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Functional state of cardiovascular system and cardiovascular risk stratification in women with postovariectomy syndrome

Arterial hypertension and heart remodeling in athletes

Chronic mesenteric ischemia. What should the general practitioner know?

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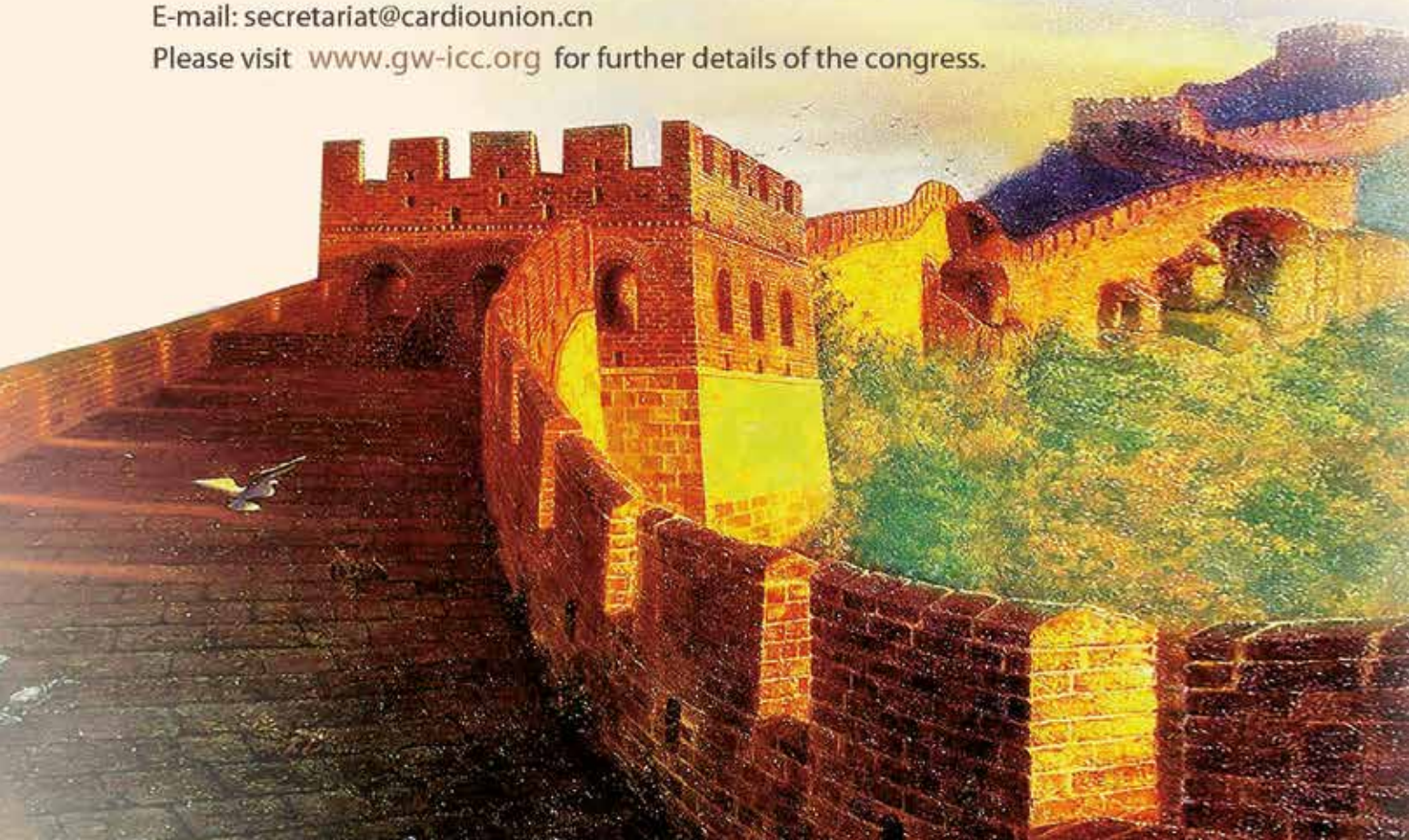

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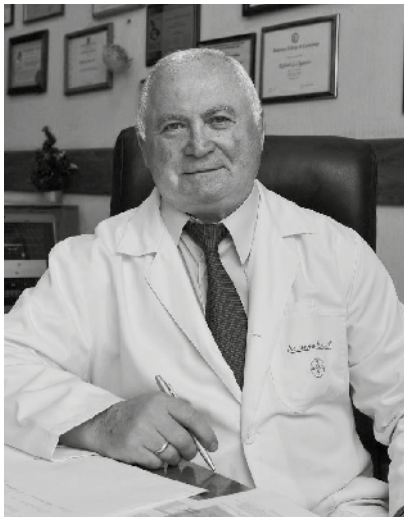

Editor's Welcome

Dear colleagues!

In the 14th issue of the International Heart and Vascular Disease Journal, there are leading article, review article, original articles, and clinical seminar.

The leading article of this issue was done by the group of Belorussian researchers and it is dedicated to identification of functional state of cardiovascular system and cardiovascular risk stratification in women with asymptomatic ST segment depression and postovariectomy syndrome

Our "Review articles" section is present with analytic review exploring the problem of connection between erectile dysfunction and anxiety-depression disorders in arterial hypertension, including their pathogenetic linkage and therapeutic options.

Traditional "Original articles" section includes 3 works of Russian authors. The first one investigated the life quality and depression intensity in patients with arterial hypertension receiving maintenance hemodialysis treatment in the Udmurt republic. According with these results, patients with AH undergoing maintenance hemodialysis had more severe depression and lowered life quality. The second original article evaluated correlation between lipid metabolism characteristics and iron-deficiency anemia in women of child-bearing age. Lately big attention is paid to investigation of cardiovascular disease markers in sportsmen. Another original article is dedicated to assessment of hemodynamic characteristics in athletes of different kinds. Although the prevalence of arterial hypertension in athletes is lower than in population, elevated BP increases the risk of myocardial hypertrophy and remodeling that is one of possible contraindications for sports with high static loads.

"Clinical seminar" session discusses an important topic of chronic mesenteric ischemia. This disease is difficult for diagnostics by general practitioners due to the lack of specific symptoms. This work covers etiology, classification of several authors, clinical manifestations depending on vascular lesions' localization, problems of diagnostics and treatment of abdominal ischemic disease. Educational review article may be useful for general practitioners.

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.

Rafael G. Oganov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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LEADING ARTICLE

Functional state of cardiovascular system and cardiovascular risk stratification in women with postovariectomy syndrome

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Summary

Objective

To reveal the features of the structural and functional state of cardiovascular system and to stratify cardiovascular risk in women with silent depression of the ST-segment and postovariectomy syndrome.

Materials and methods

The study involved 66 women with perimenopausal metabolic syndrome, including 30 females after surgical menopause (main observation group) and 36 females with naturally occurring menopause (comparison group).

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Results

In women with surgical menopause and metabolic syndrome, significant epicardial obesity and coronary calcification were identified; myocardial ischemia was more evident, myocardial hypertrophy and remodeling of the left ventricle was accompanied with violation of its diastolic function. Concentric hypertrophy of the left ventricle prevailed in the structure of geometric model disturbances.

Conclusion

The fact of detection of high risk of adverse cardiovascular events in women with surgical menopause according to single-photon emission computed tomography is clinically significant. Obtained data determine the necessity to search new criteria of cardiovascular risk stratification for the selection of patients with high cardiovascular risk and its timely correction.

