusion criteria were individuals aged 25-44 years who voluntarily provided informed consent to participate in the study. Exclusion criteria were: (1) subjects who refused to participate; (2) patients with psychiatric illnesses that interfered with the interview process; (3) individuals with cardiometabolic diseases, such as type 2 diabetes mellitus, coronary artery disease, congestive heart failure, atrial fibrillation, or chronic kidney disease; (4) those with antiphospholipid

syndrome or autoimmune inflammatory diseases; (5) individuals diagnosed with malignancies; (6) subjects with decompensation of concomitant diseases or conditions, including liver disease, kidney disease, and others that are secondary causes of obesity; (7) those with acute infectious diseases, endocrine system diseases, or other conditions that could affect the study; and (8) pregnant or lactating women, as well as (9) individuals with medical implants, such as pacemakers, silicone implants, or metal prostheses.

We conducted a comprehensive patient interview, which included a detailed medical history and physical examination. The registration card included questions about demographic information, family history, and psychosocial history, as well as questions about current smoking and physical activity. During the physical examination, height, weight, body mass index (BMI), waist circumference, and waist-to-hip ratio were measured. Body composition was assessed using a Tanita BC-601 body composition monitor (Tanita Corporation, Japan). A visceral fat rating between 1 and 12 was considered normal, while 13-59 was considered excess visceral fat [21]. Blood pressure was measured using a validated sphygmomanometer (Omron M2 Basic, Japan). The laboratory workup was performed using fasting venous blood samples in a single certified laboratory. Levels of insulin (Siemens Healthcare Diagnostics assays, England), and leptin (Diagnostics Biochem Canada Inc., Canada) were studied by enzyme immunoassay using an Immulite 1000 analyzer (Siemens, Germany).

The lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), fasting plasma glucose, oral glucose tolerance test (OGTT), glycated hemoglobin, and insulin, were assessed using automated enzymatic methods on a Beckmann Coulter automated analyzer AU480 (Beckman Coulter Inc., Brea, USA) and Beckmann Coulter assays. Serum high-sensitivity CRP (hsCRP) was measured using a high-sensitivity immunoturbidimetric method (CRP [Latex] Beckman Coulter, Japan).

We estimated insulin resistance using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). The visceral adiposity index (VAI) was estimated considering the sex and age [22]. Non-HDL-c value was estimated by subtracting HDL-c from the total cholesterol. Additionally, we also calculated the atherogenicity index. Values of laboratory tests, and calculated indices were interpreted according to respective guidelines.

A team of two cardiologists trained in advanced echocardiography and with adequate experience performed transthoracic doppler echocardiography on a Mindray DC-8 (Mindray Medical International Limited, Shenzhen, China) machine according to the guidelines [23]. We assessed common echocardiography parameters for left and right atrial and ventricular functions, and hemodynamic parameters. These include, but are not limited to, left atrial volume and size, end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), stroke volume (SV), and cardiac output (CO). Du Bois formula was used to calculate the body surface area and indices with respect to it.

Cardiometabolic risk assessment was performed using the CMDS, that considered the following risk factors [16, 17]: (RF1) abdominal obesity either as defined by waist circumference ≥80 cm and/or waist-to-hip ratio >0.85 in females and ≥94 cm and/or a waist-to-hip ratio >0.9 in males [19]; (RF2) raised systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or on antihypertensive therapy; (RF3) low HDL-c defined as HDL-c <1.3 mmol/L in females and <1.0 mmol/L in males or on lipid-lowering therapy; (RF4) fasting hypertriglyceridemia defined as triglycerides ≥1.7 mmol/l or on lipid-lowering medication. (RF5) prediabetes was defined as impaired fasting glucose (IFG - venous glucose 6.1-6.9 mmol/L) or impaired glucose tolerance (IGT - 2-hour venous glucose 7.8-11.0 mmol/L). Stage 0 comprised of metabolically healthy individuals without any risk factors; stage 1 (low risk) involved the presence of one or two risk factors (RF1-RF4). Stage 2 (medium risk) subjects included those with one of the following: ≥3 metabolic risk factors (RF1-RF4), or the presence of prediabetes. Stage 3 (high risk) involved participants with ≥3 metabolic abnormalities (RF1-RF4) + prediabetes. Individuals with stage 4 disease (end-stage disease), namely type 2 diabetes and/or vascular disease such as coronary artery disease, stroke, or peripheral artery disease.

