Volume 9, № 32, December 2021
ISSN: 2311-1623 (Print)
ISSN: 2311-1631 (OnLine)
http://www.heart-vdj.com

International Heart and Vascular Disease Journal

Journal of the Cardioprogress Foundation

Genetic determinants of hypertriglyceridemia and cardiometabolic risks

The association between aggressiveness, clinico-instrumental features and the mortality risk in patients with CAD after percutaneous coronary intervention

Secondary hyperlipidemia: definition, phenotypes, and inducing factors

International Heart and Vascular Disease Journal
Journal of the Cardioprogress Foundation

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The publication of articles within the journal is free of charge for authors. Guidelines for authors on submitting manuscripts are available at: www.heart-vdj.com

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Printed in Russia

The Journal is in the List of the leading scitntific journals and publications of the Supreme Examination Board (VAK)

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International Heart and Vascular Disease Journal

Journal of the "Cardioprogress" Foundation

Volume 9, № 32, December 2021

Contents

Editor's Welcome

Dear colleagues!

We present the 32nd issue of the International Heart and Vascular Disease Journal that includes the leading article, original and review articles.

The leading article section is opened by the original work of our colleagues from Siberia that is dedicated to the assessment of combined effect of genetic associations on the development of hypertriglyceridemia as the risk factor for the development of cardiometabolic complications among young residents of the North. The study included 883 young participants who were distributed into metabolic syndrome group and the control group. The study revealed high prevalence of hypertriglyceridemia among study participants. Hypertriglyceridemia was associated with heterozygous TG variants of the single nucleotide polymorphism rs1378942 of the CSK gene and heterozygous rs1799752 variant of the ACE gene in the majority of patients with MS. Authors conclude that the determination of genetic predictors of the hypertriglyceridemia will allow to timely identify individuals at increased cardiometabolic risk.

The original article section includes four studies. The article from Azerbaijan investigated the features of hormone homeostasis in women with coronary artery disease (CAD) at various stages of physiological development. The revealed changes confirm the hypothesis that hormonal changes in women can be considered as additional risk factor for CAD and can be used as predictors for its development. The second article evaluated myocardial structural and functional features in patients with CAD and type 2 diabetes mellitus (T2DM) compared with patients with CAD without T2DM. The study revealed that left ventricular hypertrophy, hypokinetic segments of myocardium and coronary artery stenosis are more predominantly observed in CAD patients with T2DM than in those without T2DM. The next original article assessed the cardiorenal connections in patients with chronic kidney disease (CKD) and T2DM in combination with primary hypothyroidism. The combination of primary hypothyroidism and T2DM contributes to the increase of risk of cardiovascular pathology and CKD incidence. The strongest cardiorenal connections were shown in patients with normoalbuminuric CKD. The fourth article identified the association between the aggressiveness and clinico-instrumental features in patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) and to assess the impact of aggressiveness on mortality risk during one-year follow-up after the surgery. The study revealed that the parameter of aggressiveness in patients with CAD after PCI was independently and significantly associated with gender and chronic heart failure severity, as well as with the risk of cardiovascular mortality during 1-year follow-up.

The review article examines current understanding of the secondary dyslipidemia phenotypes and its causes. In particular, the features of lipid metabolism in patients with certain internal diseases are presented.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Mekhman N. Mamedov
Editor-in-Chief
President of the "Cardioprogress" Foundation

International Heart and Vascular Disease Journal • Volume 9, № 32, December 2021

Journal of the Cardioprogress Foundation

LEADING ARTICLE

DOI 10.24412/2311-1623-2021-32-03-08

Genetic determinants of hypertriglyceridemia and cardiometabolic risks

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Summary

Objective. *To assess the combined effect of genetic associations on the development of hypertriglyceridemia as the risk factor for the development of cardiometabolic complications among young residents of the North.*

Materials and methods. *The study included 883 young participants who were examined between 2015 and 2020–749 patients had metabolic syndrome (MS), 134 — had no symptoms of MS. All the participants underwent anthropometric investigation, studies of lipid and carbohydrate metabolism, blood pressure (BP) monitoring. Using phenol-chloroform extraction genomic DNA was extracted from the peripheral blood of each individual. Gene polymorphism was assessed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) test. The following polymorphisms were studied: rs1378942 of the CSK gene, rs1801133 (C677T) of the MTHFR gene, ITGA2B, rs7903146 of the TCF7L2 gene, rs1799752 of the ACE gene.*

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Results. *The prevalence of hypertriglyceridemia among all participants was 66.6 %, and 78.1 % among participants with MS. Hypertriglyceridemia was more common among the non-indigenous population, mainly among non-indigenous rural women (83.2 %). High levels of triglycerides were revealed in 56.2 % of the examined patients. More often hypertriglyceridemia was associated with heterozygous variants of the TG single nucleotide polymorphism rs1378942 of the CSK gene (50.7 %) (OR — 1.676, 95 % CI 1.268–2.214, p=0.142) and heterozygous variant rs1799752 of the ACE gene (52.2 %) (OR 0,54, 95 % CI 0.571–0.997, p=0.142). Patients with the combination of abdominal obesity and hypertriglyceridemia more often showed intergenic interactions of heterozygous genotypes ID of the ACE, ITGA2B gene, homozygous CC genotypes of TCF7L2 and MTHFR genes, heterozygous TG genotype of the CSK gene (47.4 %), the most common among rural female population and indigenous women (22.3 %).*

Conclusion. *The study revealed high prevalence of hypertriglyceridemia among study participants. Hypertriglyceridemia was associated with heterozygous TG variants of the single nucleotide polymorphism rs1378942 of the CSK gene and heterozygous rs1799752 variant of the ACE gene in the majority of patients with MS. The determination of genetic predictors of the hypertriglyceridemia will allow to timely identify individuals at increased cardiometabolic risk.*

Keywords: *hypertriglyceridemia, metabolic syndrome, genetic polymorphism.*

Conflict of interest: None declared.

Received: 29.07.2021 Accepted: 14.09.2021

Hypertriglyceridemia (hyperTG) is a defined as triglyceride (TG) levels>1,7 mmol/l. This condition is a common form of lipid imbalance in obesity, metabolic syndrome (MS), and type 2 diabetes (T2D). Today, hyperTG is considered a major risk factor (RF) of CVD and pancreatitis. According to our research, the prevalence of hyperTG is from 10 % to 30 % [1, 2]. The European Atherosclerosis Society recommends the following thresholds: mild and moderate hyperTG (2,0–9,9 mmol/l) and severe hyperTG (≥10,0 mmol/l) [3]. Mild and moderate hyperTG is associated with CV risk. Severe hyperTG develops due to monogenic mutations, is quite rare and can lead to pancreatitis [3]. HyperTG in adults is a multifactorial condition that involves both genetic and nongenetic factors. By now over 300 genetic loci that determine clinical phenotypes including hyperTG have been identified [1]. It is known that there are common and rare types of genetic factors that predispose to hyperTG. The types of these factors include mononucleotide variants and structural variations such as inclusion, deletion, and duplication of various parts of a gene or of a complete chromosome [4].

Therefore, the objective of this study was to evaluate the role of genetic factors in the development of hyperTG — a risk factor for cardiometabolic events in the young people of the North.

Materials and methods

This is a prospective study that was carried out in Fedorov City Hospital and Surgut City Clinic № 1 from 2015 to 2020 and included 883 people. Oh those, 749 had metabolic syndrome (MS). The mean duration of residency in the North was 27,9± 0,005 years. MS was diagnosed based on the 2009 Metabolic Syndrome Clinical Guidelines: the presence of three out of five metabolic disorders — increased waist circumference (over 80 cm in women and 94 cm in men), arterial hypertension (AH) (BP over 135 and 90 mmHg), hyperTG (≥ 1,7 mmol/l), decreased levels of low-density lipoproteins (LDL) (3,0 mmol/l), fasting hyperglycemia (≥ 6,1 mmol/l). Age characteristics of the groups are presented in Table 1.

Exclusion criteria were: exacerbation of any chronic condition, age< 18 years and>45 years, pregnancy.

TG levels were considered normal if<1,7 mmol/l (low CVD risk), intermediate — 1,7–2,2 mmol/l (moderate risk) and high —>2,3 mmol/l.

Molecular genetic testing was performed in the Research Institute of Internal and Preventive Medicine — an affiliated center of The Federal Research Center Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences. DNA was isolated from venous blood using the phenol–chloroform extraction technique. Gene polymorphisms were assessed using the polymerase chain reaction (PCR) with various restrictive fragments length [5]. We studied the following gene polymorphisms: rs1378942, CSK gene; rs1801133 (C677T) MTHFR gene; ITGA2B gene; rs7903146 TCF7L2 gene; rs1799752 ACE gene.

Table 1. **Age characteristics of the groups**

Parameters	Non-native population, n=601				Native population, n= 282	
	Urban population, n=247		Rural population, n=354			
	MS, n=211	No MS, n=36	MS, n=294	No MS, n=60	MS, n=244	No MS, n=38
Men	84	19	92	16	62	14
Age, years	37,6± 0,0009	36,5± 0,0001	37,4± 0,0008	39,9± 0,001	35,0± 0,0001	37,9± 0,003
Women	127	17	202	44	182	24
Age, years	35,7± 0,0002	39,4±0,004	36,4±0,0004	37,5± 0,003	36,1± 0,0004	39,0± 0,0001

Note. MS — metabolic syndrome.

Table 2. **The prevalence of hypertriglyceridemia in patients with MS**

Parameters		Men, n=238		Women, n=511		All	
		n	%	n	%	n	%
City	MS	62	73,8	99	78,0	161	76,3
	mmol/l	2,83± 0,04		2,75± 0,05		2,79± 0,05	
Rural area	MS	73	79,3	168	83,2	241	82,0
	mmol/l	2,67± 0,02		2,75± 0,003		2,71± 0,01	
The Khanty	MS	45	72,6	138	75,8	183	75,0
	mmol/l	2,77± 0,03		2,70± 0,004		2,74± 0,02	
All	MS	180	75,6	405	79,3	585	78,1
	mmol/l	2,76± 0,03		2,73± 0,019		2,75± 0,02	

Statistical analysis was performed using the SPSS 16.0 software. First, we assessed the frequencies of genotypes and alleles of the polymorphisms of interest in patients with MS and in control group. Secondly, we checked in the genotype frequencies followed the Hardy-Weinberg equilibrium using the χ^2 test. The risk of MS in the presence of a specific allele was calculated as the odds ratio (OR) using the Fisher exact test and Pearson's chi-squared test. Confidence interval (CI) was also calculated. P<0,05 was considered statistically significant [5].

Informed consents were obtained prior to participation.

Results

The prevalence of hyperTG was 66,6% (n=588); 78,1% (n=585) in patients with MS and 2,2% in individuals without MS. In healthy participants 3 individuals who lived in rural area (2 men and 1 women) and high levels of TG (m=1,9±0,001 mmol/l). In some non-native patients with MS the prevalence of hyperTG was by 4,6% higher compared with the natives — 79,6% (n=402) and 75,0% (n=183), respectively. The prevalence of hyperTG in rural population was by 5,7% higher than in the participants with MS who lived in the urban areas and by 7,0% higher than in the natives. HyperTG was also more prevalent in women (by 3,7%) in general and in some women living in rural areas (83,2%) (Table 2). Mean levels of TG in all groups were 2,75± 0,02 mmol/l (Table 2).

More than a half of all patients with MS (56,2%, n=421) had higher mean levels of TG (>2,3 mmol/l) that were associated with high risks of coronary artery disease (CAD). Non-native participants the prevalence of hyperTG>2,3 mmol/l was 58,8% (n=297) — 8,0% higher than in native people (50,8%, n=124). Intermediate levels of TG were identified overall in 21,9%. Of those, 29,8% were non-natives, and 24,2% were natives. TG<1,7 mmol/l were present in 25,0% of native and in 20,4% non-natives (Figure 1).

We have investigated intergenic associations of mononucleotide rs1378942 polymorphisms of CSK gene, rs1801133 (C677T) polymorphisms of MTHFR genes, TCF7L2 genes, rs7903146 ITGA2B genes, rs1799752 polymorphisms of ACE genes and their prevalence in patients with MS. The results of the genotypes and polymorphism alleles prevalence analysis in patients with MS are presented in Table 3. In most patients with MS hyperTG was associated with heterozygous TG variations of of mononucleotide rs1378942 polymorphism of CSK gene (n=278, 50,7%) (OR 1,676, 95% CI 1,268–2,214, p=0,142), heterozygous rs1799752 variant of gene ACE (n=286, 52,2%) (OR — 0,754, 95% CI 0,571–0,997, p=0,142). Mutations in G allele of CKS gene were identified in 45,3% of cases (OR — 1,210, 95% ДИ 0,009–0,086, p=0,027) and D allele in ACE gene in 52,6% of cases

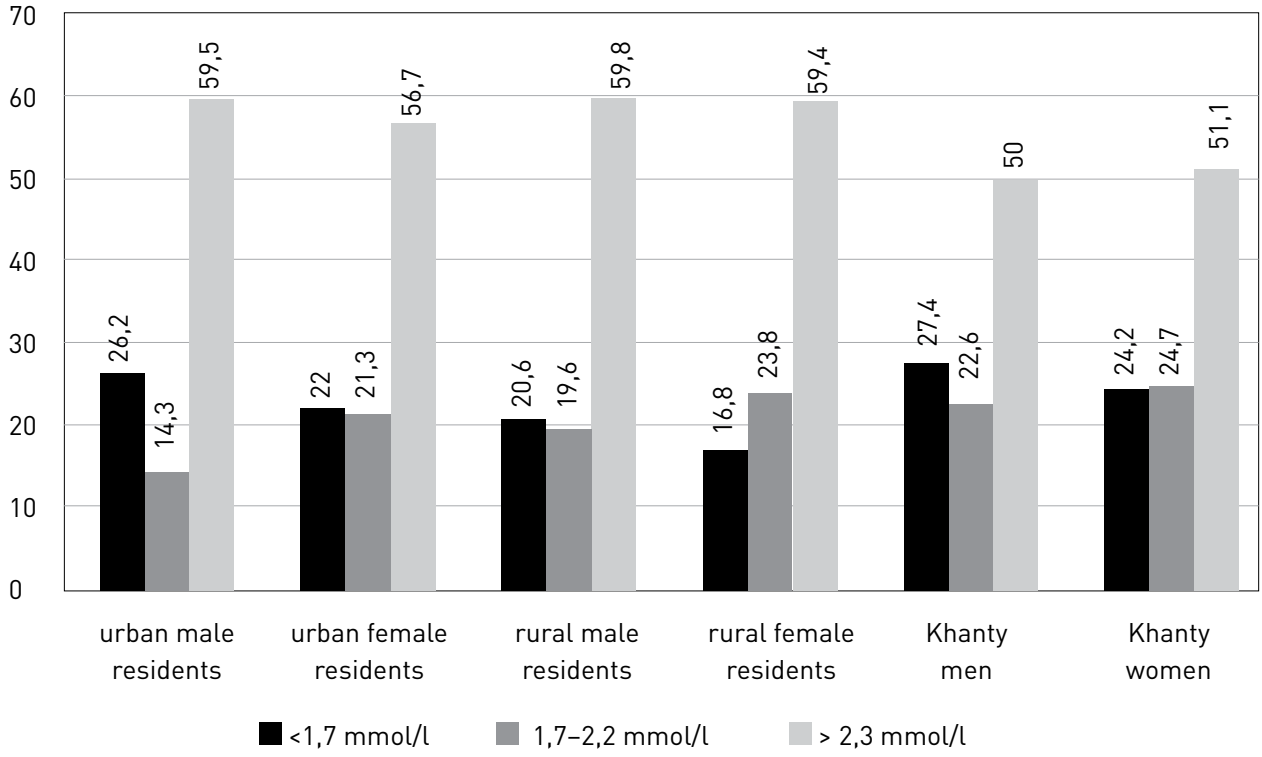

Figure 1. Coronary artery disease risks and mean triglyceride levels in patients with metabolic syndrome

(OR — 0,903, 95% ДИ 0,689–0,964, p=0,086). In patients with co-existent abdominal obesity and hyperTG heterogenous ID genotypes of ACE, ITGA2B gene, homozygous CC genotypes of TCF7L2 and MTHFR genes, heterozygous phenotype TG of CSK (47,4%), that were most prevalent in female rural (31,7%) and native (22,3%) population. The combination of mutant alleles in the homozygous genotypes of all the genes that we studied were identified in 31 patients with MS (5,7%). The prevalence was the same in urban and rural residents (22,6% respectively). The combinations of homozygous genotypes of ITGA2B and ACE, homozygous genotypes TT of CSK gene, heterozygous CT variants in MTHFR and TCF7L2 were identified in 26,4% patients with MS (n=145). They were present in more rural residents (32,4%) and native residents (22,8%) (Table 3).