Key words

Silent myocardial ischemia, postovariectomy syndrome, single-photon emission computed tomography (SPECT), epicardial adipose tissue

Introduction

In the developed countries postmenopausal period takes more than 1/3 part of women's life, and exactly this period becomes the most socially active one. Investigation of cardiovascular pathology in females is impossible without taking into account cyclic and age-related changes of the endocrine system. Estrogens' deficiency, fat tissue and biologically active molecules produced by it are interrelated, and it is associated with impaired metabolism of fat tissue, development of abdominal obesity, insulin resistance, dyslipidemia, increased activity of sympathetic nervous system and development of arterial hypertension(AH) , impaired endothelial function and thrombus formation, changed secretion of neural steroids and neural peptides participating in the regulation of food behavior and providing integrative action of different brain parts and realization of its cognitive function. Even if there is no verified correlation between cardiovascular events and estradiol plasma levels, the crucial role of visceral obesity in coronary heart disease (CHD) that can be triggered by hypoestrogenia is beyond dispute. Surgical menopause may prove the significance of sex hormones as the risk factor of cardiovascular disease (CVD), since the disorders in this condition have more evident manifestations comparing with the natural menopause. Detection of high cardiovascular risk (CVR) and detection of sublinical lesions of target organs in women with hypoestrogenia is an important problem of cardiology that has not been solved yet [1, 2, 3].

Identification of patients belonging to the high risk group of development of CVD caused by atherosclerosis and lacking of evident clinical symptoms is the priority direction of modern medicine. Patients with obesity can be considered as a part of this group since the growing epidemic of obesity and high risk of cardiovascular complications increase the social importance of this problem. Numerous studies demonstrated elevated risk of stroke and myocardial infarction in case of visceral obesity development and detected correlation between excessive body weight and big amount and early development of atherosclerotic plaques (T. Visscher, 2001, S. Yusuf, 2005, L. De Koning, 2007). Visceral fat is a hormonally active tissue that produces many biologically active molecules participating in the development of metabolic disorders, inflammation and fibrosis, thrombus formation and atherogenesis. At the same time, not all patients with obesity diagnosed according with body mass index (BMI) have high CVR, and not all patients with normal BMI do have low CVR. There are three phenotypes characterizing the role of visceral obesity in cardiovascular continuum: "uncomplicated" obesity, "complicated" obesity and "metabolically obese" but normal weight patients (M. Morelli, 2013) [4, 5]. In this case indirect detection of visceral obesity (VO) using waist circumference (WC) measurement can lead to excessive diagnostics of VO and high CVR (G. Iacobellis, 2003, Y. Chiba, 2007, G.A. Chumakova, 2012). Epicardial fat tissue (EFT) is the deposit of visceral fat around heart located between myocardium and visceral pericardium. EFT correlates with the amount of abdominal visceral fat; it is connected with the levels of C-reactive protein, fibrinogen, plasma lipids, HOMA-IR insulin resistance index and glycemic profile, it is also associated with the markers of neurohumoral activity of visceral fat, resistin, leptin, adiponectin, it can play a role in atherosclerosis development and promotes formation of myocardial atherosclerosis and arterial vascular wall (F. Natale, 2009, E. Soliman, 2010) [5, 6, 7, 8]. But up to nowa-

days the universal quantitative unit of EFT that would have allowed estimating elevated CVR has not been found yet; generalization of existing data about estimation of EFT association with metabolic disorders and cardiovascular remodeling parameters is limited by heterogeneity of visualization techniques and investigated populations of patients. Fat deposits influence adjacent organ's functioning, because of direct mechanical effect and pressure on it and secretion of biologically active molecules. Lipids, accumulated not only in adipocytes, but also in myocytes and endotheliocytes, have lipotoxic impact on them and cause their dysfunction and apoptosis. EfT produces excessive amount of angiotensin II; it increases the synthesis of fibrosis markers, promotes left ventricular myocardium remodeling and impairs cardiac diastolic function, and consequent development of chronic cardiac insufficiency [4, 6].

The objective of this study was too reveal the features of the structural and functional state of cardiovascular system and to stratify cardiovascular risk in women with silent depression of the ST-segment and postovariectomy syndrome.

Materials and methods

This study included 66 female patients in postmenopause with metabolic syndrome and asymptomatic ST segment depression detected with 24-hours electrocardiogram monitoring (24h-ECG). All women were divided in two groups depending on the mechanism of menopause development: main observation group (MOG) included 30 females after surgical menopause, whereas comparison group (CG) consisted of 36 females with naturally occurring menopause. There were no significant differences in age and CHD risk factors between two groups. WC in the main group was 92.5±8.0 cm, and in the comparison group this value was 90.0±6.0 cm.

Instrumental study included 24h-ECG, echocardiography, single-photon emission computed tomography (SPECT) with pharmacological stress test, and coronary computed tomography angiography (CCTA). Episodes of horizontal or descending ST segment depression of at least 1 mm, with duration of at least 0.08 sec after the J-point, lasting for at least 1 minute with a shift of at least 1 minute between episodes [9]. Myocardial SPECT was performed using "Nucline X-Ring" ("Mediso", Hungary) tomographic gamma scanner. ^{99m}Tc- methoxy isobutyl isonitrile (^{99m}Tc-MIBI) was used as a radiopharmaceutical(RP) for these assays. This technique allows verifying coronary ischemia and performing quantitative and qualitative analysis and estimation of the areas with impaired tissue perfusion and intensity of its reduction. Myocardial SPECT was done according with two-day protocol in the following sequence: test in rest (REST) combined with pharmacological stress test (STRESS) with dipyridamole causing vasodilatation and leading to coronary hyperemia. We used 5-points scale for analyzing severity of hypoperfusion: tracer uptake varying from 80 to 95% indicated normal perfusion (0 points), mildly reduced tracer uptake (65-79%) corresponded to 1 point, moderately reduced tracer uptake (50-64%) corresponded to 2 points, evidently reduced tracer uptake (30-49%) – 3 points, and tracer uptake less than 30% corresponded to 4 points. After it we estimated summed stress score (SSS) – the sum of points in all segments obtained using STRESS test [10].

CCTA was performed in axial scanning with prospective cardiac gating: collimation 0,6 mm, tube current 60 mA, voltage 120 kV, tube-sensor turnover time 0.25 ms. Calcium score (CS) was determined semi-automatically using licensed software "Syngo Via" Siemens. EFT was estimated using axial sexions (3,0 mm), pericardium contouring was done manually in each fourth section starting 3 mm up from the coronary arterial ostia in cranial direction down to their crossing with inferior myocardial wall. Selection and quantification of tissue volume of fat density (-190 — -30 Hounsfield units) was done automatically.

Results and discussion

According with the results of 24h-ECG, patients of the main group had higher values of ST segment depression amplitude (2.3±0.2 mm), number of episodes (9 (3.13)) and total duration of ischemia within 24h (1900±150 sec) comparing with the comparison group (1.2±0.1 mm; 4 (3; 8) episodes; 1210±110 sec, respectively, $p<0.05$). Comparison of patients' diaries and monitoring results revealed that physical exercise (MOG: 68% episodes, CG: 42% episodes) and emotional stress (22% of episodes in females with surgical menopause and 20% of episodes in females with naturally occurred menopause) acted as factors provoking significant ST depression in the main observation group. The frequency of spontaneous ST segment deviations (at rest, independent from provoking factors) was higher by 24% in patients with physiological menopause ($p< 0.05$).

Myocardial SPECT results revealed perfusion defects in all female patients with diagnostically signifi-

Table 1. **Myocardial SPECT results**

Characteristic	SPECT at rest (REST)		SPECT with pharmacological stress test (STRESS)	
	MOG, n=30	CG, n=36	MOG, n=28	CG, n=30
∑ PDV, %	6.2 (4.0; 9,0)[2]	4.8 (3.0; 9.4)	15,0 (8,6;22)[1]	8.0 (4.0; 14)
S_{PD}, cm^2	6.0 (4.2; 10,0)[2]	5.0 (3.0; 8.2)	16,0 (8;24)[1]	8.4 (3.8; 15,2)
SSS	-	-	8 (2;9)	5 (2; 8)
Percentage of patients having SSS > 8, % of abs.	-	-	46,4% (13)	16.7% (5)

Comment: Significance of differences, p<0.05.
1 – comparing with the CG,
2 – after dynamic comparison.

cant ST depression. Analysis of parameters characterizing dimensions of abnormal perfusion area: perfusion defect value (PDV) as the percentage of an area excluded from total left ventricle (LV) myocardial dimensions (%) and the square of perfusion defect (S_{PD}, cm^2), did not detect significant differences between groups during REST test. STRESS testing aggravated coronary circulation in patients of both groups, at the same time patients with surgical menopause (MOG) had more evident dynamics and created differences between groups: total PDV value and perfusion defect square were higher comparing with the CG patients (table 1).