Statistical analyses were performed using IBM SPSS Statistics 23.0 (IBM, USA). Quantitative parameters are presented as median and interquartile range (Me [25-75%]). When comparing independent groups, the Mann-Whitney U test and the Kruskal-Wallis test were used. The use of descriptive statistics was employed to generate frequencies and percentages for categorical variables. To determine statistical differences in categorical variables, we utilized either Pearson's Chi-square test or Fisher's exact test. Spearman's (r_s) correlation was used to study the relationship. Multiple logistic regression method was used. Differences were considered statistically significant at $p < 0.05$ (two-tailed).

Results and Discussion. The distribution of individuals across CMDS was as follows: CMDS 0 – 19.4%, CMDS 1 – 36.1%, CMDS 2 – 30.4, CMDS 3 – 11%, and CMDS 4 – 3.1%. On preliminary analysis, no statistically significant differences were observed in the age of the study subjects across various CMDS, both in the general and sex-based cohort ($p = 0.096$-0.568). Furthermore, the distribution of females and males was normal; therefore, subsequent analysis across various CMDS was conducted in the overall cohort.

Following workup, patients diagnosed with type 2 diabetes mellitus and heart failure (confirmed by echocardiography), were excluded from the study. The final analysis included 181 participants.

The prevalence of residual risk factors across various CMDS is presented in *Table 1*. We found that as the CMDS progressed, there was an increase in both the frequency all studied residual risk factors, which reflects a simultaneous rise in all dysmetabolic processes

and the manifestation of adiposopathy (atherogenic dyslipidemia, insulin resistance, excess visceral fat level, hyperleptinemia, and higher CRP levels) [24].

The cardiac structural and functional parameters in the general cohort and across various CMDS were within reference values *(Table 2)*.

Our results show increase in left atrial volume and dimension, interventricular septal thickness, left ventricular posterior wall thickness, left ventricular mass, end-diastolic and systolic volumes end decrease in EF with increase in CMDS. Our results align with results of previous studies that have attempted to examine the cardiac structural and functional changes in individuals with various combinations of CMRF. For instance, a Japanese study group concluded that in a population without overt cardiac diseases, insulin resistance was strongly associated with subclinical left ventricular dysfunction, as determined by assessing the left ventricular global longitudinal strain [8]. In another large echocardiographic study, investigators assessed the cardiac structure and function and observed an increased left ventricular mass index, left ventricular end-diastolic volume, left ventricular end-systolic volume and left ventricular stroke volume in obese individuals with and without metabolic syndrome compared with individuals with normal weight without metabolic syndrome [9]. Finally, in their paper Piché et al. beautifully explain, how visceral obesity results in alterations in cardiac output,