Discussion

High prevalence of hyperTG in patients with MS (78,1%) that we identified in our study is confirmed by other authors (80%) [6].

Genetic causes of lipid imbalance such as hyperTG involve mutations of genes encoding metabolism and homeostasis.

Mutations of genes that play a role in the development of hyperglycemia and insulin resistance are the main cause of MS. Insulin resistance in obesity causes increased production of very-low-density lipoprotein (VLDL) and TG because of high levels of free fatty acids that activate insulin-dependent tissues. The insulin receptor is a type of tyrosine kinase receptor that triggers autophosphorylation of the tyrosine residues [7]. Insulin binds to the extracellular alpha subunit, and in the process stimulates the autophosphorylation of the beta subunit and the expression of tyrosine kinase activity [7]. Tyrosine-protein kinase phosphorylates tyrosine residues [8]. TCF7L2 gene inhibits liver gluconeogenesis and pancreatic beta-cell proliferation and causes hyperglycemia [9, 10]. A few studies have confirmed the association between T2D and mononucleotide rs7903146 polymorphisms of TCF7L2 genes [11].

Insulin is known to increase production of endothelial NO, canal sodium reabsorption and angiotensin-converting enzyme production and, therefore, vasodilation. Obesity and hyperinsulinemia are associated with increased sympathetic activation and RAAS activity that causes rise in blood pressure [12]. Angiotensive peptides are present in all cells and tissues and have local effects on RAAS. Activation of RAAS leads to decreased satiety, less weight loss and increased adipocyte proliferation causing obesity and lipid imbalance [13, 14]. Uchiyama et al [15] have shown that angiotensin II reduces lipoprotein lipase expression in visceral adipose tissue.

Table 3. **Mononucleotide polymorphisms in patients with MS and hypertriglyceridemia**

Polymorphism	Genotype	n	%	OR, 95% CI, p
CSK rs1378942	GG	109	19,9	1,676, 1,268–2,214, p=0,142
	TG	278	50,7	
	TT	161	29,4	
	Allele G	496	45,3	1,210, 0,009–0,086, p=0,027
	Allele T	600	54,7	
MTHFR rs1801133 (C677T)	CC	288	52,6	0,163, 0,077–0,147, p=0,107
	CT	201	36,7	
	TT	58	10,6	
	Allele C	777	71,0	0,408, 0,138–0,200, p=0,094
	Allele T	317	29,0	
ITGA2B	DD	76	13,9	0,178, 0,133–0,239, p=0,150
	ID	260	47,4	
	II	212	38,7	
	Allele D	412	37,6	0,363, 0,305–0,431, p=0,088
	Allele I	684	62,4	
TCF7L2 rs7903146	CC	347	63,3	0,060, 0,023–0,052, p=0,205
	CT	170	31,0	
	TT	31	5,7	
	Allele C	864	78,8	0,269, 0,059–0,089, p=0,072
	Allele T	232	21,2	
ACE rs1799752	DD	117	21,4	0,754, 0,571–0,997, p=0,142
	ID	286	52,2	
	II	145	26,4	
	Allele D	520	52,6	0,903, 0,689–0,964, p=0,086
	Allele I	576	47,4	

Note. CSK — C-terminal Src kinase gene, MTHFR — Methylenetetrahydrofolate reductase, ITGA2B — Integrin Subunit Alpha 2b, TCF7L2 — Transcription Factor 7 Like 2, ACE — angiotensin converting enzyme gene.

Insulin resistance in MS increases thrombogenesis and changes blood rheology and, therefore, has toxic effects on vascular wall. ITGA2B and MTHFR cause these effects. It leads to hyperhomocysteinemia and atherosclerotic changes in vascular wall.

The genes that we described in the current paper play a role in the development of hypeTG and MS and, therefore, their mutations predispose to cardiometabolic syndrome.

Conclusion

We have identified high prevalence of hypertriglyceridemia in all young people that we've examined (66,6%) and in 78,1% patients with metabolic syndrome. ACE, TCF7L2, ITGA2B, CSK, MTHFR gene polymorphism play a role in hyperTG that is usually associated with heterozygous TG variants of mononucleotide rs1378942 polymorphism of CSK gene and heterozygous rs1799752 variant of ACE gene.

Conflict of interest: None declared.

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International Heart and Vascular Disease Journal • Volume 9, № 32, December 2021

Journal of the Cardioprogress Foundation

ORIGINAL ARTICLES

DOI 10.24412/2311-1623-2021-32-09-14

The features of the hormone homeostasis in women with coronary artery disease at various stages of physiological development according to clinical and epidemiological research

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Summary

Objective. *To assess and compare the features of hormone homeostasis in women with coronary artery disease (CAD) at various stages of physiological development according to clinical and epidemiological research.*

Materials and methods. *The study included 200 women with CAD, who were divided into 2 groups: I — epidemiological and II — clinical (99 and 101 patients, respectively). To verify CAD, patients underwent full range of epidemiological and clinical instrumental studies. Sex hormones — estradiol (E), testosterone (T), progesterone (P) and the adrenal cortex hormone — cortisol (K) were investigated in all participants in different age groups and were compared with the control group of healthy individuals.*

Results. *The study revealed heterogeneous changes in hormone homeostasis in women with CAD of reproductive age and at menopause, which also differed between groups of epidemiological and clinical examination. Thus, young women from group I showed significant decrease of E with a reciprocal increase of T, while women at menopause had statistically significant decrease of the P level in both groups. The decrease of K production was observed in both age groups. Young women of childbearing age mostly had the decrease of E: P ratio, and during menopause — of E: T ratio.*

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Conclusion. *Women with CAD have certain changes of hormone homeostasis according to epidemiological and clinical research, which differ between groups of reproductive and menopause age. The revealed changes confirm the hypothesis that hormonal changes in women can be considered as additional risk factors for CAD and can be used as predictors for its development.*

Keywords: *coronary artery disease, women, sex hormones, hormone homeostasis.*

Conflict of Interest: None declared.

Received: 08.11.2021 Accepted: 18.07.2021

Coronary artery disease (CAD) is one of the most important issues in cardiology. It is still one of the leading causes of morbidity and mortality in young people (the working age population) [1]. For a long time, cardiovascular diseases (CVD) have been considered the leading cause of disability and mortality primarily in men. However, recently it has been shown that women are at 2–4 times higher risk of CV complications compared with men [2].

Previously it had been thought that early CAD in women were caused by the same risk factors (RF) as in men (mostly genetic conditions that result in metabolism problems), but now it has been reconsidered [3]. According to the recent studies, there are female-specific risk factors associated with women's reproductive health including the age of menopause, use of hormonal contraceptives and history of gynecological problems [2, 3].

CVD is the leading cause of mortality in women. According to the latest American Heart Association (AHA) studies, over 30 % of women have some form of CVD. Among women, annual CVD incidence rate is 35 per 1,000 persons aged 45–54 years [4]. According to the World Health Organization (WHO), the top causes of mortality in women over 45 are CVD, followed by lung disease, diabetes, and cancer [5]. In women aged 45–65 years, some form of CVD is present in 1 in every 9 women, in women over 65 years — in 1 in every 3 women. Premenopausal women are at twice the risk of CVD compared with postmenopausal women [6]. However, the incidence of CVD has recently increased both in young and older women including premenopausal women. That led to the introduction of the term "early CAD" meaning CAD in women younger than 55 years [6, 7]. Therefore, menopause provokes multiple problems including CVD [8].

Later manifestation of CAD in women is associated with protective effects of estrogens [1]. After menopause these effects wear off and leads to greater risk of CVD [9, 10]. The risk of CAD increases 7 times each decade after 40–45 years [11, 12].

Therefore, female sex hormones can be considered additional gender RF of CAD. The effects of menopausal hormone changes and other RF and predictors still need to be further investigated for more effective CVD prevention. CAD predictors include main or additional risk factors, that vary in different groups. Based on this information we divided all the participants into two groups: the epidemiologic group and clinical group.

Objective of this study was to assess and compare the features of endocrine homeostasis in women with coronary artery disease (CAD) at various stages of physiological development according to clinical and epidemiological research.

Materials and methods

The study was conducted in two separate phases. First, we carried out a cross-sectional epidemiologic study that included 952 women from the city of Sumgait; 228 (23,9 %) had CAD. Then, 99 women were randomly selected from all the participants with CAD and included into the final study.

The study group included 101 outpatient and inpatient females with CAD. CAD was verified with a thorough examination during hospital stay (40 women) or outpatient visit (61 women) in the M. A. Mirqasimov Clinical Hospital, Baku, Azerbaijan. Overall, 101 women were examined.

The final study included 200 women with CAD who were further divided into two groups..The first group included 99 participants with CAD that was identified epidemiologically. The second group included 101 participants with CAD verified with a thorough examination during hospital stay or outpatient visit.

We performed anthropometric measurements, laboratory evaluation that included biochemical parameters such as a lipid panel and other well-known

predictors of CAD. Sex hormones — estradiol (E), testosterone (T), progesterone (P) and the adrenal cortex hormone — cortisol (K) were investigated in all participants in different age groups and were compared with the control group of healthy individuals. Sex hormones were evaluated at the 6–8 days of the menstrual cycle (follicular phase).

The control group included 23 healthy women. Of those, there were 10 women of reproductive age (mean age 38± 2,5 years) and 13 women of postmenopausal age (mean age 53,4± 3,6 years).

We analyzed hormonal profile in healthy women of reproductive and postmenopausal age without CAD and compared them with each other and with populational data. According to our results, the levels of all hormones except for estrogen were similar in different age groups and in the two groups in general. Therefore, based on these findings, we further used hormonal profile of healthy women. Age and estrogen levels were excluded from the final analysis (Table 1).

Table 1. **Hormonal profile in healthy women of different ages**

Hormones	Control group of healthy women (n=20)	Fertile (n=10)	Post-menopausal (n=13)	p
Estrogen (pg/ml) M±m	45,6± 3,8	49,8± 2,1	36,7± 1,2	p1< 0,05 p2< 0,01 p3< 0,001
Progesterone (ng/ml) M±m	0,46± 0,11	0,64± 0,06	0,38± 0,09	NA
Testosterone (ng/ml) M±m	0,34± 0,05	0,46± 0,05	0,38± 0,05	NA
Cortisol (ng/ml) M±m	138± 9,9	136,5± 7,8	135,0± 6,5	NA

Note. P1 — difference between healthy women and women of reproductive age with CAD, p2 — difference between healthy women and women of postmenopausal age with CAD; p3- difference between fertile and postmenopausal women with CAD.

Sex hormone levels were measured in the morning after overnight fasting using the «BioScreen-500» reader system (USA) with HUMAN's system reagents. 10–15 ml of blood were drawn from the cubital vein. Reference hormone ranges according to HUMAN are the following: estrogen in healthy women — 30–120 pg/ml during follicular phase; 15–60 pg/ml; after menopause; progesterone 0,2–1,4 ng/ml during follicular phase, 0,1–1 ng/ml after menopause; testosterone In healthy women <0,6 ng/ml during follicular phase, <0,8 ng/ml after menopause; cortisol in adults 50–250 ng/ml.

Statistical analysis was performed using the SAS statistical software and Statistic for Windows. The groups were compared using Student's t-test. The mean (M), standard error of mean (m), minimal (min) and maximal (max) values were calculated. P<0,05 was considered statistically significant.

Results

Of 200 participants, 79 were of reproductive age and 121 in postmenopausal age; in group I, 55 patients were of reproductive age and 44 of menopausal age, in group 2–24 were o reproductive age and 77 were in postmenopausal age.

We compared the levels of hormones in various physiological phases in women of reproductive and postmenopausal age with CAD (Table 2).

As shown in Table 2, both patients of reproductive and postmenopausal age in group I have lower levels of estrogen, but these differences aren't statistically significant. However, estrogen levels were lower in women of reproductive age from this group compared with healthy females of the same age group (p<0,05). Patients in group II had higher levels of estrogen but the differences between fertile and postmenopausal women and women in group II and I weren't statis-

Table 2. **Mean hormone levels in women of reproductive and postmenopausal age**

Groups		Estradiol (pg/ml)	Progesterone (ng/ml)	E:P	Testosterone (ng/ml)	E:T	Cortisol (ng/ml)
Group I (n=99)	Fertile (n=55)	40,5±3,9^	0,7±0,1	57,85	0,76±0,1^^	53,3	139,1±4,6
	Postmenopausal (n=44)	40,9±5,0	0,29±0,05**	141,0	0,66±0,8	61,9	154,3±6,5*^
Group II (n=101)	Fertile (n=24)	48,9±7,8	0,65±0,17	75,23	0,34±0,06^^^	143,8	121,4±7,6
	Postmenopausal (n=77)	45,3±4,3^	0,24±0,02**^	188,7	0,47±0,04^	96,4	140,3±5,2*
Здоровые лица (n=23)	Fertile (n=10)	49,8±2,1	0,64± 0,06	77,8	0,46± 0,05	108,3	136,5±7,8
	Postmenopausal (n=13)	36,7±1,2	0,38± 0,09	96,6	0,38± 0,05	96,6	135,0±6,5

Note. P — difference between I and II groups in women of reproductive and postmenopausal age (*— p< 0,05; **— p< 0,01; ***— p< 0,001); ^ — difference between women with CAD and healthy women.

tically significant. Climacteric women from group II had statistically higher levels of estrogen compared with control group (45,3±4,3 vs 36,7±1,2, p<0,05).