Summed stress score (SSS) estimation is used for the stratification of coronary events' risk. If SSS is less than 4 the probability to develop CHD and possible myocardial infarction (MI) is low; if SSS is between 4 and 8, there is high possibility of CHD, moderate MI risk and low risk of cardiac death; if SSS is above 8, there is high possibility of CHD, moderate MI and cardiac death risk. SSS in the MOG (females with postovariectomy syndrome) was 8 (2; 9) points and corresponded to high probability of CHD development, moderate risk of MI and cardiac death. SSS value in comparison group was 8 (2; 8) points and it matched high probability of CHD, moderate MI risk and low cardiac death risk. The percentage of female patients with SSS value of 8 points and more was 46.4% for the MOG and 16.7% for the CG (Table 1). Thus, around one half of women without ECG symptoms and impaired endocrine homeostasis (postovariectomy syndrome) have high possibility of CHD and moderate risk of MI development and cardiac death.

Several studies demonstrated association of anthropometric characteristics and indexes with the risk of cardiovascular events development: WC is a sign of abdominal obesity and predictor of impaired carbohydrate metabolism, it also correlates with secretory activity of fat tissue and the risk of cardiovascular catastrophes development. At the same time, females with metabolic syndrome included in this study had significant differences of abnormal myocardial perfusion (SPECT results) and severity of ischemia (CCTA results), even if WC values were comparable between two groups. To evaluate the influence of regional characteristics of fat tissue distribution on cardiovascular risk, we estimated EFT volume, since this tissue is a metabolically active substrate participating in synthesis of biologically active local and systemic action substances involved in CHD pathogenesis. CCTA revealed significant difference of EFT volume: in the MOG this value was 149,13 (82, 28-227, 29) cm^3, and in the CG this value was 117.14 (51.11-130.21) cm^3, p<0,05. Calcium index quantified using A.S. Agatston (AJ-130) formula was 115 (34; 380) units in females with postovariectomy syndrome and 60 (17, 100) units in the CG patients, another quantification method (Volume) resulted in values of 130 – 140 (41; 354) mm^2 and 130 – 68 (14; 130) mm^2, p<0,05, in MOG and CG patients, respectively.

Echocardiography assay demonstrated that LV myocardial mass index (LVMMI) in patients of the MOG was higher than in CG patients (99,5±9,5 g/m^2; 88,0±8,4 g/m^2, p<0,05, respectively). Myocardial hypertrophy (LVMMI more than 95 g/m^2 for females) and pathologic deviation of LV geometric model were more frequent in patients after surgical menopause. The percentage of patients with LV myocardial hypertrophy (LVMH) in the MOG was 53.3% (16 persons), and 25% in the CG (9 persons). Concentric LVMH was present in 50% of female patients after surgical menopause, making it the most frequent form of impaired LV geometrical model. We performed the analysis of LV diastolic function using transmitral blood flow peak velocities accessed by Doppler echocardiography in impulse mode. Comparing with CG patients, patients of the MOG had reduced early filling velocity (peak E), increased late filling velocity (peak A), and reduced E/A ratio of transmitral blood flow that indicates diastolic dysfunction of LV myocardium in patients with postovariectomy syndrome (Table 2).

Table 2. **LV diastolic function characteristics**

Characteristic, Me (25%-75%)	MOG, n=30	CG, n=36
E peak, m/sec	56 (54; 68)*	70 (60; 74)
A peak, m/secc	66 (56; 72)*	62 (50; 64)
E/A ratio	0.8 (0.8; 1.0)*	1.1 (1.0; 1,3)
Symptom, % (abs.)		
LV diastolic dysfunction	83.3% (25)*	53.3% (16)

* Significance of differences comparing with the CG, p<0.05.

Conclusion

Women with metabolic syndrome who went into surgical menopause have evident increase of epicardial fat thickness, coronary calcinosis (EFT volume measured with CCTA was higher comparing with the women with naturally occurring menopause), and more severe myocardial ischemia (according with 24h-ECG results, they had significantly higher amplitude of ST segment depression, higher number of episode and total ischemia duration within 24h, SPECT demonstrated statistically significant increase of total PDV and perfusion defect dimensions). In females with postovariectomy syndrome myocardial hypertrophy and LV remodeling are combined with impaired LV diastolic function, and concentric LVMH is the prevailing form of LV impaired geometrical model.

The fact that females who went into surgical menopause had high risk of unfavorable cardiovascular events (SSS values of 8 (2; 9) points), high percentage of patients with high CHD probability, moderate risk of MI development and cardiac death, is clinically significant. These data determine the necessity to search new criteria of cardiovascular risk stratification for selection of female patients with high cardiovascular risk and its well-timed correction.

Conflict of interest: None declared.

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Erectile dysfunction, anxiety and depressive disorders in arterial hypertension: pathogenetic communication and approaches to treatment

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Summary

Erectile dysfunction (ED) is very common in patients with arterial hypertension (AH), reaching the frequency of 70% according to various authors, and accompanying psychoemotional disorders aggravating the course of sexual and somatic disorders. Associated pathology increases the risk of premature death, worsens the prognosis and reduces social functioning of these patients. Common pathogenetic mechanisms of ED, anxiety and depressive disorders and AH include endothelial dysfunction with decreased nitric oxide production, low levels of androgens, violation of cortico-visceral connections with imbalance of the hypothalamic-pituitary-adrenal system, and sympathicotonia. Complex pathophysiology requires prescription of adequate antihypertensive and psycho-corrective therapy, together with effective ED treatment.

Key words

Erectile dysfunction, anxiety and depressive disorders, arterial hypertension, pathogenetic relationship, Phosphodiesterase type 5 inhibitors, adaptogens.

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Introduction

Combination of erectile dysf unction (ED), anxiety and depressive disorders (ADD) and arterial hypertension (AH), so-called «Mutually reinforcing triad», is rightfully considered one of the most important men's problems of the XXI century. [1]. It is caused by their high prevalence, medical and social importance and several pathogenetic mechanisms common between these conditions [2].

Erectile dysfunction is described as inability to reach and/or support adequate erection necessary for coitus [2]. Around 400mln men have ED and it is predicted this number will reach 900 mln persons that is related to negative influence of a growing number of ED risk factors (AH, smoking, obesity, dyslipidemia, and diabetes mellitus) and increased lifespan of male population that is associated with another important ED risk factor – aging and age-related androgene deficiency [3, 4]. The first large-scale study that assessed ED prevalence was held in 2012 and it demonstrated that 1101 respondents (89.9%) out of 1225 had ED symptoms [5].

Sexual functioning is tightly linked with physical and psychosocial health of men and strongly influences the life quality of men and their families. Significant results of E.O. Laumann e coauthors demonstrated, that erection disorders often accompanied with anxiety, despondence and lack of self-confidence cause 4-fold and 6-fold reduction of physical and psychoemotional component of life quality, respectively [6]. Other authors reported that sexual activity directly correlated with men's lifespan. Results of prospective Cayerphilly study that had lasted 10 years demonstrated that the mortality between men with low sexual activity (less than 1 sexual contact per month) was 50% higher comparing with the men who had sexual contacts twice per week and more often [7].

Individual reports of men and women above 55 years old that had been obtained during recent study held in Florida demonstrated that preserved sexual activity is associated with positive physical, social and emotional health characteristics [8].

Pathogenetic correlation between ED, anxiety/depression and AH

Previously the problems of psychogenic origin had been considered the main reason of ED, nowadays it is established that ED is mostly caused by organic and mixed nature. In any case, concomitant anxiety and depression aggravate the course of sexual and somatic disorders.