Table 1

Frequency of residual risk factors across various CMDS

Таблица 1

Частота встречаемости факторов остаточного риска на различных стадиях CMDS

CMRF	CMDS 0 (n = 36)	CMDS 1 (n = 69)	CMDS 2 (n = 57)	CMDS 3 (n = 19)	p-value
	1	2	3	**4**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Excess level of visceral fat	0	4 (5.8)	2 (3.5)	5 (26.3)	$p_{1,2}$ – 0.135 $p_{1,3}$ – 0.249 **$p_{1,4}$ – 0.002** $p_{2,3}$ – 0.548 **$p_{2,4}$ – 0.016** **$p_{3,4}$ – 0.005**
VAI	0 (0)	3 (4.3)	14 (24.6)	17 (89.5)	$p_{1,2}$ – 0.198 **$p_{1,3}$ – 0.001** **$p_{1,4}$ – 0.000** **$p_{2,3}$ – 0.001** **$p_{2,4}$ – 0.000** **$p_{3,4}$ – 0.000**
Leptin >11.1 ng/mL	17 (47.2)	34 (49.3)	36 (63.1)	19 (100)	**$p_{1,2}$ –** 0.345 **$p_{1,3}$ –** 0.053 **$p_{1,4}$ – 0.000** **$p_{2,3}$ –** 0.248 **$p_{2,4}$ – 0.001** **$p_{3,4}$ – 0.006**
Atherogenicity index	4 (11.1)	24 (34.8)	27 (47.4)	18 (94.7)	**$p_{1,2}$ – 0.007** **$p_{1,3}$ – 0.000** **$p_{1,4}$ – 0.000** $p_{2,3}$ – 0.171 **$p_{2,4}$ – 0.000** **$p_{3,4}$ – 0.002**
HOMA-IR >2.52	1 (2.7)	15 (21.7)	14 (24.6)	14 (73.7)	**$p_{1,2}$ – 0.009** **$p_{1,3}$ – 0.005** **$p_{1,4}$ – 0.000** $p_{2,3}$ – 0.748 **$p_{2,4}$ – 0.000** **$p_{3,4}$ – 0.000**
CRP >3 mg/L	1 (2.8)	23 (33.3)	12 (21.0)	12 (63.1)	**$p_{1,2}$ – 0.000** **$p_{1,3}$ – 0.013** **$p_{1,4}$ – 0.000** $p_{2,3}$ – 0.112 **$p_{2,4}$ – 0.050** **$p_{3,4}$ – 0.002**

Note: n – number of participants with deranged parameters; % – proportion of subjects, with deranged parameters presented as percent; $p_{1,2}$ – significance between CMDS 0 and CMDS 1; $p_{1,3}$ – significance between CMDS 0 and CMDS 2; $p_{1,4}$ – significance between CMDS 0 and CMDS 3 calculated using the Mann-Whitney U-test. p-values < 0.05 are in bold. Abbreviations: CMRF – cardiometabolic risk factor; BMI – body mass index; HOMA-IR – homeostatic model assessment of insulin resistance; non-HDL-c – non-high- density lipoprotein cholesterol; VAI – visceral adiposity index; CRP – C-reactive protein.

Table 2

Median of key structural and functional parameters of the heart in various CMDS

Таблица 2

Средние значения структурных и функциональных параметров сердца на различных стадиях CMDS