Of note is that progesterone levels were lower only in postmenopausal women compared with women of reproductive age (p<0,001 in group I и p<0,001 — in group II). Levels of testosterone were higher in patients in group I compated both with women of postmenopausal age (0,76±0,1 vs 0,66±0,8, p<0,001), and with healthy fertile wonen (0,76±0,1 vs 0,46±0,05, p<0,001). However, fertile women in group II had lower levels of testosterone compared with healthy individuals (0,34±0,06 vs 0,46±0,05, p<0,001). There was no statistically significant difference between the levels of testosterone in women of reproductive and postmenopausal age.

At the same time, E:P and E:T ratios in group I are significantly lower in fertile women with CAD compared with those of postmenopausal age (57,85 и 53,3 vs 141,0 and 61,9 respectively).

Cortisol levels in fertile women with CAD were lower in both groups compared with climacteric patients (p<0,05) and were also lower in patients from group II compared with women of all age groups with CAD from group I (p<0,01). Compared with healthy individuals, only postmenopausal patients from group I had higher levels of cortisol that were statistically significant (154,3±6,5 in women with CAD vs 135,0±6,5 in menopausal women from control group, p<0,05). The changes in hormonal levels such as rise in cortisol and decrease in progesterone in postmenopausal women with CAD can be due to increased activity of steroidogenesis in adrenal glands and reduced function of corpus luteum [13]. These findings are similar to epidemiologic populational data but nevertheless there were some differences in postmenopausal women: compared with populational data and women of reproductive age they had lower levels of progesterone, higher cortisol and lower E:P ratio. These changes in postmenopausal women with CAD are most likely associated with lower cardioprotective effects of estrogen and progesterone [14].

Postmenopausal women had higher estrogen levels and lower progesterone levels compared with the general group data (p<0,05 and p<0,01, respectively). However, E:P ratio was significantly higher in these patients compared with healthy individuals. E:T ratio was similar in both groups. Progesterone levels in women of reproductive age were similar to those in the control group (0,65±0,17 vs 0,64±0,06 in healthy women), but higher than in women of postmenopausal age (0,65±0,17 vs 0,24±0,02, p<0,01). At the same time cortisol levels were higher in postmenopausal women than in young women of reproductive age (140,3±5,2 vs 121,4±7,6, p<0,05). Lower levels of progesterone together with higher levels of estrogen and testosterone as well as higher levels of cortisol in women with CAD from group II can be a sign of adrenal hyperfunction [13]. E:P ratio is lower in women of reproductive age and E:T ratio in women if postmenopausal age. E:P is one of the negative predictors of CAD and hormonal imbalance is an important risk factor in young women of reproductive age [13, 15].

Discussion

In this study we demonstrated the changes in endocrine homeostasis in women of different age and from different epidemiologic and clinical groups. These changes of hormonal levels in both groups can be explained by the fact that patients from group II had atherosclerosis and active forms of CAD. According to the existing studies estrogen effects depend on the length of estrogen deficiency and can change from antiatherosclerotic to proatherosclerotic [16]. These affects were first described in WISE, HERS and WHI studies in which hormonal replacement therapy (HRT) didn't lead to reduction of CVD risk. These studies included older patients in late menopause with worse atherosclerosis and therefore exogenous estrogens didn't have any cardioprotective effects [17]. Lower levels of progesterone can be associated with poor cardioprotective effects of estrogens. At the same time, protective effects of female hormones can also be alleviated by their imbalance. Many authors note that the main CAD predictor in both women and men is the reduced E:P [15]. Progesterone, as well as estrogen, binds to specific myocardial and coronary vessel progesterone receptors. The number of progesterone receptors is modulated by estrogen. Progesterone reduces endothelial estrogen-mediated vasodilation [17]. Therefore, it is likely that in fertile women from group I with CAD but without severe atherosclerosis hormonal imbalance is associated with low levels of estrogen, increased levels of progesterone and testosterone that lead to androgenization and the loss of cardioprotective effects of estrogens [17]. Increased levels of progesterone inhibit endothelial vasodilation caused by estrogen [13]. Therefore, decrease in estrogen and rise in progesterone lead to vasoconstriction, worse coronary blood flow and endothelial dysfunction that causes CAD in young fertile women [18]. In postmenopausal women, higher levels of estrogen

lead to atherosclerotic effects. Reduction in progesterone leads to vasoconstriction and fluid retention due to higher aldosterone activity and Na reabsorption [19].

Women with CAD have different endocrine profiles. These differences were noted in women in different physiologic phases and also in epidemiologic and clinical study groups. According to the epidemiological study results, fertile women with CAD have lower levels of estrogen, higher levels of testosterone and reduced production of cortisol. On the contrary, clinical study results women had higher levels of estrogen and lower levels of testosterone compared with healthy control group. Changes in cortisol production were similar in both groups: cortisol production was lower in fertile women, especially in group II, compared with menopausal women. Postmenopausal women had higher levels of estrogen compared with healthy individuals according to clinical examination, as well as lower progesterone and higher cortisol in both groups.

In our study we have demonstrated the different hormonal changes in women with CAD in different physiologic phases, with different stage and length of atherosclerosis and also in epidemiologic and clinical study groups. These changes between groups I and II can become the foundation for CAD predictor research. The results of this study should be considered during the development of national CAD prevention program in women.

Conclusion

Estrogen levels were lower in women of reproductive age compared with healthy females of the same age group ($p<0,05$) according to epidemiological study and higher in climacteric women compared with control group according to clinical study ($p<0,05$).

Progesterone levels were lower in postmenopausal women according to both clinical and epidemiological investigations.

Changes in testosterone production were noted only in women of reproductive age: testosterone levels were higher in patients from group I compared with group II and with healthy individuals and lower in group II compared with control group.

Cortisol production was reduced in women of reproductive age according both to epidemiological and clinical investigations. Cortisol levels in group II were lower compared with group I both in fertile and postmenopausal women.

Conflict of interest: none declared.

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International Heart and Vascular Disease Journal • Volume 9, № 32, December 2021

Journal of the Cardioprogress Foundation

DOI 10.24412/2311-1623-2021-32-15-20

Changes in myocardial structure and function in patients with coronary artery disease and type 2 diabetes mellitus

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Abstract

Objective. *Our study aimed to evaluate myocardial structural and functional features in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) compared with patients with CAD without T2DM.*

Methods. *The comparative cohort study included 82 men and 68 women with 2–3 classes of angina. Patients were divided into 4 groups based on the presence of T2DM and their gender. Glycemic status and lipid profile parameters were assessed in all patients. Invasive and non-invasive procedures were performed to assess myocardial and coronary artery structure.*

Results. *Transthoracic echocardiogram (TTE) and electrocardiography (ECG) detected left ventricular hypertrophy (LVH) in 57% of men with CAD and T2DM compared to 35% in those without T2DM. Hypokinetic segments of myocardium were identified on average in 35% of patients (39% men and 34% women) with CAD and T2DM while in patients without T2DM, hypokinesis was detected in 27% of cases (30% men and 23% women). Stenosis of the right coronary artery was detected in 30% of patients with T2DM and in 25% of patients without T2DM. The frequency of coronary artery stenosis in distal segments in patients with T2DM was 3 times higher relative to the non-diabetic group (43% vs 14% in men; 47% vs 16% in women).*

Conclusion. *LV hypertrophy, hypokinetic segments of myocardium and coronary artery stenosis are more predominantly observed in CAD patients with T2DM than in those without T2DM. This should be considered during treatment.*

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Key words: *angina pectoris, coronary artery disease, type 2 diabetes mellitus.*

Conflict of interest: None declared.

Received: 30.04.2021 Accepted: 28.07.2021

Introduction

T2DM is one of the top five diseases with various complications among adults around the world [1]. Experts note its continuous growth in both developed (USA) and developing countries (India, China, Mexico, etc.). According to World Health Organization (WHO), Russia is included in the top ten countries with the highest risk of T2DM. In general, the prevalence of T2DM is from 8 to 10 % [2]. The decrease in average age at the onset of T2DM, potentially associated with lifestyle changes, is of particular concern [3].

Vascular lesions and primarily macrovascular complications predominate among the patients with complications and fatal outcomes of T2DM [4].

It is known that there are 3 types of myocardial damage in patients with T2DM: atherosclerotic coronary lesion, diabetic (metabolic) cardiomyopathy and autonomic neuropathy [2]. Coronary Artery Disease (CAD) is the main cause of death and complications in patients with T2DM [5]. Given these findings, experts tend to consider T2DM as an equivalent to CAD [2]. In addition to the severity of CAD, it is necessary to emphasize the frequency of silent myocardial ischemia in patients with T2DM [6, 7]. Prospective studies have shown that glycemic status is directly associated with macrovascular complications and the prognosis [8, 9].

CAD diagnosis in patients with T2DM, include both invasive and non-invasive methods. This allows to determine further management strategies for patients with CAD and T2DM [10].

Complex assessment of clinical and anatomical myocardial features will allow us to estimate the prognosis and to develop secondary prophylaxis measures in patients with high risk of cardiovascular complications.

Comparative cohort study on myocardial structure and function was performed using invasive and non-invasive procedures to assess the state of myocardium in patients with CAD and T2DM.

Materials and methods

The clinical cross-sectional study after the initial screening (n=180) included 82 men and 68 women with 2–3 classes of angina severity according to the Canadian Cardiovascular Society Angina Grading Scale (1976), who were admitted to the cardiology department of the Domodedovo Central City hospital (Moscow region, Russia). Patients were divided into 4 groups based on the presence of T2DM and gender: group 1 — men with T2DM (n=42), group 2 — women with T2DM (n=38), group 3 — men without T2DM (n=40), group 4 — women without T2DM (n=30). All patients were diagnosed with CAD. The exclusion criteria were: stages 2–4 of chronic heart failure, chronic kidney disease, chronic liver failure, life-threatening heart rhythm disturbances, hypertrophic cardiomyopathy, severe valvular heart disease, type 1 diabetes mellitus, decompensation of T2DM, oncology and blood disorders.

All patients underwent questioning on sociodemographic parameters as well as biological and behavioral risk factors. Patients underwent instrumental and laboratory investigations: blood pressure, resting heart rate, anthropometric parameters (waist circumference, body weight and height with the calculation of body mass index), glycemic status, and lipid profile parameters measurement.

We performed the following invasive and non-invasive studies to determine structural and functional parameters of the myocardium and coronary arteries: standard 12-lead ECG at rest (Schiller AT-10 plus, Switzerland), M- and B-modes TTE (Acuson-128Xp, Siemens, Germany), and invasive coronary angiography (CAG) using GE Innova 4100 apparatus, manufactured in the USA. We also performed polypositional selective CAG of left coronary artery in five standard positions and right coronary artery in three standard positions. We used the Sokolow-Lyon criteria (SV1+ RV5>3.5 mB, RaVL> 1.1 mB) and the Cornell voltage index (>244 mBxmsec) for the diagnosis of LVH using ECG, as well as left ventricular mass index by TTE (>115 g/m² in men, and> 95 g/m² in women).

CAD and the history of myocardial infarction were determined via medical examination, as well as ECG and TTE criteria. The presence of pathological Q or QS wave, ST segment elevation and inverted T wave (along with cardio specific enzymes) were considered as ECG signs of myocardial infarction, inverted T wave with horizontal or oblique ST segment depression —

as CAD. The following parameters were evaluated during CAG: stenosis by segments, by localization, by the degree of narrowing and the frequency of vascular lesions. Informed consent was obtained from all participants prior to the study.

The diagnosis of T2DM was based on patient's historical data, clinical examination, the fasting blood glucose level (over 110 mg/dL for capillary blood, over 126 mg/dL — for venous blood), glycated hemoglobin (≥6,5 %) according to WHO criteria (1999–2013).

Data entry was carried out using ACCESS MS OFFICE system, editing and statistical processing was performed using statistical software SAS version 9.4 (Statistical Analysis System, SAS Institute Inc., USA). Standard criteria were used to determine statistical significance: chi-squared test, Student's t-test for 2 samples and Fisher's exact test for variances. The chosen significance level for all tests was set as $p<0.05$.

Results

Age distribution did not differ significantly among 4 studied groups, and, therefore, could not affect outcomes among groups of patients with and without T2DM. Sociodemographic indicators were also comparable between analyzed groups, with the exception of body mass index, that was significantly higher in patients with T2DM ($p<0.05$), regardless of gender (table 1). Patients with T2DM had hyperglycemia as the level of glycated hemoglobin was by 25 % higher compared with patients without T2DM ($p<0.01$). Smoking rates were lower in men with T2DM compared with non-diabetic group ($p<0.05$).

According to the results of TTE and ECG at rest, LVH was detected in 57 % of men with CAD and T2DM and was 1.5 times lower (35 %, $p<0.05$) in non-diabetic group. We did not reveal statistically significant differences in the frequency of LVH between women with and without T2DM — 40 % and 33 %, respectively (Figure 1).

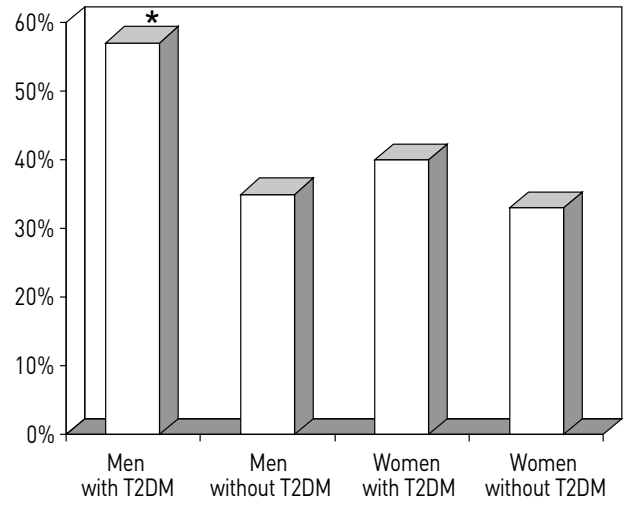

Figure 1. The prevalence of LVH.
LVH — left ventricular hypertrophy, CAD — coronary artery disease, T2DM — type 2 diabetes mellitus, [a]$p< 0.05$ from the result of comparison with other groups.