Clinical studies demonstrate tight connection between ED and cardiovascular diseases [9]. The study of F.A. Giuliano and coauthors [10] revealed ED in 70% of men with AH, and severe AD was diagnosed in 45.2% of males with AH comparing with 10% frequency of this disorder in general population. Doppler scan of penis vessels reveals ED in 87% of patients with AH [11]. The most important pathogenetic mechanism of AH and ED is endothelial dysfunction and insufficient production of nitrogen oxide (NO), main moderator of systemic and organ blood supply. Elevated blood pressure with senescent background is accompanied with impaired endothelium-dependent vasodilatation and consequent structural remodeling, atherosclerosis development, and stenosis of vessels providing blood supply during erection (Figure 1) [12, 13].

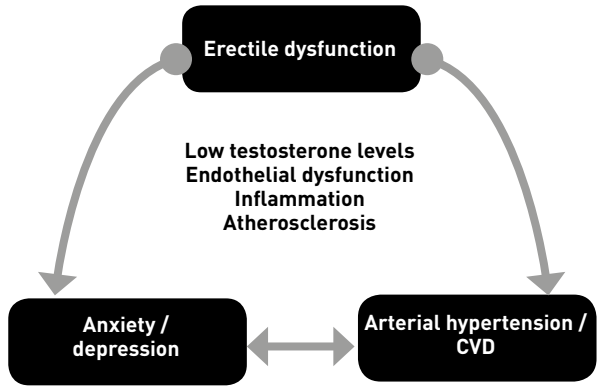


Figure 1. Common mechanisms between ED, ADD, and AH pathogenesis: low testosterone, endothelial dysfunction, slowly progressing systemic vascular inflammation

Chronic vascular inflammation promotes aggravation of endothelial dysfunction and ED development. Increased levels of inflammation markers and mediators (C-reactive protein, intercellular adhesion molecule 1 (ICAM-1), interleukins 6, 10, 1β (IL-6, IL-10, IL-10β, respectively), tumor necrosis factor-α (TNF-α) and endothelial/prothrombotic factors (von Willebrand factor, tissue plasminogen activator, plasminogen activator inhibitor-1, fibrinogen) have been detected in patients with ED [14, 15].

It has been proved that ED is an early marker and predictor of cardiovascular disease. P. Montsori and coauthors demonstrated that ED precedes the development of acute coronary syndrome and angina pectoris in the majority of cases. The average time interval between this events is 12-36 months. It is explained by the fact that diameter of penile artery is 2-3 times less than the diameter of coronary arteries and 3-4 times smaller than the diameter of carotid

arteries, thus manifestations of endothelial dysfunction and atherosclerotic lesions of penile arteries become evident much earlier than the same abnormalities of major coronary and peripheral vessels [16].

Low androgens' level (hypogonadism) is another one important mechanism of combined pathology. Nowadays it has been established that testosterone and its active metabolites not only control adequate sexual functioning but also determine the risk of unfavorable cardiovascular events development and cardiovascular mortality. AH is one of the main cardiovascular disease risk factors and it is connected with low testosterone levels. C. Vlachopoulos and coauthors estimated correlation of low testosterone levels and development of severe cardiovascular event (SCVE) in 228 patients with AH without clinically evident atherosclerosis. They demonstrated that during 44 months observation period 19 participants (8.3%) had developed SCVE like cardiovascular death, myocardial infarction or stroke. Comparing with the patients who did not develop SCVE, men with AH had lower total testosterone (TT) levels (13.5 ± 2.4 nmol/L vs 15.9 ± 5.2 nmol/L, p <0.01) and higher prevalence of hypogonadism (36% vs 16%, p < 0.05) [17]. Testosteron has vasoprotective and cardioprotective effect mediated through NO, its influence on endothelium and inflammation markers, and its deficiency is manifested as cardiovascular disorders like refractory AH, impaired lipid and carbohydrate metabolism, and progressing atherosclerotic remodeling of vessels [18, 19]. Apart from it, androgenic deficiency lowers down psychophysical activity and libido, increases ED and psychoemotional disorders like anxiety and depression that correlates with laboratory test results (TT ⩽ 15nmol/L) [20]. International society of sexual medicine recommends to check TT concentration in patients with ED and/or decreased libido [21].

The presence of anxiety and depression in patients with ED and AH complicates the clinical course of comorbid pathology and becomes a risk factor of premature death, aggravates prognosis and decreases social functioning of these patients [22]. If patients with AH have just depressive disorders, they have 18% higher risk of stroke and 25% higher risk of cardiovascular death [23]. Nowadays several possible common mechanisms of ADD influencing AH, cardiovascular disorders and ED are under investigation. The most important ones are hyperactivation of hypothalamo-pituitary-adrenal system and imbalanced vegetative nervous system with prevailing sympathicotonia [24, 25], impaired functional activity of platelets, increased blood viscosity, endothelial dysfunction [24], and increased chronic inflammatory response [24-26].

Depressive disorders significantly decrease compliance to antihypertensive therapy [27]. These patients do not follow therapeutic regimen and healthy lifestyle in terms of diet, smoking refusal, increased physical activity, and restricted alcohol consumption [28]. European guideline for cardiovascular disease prevention in clinical practice (2016) considers depression and anxiety as significant obstacles for modification of patients' lifestyle in desirable direction that require psycho-correcting work [29].

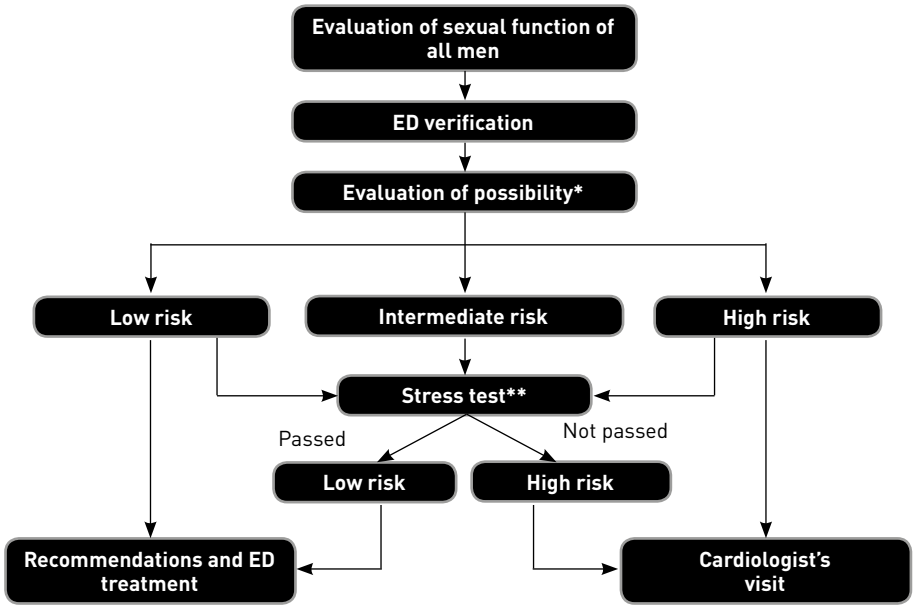
It is necessary to remember that antihypertensive drugs by themselves (non-selective ß-blockers, thiazide diuretics [30-32], and psychotropic drugs like antidepressants and tranquilizers [33]) have a negative impact on ED development. Sings of drug-induced ED include relatively fast development, presence of temporal connection with therapy and reduced intensity or disappearance of ED after drug withdrawal. It explains the fact that ED, ADD and AH triad requires prescription of adequate hypotensive therapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) [30-32] and psychotropic treatment with atypical antidepressants like bupropion – selective inhibitor of noradrenalin and dopamine reuptake, trazodone – antagonist of 5-HTA/2C serotonin receptors, agomelatine – MT1 and MT2 melatonergic receptors agonist [33]. The drugs listed above have positive effect on ED without aggravating erectile function.