Echo parameter	General cohort (n = 181)	CMDS 0 (n = 36)	CMDS 1 (n = 69)	CMDS 2 (n = 57)	CMDS 3 (n = 19)	p_{K-W}
		1	2	3	4	
	Me [25-75%]	Me [25-75%]	Me [25-75%]	Me [25-75%]	**Me [25-75%]**	
LA volume, ml	47.0 [45.0-49.0]	46.0 [45.0-47.0]	47.0 [46.0-49.0]	47.0 [46.0-49.0]	47.0 [46.0-50.0]	0.012
LA dimension, cm	3.5 [3.4-3.6]	3.4 [3.4-3.5]	3.5 [3.4-3.62]	3.5 [3.4-3.7]	3.5 [3.4-3.7]	0.001
End-diastolic interventricular septal thickness (IVST), cm	0.9 [0.79-0.91]	0.8 [0.78-0.9]	0.9 [0.8-0.96]	0.9 [0.8-1.0]	0.9 [0.8-0.99]	0.016
End-diastolic LV posterior wall thickness (PWT), cm	0.91 [0.82-1.0]	0.9 [0.81-0.94]	0.96 [0.81-1.0]	0.95 [0.88-1.0]	0.99 [0.9-1.0]	0.028
Relative wall thickness (RWT)	0.4 [0.37-0.43]	0.39 [0.36-0.42]	0.4 [0.37-0.43]	0.4 [0.38-0.42]	0.4 [0.39-0.43]	0.390
LV mass, gm	135.28 [113.83-163.92]	121.63 [102.08-138.44]	135.28 [118.35-162.36]	145.03 [114.82-179.8]	146.76 [116.58-179.8]	0.007
LV mass index (g/m²)	72.1 [61.49-83.76]	67.47 [60.91-76.5]	75.22 [63.0-86.85]	77.59 [61.92-87.19]	68.61 [59.07-88.39]	0.194
EDD, cm	4.5 [4.2-4.9]	4.3 [4.1-4.67]	4.6 [4.3-4.9]	4.8 [4.2-4.9]	4.8 [4.2-4.9]	0.084
EDV, ml	78.0 [70.0-79.5]	77.0 [69.0-78.0]	78.0 [69.0-79.0]	78.0 [70.0-87.0]	79.0 [78.0-89.0]	0.004
ESD, cm	2.9 [2.8-3.0]	2.9 [2.73-2.9]	2.9 [2.8-3.0]	2.9 [2.8-3.0]	2.9 [2.8-3.0]	0.273
ESV, ml	29.23 [26.1-31.2]	27.64 [24.93-29.14]	29.41 [25.98-31.2]	30.26 [26.6-32.76]	30.42 [29.23-35.6]	0.002
EF, %	62.0 [61.0-63.0]	63.0 [61.0-64.75]	62.0 [60.0-63.0]	61.2 [60.0-63.0]	62.0 [60.0-62.0]	0.010
SV, ml	47.58 [43.4-50.7]	47.19 [42.37-49.6]	47.4 [43.55-50.7]	48.36 [43.4-52.2]	48.36 [47.4-53.4]	0.090
CO, L/min	3.52 [3.17-4.0]	3.45 [3.09-3.84]	3.51 [3.17-3.95]	3.52 [3.11-4.2]	3.79 [3.38-4.35]	0.062

Note: n – number of participants in a particular group; Me – median [interquartile range, 25th –75th percentile], p_{K-W} – p-value using Kruskal-Wallis test to compare four groups. p-values < 0.05 are in bold. Abbreviations: LA – left atrium; LV – left ventricle; EDD – End-diastolic dimension; EDV – End-diastolic volume; ESD – End-systolic dimension; ESV – End-systolic volume; EF – Ejection fraction; SV – Stroke volume; CO – Cardiac output.

left ventricular hypertrophy and diastolic and systolic dysfunction of both ventricles [25].

Undoubtedly, any research conducted to detect early cardiac changes pertaining to heart failure are incomplete without studying the level of natriuretic peptide, a marker of heart failure. Thus, considering that on the one hand, our study subjects were at risk for the development of heart failure, and on the other hand, the presence of heart failure was an exclusion criterion, we were curious to study N-terminal pro-Brain Natriuretic Peptide (Nt-proBNP) at various cardiometabolic risks.

Nt-proBNP levels were investigated in 165 patients. An increase in Nt-proBNP level > 125 pg/ml (167.5 [143.5 – 207.25] pg/ml) was found in 26 patients (15.8%). These patients were analyzed for heart failure with preserved ejection fraction using the appropriate diagnostic criteria. We did not see any characteristic symptoms and signs of heart failure.

On comparing the echocardiography data in individuals with increased and normal Nt-proBNP levels, we found lower values of interventricular septal thickness (0.80 [0.77 – 0.90] cm *versus* 0.90 [0.80 – 0.94] cm, p = 0.011) and left ventricular posterior wall thickness (0.88 [0.80 – 0.92] cm *versus* 0.92 [0.85 – 1.00] cm, p = 0.016). The remaining structural echocardiographic parameters in the compared groups, both in the overall and sex-based cohort, were comparable (p = 0.134 – 0.435). At the same time, hemodynamic parameters (end diastolic volume and end systolic volume) had a tendency toward lower values in the group of people with increased Nt-proBNP (p = 0.084 – 0.099), whereas left ventricular ejection fraction was comparable (p = 0.220). The median values of Nt-proBNP in patients across various CMDS stages did not differ significantly (p = 0.260). Lastly, the correlation analysis established a weak inverse relationship between the Nt-proBNP levels and waist circumference (r_s = -0.257; p = 0.001), waist-to-hip ratio (r_s = - 0.332; p = 0.000), and the level of visceral fat (r_s = -0.205; p = 0.011). These findings may be explained by the so-called “natriuretic peptide deficiency” in asymptomatic obese individuals [26].