Hypokinesis of individual myocardial segments according to TTE was detected in 36 % of patients with CAD and T2DM (39 % of men and 34 % of women) and in 26 % of patients without T2DM (30 % of men and 23 % of women). These differences were not statistically significant.

According to TTE data, left ventricular ejection fraction was significantly lower in men and women with T2DM compared with those without T2DM (51.9±1.2 % and 53.4±1.2 %, $p<0.05$).

Table 1. **Clinical characteristics of study patients**

Groups	CAD with T2DM, men (n=42)	CAD with T2DM, women (n= 38)	CAD without T2DM, men (n= 40)	CAD without T2DM, women (n= 30)
Age, years	56.9±0.8	58.4±1.1	57.1±1.1	59.1±1.9
Employment status	Unemployed 15 (36 %)	Unemployed 9 (24 %)	Unemployed 13 (32 %)	Unemployed 8 (27 %)
Smoking	10 (24 %)	4 (10 %)	18 (45 %)*	5 (17 %)
Body mass index, kg/m^2	29.1±0.5*	30.8±0.7*	27.3±0.7	28.4±0.5
HbAc1, %	8.4±0.13**	8.1±0.12*	6.1±0.1	5.9±0.1
Arterial hypertension	31 (74 %)	26 (69 %)	28 (70 %)	19 (67 %)
Average CAD duration, years	6.4±0.5	6.1±0.3	5.9±0.5	5.2±0.4
Average T2DM duration, years	8.2±0.7	7.4±0.4	–	–
Antihypertensive therapy (sartans, ACE inhibitors, beta blockers, calcium antagonists, diuretics)	57.1 %	63.1 %	55 %	63.3 %
Statin therapy (atorvastatin, rosuvastatin)	35.7 %	44.7 %	30 %	40 %
Antiplatelet agents (aspirin, clopidogrel)	80.9 %	81.6 %	80 %	83.3 %
Hypoglycemic agents, including insulin therapy (metformin, sulfonylureas medications)	59.5 %	73.6 %	–	–

ACE inhibitors — angiotensin-converting-enzyme inhibitors, CAD — coronary artery disease, T2DM — type 2 diabetes mellitus, *$p< 0.05$, **$p<0.01$ from the result of comparison between patients with and without T2DM in the same sex group.

Present study included patients who underwent diagnostic CAG with possible further revascularization. The following parameters were assessed: frequency of stenosis by segments, by localization, by the degree of narrowing and the frequency of vascular lesions.

According to CAG, 69 % of men and 50 % of women had stenosis of the anterior interventricular branch of left coronary artery ($p<0.05$ compared with men without T2DM). Stenosis was revealed in 48 % and 32 % of men and women from non-diabetic groups, respectively. Stenosis of the right coronary artery was detected in 30 % of patients with T2DM and in 25 % of patients without T2DM. The stenosis rates of more than 2 coronary arteries were comparable between groups (54 % in patients with T2DM and 45 % in patients without T2DM). The frequency of distal coronary artery segments stenosis in patients with T2DM was 3 times higher compared with patients without T2DM ($p<0.05$) (Figure 2).

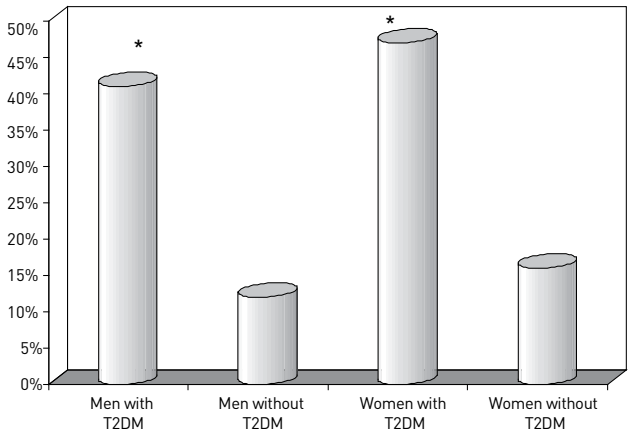

Figure 2. The prevalence of distal segment CAD.
T2DM — type 2 diabetes mellitus, [a] $p<0.05$ from the result of comparison with patients without T2DM in the same sex groups.

Discussion

This study was cross-sectional and aimed to estimate complex clinical and anatomical changes in the myocardium in patients with T2DM. Therefore, we performed comparative analysis of groups of patients with and without T2DM. The groups of patients were comparable by age. In order to assess gender differences, we also compared groups by gender. Thus, the study included 4 groups of patients.

The issue of the study is relevant as the number of patients with acute and chronic CAD among those with T2DM is constantly increasing worldwide [5, 9]. According to the data of multicentral Euroaspire study, the number of new T2DM cases increased when the control of hypercholesterinemia and arterial hypertension significantly decreased compared with previous follow-up studies. In other words, cardiometabolic disturbances and T2DM in particular seem to be the main cardiovascular disease risk factors [2].

Complex assessment of myocardial changes in patients with T2DM is important for the development of complex measures for the prevention of cardiovascular diseases.

The analyzed groups differ by body mass index that indicates the association between overall obesity and T2DM. Lower number of smokers among patients with T2DM can be associated with higher adherence to lifestyle modifications of such patients. People with diabetes are generally more likely to have a chance of education or training for lifestyle changes.

In this study we assessed 2 main aspects that characterize myocardial state: left ventricular hypertrophy and CAG changes. According to experts, only complex diagnostic methods, including imaging methods, can provide additional predictive value when studying the state of myocardium in patients with T2DM [12, 13].

LVH is known to be an independent risk factor for cardiovascular disease that is directly associated with arterial hypertension. Moreover, LVH is one of the main factor that contributes to the development of myocardial dysfunction and heart failure in patients with T2DM [4]. According to the multicenter study, T2DM increases the risk of LVH by approximately 1.5 times which may be associated with abdominal obesity [11]. The frequency of arterial hypertension was comparable between groups. LVH has 1.5 more frequent among men and women with T2DM compared with those without T2DM. Moreover, LVH was associated with the gender and was more pronounced in men with T2DM compared with other groups. This may be associated with 2 main reasons. First, not only arterial hypertension but also neurohumoral components and insulin resistance play a pivotal role in the development of LVH. According to the theory of G Reaven, which describes the association between arterial hypertension and insulin resistance, this state causes a cascade of disturbances including direct effect on target organs [14]. This also highlights the importance of target antihypertensive therapy in patients with LVH and T2DM. In current study most patients received antihypertensive therapy and, obviously, its effect was not so pronounced.

Anatomy of the coronary arteries affect the prognosis of patients with T2DM [15, 16]. Patients with T2DM have several CAD features such as the preva-

lence of painless ischemia that is associated with decreased pain sensitivity in such patients. CAG is still a gold standard diagnostic tool for the diagnosis of CAD including patients with T2DM [17]. Several clinical studies have shown that diffuse coronary artery atherosclerosis, decreased coronary reserve, and multifocal vascular lesions are often observed in such patients [2, 15, 18]. The study showed that the distal coronary arteries lesions predominated in patients with T2DM.

According to the European clinical practice guidelines for acute coronary syndrome, percutaneous coronary intervention is the main revascularization method in patients with T2DM and acute myocardial infarction. It is also recommended to use drug-eluting stents in patients with T2DM. Coronary artery bypass grafting is superior to percutaneous coronary interventions due to common multifocal vascular lesions in patients with T2DM [13, 15]. It should be noted that patients with T2DM often have concomitant diseases (chronic kidney disease and cerebrovascular diseases) that adversely affect coronary revascularization outcomes [2].

Moreover, our study had some limitations. The sample size was relatively small due to inclusion and exclusion criteria. Other limitations included cross-sectional design of the study and the absence of multivariate analysis.

Conclusion

LVH, hypokinetic segments of myocardium and coronary artery stenosis predominated in CAD patients with T2DM than those without T2DM which should be a consideration during treatment. LVH was also associated with gender and predominated in men with T2DM. Multicenter clinical study based on the protocol of our investigation in the future will allow to propose diagnostic algorithms for risk stratification and to develop preventive strategies for the patients with CAD and T2DM.

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International Heart and Vascular Disease Journal • Volume 9, № 32, December 2021

Journal of the Cardioprogress Foundation

ORIGINAL ARTICLES

DOI 10.24412/2311-1623-2021-32-21-27

Cardiorenal connections in patients with type 2 diabetes mellitus and hypothyroidism

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Summary

Objective. *To study the cardiorenal connections in patients with chronic kidney disease (CKD) and type 2 diabetes mellitus (DM) in combination with primary hypothyroidism.*

Materials and methods. *The study included 203 patients: group 1 (76 patients) with type 2 DM and primary hypothyroidism, group 2 (127 patients) with type 2 DM without thyroid disease. All the participants underwent standard clinical examination, determination of the glomerular filtration rate by the level of creatinine and cystatin C (GFR-creat, GFR-cys), echocardiography, doppler ultrasonography of the lower extremity arteries, 24-hour ambulatory blood pressure monitoring (ABPM), endothelium-dependent vasodilation (Δd) assessment.*

Results. *The prevalence of CKD was 64.47±5.49% in group 1, and 44.88±4.41% in group 2 (p= 0.0059); the frequency of normoalbuminuric CKD (NA-CKD) was 32.89±5.39% and 16.54±3.3%, respectively (p=0.0103). Cardiovascular pathology was significantly more common in patients with NA-CKD compared with patients with diabetic nephropathy.*

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According to echocardiography, the left ventricular (LV) ejection fraction correlated with the level of creatinine (r= –0.2737; p= 0.0470), in group 1 — with albuminuria (r= –0.7871, p= 0.0005); in group 2 — with GFR-creat (r= 0.2148, p= 0.0407). LV isovolumic relaxation was associated with GFR-creat (r= –0.299, p= 0.0365) and GFR-cys (r= –0.9064, p= 0.0093) in group 2; LV myocardial mass index — with GFR-creat in group 1 (r= –0.5410, p=0.0305), GFR-creat in group 2 (r= –0.4235, p= 0.0252), GFR-cys in group 2 (r= –0.4207, p= 0.0634) and with albuminuria in both groups (r=0.3843, p=0.0157).

The concentration of cystatin C in both groups positively correlated with several ABPM and echocardiography parameters and negatively correlated with Δd.

Conclusion. *The combination of primary hypothyroidism and type 2 DM contributes to the increase of risk of cardiovascular pathology and CKD incidence. The strongest cardiorenal connections were shown in patients with normoalbuminuric CKD. The obtained data showed the importance of screening for thyroid dysfunction in patients with type 2 DM and cardiorenal pathology.*

Keywords: *cardiorenal syndrome, chronic kidney disease, diabetes mellitus, hypothyroidism, cystatin C.*

Conflict of interest: None declared.

Received: 30.04.2021 Accepted: 28.07.2021

Introduction

Today, the connections between cardiovascular disease (CVD) and chronic kidney disease (CKD) in patients with diabetes mellitus (DM) are thoroughly investigated. Epidemiologic studies have shown that CKD is an independent risk factor of congestive heart failure (CHF), cardiovascular mortality [1] and significantly reduced quality of life [2]. CKD is associated with myocardial infarction (MI), stroke, peripheral artery disease (PAD) [1].

Cardiorenal syndrome (CRS) is a term that defines "disorders involving both the heart and the kidneys in which acute or chronic dysfunction in 1 organ may induce acute or chronic dysfunction in the other organ" [3].

Reduced glomerular filtration leads to sodium and water retention and hypervolemia, arterial hypertension (AH), increased left ventricular (LV) afterload with LV hypertrophy (LVH) [4]. CVD progression in diabetic patients with diabetic nephropathy and CKD is caused by additional risk factors (RF) such as albuminuria, systemic inflammation, autonomic neuropathy, anemia, oxidative stress, hyperparathyroidism, hyperphosphatemia, vitamin D deficiency [5].

Along with DM, thyroid disorders are also highly prevalent. According to epidemiological data, the incidence of hypothyroidism manifestation is up to 10 % in general population and up to 6.9–35 % in diabetic individuals [6, 7]. Thyroid hormones play a major role in normal kidney and CVS functioning. Studies have shown that diabetic patients with concurrent symptomatic and subclinical hypothyroidism have earlier development of albuminuria, proteinuria and reduced glomerular filtration rate (GFR) [8].

Thyroid hormones not only directly regulate kidney function (filtration, secretion and reabsorption) but also have prerenal (indirect) effects on CVD and kidney perfusion [9].

Hypothyroidism is highly prevalent in diabetic patients. Negative effects of hypothyroidism include dyslipidemia, endothelial dysfunction, rise in peripheral vascular resistance and antidiuretic hormone production and are associated with CVD and CKD. Therefore, the objective of this study was to investigate cardiorenal connections in patients with CKD and coexistent DM and hypothyroidism; evaluate diagnostic values of cystatin C as a marker of CRS in this group of patients.

Materials and methods

Our study included 203 patients with DM that were divided into two groups: group I — 76 participants with type 2 diabetes (T2D) and primary hypothyroidism (PH) (T2D+PH) (n=76, 21 men, 55 women): autoimmune thyroiditis — n=45, postoperative hypothyroidism — n=31; group II — patients with T2D without thyroid disease (T2D) (n=127, 38 men, 89 women). The two groups didn't have any statistically significant differences in the age, sex and the duration of T2D of the participants (Table 1) and also in the type of antihypertensive, anti-anginal, hypoglycemic and hypolipidemic therapy.

We collected anthropometric parameters, evaluated the levels of hemoglobin A1C, total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerids (TG), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), thyroid-stimulating hormone (TSH), thyroxine (T4). Cystatin C levels were evaluated using the Human Cystatin C ELISA. Albuminuria was evaluated in a single urine portion with the NycoCard reader. GFR was calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula based on the creatinine level (CKD-EPI-creat) and cystatin C (CKD-EPI-cys). 24-hour blood pressure monitoring was performed with Valento monitor, Russia. Echocardiography (Echo) was performed with the Acuson Sequoia 512 (Siemens, USA) system. PAD was verified using the LOGIQbookXP, China ultrasound machine. Endothelium-dependent vasodilation was assessed with the D. Celermajer (1999 r.) method based on the brachial artery diameter changes (Δd).

Patients with active urine tract infections (UTI) and CKD stages 4–5 were excluded from the study.

Statistical analysis was performed using the "Statistica 10.0" software. The Kolmogorov-Smirnov test was used to check if the set of data came from a normal distribution. Quantitative (numeric) values were summarized using the median with the upper and lower quartiles — Me [Q25; Q75]. Qualitative (ategorical) values summarized using the proportions (%). The Mann-Whitney U test was used to compare differences between two independent groups. The Spearman rank correlation coefficient (Spearman ρ) was used to determine the relation existing between two sets of numeric data.$p<0.05$ was considered statistically significant.