Treatment of ED and ADD in patients with AH

Complicated pathogenetic connections between ED and ADD in AH require particular treatment approach. Safety of sexual activity in AH is an important question for patients and internal medicine specialists. According with the Princeton Consensus II (Figure 2) [3], patients with controllable AH belong to the low risk group and had can safely continue sexual relationships and use the drugs for ED treatment. Patients with uncontrollable AH having 10-fold increased risk of developing cardiovascular events during coitus and 2 hours after belong to the group of high risk and should visit cardiologist and avoid sexual activity until their condition would be stabilized. Algorithm of management of patients according to cardiac risk is present at Figure 3 [3, 34].

Low risk	Intermediate risk	High risk
• Asymptomatic course or <3 CHD risk factors • Controllable AH • Angina pectoris (FC I-II) • Condition after successful revascularization of coronary arteries • MI without complications (>8 weeks after it) • mild valvular lesions • HF (FC I)	• >3 CHD risk factors • stable angina • MI (2-6 weeks after it) • other manifestations of atherosclerosis (peripheral vascular disorders, transitory ischemic attacks)	• Unstable or refractory angina • Uncontrollable AH • Hf (fC III-IV) • MI or stroke (less than 2 weeks after it) • life-threatening arrhythmias • hypertrophic cardiomyopathy • severe valvular lesions

Figure 2. II Princeton consensus – identification of cardiac risk groups and sexual activity



* Sexual activity is equivalent to walking 1 mile during 20 minutes or going up 2 flights of stairs during 10 seconds
** Sexual activity is equivalent to 4 minutes of Bruce treadmill protocol.

Figure 3. Algorithm of management of patients with ED according to cardiovascular risk [3].

Phosphodiesterase type 5 (PDE-5) inhibitors can be recommended after selection of antihypertensive drugs that are the "golden standard" of ED treatment: sildenafil, tadalafil, valdenafil [35]. At the same time several problems like adverse effects of PDE-5 inhibitors (headache, face hyperemia, dyspepsia, stuffiness in the nose, myalgia) and insensitivity to therapy in 15-40% of patients remain unsolved. It is known that these drugs are able to potentiate relaxing action of NO on smooth muscular cells of trabecular tissue. But central nervous system impulses are required for triggering NO release. Their intensity depends on patient's reaction on sexual stimulus. Due to the lack of substrate of action, monotherapy with PDE-5 inhibitors is not very effective in case of strong reduction of libido and it is heavily suppressed with age. That's why nowadays it is strictly important to optimize clinical usage of PDE-5 inhibitors for treatment of patients with ED [36]. In case of androgen replacement therapy several problems like suppression of endogenous androsteroids production, negative effect on liver and prostate, remain unsolved.

Use of nature—derived drugs, that have minimal number of adverse effects and are capable to increase sexual desire, improve the quality of erection and mood, and stabilize vegetative nervous system, is a good alternative and addition to ED treatment in men with AH. The authors of this article participated in the study of dynamical clinical evaluation of ED and ADD in 78 male patients with AH I-III stage during complex therapy [37-39], which included antihypertensive drugs together with adaptogen Eromax produced in Russia and containing drone brood, pollen pellet, ginseng root, L-arginine, zinc citrate, and pyridoxine hydrochloride. All patients were divided into two groups with comparable age and severity of

Table 1. **Dynamics of testosterone, prolactin, and DHEAS levels in serum during therapy**

Parameters	Day 0		Day 28		Reference values	p
	Group 1	Group 2	Group 1	Group 2		
TT	11.8 ± 4.4	11.4 ± 3.8	17.1 ± 5.7*	13.4 ± 3.1	12.1-38.3 nM/L	<0.02
Prolactin	521 ± 36	517 ± 29	285 ± 60*	460 ± 69	24.5-467 mU/L	<0.02
DHEAS	1.2 ± 0.3	1.3 ± 0.1	1.4 ± 0.7	1.3 ± 0.2	1.0-4.2 μg/mL	>0.054
* Significant differences						

Table 2. **IIEF characteristics' dynamics**

Characteristic	Day 0		Day 28	
	Group 1	Group 2	Group 1	Group 2
ED	13.4 ± 0.7	12.9 ± 0.8	19.8 ± 0.6*	14.8 ± 0.7
Satisfaction with coitus	9.6 ± 0.4	9.8 ± 0.5	14.1 ± 0.7*	12.8 ± 0.4
Orgasm	5.1 ± 0.4	5.7 ± 0.2	8.8 ± 0.2*	5.9 ± 0.8
Libido	6.1 ± 0.5	6.3 ± 0.1	10.9 ± 0.3**	8.1 ± 0.1
General satisfaction	5.8 ± 0.1	5.9 ± 0.7	10.1 ± 0.9**	7.0 ± 0.7
Significant differences - * p<0,05, ** p<0,02.				

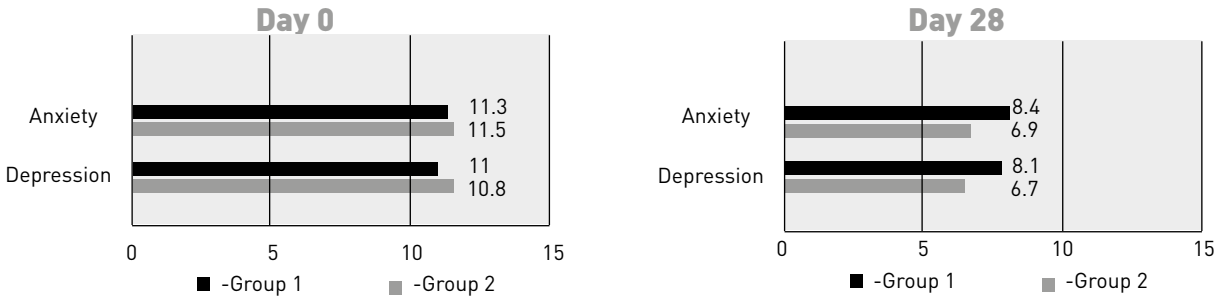


Figure 4. Dynamics of pshycoemotional characteristics

health problems. Patients of the first group (n=55) received hypotensive therapy and adaptogen, the second group (n=23) received only antihypertensive drugs. Small doses of antidepressants (trazodone 50-150 mg/day) were used in both groups in order to reduce evident affective pathology. Common procedures included also individual and/or family cognitive-behavioral psychotherapy. By the moment of the end of treatment, investigation of hormonal status in the first group demonstrated significant increase of TT levels (from 11.8 ± 4.4 to 17.1 ± 5.7 nmol/L, p<0.02) and tendency to increase of dehydroepiandrosterone sulfate (DHEAS) concentration (from 1.2 ± 0.3 to 1.4 ± 0.7 μg/mL, p<0.05) together with decreased prolactin levels (from 521 ± 36 to 285 ± 60 mU/L, p<0.02), whereas the patients of the second group had no significant changes of hormones' levels (Table 1). All parameters of the "International Index of Erectile Function (IIEF) questionnaire increased significantly in the first group (Table 2). Hospital Anxiety and Depression Scale (HADS) revealed more significant reduction of anxiety and depression in the patients of the first group (Figure 2). Before treatment the average level of depression was evaluated as clinical and was comparable in both groups (11.5 ± 0.6 and 11.3 ± 0.7 points, respectively). After treatment this parameter came back to normal values in the patients of the first group (6.9 ± 0.3 points, p<0.02), whereas in the second group its values stayed at subclinical level. Average depression level estimated with the HADS scale was close to clinical level in the beginning of treatment (10.8 ± 0.5 points in the first group versus 11.0 ± 0.2 points in the second group); by the end of treatment (28 days) depression characteristics reached the normal levels only in the first group (6.7 ± 0.3 (p<0.02)) (Figure 4).

Conclusion

ED and ADD are frequently present in men with AH. Combined pathology increases significantly the risk of premature death, aggravates prognosis and lowers down the quality of patients' life. Common pathogenetic mechanisms of ED, ADD, and AH include endothelial dysfunction, low androgene levels, impaired balance of hypothalamo-pituitary-adrenal system, and sympathicotonia. ED is an early marker or prede-

cessor of cardiovascular disorders and appears to be a valuable diagnostic symptom for internal medicine specialists. The triad of ED, ADD and AH requires the prescription of adequate antihypertensive and psychocorrecting therapy, complex restoration of sexual function and consequently becomes the problem of interdisciplinary interaction between cardiologists, psychiatrists, sexologists, urologists and endocrinologists.