In next step we performed correlation analysis to investigate the association between CMRF and echocardiographic parameters. Derangements in carbohydrate and lipid metabolism, increases in BMI, waist circumference, waist-to-hip ratio, and visceral obesity parameters were most closely associated with an increase in pre- and afterload. Among these factors, visceral fat level demonstrated the strongest correlation with key echocardiographic parameters such as, left atrial volume (r_s = 0.471; p = 0.000), stroke volume (r_s = 0.464; p = 0.000), ejection fraction (r_s = -0.351; p = 0.000), and end-diastolic volume (r_s = 0.563; p = 0.000), end-diastolic dimension (r_s = 0.450; p = 0.000), end-systolic volume (r_s = 0.568; p = 0.000) and end-systolic dimension (r_s = 0.343; p = 0.000).

Considering the relationship between various metabolic abnormalities and their parameters, we conducted a regression analysis to determine independent predictors of changes in echocardiographic parameters. Since different phenotypic features of CMRF were identified in males and females, we conducted a regression analysis separately for each of these groups. The results of most significant models are presented in *Table 3*.

Thus, an increase in left ventricular and left atrial volumes and a decrease in ejection fraction in males were associated with an increase in BMI and atherogenic cholesterol fractions. In females, the predictors were visceral fat level and insulin resistance.

Since the level of visceral fat contributes to the increase in end-diastolic and systolic volumes, an analysis of hemodynamic parameters was conducted in cohort that had normal and higher levels of visceral fat *(Table 4)*. Patients with excess visceral fat levels had higher left atrial volume and size, end-diastolic dimension, and end-diastolic and systolic volumes (p = 0.000–0.010).

Considering the significant influence of elevated visceral fat levels on left atrial and ventricular dimensions as well as volumes and the fact that the highest proportion of these patients was found in the CMDS 3 group, we identified a subset of individuals within the CMDS 3 group who had excess visceral fat levels. This group also had the highest number of metabolic disorders and the highest cardiometabolic risk (CMDS 3). Consequently, we labeled this new group CMDS 3-overly high. *Figure 1* demonstrates changes in the cardiometabolic profile and hemodynamics with increasing risk factors.

According to various studies [5, 16, 18], as well as the echocardiographic data obtained in our study, young adults with CMDS 3 and CMDS 3-overly high represent a risk group for the development of not only CHF, but also CAD and atrial fibrillation which has a multifactorial origin. Therefore, this group needs to be promptly examined by a cardiologist for early detection of these cardiovascular complications and plan early screening and management strategies. The algorithm of identification and management is shown in *Figure 2*.

Analysis of cardiac structure and functional changes in accordance with their integral risk based on the CMDS system and demonstrated the alterations in

Table 3

Predictors of changes in echocardiographic parameters obtained using multiple regression analysis

Таблица 3

Предикторы изменений эхокардиографических параметров по результатам множественного регрессионного анализа