Study protocol was approved by the local Ethics Committee. Informed consents were obtained prior to participation in the study.

Results and discussion

The main clinical and laboratory values are presented in Table 1. The comparison of the two groups identified higher levels of hemoglobin A1c, lipids, HOMA-IR in group I that is similar to the data presented in other research works: most studies have shown that patients with T2D and hypothyroidism have increased insulin resistance and reduced glucose uptake. Primary hypothyroidism is associated with atherogenic dyslipidemia [10].

The prevalence of AH, CAD, PAD, as well as history of MI, arrythmias and AF was higher in patients with T2D and PH (Figure 1).

Today, along with the rising number of cases of classic albuminuria there's an increase in normoalbuminuric diabetic kidney disease (NADKD) prevalence especially in diabetic patients. This is possibly due to the use of antihypertensive medications with antialbuminuric effects; increased effectiveness of hypolipidemic therapy; the use of new hypoglycemic medications with nephprotective effects. On the one hand, NADKD is associated with lower risk of end-stage renal disease; on the other hand, the risks of MI, stroke, cardiovascular and all-cause mortality in T2D [11].

Table 1. **The main clinical and laboratory values**

Value	Group I (T2D+PH)	Group II (T2D)	p*
Age, years	60.5 [55.0;66.0]	59.0 [53.5;63.0]	0.4118
Duration of T2D, years	11.0 [5.0;16.0]	10.0 [7.0;14.0]	0.6209
TSH, mU/L	5.51 [2.93;11.08]	1.655 [1.26;2.5]	0.00000000007
T4., nmol/L	12.7 [10.8;14.1]	13.85 [12.3;15.8]	0.0404
HbA1c, %	8.9 [7.9;11.3]	8.0 [7.1;9.0]	0.0253
HOMA-IR	5.7 [3.14;8.32]	2.83 [1.9;9.36]	0.027
Total cholesterol, mmol/L	6.29 [5.55;7.43]	5.75 [5.0;6.6]	0.0011
LDL, mmol/L	3.84 [3.38;4.58]	3.41 [2.8;4.0]	0.0062
HDL, mmol/L	1.1 [0.89;1.22]	1.27 [1.05;1.46]	0.0062
TG, mmol/L	2.27 [1.76;2.8]	1.635 [1.225;2.15]	0.0012
Albuminuria, mg/L	16.0 [5.0;50.0]	5.5 [0;20.0]	0.018
Creatinine, μmol/L	88.0 [78.0;99.0]	85.5 [72.0;95.0]	0.044
GFR, ml/min/1.73 m^2 (CKD-EPI-creat)	59.0 [50.0;72.0]	66.0 [54.0;81.0]	0.0281
Cystatin, ng/ml	1058.0 [976.55;1110.0]	1282.5 [1087.0;1417.0]	0.0321
GFR, ml/min/1.73 m^2 (CKD-EPI-cys)	67.0 [63.0;74.0]	51.5 [45.0;65.0]	0.0271

Note. CKD — EPI — The CKD Epidemiology Collaboration, GFR — glomerular filtration rate, HbA1c — hemoglobin A1c, HDL — high-density lipoprotein, HOMA-IR — Homeostatic Model Assessment for Insulin Resistance, LDL — low-density lipoprotein, PH — primary hypothyroidism, T2D — type 2 diabetes, T4 — free thyroxine, TSH — thyroid-stimulating hormone. * — $p<0.05$ is considered statistically significant.

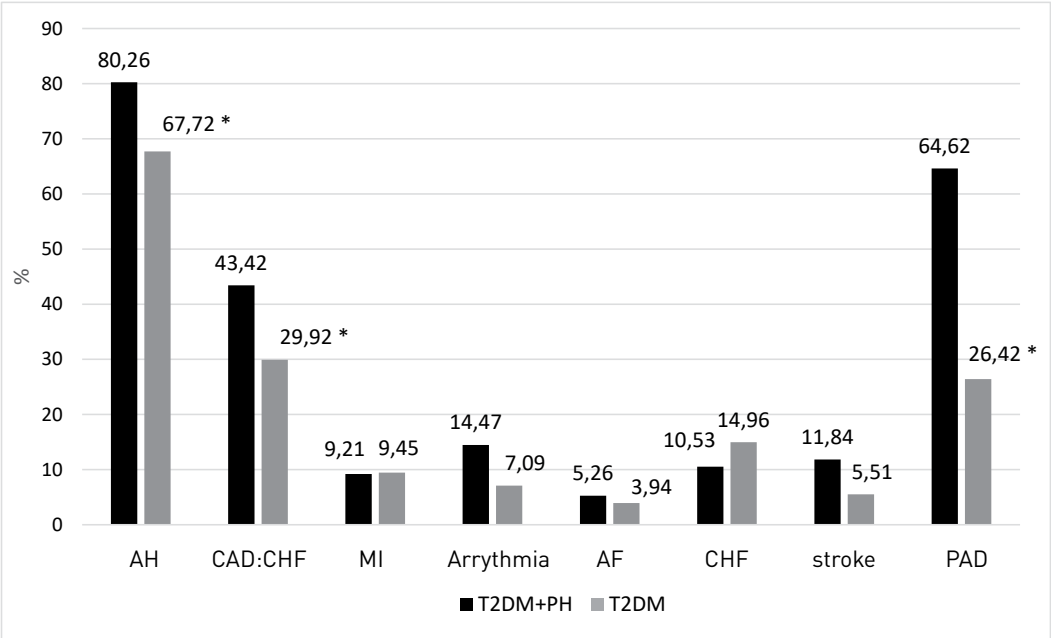

Figure 1. Cardiovascular disease prevalence in the T2D+PH and T2D groups.
Note. AF — atrial fibrillation, AH — arterial hypertension, CAD — coronary artery disease, CHF — congestive heart failure, PAD — peripheral artery disease, PH — primary hypothyroidism. T2D — type 2 diabetes. * — p<0.05 is considered statistically significant.

In this study, the prevalence of CKD in the 1st group was higher than in the 2nd group. The prevalence of classic albuminuric diabetic nephropathy was similar in both groups, and the prevalence of NADKD was twice as high in T2D-PH group as in T2D group (Table 2).

More patients with NADKD had CVD (Figures 2, 3). Diabetic nephropathy often co-existed with diabetic retinopathy — in 43.75±12.81 % and 72.73±9.72 % cas-

Table 2. **Kidney dysfunction in patients with T2D and PH**

Value	Group I (T2D+PH)	Group II (T2D)	p*
Diabetic nephropathy, %	21.05±4.68	17.32±3.36	0.518
NADKD, %	32.89±5.39	16.54±3.3	0.0103
Kidney stones, chronic pyelonephritis, %	10.53±3.52	11.02±2.78	0.9129
Total cases of CKD, %	64.47±5.49	44.88±4.41	0.0058

Note. CKD — chronic kidney disease, NADKD — normoalbuminuric diabetic kidney disease, PH — primary hypothyroidism. T2D — type 2 diabetes. * — p<0.05 is considered statistically significant.

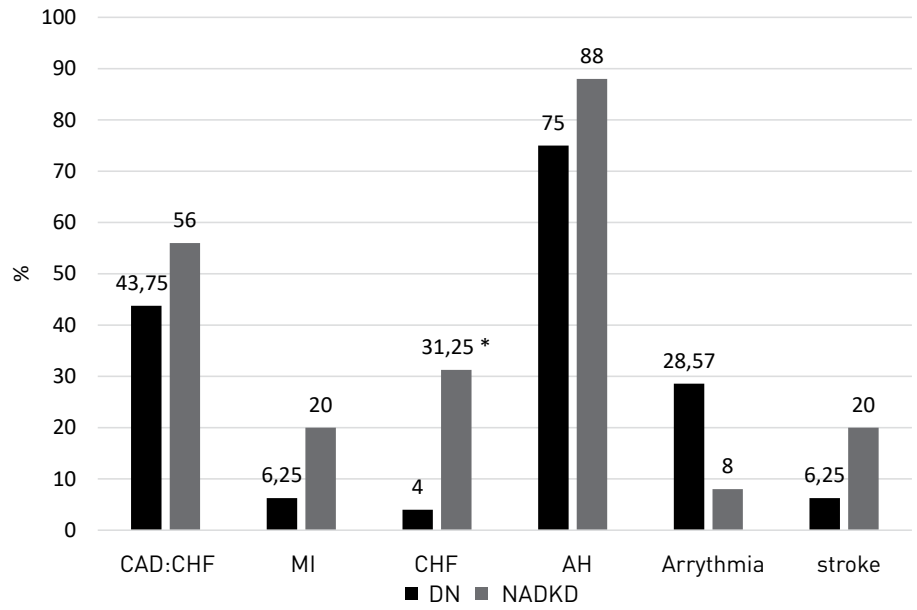

Figure 2. Prevalence of cardiovascular disease in patients with DN and NADKD in the T2D group.
Note. AH — arterial hypertension, CAD — coronary artery disease, CHF — congestive heart failure, DN — diabetic nephropathy, NADKD — normoalbuminuric diabetic kidney disease, T2D — type 2 diabetes. * — p<0.05 is considered statistically significant.

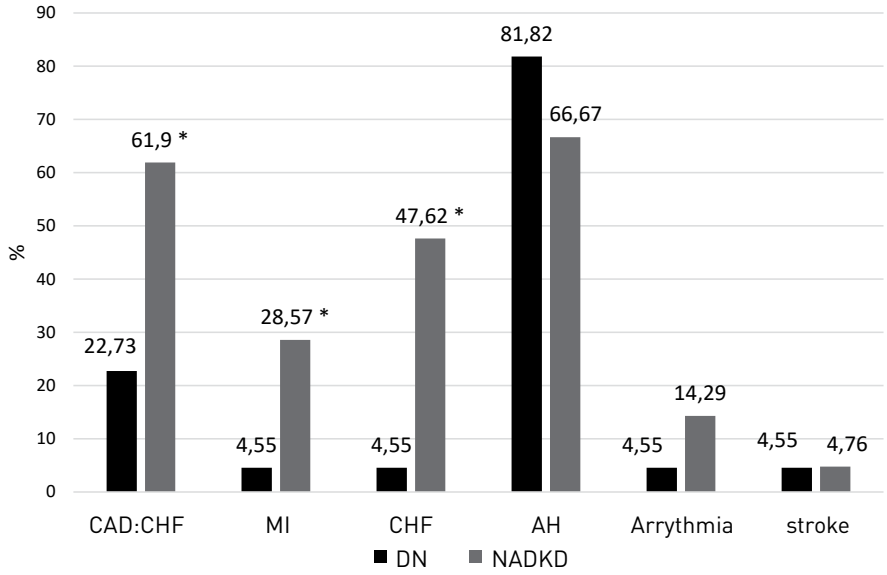

Figure 3. Prevalence of cardiovascular disease in patients with DN and NADKD in the T2D group.
Note. AH — arterial hypertension, CAD — coronary artery disease, CHF — congestive heart failure, DN — diabetic nephropathy, NADKD - normoalbuminuric diabetic kidney disease, T2D — type 2 diabetes. * — p<0,05 is considered statistically significant.

es in groups 1 and 2, respectively (p=0.0801). That is a sign of the nephron-retinal syndrome development.

The analysis of AH and CKD connection using the 24-hour blood pressure monitoring has shown that the 24-hour systolic and diastolic blood pressure indices were higher in patients with stage C3a and C3b CKD compared with in those with GFR>60 ml/min/1.73 m^2 in both groups. This is a sign of the 24-hour blood pressure rhythm imbalance and insufficient blood pressure decrease during nighttime (Figure 4). Patients with stage C3a and C3b CKD had faster and more pronounced systolic and diastolic blood pressure elevation in the morning.

According to echocardiography findings in patients with stage C3 CKD the median thickness of interventricular wall was 13.0 [12.0; 14.0] mm, the median thickness of left ventricular posterior wall was 12.85 [12.0;13.5] mm; in patients with GFR>60 ml/min/1.73 m^2–12.0 [11.0; 13.0] mm (p=0.0462) and 12.0 [11.0;13.0] mm (p=0.0593), respectively. The maximal IVRT was identified in patients with stage 3 CKD — –0.12 [0.10; 0.12] sec, in СКФ≥90 ml/min/1.73m^2–0.095 [0.09; 0.1] sec (p=0.0296).

Left ventricular ejection fraction (LVEF) reversely correlated with creatinine level (r=–0.2737, p=0.047) and with albuminuria in group I (r=–0.7871, p=0.0005);

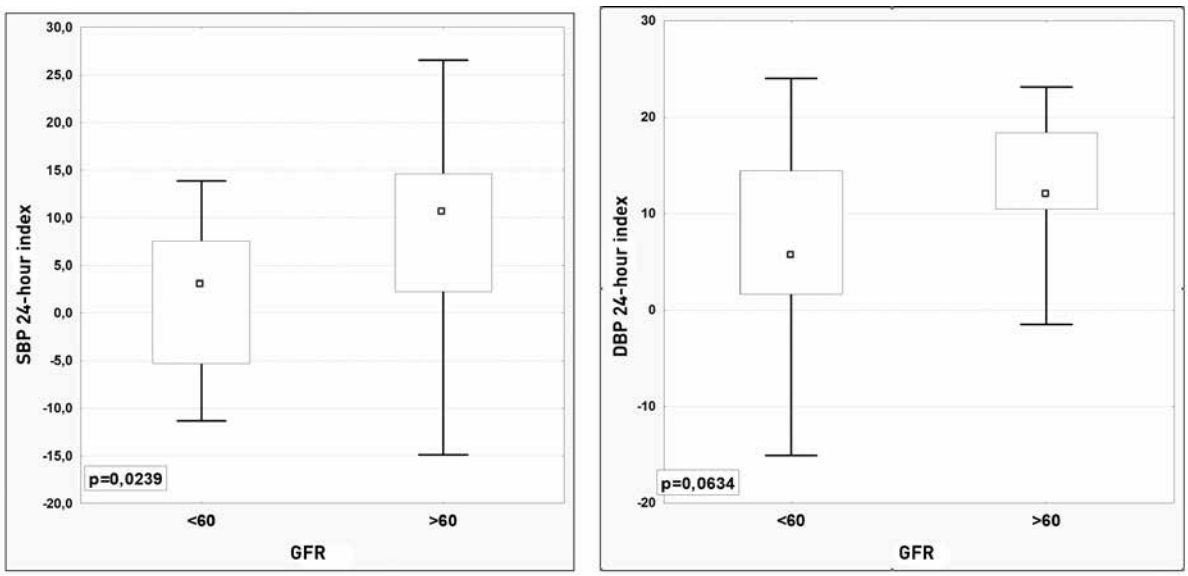

Figure 4. Systolic (SBP) and diastolic (DBP) blood pressure 24-hour indices in patients with different glomerular filtration rate (GFR) values

and positively correlated with GFR-creat in group II (r=0.2148, p=0.0407). IVRT correlated with GFR-creat and GFR-cys in group II: r=–0.299 (p=0.0365) и r=–0.9064 (p=0.0093), respectively. A strong correlation between the left ventricular (LV) mass with GFR-creat in group I (r=–0.541, p=0.0305), GFR-creat in group II (r=–0.4235, p=0.0252), GFR-cys in group II (r=–0.4207, p=0.0634); with albuminuria in both groups (r=0.3843, p=0.0157).