Conflict of interest: None declared.

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Investigation of life quality and depression intensity in patients with arterial hypertension receiving maintenance hemodialysis treatment

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Summary

Objective

To detect the characteristics of life quality (LQ) and depression intensity in patients with arterial hypertension receiving maintenance hemodialysis treatment in the Udmurt Republic.

Materials and methods

We performed the analysis of LQ in 248 patients with chronic kidney disease (CKD), stage 5, receiving maintenance hemodialysis treatment in the Udmurt Republic. The average duration of dialysis in this patients was 5.6±5.5 years. Analysis was performed using Beck's Depression Inventory (1961) and specific questionnaire Kidney Disease Quality of Life Short Form (KDQOL-SF™), Russified by I.A.Vasilieva in 2006.

Results

We identified that LQ characteristics in people with AH receiving maintenance hemodyalysis were lower than the ones of patients with normal and low AH according with the majority of scales. mostly due to the reduction of mental component: 38.6±9.5 versus 44.4±12.6 ($p<0.01$) and 49.5±8.4 ($p<0.001$), correspondingly. Patients with AH demonstrated lower values for the majority of scales reflecting specific kidney disorders in patients with AH. Significant difference between studied group and both comparison groups was found for scales "Symptoms/problems", "Cognitive functions", "Sexual function". The differences in scales "Labour ability" and "Support by dialysis

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staff" was not found. It was detected that the patients with AH have more evident depression symptoms. We also identified the correlation between depression and scales of LQ related to mental component. We did not detect the connection of depression with LQ scales characterizing the quality of medical services and psychological support by dialysis staff.

Conclusion

The results of this study demonstrate that the patients with AH receiving maintenance hemodialysis had more evident depression and lowered life quality according with all scales, dominantly because of the mental component. Patients with AH, 3 stage, demonstrated low values in all scales reflecting the prominence of disease symptoms and their influence on physical component.

Key words

Arterial hypertension, chronic kidney disease, life quality, depression, sexual function

Improvement of renal replacement therapy's (RRT) techniques provided significant reduction of mortality rate and exposed the problem of life quality (LQ) in patients with chronic kidney disease (CKD). It is particularly important for modern cardiology and nephrology to bring LQ parameters of the patients undergoing hemodialysis (HD) to the level of population ones. Russian and foreign authors mark out some aspects of LQ investigation in patients undergoing HD: morbidity and mortality predictors, influence of dialysis type and treatment efficiency on LQ. Patients undergoing HD have to constantly follow particular diet, restrict liquid intake, they depend on HD procedures, medical staff, additional medications, they suffer the loss of work and inability to travel, and some of them live through sexual dysfunction. Several Russian studies assessed the influence of minimal and average pulse blood pressure (BP) during HD procedure on the severity of pain syndrome [1, 2].

The works of I.A.Vasilyeva (2010) demonstrated that self-estimation of their condition of HD patients is as much important predictor of survivability as well-known clinical manifestations and laboratory test results characterizing the severity of the disease. For example, if physical functioning (PF) characteristic exceeds 56.8 points, the 5-year survivability is 69% comparing with 31% in the group where the value of this LQ parameter is less than 56.8. 6-year survivability in the patients with the values of total physical component (TPC) not higher than 34.6 is 0, whereas 6-year survivability in patients with TPC higher than 34.6 is 54% [3, 4, 5].

Several works investigated LQ correlation with the type of RRT, gender and HD duration in patients with CKD 5D stage [6, 7]. Some other articles estimated LQ in patients with AH [6, 7]. At the same time, LQ is rarely evaluated in patients with CKD 5D stage and AH. Single studies have proved the correlation between LQ, central hemodynamics and the adequacy of HD treatment [8].

Depression, associated with increased mortality, is very common in patients with terminal CKD [9, 10, 11, 12]. In particular, P. Kimmel and coauthors (2005) consider depression as the most frequent mental disorder in patients with CKD 5stage [13]. Depression frequency in HD population is high, and its comorbidity with AH is around 30%. Depressive disorders in patients with AH make treatment more complicated and can be the cause of patients' refusal of adequate antihypertensive therapy [14, 15, 16].

Thus, it is necessary to perform further LQ estimation in HD patients and to study if these deviations should undergo psychopharmacological correction.

The objective of this study was to detect the characteristics of life quality (LQ) and depression intensity in patients with arterial hypertension receiving maintenance hemodialysis treatment in the Udmurt Republic.

Materials and methods

This study involved 248 patients with CKD 5D stage, among them 129/119 males/females, aged between 18 and 61 years, receiving maintenance HD treatment in HD departments of the Udmurt Republic (cities Izhevsk, Glazov, Votkinsk, Mozhga, Sarapul). 4008S ("Fresenius", Germany) and Dialog+ (B. Braun, Germany) HD apparatus was used for HD procedure that has been done 3 times per week for 4-4.5 hours each using polysulfonic dialysis membranes. The adequacy index Kt/V of urea was higher than 1.2 with the average value of 1.43±0.09 All patients were divided in 3 groups of comparable age and gender. The first group consisted of 173 patients with elevated BP: 120 patients with stage I hypertension, 42 patients with stage II hypertension, and 11 patients with stage III hypertension according with the guidelines of the

World Health Organization/International Society of Hypertension (WHO/ISH, 1999, with the updates of 2003), the Russian Society of Cardiology (RSC, 2004, 2010), the European Society of Hypertension/the European Society of Cardiology (ESH/ESC, 2013). AH duration was 13.4±1.1 years. The second group consisted of 28 patients with normal BP (systolic BP, SBP was 100-139 mm Hg, diastolic BP, DB was 60-89 mm Hg). The third group included 47 patients with low BP (SBP 99 and less mm Hg, DBP 59 and less mm Hg). Patients with different BP had comparable age and gender.

Kidney Disease Quality of Life Short Form (KDQOL-SF™) questionnaire (R.D. Heys and coauthors, USA, 1994, Russian version by I.A. Vasilyeva, 2006) and the Beck depression inventory were used for estimation of LQ level and intensity of depression.

Statistical analysis was performed using "BioStat" v.4.03 (2009) and Microsoft Excel 2010 software. Statistical analysis involved parametric and non-parametric methods. Results are presented as M±m. Results' significance was proved using Student's t-test and Mann-Whitney (T) test. Correlation analysis was done using Pearson's (r) and Spearman's (rs) tests.

Results

Patients with AH undergoing maintenance HD had low values of the following scales of the questionnaire: "Emotional wellbeing", "Emotional role restriction', "Social functioning", "Vitality". Several parameters of physical component like "Pain" and "Physical role restriction" were low in this group of patients. The level of additional scale "General perception of health" was also significantly lower comparing with the patients with normal BP (Table 2). The majority of scales reflecting specificity of kidney disorders in patients with AH were characterized with lower values. Significant difference between investigated group and comparison groups was found for the scale "Sexual function" (Table 1). Correlation analysis revealed connection between parameters of the scale "Sexual function" and renal parenchymal thickness for both kidneys: r= -0.75 (p<0.001) and r= -0.84 (p<0.001) for the right and left kidney, respectively.

Patients with AH had significantly lower values of such specific scales like "KS", "KDI", "CF", "SQ" (Table 1), comparing with the patients with hypotension. Patients with normal BP had higher scores in such scales like "KS" and "SIQ" comparing with the persons with low BP. At the same time, they noticed that kidney disorders influenced more their everyday life. We did not find significant differences in scales "LA" and "DSS" (Table 2).

Comparison of obtained results in patients with different stages of AH revealed that persons with AH 3 stage had lower LQ score. In particular, significant differences have been found for specific scales ("Feeling of being burdened with CKD", "SF", "SQ") and additional scales ("GHE"). The same group was characterized with a tendency to high values of such scales like: "MSS", "DSS", "SSF ", "SIQ", and "KDI". Thus, socio-psychological component was more favorable in the group of patients with AH 3 stage, and the scores of the scales reflecting severity of disease symptoms and their influence on patient's everyday functioning were significantly lower.