Echo parameter	Model	Unstandardized coefficients		Standardized coefficient	t	p-value	R square
		B	**Standard error**	**Beta**			
Females							
EDV	(Constant)	69.621	1.986		35.054	< 0.001	0.152
	VFL	1.064	0.286	0.390	3.716	< 0.001	
ESV	(Constant)	25.965	0.939		27.651	< 0.001	0.143
	VFL	0.486	0.135	0.379	3.588	< 0.001	
LA volume	(Constant)	46.019	0.455		101.083	< 0.001	0.089
	VFL	0.178	0.065	0.298	2.718	0.008	
EF	(Constant)	62.605	0.340		184.345	< 0.001	0.052
	HOMA-IR	-0.288	0.140	-0.227	-2.048	0.044	
Males							
EDV	(Constant)	51.307	5.464		9.390	< 0.001	0.248
	BMI	1.002	0.198	0.498	5.070	< 0.001	
ESV	(Constant)	14.354	2.445		5.871	< 0.001	0.353
	BMI	0.469	0.092	0.493	5.104	< 0.001	
	AI	0.899	0.409	0.212	2.200	0.031	
LA volume	(Constant)	40.374	1.062		38.028	< 0.001	0.348
	BMI	0.178	0.040	0.449	4.464	< 0.001	
	LDL-c	0.556	0.227	0.246	2.450	0.017	
EF	(Constant)	66.988	1.141		58.722	< 0.001	0.185
	BMI	-0.174	0.041	-0.431	-4.214	< 0.001	

Note: Abbreviations: LA – left atrium; EDV - End-diastolic volume; ESV – End-systolic volume; EF – Ejection fraction; VFL – visceral fat level; BMI – body-mass index; LDL-c – low density lipoprotein cholesterol; AI – atherogenicity index; HOMA-IR – homeostatic model assessment of insulin resistance.

Table 4

Quantitative characteristics of cardiac structural and functional parameters based on the visceral fat level

Таблица 4

Количественная характеристика структурно-функциональных показателей сердца с учетом уровня висцерального жира

Parameter	Normal visceral fat level (n = 171)	Excess visceral fat level (n = 10)	$p_{1,2}$
	1	2	
	Me [25-75%]	Me [25-75%]	
LA volume, ml	47.0 [45.0-48.0]	49.0 [47.5-51.2]	0.005
LA dimension, cm	3.5 [3.4-3.6]	3.7 [3.5-3.9]	0.000
EDD, cm	4.4 [4.2-4.9]	4.9 [4.8-5.1]	0.001
EDV, ml	78.0 [70.0-79.0]	87.0 [78.0-99.7]	0.007
ESV, ml	29.1 [26.1-31.2]	33.1 [29.7-38.9]	0.010
EF, %	62.0 [61.0-63.0]	61.0 [60.0-62.2]	0.206

Note: n – number of participants in a particular group; Me – median [interquartile range, 25th –75th percentile], $p_{1,2}$ – Mann-Whitney significance between normal (1) and higher (2) visceral fat levels. Abbreviations: LA – left atrium; EDD – End-diastolic dimension; EDV – End-diastolic volume; ESV – End-systolic volume; EF – Ejection fraction; VFL – visceral fat level.