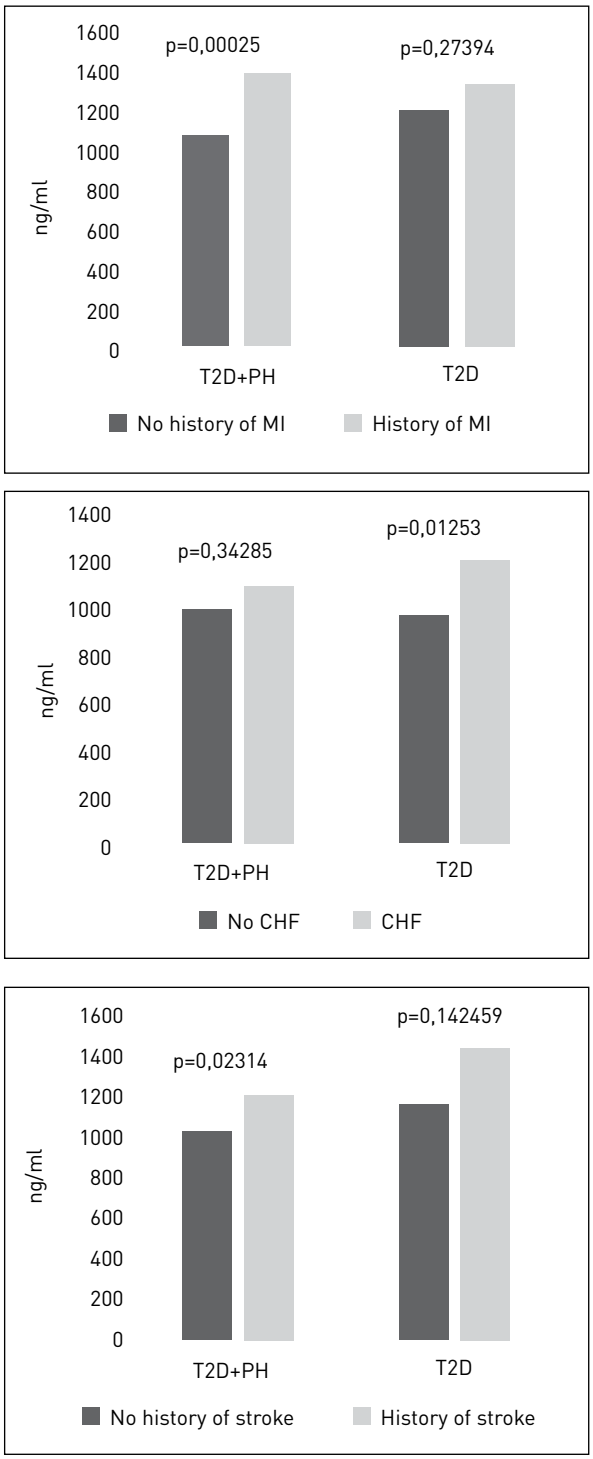

Figure 5. Cystatin C values in patients from T2D+PH and T2D groups with cardiovascular disease

The latest data show that cystatin C is not only an early marker of kidney dysfunction but also of cardiorenal syndrome, CHF, ACS, and a cardiovascular risk factor in general. Cystatin C is thought to play a role in systemic inflammation [12]. Some studies have also shown that thyroid hypothyroidism is associated with lower levels of Cystatin C [13].

According to our results, the levels of cystatin C were lower in group I compared with group II — 1019.0 [976.55;1097.5] and 1350 [1087.0;1485.0] ng/ml, respectively, (p=0.008542) and correlated with T4 levels (r=0.5798, p=0.0278).

In group II cystatin C levels correlated with age (r=0.5934, p=0.0032), 24-hour blood pressure monitoring parameters: DBP variability (r=0.585, p=0.0269), DBP index (r=0.6585, p=0.0269), 24-hour SBP index (r=–0.4661, p=0.0028); echocardiography parameters — IVS thickness (r=0.3625, p=0.1243) and left ventricular posterior wall thickness (r=0.4566, p=0.0033), LV IVRT (r=0.7121, p=0.0679), LV mass (r=0.5666, p=0.0056), endothelium-dependent vasodilation parameter Δd (r=–0.6868, p=0.0332).

In T2D+PH group cystatin C levels correlated with DBP (r=0.4958, p=0.0044), LVEF (r=–0.3633, p=0.0764), LV IVRT (r=0.3286, p=0.0893), aortic wall thickness (r=0.7595, p=0.0028), and Δd (r=–0.2765, p=0.1386).

Cystatin C levels were increased in patients with CHF with a history of prior MI and with a history of stroke (Figure 5). Cystatin C levels were also increased in patients with LVH and LV diastolic dysfunction according to echocardiography. However, these differences weren't statistically significant.

Conclusion

Primary hypothyroidism together with type 2 diabetes causes increased insulin resistance, lipid and carbohydrate imbalance, increased risk of cardiovascular and chronic kidney disease. There is also a mild risk of CVD and CKD in normoalbuminuric CKD.

High prevalence of CKD and CVD in patients with co-existent T2D and hypothyroidism means that PH screening is necessary in patients with T2D and CVD.

The associations between cystatin C and 24-hour blood pressure monitoring and echocardiography parameters allow us to recommend it as a cardiorenal syndrome marker in patients with T2D.

Conflict of interest: none declared.

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International Heart and Vascular Disease Journal • Volume 9, № 32, December 2021
Journal of the Cardioprogress Foundation

ORIGINAL ARTICLES

DOI 10.24412/2311-1623-2021-32-28-33

The association between aggressiveness, clinico-instrumental features and the mortality risk in patients with CAD after percutaneous coronary intervention

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Summary

Objective. *To identify the association between the aggressiveness and clinico-instrumental features in patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) and to assess the impact of aggressiveness on mortality risk during one-year follow-up after the surgery.*

Materials and methods. *The study was based on the data of "Prospective Registry of PCI". The registry contains the information about 1080 patients (764 men and 254 women) aged from 33 to 90 years (average age — 58,9±9,7 years). The Russian version of Cook and Medley hostility scale was used to assess the level of aggressiveness. Life status after one year of prospective observation was determined in 986 patients (96.9 %). The statistical analysis included: binary logistic regression and Cox proportional hazards model.*

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Results. *The binary logistic regression analysis revealed significant association between the level of aggressiveness, gender, and the severity of chronic heart failure (CHF). During the follow-up, 24 (2,4 %) of patients died from all causes and 21 (2.1 %) — from cardiovascular diseases (CVDs). Relative risk (RR) for the parameter of aggressiveness, which was assessed in points, for all-cause mortality was 1,05 (95 % CI 0,98–1,13, p=0,04), for cardiovascular mortality — 1,08 (95 % CI 1,01–1,17, p=0,04). The analysis of categorical variables revealed that in patients with high level of aggressiveness the RR for all-cause mortality was 2,28 with 95 % CI from 0,93 to 5,61, p=0,07, and for cardiovascular mortality 3,01 with 95 % CI from 1,14 to 7,94, p=0,03 compared with patients from the control group.*

Conclusion. *The parameter of aggressiveness in patients with CAD after PCI was independently and significantly associated with gender and CHF severity, as well as with the risk of cardiovascular mortality during 1-year follow-up.*

Keywords: *coronary artery disease, aggressiveness, psychosocial risk factors, percutaneous coronary interventions.*

Conflict of interest: None declared.

Received: 15.06.2021 Accepted: 25.08.2021

Introduction

Cardiovascular diseases are still the main cause of mortality in developed and most developing countries [1]. In our country psychosocial risk factors (RF) contribute to the development, progression and mortality from cardiovascular diseases [2]. The analysis of the literature data shows that today the main focus is on the association between psychosocial RF and the severity of cardiovascular diseases, in particular coronary artery disease (CAD) and chronic heart failure (CHF) [3]. For example, it has been shown that social isolation, hostility, depression negatively affect the prognosis in patients with cardiovascular pathology and significantly increase their mortality [4].

Objective

To access the prevalence of high level of aggressiveness in patients with coronary artery disease (CAD) according to the data from "Prospective Registry of PCI" that allows to identify the association between the aggressiveness and clinico-instrumental features and to assess its impact on mortality risk during one-year follow-up after the coronary artery stenting (CAS).

Materials and methods

The study was based on the data of "Prospective Registry of PCI" that has state registration database No. 2020621655 [5]. The registry contains the information on 1018 patients (764 men and 254 women) aged from 33 to 90 years (mean age 58.9± 9.7 years). The clinical part of the database contains information on medical history, concomitant pathology, smoking, alcohol consumption, basic anthropometric data (office blood pressure (BP), height, weight, body mass index (BMI), waist circumference (WC)), as well as the results of biochemical blood test, including lipid panel. In addition, the electronic database contains the results of ECG, echocardiography and coronary angiography of patients before PCI. The prospective part of the registry contains information on the status of 986 patients (96.9 %) obtained one year after the intervention.

Data on the stable character trait — aggressiveness, were obtained using the Cook-Medley Hostility Scale adapted by Sobchik L.N. [6]. The scale is highly reliable and valid [7]. The questionnaire includes 27 questions and 3 subscales: subscale of cynicism, subscale of aggressiveness and subscale of hostility. The Cook-Medley scale adapted by L.N. Sobchik uses the Likert scale that consist of 6 items that grades from 1 ("Never") to 6 ("Usually"). The final score was calculated by summing the scores of aggressiveness subscale questions. The scores were split into 2 categories according to percentiles. Patients with the score of over 75th percentiles by the aggressiveness subscale were assigned to the group with high aggressiveness. Patients with the total score less than

the 75th percentile were assigned to the comparison group. The "Prospective Registry of PCI" contains complete information on 947 patients. Thus, the survey response rate was 93%. The study was approved by the local Ethics committee, informed consent was waived from all the participants before the study.

Statistical analysis was performed using SPSS software (SPSS Inc., version 21). The results are presented as M± SD (mean± standard deviation). The normality of distribution was assessed using Kolmogorov — Smirnov test. Student's t-test was used to compare normally distributed quantitative variables, and nonparametric Mann — Whitney test — for the variables that significantly deviated from the normal distribution. The Chi-squared test (χ^2) was used to assess the significance of differences between qualitative variables. Multivariate analysis was performed using binary logistic regression, and the odds ratio (OR) with 95% confidence interval (CI) were calculated. A multivariate analysis by Cox proportional hazard regression model was performed to estimate the relative risk (RR) of death and its 95% CI. Confounding factors included: gender, age, alcohol abuse, smoking, BMI and blood pressure (systolic and diastolic), total cholesterol, atrial fibrillation (AF), diabetes mellitus (DM), left ventricular (LV) ejection fraction, the severity of CHF (functional class (FC) according to NYHA)), as well as acute coronary syndrome (ACS) during admission and the severity of coronary stenosis according to the SYNTAX score.

Results

The mean of aggressiveness by Cook-Medley hostility scale was 29.6±6.6 points. High level of aggressiveness was observed in 217 patients (22.9%). Clinical and instrumental characteristics of patients depending on the level of aggressiveness are presented in Table 1.

Compared groups significantly differed by gender. The proportion of men was higher in group with high level of aggressiveness (p=0.004). Patients with high level of aggressiveness had lower values of systolic blood pressure (p=0.058) and higher functional class of chromic heart failure (p=0.058). Patients with high level of aggressiveness had lower LV ejection fraction (p=0.009). Other parameters did not differ significantly between groups.

The results of coronary angiography and PCI did not differ significantly between groups with different levels of aggressiveness (Table 2). There was a tendency towards more frequent lesion of the anterior interventricular artery in patients with high level of aggressiveness (p=0.07).

Table 1. **Clinical and instrumental parameters in patients depending on the level of aggressiveness**

Parameters		Comparative group (n=730)	Group with high level of aggressiveness (n=217)	p
Men, %		74,4	83,9	0,004
Age, years		58,3±9,0	58,4±9,5	0,96
Postinfarction cardiosclerosis, %		44,1	43,3	0,84
Smoking, %		40,1	40,1	0,99
Alcohol abuse, %		8,4	8,8	0,85
BMI, kg/m²		30,4±5,2	30,9±5,0	0,38
WC, cm		101,3±12,7	102,2±11,0	0,29
Arterial hypertension, %		89,7	87,6	0,37
Systolic BP, mmHg		135,7 20,4	131,6/20,3	0,058
Diastolic BP, mmHg		83,7 11,2	82,0/12,8	0,21
Hypercholesterolemia, %		61,4	63,6	0,56
Total cholesterol, mmol/l		4,98±1,27	5,02±1,32	0,73
Low-density lipoproteins, mmol/l		3,18±1,11	3,24±1,17	0,73
High-density lipoproteins, mmol/l		1,16±0,37	1,11±0,31	0,10
Triglycerides, mmol/l		1,74±1,06	1,80±1,14	0,51
Chronic Heart Failure FC (NYHA), %	I–II	79,3	73,1	0,058
	III–IV	20,7	26,9	
DM, %		20,8	22,6	0,58
AF, %		9,2	11,1	0,42
ACS at admission, %		31,8	35,5	0,31
LV ejection fraction, %		54,1±8,4	52,2±9,3	0,009

ACS — acute coronary syndrome, AF — atrial fibrillation, DM — diabetes mellitus, FC — functional class, BMI — body mass index, BP — blood pressure, LV — left ventricular, WC — waist circumfluence.

Multivariative analysis regression model included as covariates all variables with statistically significant differences or with tendency for this difference. The binary logistic regression analysis showed independent association between high level of aggressiveness, sex and FC of CHF (Figure 1). Thus, the probability of high level of aggressiveness was approximately 2 times lower in women compared with men

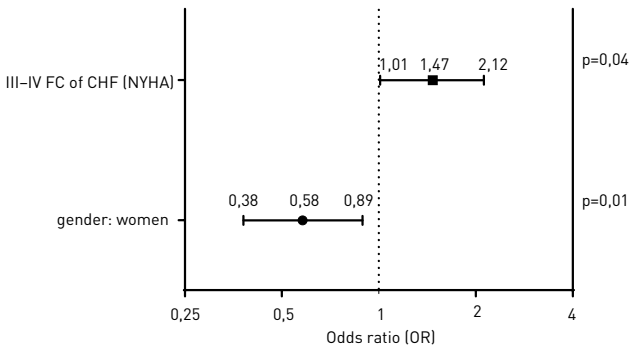

Figure 1. Independent associations between parameters and high level of aggressiveness in patients with coronary artery disease after PCI.