Patients with AH 3 stage had low scores of questionnaire's general scales like "Pf", "PRR", "GHP", "EW". These persons had a trend for low scores of the "TPC" scales comparing to high values of the "TMC" scale (Table 2).

Analysis of Beck depression inventory revealed that among the patients receiving maintenance HD, depression was present in 167 (96.5%) persons with AH, in 17 (60.7%) people with normal BP, and in 23 (48.9%) patients with hypotension (Table 3). Severe depression occurred in 16 (9.2%) patients with high BP, in 2 (7.2%) patients with normal BP, and in 3 (6.4%) patients with hypotension. Average intensity of depression in patients with AH was 20.6±1.1 points, the same value in patients with normal BP and hypotension was 18.6±2.7 and 11.6±1.5 points, respectively (p_{1-3}<0.001; p_{2-3}<0.001).

Depression symptoms were detected in 114 (95%) patients with AH 1 stage and in all patients with AH 2-3 stage. Subdepression was detected in 42 (35%) and 12 (28.6%) patients with AH 1 and 2 stage, respectively. Moderate and evident depression prevailed in persons with AH 1 stage, and patients with AH 2-3 stage had mostly evident and severe depression (Table 4). As it may be seen in the table, percentage of patients with severe depression increased accordingly with the stage of AH. The same pattern could be observed for average depression score: 17.9±1.3 for AH 1 stage, 20.9±2.5 for AH 2 stage, 26±2.7 for AH 3 stage (p_{1-3}=0.0003).

Correlation analysis revealed connection between depression intensity mostly with the LQ scales reflecting mental component: "ERR" (r=-0.74; p<0.001), "EW" (r=-0.45; p<0.01), "SOCF" (r=-0.37; p<0.01). We identified correlation between the intensity of depres-

Table 1. **Comparison of specific and additional scales' parameters in groups of patients with different BP levels**

Scales of the KDQOL-SF™ questionnaire	AH N=173			Normal BP N=28	Hypotension N=47	p-value
	1stage N=120	2stage N=42	3stage N=11			
Kidney symptoms (KS)	56 4±3.2	56.3±4.8	45.1±7.7	73.1±2.6	66.4±2.5	p_{1-4}=0.0000 p_{2-4}=0.0000 p_{3-4}=0.0000 p_{1-5}=0.0001 p_{2-5}=0.0002 p_{3-5}=0.0000 p_{4-5}=0.0032
Kidney disease impact (KDI)	47.7±3.8	52.8±3.7	57.9±7.8	49.6±5.0	62.6±14.7	p_{1-5}=0.0000 p_{2-5}=0.0005 p_{4-5}=0.0000
Feeling of being burdened with CKD	24.2±3.9	22.5±4.8	6.2±3.2	31.9±3.2	35.1±5.1	p_{1-4}=0.0106 p_{2-4}=0.0035 p_{3-4}=0.0000 p_{1-5}=0.0003 p_{2-5}=0.0009 p_{3-5}=0.0000 p_{1-3}=0.0012 p_{2-3}=0.002
Labor ability (LA)	17.3±5.5	15.0±6.6	16.6±7.5	22.2±14.6	21.8±7.8	-
Cognitive functions (CF)	72.5±4.1	63.6±5.0	61.1±12.8	81.5±4.9	83.1±3.4	p_{1-4}=0.0186 p_{2-4}=0.0000 p_{3-4}=0.0012 p_{1-5}=0.001 p_{2-5}=0.0000 p_{3-5}=0.0001
Quality of social interactions (SIQ)	72.6±3.1	72.6±3.5	79.6±4.5	85.9±4.8	74.6±4.1	p_{1-4}=0.0001 p_{2-4}=0.0000 p_{4-5}=0.0026
Sexual functions (SF)	67.0±9.7	75.0±10.2	40.8±12.3	87.5±5.1	87.5±5.5	p_{1-4}=0.0007 p_{2-4}=0.0412 p_{3-4}=0.0000 p_{1-5}=0.0000 p_{2-5}=0.0165 p_{3-5}=0.0000 p_{1-3}=0.0162 p_{2-3}=0.0046
Sleep quality (SQ)	44.6±3.7	38.7±6.2	23.3±7.2	51.2±2.9	56.1±4.2	p_{1-4}=0.0424 p_{2-4}=0.0013 p_{3-4}=0.0000 p_{1-5}=0.002 p_{2-5}=0.0000 p_{3-5}=0.0000 p_{1-3}=0.001 p_{2-3}=0.0237
Feeling of social support (SSF)	62.4±5.2	68.3±5.7	77.7±12.5	74.1±5.6	79.2±4.1	p_{1-4}=0.0163 p_{2-4}=0.0004 p_{1-4}=0.0001 p_{2-5}=0.0000
Dialysis staff's support (DSS)	65±4.8	65±5.5	75±12.5	69.4±6.2	67.9±7.3	-
General perception of health (GHP)	39.2±3.2	34±4.5	16.6±3.3	50±2.1	48.1±3.7	p_{1-4}=0.0007 p_{2-4}=0.0000 p_{3-4}=0.0000 p_{1-5}=0.0009 p_{2-5}=0.0000 p_{3-5}=0.0000 p_{1-3}=0.0000 p2-.3=0.0004
Medical service satisfaction (MSS)	47.9±6.1	49.9±7.4	61.1±15.2	66.7±7.3	62.4±6.3	p_{1-4}=0.0013 p_{2-4}=0.002 p_{1-5}=0.0023 p_{2-5}=0.00101

Table 2. **Comparison of general scales' parameters in groups of patients with different BP levels**

Scales of the KDQOL-SF™ questionnaire	AH N=173			Normal BP N=28	Hypotension N=47	p-value
	1stage N=120	2stage N=42	3stage N=11			
Physical functioning (PF)	43.4±4.9	32.8±7.9	19.4±10.0	48.6±9.1	55.6±6.0	p_{2-4}=0.0084 p_{3-4}=0.0016 p_{1-5}=0.0031 p_{2-5}=0.0000 p_{3-5}=0.0000 p_{1-3}=0.0049
Physical role restriction (PRO)	12.9±4.8	18.3±7.6	11.1±8.4	33.3±14.1	24.5±9.8	p_{1-4}=0.0007 p_{1-5}=0.0134
Pain (P)	39.8±3.9	44.5±6.1	37.5±8.6	60.6±2.6	59.5±5.9	p_{1-4}=0.0000 p_{2-4}=0.0001 p_{3-4}=0.0000 p_{1-5}=0.0000 p_{2-5}=0.0011 p_{3-5}=0.0059
General health evaluation (GHE)	30.9±2.8	20.7±5.2	11.6±6.0	39.4±3.2	38.5±4.1	p_{1-4}=0.0028 p_{2-4}=0.0000 p_{3-4}=0.0000 p_{1-5}=0.0028 p_{2-5}=0.0000 p_{3-5}=0.0000 p_{1-3}=0.0001
Emotional wellbeing (EW)	53.2±3.8	38.2±6.8	28.0±9.6	64.8±6.2	66.3±6.5	p_{1-4}=0.0031 p_{2-4}=0.0000 p_{3-4}=0.0000 p_{1-5}=0.0003 p_{2-5}=0.0000 p_{3-5}=0.0000 p_{1-3}=0.0002
Emotional role restriction (ERR)	19.4±5.6	30±8.5	33.3±13.2	66.6±16.6	60.4±9.7	p_{1-4}=0.0000 p_{2-4}=0.0014 p_{3-4}=0.0284 p_{1-5}=0.0000 p_{2-5}=0.0003 p_{3-5}=0.0286
Social functioning (SOCF)	50.8±5.3	53.7±6.4	58.3±8.3	68.1±5.6	72.6±5.2	p_{1-4}=0.0011 p_{2-4}=0.0008 p_{1-5}=0.0000 p_{2-5}=0.0000 p_{3-5}=0.0228
Vitality (V)	38.9±3.3	38.8±3.7	41.6±3.3	51.1±5.7	54.5±2.9	p_{1-4}=0.0007 p_{2-4}=0.0003 p_{3-4}=0.0497 p_{1-5}=0.0000 p_{2-5}=0.0000 p_{3-5}=0.0004
Total physical component (TPC)	33.1±1.6	32.9±4.2	30.6±5.3	35.2±0.8	35.2±2.1	p_{3-4}=0.0081
Total mental component (TMC)	37.8±2.1	36.6±5.2	40.4±4.0	44.4±5.1	49.5±2.2	p_{1-4}=0.0014 p_{2-4}=0.0079 p_{1-5}=0.0000 p_{2-5}=0.0000 p_{3-5}=0.0012 p_{4-5}=0.0389