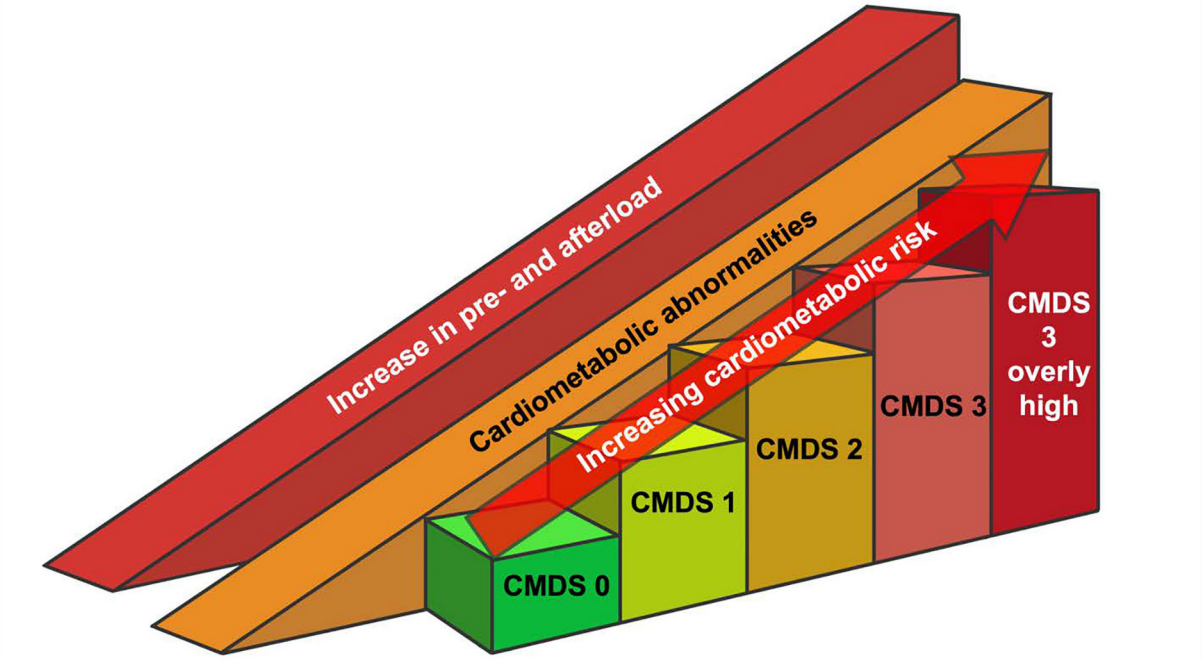

Figure 1. Schematic representation of increasing cardiometabolic abnormalities, pre- and afterload with progression of CMDS stage.

Рисунок 1. Схематичное изображение нарастания кардиометаболических нарушений, повышения пред- и постнагрузки на сердце при увеличении стадии CMDS.

echocardiographic parameters at various stages of cardiometabolic risk. Considering the assessment of a combination of factors, they showed that there is an increase left atrial volume and dimension, interventricular septal thickness, left ventricular posterior wall thickness, relative wall thickness and LV mass. Similarly, we saw a statistically significant increase in end-diastolic and systolic volumes and a decrease in ejection fraction with an increase in the cardiometabolic risk.

To summarize, our results reflect alterations in cardiac structure and function with rise in cardiometabolic risk. With the progression in CMDS there is an increase in pre- and after-load. Furthermore, these changes were also associated with an excess level of visceral fat, the independent contribution of which was shown in various statistical analyses. This has allowed us to identify a subgroup CMDS 3-overly high among young adults within CMDS 3. Excess levels of visceral fat were associated with an additional increase in dysmetabolic changes reflective of adiposopathy (increased levels C-reactive protein, leptin and insulin, and indices such as visceral adiposity index and HOMA-IR) as well as additional increase in the pre- and afterload. Considering these, we designed an algorithm that helps in stratifying