Table 2. **Comparative characteristics of coronary angiography and PCI results depending on the level of aggressiveness**

Parameters		Comparison group (n=730)	Group with high level of aggressiveness (n=217)	p
Stenosis of the trunk of the left coronary artery	%	1,5	1,4	0,89
Stenosis of the anterior intraventricular artery	%	57,3	64,1	0,07
Stenoses of the circumflex artery	%	25,3	26,7	0,68
Stenoses of the right coronary artery	%	44,2	43,3	0,81
Stenosis of second-order coronary arteries	%	26,4	27,6	0,72
Single-vessel coronary artery disease	%	60,8	58,5	0,41
Double-vessel coronary artery disease	%	25,8	24,4	
Multivessel coronary artery disease	%	13,4	17,1	
SYNTAX score	units	10,1±7,4	11,1±8,7	0,25
Number of stents	number	1,33±0,67	1,33±0,69	0,93
Optimal PCI outcome	%	98,1	98,2	0,94
Arterial dissection	%	2,6	1,9	0,51

(p=0.01). Patients with III–IV FC of CHF had 1.5 times greater chance of high aggressiveness compared with lower FC (p=0.04).

During the prospective follow-up, 24 (2.4%) patients died from all causes and 21 (2.1%) patients from cardiovascular diseases. As seen from Fig. 2–3, after adjusting for associated factors, aggressiveness was statistically significantly associated with cardiovascular mortality. Thus, with the increase of aggressiveness by one point, the risk of death from cardio-

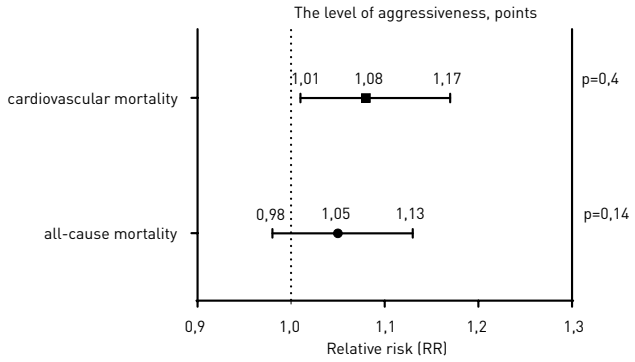

Figure 2. Associations between the quantitative variable aggressiveness in points and the risk of cardiovascular and all-cause mortality (multivariate model)

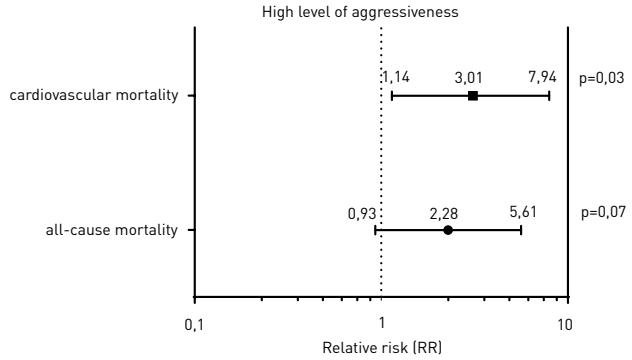

Figure 3. Associations between the categorical variable of aggressiveness and the risk of cardiovascular and all-cause mortality (multivariate model).

vascular disease increased by 8% (p=0.04). Patients with high level of aggressiveness had 3 times higher relative risk of cardiovascular mortality compared with the control group (p=0.03).

Discussion

Several studies have shown that male gender is associated with higher aggressiveness [8] that can be explained by greater level of sex hormone testosterone. Nowadays the connection between aggressive behavior and high level of testosterone is unambiguous [9, 10].

According to the literature data, aggressiveness is the risk factor for the development of arterial hypertension [11]. However, according to the results of the analysis, there is a tendency towards the decrease of systolic blood pressure in patients with higher level of aggressiveness. However, the influence of confounding factors cannot be excluded. For example, patients with high level of aggressiveness had higher CHF class and, accordingly, lower LV ejection fraction, which probably caused lower systolic blood pressure in this group of patients. The most common mechanisms of the effect of aggressiveness on the development and progression of cardiovascular diseases include endothelial dysfunction, platelet and proinflammatory cytokines activation [12, 13]. On the other hand, behavioral mechanisms such as low compliance, resistance to lifestyle changes and insufficient cardiac rehabilitation, which are common in patients with high aggressiveness, can also aggravate the clinical picture of cardiovascular diseases, including CHF. This, probably, can explain the association between aggressiveness and a more severe course of CHF, according to the data of binary logistic regression [14]. There are studies that show the relationship between aggressiveness and the frequency of admissions of patients with CHF [15]. Thus, it can be

assumed that high level of aggressiveness serves as an independent RF for more severe course of CHF.

Present study demonstrates that high level of aggressiveness is independently associated with threefold increase of cardiovascular mortality. K.M. Appleton et al. [16] also found an independent association between the Cook-Medley hostility score and all-cause mortality (RR 1.14, 95% CI 1.01–2.29). According to the results of the meta-analysis by Y. Chida et al., aggressiveness and hostility were associated with increased risk of cardiovascular complications in both healthy controls (1.19; 95% confidence interval [CI]: 1.05 to 1.35, p=0.008)), and patients with cardiovascular pathology (1.24; 95% CI: 1.08 to 1.42, p=0.002) [17]. According to other studies, the relationship between hostility and adverse events is not clear [12] or completely absent [18]. For example, Wong J.M. et al. showed that aggressiveness was associated with a poor prognosis (RR 1.68, p<0.0001), but this association lost its statistical significance when behavioral risk factors such as smoking and physical inactivity were added to the multivariate model (RR 1.25, p<0,13) [18]. The authors, who in their studies did not confirm the independent association of aggressiveness with cardiovascular mortality, assume that aggressiveness realizes its negative effect through other biological and behavioral risk factors [12], such as unhealthy lifestyle (insufficient physical activity, excessive alcohol consumption, smoking, unhealthy diet, etc.) [17]. A number of studies have demonstrated the connection between hostility / aggressiveness and low socioeconomic status, low educational level and social support, as well as with general dissatisfaction with family relations [19]. These aspects could also exacerbate negative influence of considered risk factors.

Conclusion

Thus, the parameter of aggressiveness in patients with CAD after PCI was independently and significantly associated with gender and CHF severity, as well as with the risk of cardiovascular mortality during 1-year follow-up.

Conflict of interest: None declared.

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International Heart and Vascular Disease Journal • Volume 9, № 32, December 2021

Journal of the Cardioprogress Foundation

REVIEW ARTICLES

DOI 10.24412/2311-1623-2021-32-34-40

Secondary hyperlipidemia: definition, phenotypes, and inducing factors

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Abstract. *The investigations related to lipid metabolism disorders have been relevant for many years, due to its correlation with cardiovascular risk and the leading positions of cardiovascular mortality. Timely diagnosis and treatment of dyslipidemia increases therapy effectiveness and, therefore, improves the quality and increases life expectancy. This review article examines current understanding of the secondary dyslipidemia phenotypes and its causes.*

Key words: *secondary hyperlipidemia, risk factors for dyslipidemia, phenotypes of secondary hyperlipidemia.*

Conflict of interest: none declared.

Received: 15.07.2021 Accepted: 02.09.2021

Cardiovascular diseases (CVDs) are still the leading cause of death and disability. According to Rosstat, 938538 people deceased due to CVDs in 2020 that by 11.6% higher than in 2019 [11, 33]. The increase of cardiovascular mortality may be associated with the COVID-19 pandemic, since this disease is accompanied by multiorgan failure, including the cardiovascular system (CVS) [4]. High prevalence of CVDs ensues the need for preventive measures aimed to improve the quality of patient's life by minimizing modifiable risk factors.

At this stage, dyslipidemia (DLP) is considered as the main factor in the development and progression of atherosclerosis in patients with various diseases, therefore, the improvement of lipid profile is essential for the reduction of cardiovascular risk [7]. In recent years, the prevalence of diabetes mellitus (DM), obesity, etc. has significantly increased that contributed to the rise of the diseases predisposing to the development of secondary hyperlipidemias (HLP) [10]. The epidemiological ESSE-RF study established high prevalence of atherogenic dyslipidemias in

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Table 1. **The Frendrickson classification of hyperlipidemias recommended by WHO and the most common causes of lipid metabolism disorders development and progression**

Type	Synonym	Elevated plasma lipoprotein	Plasmatic cholesterol and triglycerides	Atherogenicity	DLP structure (%)	Secondary causes
I	Hyperchylomicronemia	Chylomicrones	TG, TC	—+	<1	Systemic lupus erythematosus
IIa	Hypercholesterolemia	LDL	TC	+++	10	Hypothyroidism
IIb	Combined hyperlipidemia	LDL, VLDL	TC, TG	+++	40	DM, nephrotic syndrome, anorexia nervosa
III	Familial dysbetalipoproteimemia	IDL	TG, TC	+++	<1	Abdominal obesity, DM, hypothyroidism
IV	Familial hypertriglyceridemia	VLDL	TG	+	45	CKD, DM, alcohol
V	Combined hyperlipidemia	Chylomicrones, VLDL	TG, TC	+	5	Thiazide diuretics, oral contraceptives, beta-blockers, alcohol

HDL-high density lipoproteins, LDL — low density lipoproteins, TG — triglycerides, TC — total cholesterol, VLDL — very low-density lipoproteins, IDL — intermediate-density lipoproteins, DM — diabetes mellitus, CKD — chronic kidney disease.

Table 2. **Modern classification of hyperlipidemias**

Type	TC	LDL	TG	HDL
Hypercholesteremia	+	+	Within reference values	Within reference values
Hypertriglyceridemia	Within reference values	Within reference values	+	Within reference values
Combined hyperlipidemia	+	+	+	Within reference values
Atherogenic hyperlipidemia	+ / Within reference values	+ / Within reference values	+	Decreased

HDL-high density lipoproteins, LDL — low density lipoproteins, TG — triglycerides, TC — total cholesterol

Russian Federation [26]. According to various sources, up to 30% of people with DLP have secondary hyperlipidemia [5]. The study of DLP becomes even more relevant during the COVID-19 pandemic, since DLP decrease organism's environmental resistance and increases the risk of viral infection [2, 38].

This review article presents current understanding of the secondary dyslipidemia phenotypes and its causes.

The definition of secondary hyperlipidemia

Secondary hyperlipidemia is the disorder of lipid metabolism induced by certain diseases, hormonal changes, and medication. It is necessary to differ primary (hereditary) and secondary (acquired) hyperlipidemia, since its management varies depending on the etiology [21]. Changes of lipid metabolism are usually of moderate severity and atherosclerotic plaques may not be present in patients with secondary hyperlipidemia unlike those with primary hyperlipidemia. However, as the pathological process develops, atherogenesis starts.

Secondary hyperlipidemia phenotypes

There are several classifications of hyperlipidemia. Currently, the World Health Organization (WHO) has approved the classification developed by D. Frendrickson (1965) that is based on the biochemical signs of DLM [21]. However, this classification is rarely used in everyday clinical practice, since there are several difficulties associated with the technique [5]. Therefore, Frendrickson's classification is more often used for scientific research. It should be noted that the classification (Table 1) establishes the type of hyperlipidemia regardless of etiology, as well as the risk of atherogenesis depending on the type of DLM: IIa, IIb and III types are atherogenic; I, IV and V types are "relatively" atherogenic [21].

Today, simplified version based on fasting lipid pannel (total cholesterol (TC), triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL)) is used. This classification includes predominant hypercholesteremia, predominant hypertriglyceridemia, combined hyperlipidemia and atherogenic hyperlipidemia (Table 2) [7] It is based on clinical studies indicating different degree of cardiovascular risk depending on the increase of various lipid fractions [5].

Inducing factors

The most common endocrine causes of hyperlipidemia include: hypothyroidism, Cushing's syndrome, uncontrolled diabetes mellitus (DM), obesity, hyperparathyroidism, growth hormone deficiency, pregnancy [5]. Certain medications can also induce the development of secondary hyperlipidemia such as: non-selective beta-blockers without intrinsic sympathomimetic activity, glucocorticoids, estrogens, psy-

chotropic medications, anabolic steroids, antiretroviral medications (protease inhibitors), thiazide diuretics, cyclosporine, barbiturates, cimetidine, retinoids [7 23, 24]. Other conditions that induce the development of hyperlipidemia are: chronic kidney disease, primary biliary cholangitis, biliary atresia, systemic lupus erythematosus, anorexia nervosa, arterial hypertension, paraproteinemia, burns, infections, alcohol abuse, smoking, carbohydrates and trans fats rich diet [1, 10, 20, 29]. We believe that it is important to assess the contribution of various risk factors to the development of pathological conditions associated with lipid metabolism disorders, based the latest literature data.

Diet impairment

Diet, alcohol consumption, and chronic stress contribute significantly to the development of DLM.

Trans fats

Trans fats induce the synthesis of endogenous cholesterol by the liver and apolipoprotein B (ApoB-100) that increases LDL cholesterol and atherogenic index and decreases HDL cholesterol.

Saturated fats

Saturated fatty acids affect the translation of LDL cholesterol receptors by decreasing the expression of mRNA that causes the elevation of their concentration. It should be emphasized that, not only molecular changes, but also the metabolism of saturated fatty acids contributes to the development of hyperlipidemia: chylomicrons and VLDL (very low-density lipoproteins) cholesterol, which have small size and high atherogenicity, are formed during the processing of saturated fats [7].

Fast digesting carbohydrates

The consumption of high glycemic index foods increases the secretion of insulin by the pancreas and activates GLUT-4 transporter that supplies glucose into adipose and muscle tissue cells. Due to the increased synthesis of reduced nicotinamide adenine dinucleotide (NADH), the monosaccharides convert into fatty acids and cause hypertriglyceridemia [9].

Alcohol

Alcohol abuse negatively affects blood triglyceride levels, causing hypertriglyceridemia. Ethanol damages hepatocyte mitochondria, impairs the oxidation of fatty acids and leads to hepatic steatosis [7]. The reduced NADH is produced by the metabolism of ethanol that triggers the biosynthesis of fatty acids. Acetaldehyde, a metabolite formed during ethanol catabolism, activates lipogenesis by suppressing the genes involved in fatty acid metabolism. Due to active synthesis of fatty acids, malonylcoenzyme A accumulates and suppresses their transport into mitochondria, which leads to their increase in blood plasma [6, 32]. Alcohol reduces the secretion of VLDL cholesterol by inhibiting the synthesis of apolipoproteins and phosphatidylcholine, the main phospholipid of cell membranes [10, 32].

Stress

Stress promotes the development of DLM through the increase of glucocorticoids, catecholamines and neuropeptide Y that enhance appetite and lead to stress-related overeating, primarily with high in saturated fat and cholesterol foods. It should be noted that stress hormones affect the hypothalamic-pituitary-adrenal axis, causing the increase of triglycerides blood concentration [10].

Internal diseases that cause of secondary dyslipidemias

The main diseases that affect lipid metabolism are presented in table 3 [10, 12, 14, 18, 19, 27, 28, 36, 37], however, certain disorders should be described further in detail.

COVID-19

Articles dedicated to the investigation of the new coronavirus infection (caused by SARS-CoV-2 virus) are of special relevance nowadays since the pandemic plays an important social, medical and economic role [16]. Foreign studies analyzed lipid profile in patients with a confirmed diagnosis of COVID-19. The following data were obtained in such patients: hypertriglyceridemia, decreased level of TC and HDL cholesterol, and elevated VLDL cholesterol. It is with noting the approximately 2 time increase of the Apo-B to Apo-A1 ratio that indicates the elevation of cardiovascular risk in patients with COVID-19 [3, 34]. Such changes may be partially explained by hepatopathy that is often observed in patients with SARS-CoV-2 [22].

Acquired immunodeficiency syndrome (AIDS)

It is well-known fact that antiretroviral pharmacotherapy can induce the development of secondary hyperlipidemia [15]. But there is also evidence that human immunodeficiency virus (HIV) can cause dys-

lipidemia itself. Patients have elevated level of triglycerides and reduced level of HDL and LDL cholesterol. There is an opinion that the pathogenesis of lipid metabolism disorders in patients with HIV infection is associated with increased production of interferon α that limits triglyceride clearance [13].

Obesity

Triglycerides accumulate in the liver due to increased concentration of free fatty acids in the blood in patients with obesity. This stimulates the secretion of VLDL cholesterol that inhibits the lipolysis of chylomicrons due to competitive inhibition of LPL. Lipolysis is complicated by decreased expression of lipoprotein lipase mRNA in adipose and muscle tissue. The level of HDL and LDL cholesterol as well as TG decrease due to the exchange of esters by CETP between high, low and very low-density lipoproteins. DLM in patients with obesity is typical for metabolic syndrome (MS) [10].

Type 2 diabetes mellitus

Endocrine disorders occupy a special place among the causes of lipid metabolism disorders due to high prevalence, especially type 1 and type 2 diabetes mellitus. Dyslipidemia develops in 72–85 % of patients with type 2 diabetes mellitus [10]. The insulin effect decreases and induces lipolysis and the synthesis of VLDL cholesterol, their catabolism decreases due to low LPL activity and the elevation of ApoC–III level, therefore, the atherogenic index increases. The activity of intestinotrophic hormone, glucagon-like peptide 2 (GLP-2), increases with insulin resistance, and the concentration of ApoB48 rises. Increased secretion of ApoB48 and the expression of the microsomal triglyceride transfer protein stimulates the synthesis of chylomicrones that contributes to the development of postprandial hyperlipidemia [25]. Due to low lipoprotein lipase activity and elevated plasma levels of ApoC–III, an LPL inhibitor, chylomicron catabolism decreases in patients with insulin resistance [10].

The CETP activity in patients with hypertriglyceridemia together with hepatic lipase activity results in the formation of small dense LDL cholesterol and the reduction of large cholesterol-rich HDL cholesterol [18]. Patients with type 2 diabetes have HDL cholesterol with impaired ability to acquire cholesterol from cells that can be explained by decreased expression of the membrane ABCA1 transporter, which is responsible for the first stage of cholesterol transfer from cell membranes to HDL cholesterol. The decrease of the ABCA1 activity may be associated with its glycation.

Type 1 diabetes mellitus

The lipid profile of patients with type 1 diabetes is usually within reference values [10] due to the effects of subcutaneous insulin infusions (Table 3). However, in severe cases, insufficient insulin levels or the development of insulin resistance can lead to atherogenic hyperlipidemia [12].

Hypothyroidism

Uncompensated hypothyroidism is associated with low life quality and significant cardiometabolic disorders. The degree of dyslipidemia is affected by the severity of hypothyroidism, age, lifestyle (physical activity and nutrition) and genetic background [24]. Reduced expression of CYP7A1, which encodes the key enzyme of bile acid anabolism, and genes that code ATP-binding cassette transporters (ABCG5 / 8), which transfer cholesterol from hepatocytes to bile, increases the level of plasma cholesterol. Low serum thyroid hormone levels lead to lipoprotein lipase inactivation due to the expression genes that inhibit it [10].

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) can be considered as hepatic type of metabolic syndrome that manifests with intrahepatic lipid accumulation (steatosis, fatty liver degeneration) in patients without other liver diseases and alcohol abuse. Atherogenic hyperlipidemia usually develops (see Table 3). It should be emphasized that the concentration of adiponectin with antiatherogenic properties [27, 31] is reduced compared with healthy controls, despite intense lipolysis and high fatty acid concentrations associated with increased fatty acid oxidation. Thus, low levels of adiponectin in patients with NAFLD can be considered as factors that limit the ability to increase lipid oxidation in response to fatty acid overload, and that induce their transesterification.

Cholestasis

Hyperlipidemia in patients with cholestasis is associated with the inhibition of 7-alpha-hydroxylase by bile acids that accumulate in the liver. The hydroxylase catalyzes the rate-limiting step in bile acid biosynthesis from cholesterol. Bile acids affect hepatic nuclear farnesoid X receptors (FXR) and inhibit the expression of the CYP7A1 gene encoding this enzyme [17]. Fibroblast growth factor 19, which accumulates during cholestasis, is also considered as CYP7A1 inhibitor [10].

Table 3. **Lipid metabolism impairment in patients with various internal diseases**

	Changes of lipid fractions			The pathogenesis of the observed phenomena
	TG	LDL	HDL	
Infectious diseases				
COVID-19	↑	↑	↓	The exact mechanism is unclear
AIDS	↑	↓	↓	Decreased TG clearance
Endocrine and metabolic disorders				
Obesity	↑	↑	↓	The secretion of VLDL cholesterol is stimulated, lipolysis of chylomicrons is inhibited. The exchange of cholesterol and triglyceride esters between HDL cholesterol, VLDL cholesterol and LDL cholesterol is activated
Anorexia nervosa	↑	↑	↑	Changes in the intestinal microbiota, resulting in increased absorption of fats and decreased concentration of thyroid hormones.
Type 2 DM	↑↑	↑	↓	Insulin resistance, glycation of apolipoproteins that impairs their metabolism. Activation of the cholesteryl ester transfer protein (CETP).
Type 1 DM	↓	↓	↑ or within reference values	Activation of lipoprotein lipase (LPL) in skeletal muscles and adipose tissue that intensifies VLDL cholesterol catabolism, regulatory effects of insulin.
Hypothyroidism	↑	↑↑		Impaired bile acids synthesis. Deceleration of the hepatic cholesterol uptake from the bloodstream. The number of LDL cholesterol receptors decreases that increases the time of their circulation. Decreased LPL activity.
Cushing's syndrome	↑	↑		Appetite stimulation. Inducing effect on the liver lipogenesis that increases the level of VLDL cholesterol. LPL activation resulting in the increase of fatty acids plasma concentration.
Polycystic ovary syndrome	↑	↑	↓	Metabolic syndrome.
Diseases of the gastrointestinal tract				
Non-alcoholic fatty liver disease (NAFLD)	↑↑	↑	↓	Imbalance between lipid absorption and excretion due to insulin resistance.
Cholestasis		↑↑↑		Inhibition of the conversion of cholesterol to bile acids.
Kidney diseases				
Nephrotic syndrome	↑↑	↑↑	↓	Increased hepatic lipogenesis. Decreased number of LDL cholesterol receptors and LPL activity.
Chronic kidney disease (CKD), stages 3–5	↑	↑	↓	A sharp decline of LDL cholesterol catabolism. Changes correlate with the decrease glomerular filtration rate.
Chronic renal failure	↑	↑↑	↓	
Hematologic diseases				
Paraproteinemia		↑		The affinity of paraproteins to blood plasma lipids that which makes them insensitive to the action of LPL.
Systemic diseases				
Systemic lupus erythematosus (SLE)	↑	↑	↓	Metabolic syndrome. Suppression of lipoprotein lipase. Elevation of C-reactive protein, which binds to lipoproteins and depresses their metabolism.
Rheumatoid arthritis	↑	↑	↓	The pathogenesis is similar to systemic lupus erythematosus.
Psoriasis	↑	↑	↓	Insulin resistance.

Nephrotic syndrome/ chronic kidney disease

Kidney diseases are often associated with lipid metabolism disorders. Patients with nephrotic syndrome have low lipid catabolism due to impaired synthesis of proteins that affect lipoprotein lipase activity (GPIHBP1, ANGPTL4), and increased hepatic lipid synthesis [10]. The main factors that affect lipogenesis in patients with nephrotic syndrome include: changes in plasma albumin concentration, plasma oncotic pressure, local viscosity of the liver sinusoid, loss of urine proteins or other liporegulatory substances.

Patients with 1–2 stage of CKD usually have DLM characterized by the increase of triglycerides, decreased HDL cholesterol. Total cholesterol and LDL cholesterol stay unaltered at these stages of the disease [7].

Systemic lupus erythematosus

The prevalence of dyslipidemia with increased total cholesterol, triglycerides and ApoB-containing lipoproteins (VLDL cholesterol and LDL cholesterol), as well as decreased HDL cholesterol is about 30 % at the initial stage of the disease, and it increases up to 60 % in 3 years [37]. Active stage of systemic lupus erythematosus is usually characterized by the increase of triglycerides and the decrease of HDL cholesterol. Their paraments improve during treatment, while total cholesterol and LDL cholesterol levels remain elevated.

Rheumatoid arthritis

The main cause of premature mortality in patients with rheumatoid arthritis (RA) is atherosclerosis and

its complications. Atherosclerosis develops due to the presence of many traditional risk factors (obesity, arterial hypertension, carbohydrate metabolism disorders, hypodynamia) in these patients [35], stimulated by anti-inflammatory therapy and high inflammatory activity in RA. The severity of lipid disorders correlates with the intensity of arthritis and are most pronounced in systemic RA.

DLM often develops at the onset of the disease in young patients and children, before the prescription of glucocorticoids (see table 3). Moreover, secondary DLM in those with early development of RA can extend to adulthood and, therefore, shorten the duration and affects the quality of life in such patients. DLM is caused by inflammation that affects enzyme activity (increases the action of hepatic lipase, lipid-transfer proteins), induces the increase of serum phospholipase A2 and sphingolipids, and the accumulation of serum amyloid A.

Radiation injury

It is usually thought that radiation can induce the development of atherogenic dyslipidemia that can be explained by the impairment of forward and reverse lipid transport [8].

Pregnancy

Physiological conditions can also cause hyperlipidemia. Thus, all lipid fractions increase during pregnancy [30]. Lipid anabolism predominate during first two trimesters of pregnancy, as the women's organism prepares to increase fetus energy that will be required at the final stage of pregnancy. Insulin sensitivity decreases, which induces lipolysis and decreases the activity of lipoprotein lipase and leads to hypertriglyceridemia during the third trimester. In addition, placental lactogen stimulate lipolysis [10, 30].

Conclusion

This review article analyzed wide range of secondary hyperlipidemia. The main factor that decreases cardiovascular risk is the achievement of target blood lipids levels, therefore, modern diagnostics should focus on timely detection and correction of lipid metabolism disorders.

Conflict of interest: none declared.

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International Heart and Vascular Disease
Journal • Volume 9, № 32, December 2021

Journal of the Cardioprogress Foundation

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[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

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The first reference to an abbreviation is always accompanied by the full spelling of the abbreviated concept, and the abbreviation is indicated in brackets. For example, blood pressure (BP); heart rate (HR). Capital letters are more often used to denote abbreviations. If abbreviations are used only in tables and figures, and are not used in the text, they should not be included in the list of abbreviations, but should be given a transcript in the note to the table or figure. The summary of the article, as a separate document, is subject to the same rules as the article (abbreviations are made when they are used 3 or more times).

Abbreviations should be generally accepted and understandable to the reader, in accordance with the generally accepted norms in the scientific literature. Undesirable abbreviations that coincide in writing with others that have a different meaning.

Abbreviations in the list of abbreviations are written in alphabetical order, separated by commas, in solid text, using "dash". **Example of design:** BP-blood pressure, HR-heart rate.

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The article should be carefully verified by the author (s). The authors are responsible for the correctness of citation, doses and other factual materials.

Introduction — it is necessary to describe the context and prerequisites of the work (what is the essence of the problem and its significance). It sets certain goals or describes the object of the study, or a hypothesis that needs to be tested by comparison or observation. Only those sources that directly indicate the problem are cited.

Statistics — all published materials are reviewed by an expert in statistics and must meet "Uniform requirements for manuscripts submitted to biomedical journals" (Uniform Requirements for Manuscripts Submitted to Biomedical Journals, Ann Intern Med 1997, 126: 36–47). In the preparation of the statistical part of the work it is recommended to use special guidelines, for example, the European journal of cardiology: www.oxfordjournals.org/our_journals/eurheartj/for_authors/stat_guide.html

Statistical methods are described in detail in the Material and methods section.

Acknowledgements — all participants who do not meet the authorship criteria should be listed in the Acknowledgements section, which is located at the end of the article before the Literature section.

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Tables should contain the compressed, necessary data. Each table is placed at the end of the text (after the list of references) with the number, name and explanation (note, abbreviations).

The tables should clearly indicate the dimension of the indicators and the form of data (M±m; M±SD; Me; Mo; percentiles, etc.). All figures, totals and percentages should be carefully verified, and also correspond to the mention in the text. The explanatory notes are given below the table, if necessary. The footnotes must be in the following order: *, †, §, ||, ¶, #, **, †† etc.

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Book:

Shlyakhto EV, Konradi AO, Tsyrlin VA. The autonomic nervous system and hypertension. SPb.: Meditsinskoe izdatel'stvo; 2008. Russian. Шляхто Е. В., Конради А. О., Цырлин В. А. Вегетативная нервная система и артериальная гипертензия. СПб.: Медицинское издательство; 2008. ISBN 0000–0000.

Chapter:

Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger; 1990. p.398–420. ISBN 0000–0000.

Russian chapter:

Diagnostics and treatment of chronic heart failure. In. National clinical guidelines 4th ed. Moscow: Silicea-Polygraf; 2011. pp.203–93. Russian Диагностика и лечение хронической сердечной недостаточности. В кн: Национальные клинические рекомендации. 4-е издание. М.: Силицея-Полиграф; 2011.сс.203–96. ISBN 0000–0000.

Webpage:

Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

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ISSN: 2309-0901 (Print)

ISSN: 2311-1631 (Online)

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