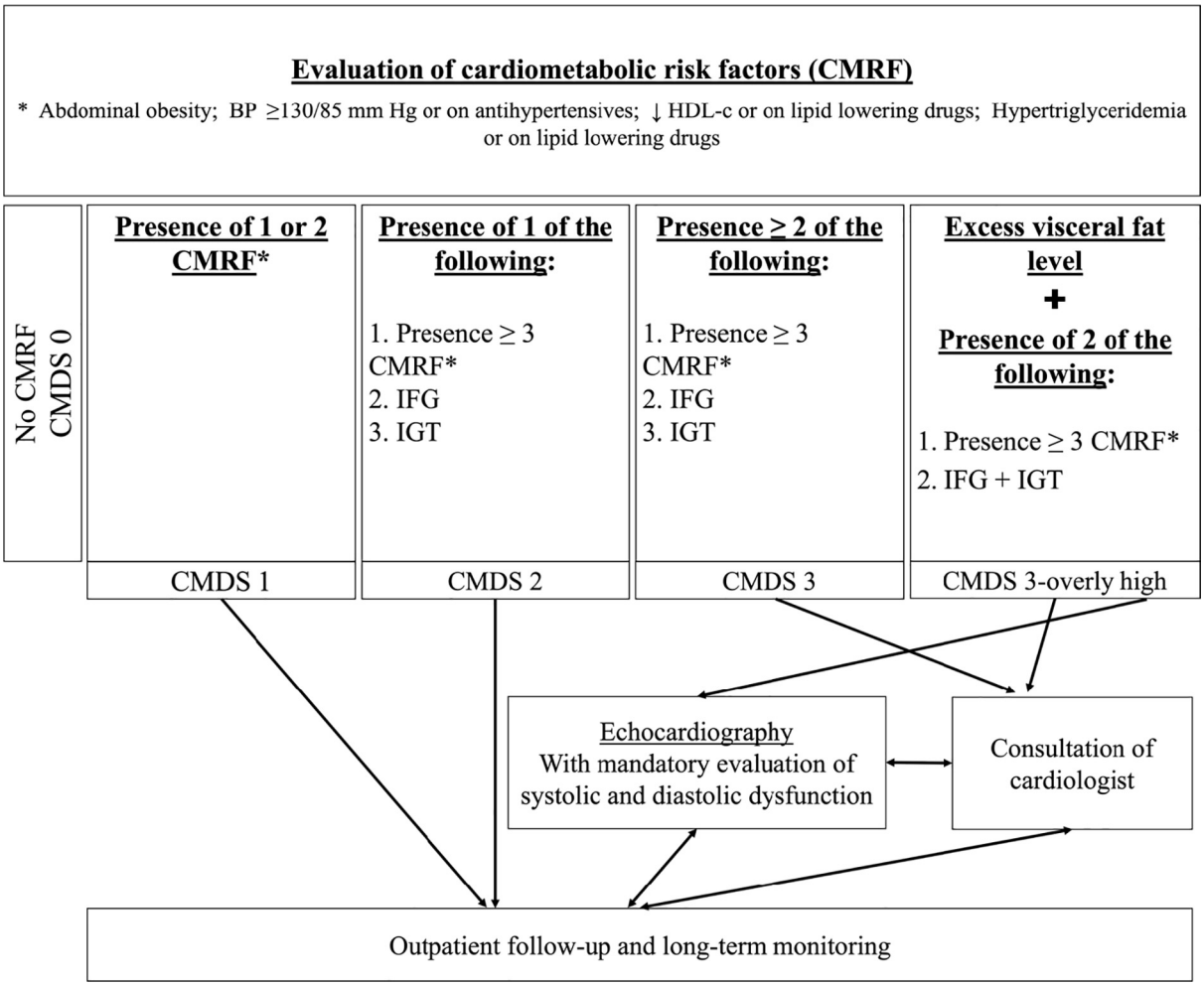

Figure 2. Algorithm depicting a differentiated approach for management of patients at various CMDS to determine indications for echocardiography and cardiology consultation
Рисунок 2. Алгоритм дифференцированного подхода к ведению пациентов на различных стадиях CMDS с целью определения показаний к проведению эхокардиографии и консультации кардиолога

individuals prone to higher risk of developing CHF, CAD and atrial fibrillation. This is a case-control and has its weaknesses, for instance, it is prone to selection bias and there is no prospective component involved.

Conclusion. In young adults, as the CMDS stage progresses, there is an increase in the frequency of insulin resistance, hyperleptinemia, raised non-HDL cholesterol, raised atherogenicity index, excess visceral fat level, visceral adiposity index, and levels of CRP. Furthermore, with an increase in the stage of CMDS, there is an increase in the left ventricular end-systolic and diastolic volumes, left atrial volume, and a reduction in left ventricular ejection fraction. As shown by various statistical analysis, visceral fat level resulted in additional increase in cardiac pre- and afterload, which helped us to identify the group CMDS 3-overly high. Based on these findings, we designed an algorithm to determine indications for echocardiography and cardiology consultation especially in individuals with higher CMDS.

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