sion and physical component's scales" "P" (r=-0.56; p<0.01), PF (r=-0.34; p<0.01), that by itself proves the presence of several factors promoting the development of depression, as external ones (social, psychological, emotional), as internal ones (rough pathophysiological deviance). Specific scales like "KS" (r=-0.4; p<0.01), "Feeling of being burdened with CKD" (r=-0.67; p<0.001), "KDI" (r=-0.62; p<0.001), "CF" (r=-0.6; p<0.001), "SQ" (r=-0.4; p<0.01), "SF" (r=-0.5; p<0.001), "SSF" (r=-0.35; p<0.01; Table 4). There was no significant correlation between depression and additional LQ scales: "MSS" (r=-0.15; p>0.05), "DSS" (r=-0.1; p>0.05), "GHP" (r=-0.2; p>0.05).

Discussion

This study demonstrated that all patients with AH, independently on its stage, had significant reduction of specific and general LQ scales reflecting prevalently mental component (p<0.001). Thus, these patients had the symptoms of neurotic disorders, tiredness,

Table 3. **Severity of depression in patients with CKD with different BP levels**

Depression intensity	High BP N=173 Persons (%)	Normal N=28 Persons (%)	Arterial hypotension N=47 Persons (%)	p-value
Absence	6(3.5)	11(39.3)	24(51.1)	p_{1-2}<0.0001 p_{1-3}<0.0001 p_{2-3}>0.05
Subdepression	54(31.2)	4(14.3)	8(17.0)	p_{1-2}>0.05 p_{1-3}>0.05 p_{2-3}>0.05
Moderate	43(24.9)	4(14.3)	2(4.3)	p_{1-2}>0.05 p_{1-3}<0.01 p_{2-3}>0.05
Evident	54(31.2)	7(25.0)	10(21.2)	p_{1-2}>0.05 p_{1-3}>0.05 p_{2-3}>0.05
Severe	16(9.2)	2(7.1)	3(6.4)	p_{1-2}>0.05 p_{1-3}>0.05 p_{2-3}>0.05

Comment: p – significance of differences between the groups according with the Pearson's chi-squared test.

Table 4. **Depression intensity in patients with CKD 5D stage combined with AH of different stages**

Depression intensity	AH 1 stage N=120 patients (%)	AH 2 stage N=42 patients (%)	AH 3 stage N=11 patients (%)	p-value
Absence	6(5)	0(0)	0(0)	p_{1-2}>0,05 p_{1-3}>0,05 p_{2-3} -
Subdepression	42(35)	12(28,6)	0(0)	p_{1-2}>0,05 p_{1-3}<0,05 p_{2-3}<0,05
Moderate	35(29,1)	6(14,3)	2(18,2)	p_{1-2}>0,05 p_{1-3}>0,05 p_{2-3}>0,05
Evident	32(26,7)	16(38,1)	6(54,5)	p_{1-2}>0,05 p_{1-3}>0,05 p_{2-3}>0,05
Severe	5(4,2)	8(19,0)	3(27,3)	p_{1-2}<0,01 p_{1-3}<0,01 p_{2-3}>0,05

Comment: p – significance of differences between the groups according with the Pearson's chi-squared test.

sorrow, emotional exhaustion and did not have "the feeling of happiness". This group of patients had low scores both of physical component scales like "P" and "PRR" (p<0.01), that can indicate significant restriction of physical exercises in everyday life, in particular, osteodystrophy and related to it pain syndrome, the presence of chronic inflammation (polyneuropathy). Patients with AH reported stronger impact of kidney disorders on social functioning related to the necessity to follow a diet and reduce liquid intake, the inability to do house duties, and disease's influence on appearance or social functioning. Significant difference between the studied group and normal BP and hypotension groups was found for the "SF" scale (p<0.001). The questionnaire reflects subjective evaluation by patient, but it does not reduce the significance of this scale that can correspond to the intensity of erectile dysfunction. According with several authors, erectile dysfunction is a sign of severity of endothelial dysfunction in cavernous bodies and may be considered as cardiovascular complications risk factor [17.18.19], that was proved in our study by strong correlation between "SF" scale and renal parenchymal thickness (p<0.001). In our study patients with AH related low social support including friends and family, at the same time perception of dialysis staff's psychological support was comparable with the groups of normal and low BP.

Comparison of the results obtained in patients with AH of different stages revealed that patients with AH 3 stage had lower LQ scores. This reduction was present for scales reflecting physical component and symptoms including the "SF" scale. Patients reported that kidney disorders prevented them from living

normal life, took much time and made them feel as a burden for their families. CKD complications like cramps, skin itch, numbness of hands and feet, chest pain, reduced sleep quality become more evident in higher stages of AH.

In the Udmurt Republic depression is a common mental disorder in patients with AH undergoing maintenance HD (96.5%). Occurrence and intensity of depression symptoms increased accordingly with AH stage($p<0.05$). It may be caused by crossing mechanisms of AH and depression pathogenesis, in particular, by hyperactivation of sympathetic nervous system and activation of thalamo-pituitary-adrenal system [20, 21].

Correlation analysis revealed connection between depression intensity and LQ scales, mostly with the ones reflecting mental component ($p<0.01$), that proves the presence of external (social, psychological, emotional) and internal (rough pathophysiological deviance) factors promoting the development of depression [22]. The presence of significant correlation demonstrates burdening influence of depression on LQ parameters. Since depression intensity has no correlation with the scales "MSS" and "DSS", professional psychological help is required in this category of patients. Taking into account prevalence and intensity of depression in patients undergoing maintenance HD that is aggravated in case of AH, not only psychotherapeutic but also psychopharmacological support may be required in these patients. Unfortunately, nowadays there are no psychotherapists in HD departments of the Udmurt Republic.

Reduction of LQ characteristics and more severe depression in patients with AH undergoing maintenance HD increases the risk of unfavorable cardiovascular complications.

Conclusion

Taking into account all mentioned above facts, we can conclude that patients with AH undergoing maintenance HD had reduced LQ according with all scales of the questionnaire, mostly because of the mental component. Patients with AH 3 stage had low scores of the scales reflecting the severity of disease symptoms and physical component. Patients with AH have higher risk of developing depression. Intensity of depression symptoms increases with the increase of AH stage. Due to this it is necessary not only to correct BP levels in patients with AH undergoing HD, but also give these patients necessary psychological support and/or psychopharmacological treatment.

Conflict of interest: None declared.

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Lipid metabolism characteristics in women of child-bearing age with iron-deficiency anemia

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Summary

Objective

To determine interrelation between lipid metabolism characteristics with iron-deficiency anemia and other cardiovascular risk factors in women of child-bearing age.

Materials and methods

Using the results of complex population study of rural dwellers, we performed analysis of lipid metabolism characteristics and other cardiovascular risk factors in 506 women of child-bearing age.

Results

Women with iron-deficiency anemia (n=26) had significantly lower levels of total cholesterol (p=0,009), low density lipoproteins cholesterol (p=0,003) and significantly lower atherogenic index (p=0,003). Regression analysis demonstrated that the presence of iron-deficiency anemia is an independent factor that significantly reduces the possibility to have atherogenic dyslipidemia in females of studied population (OR=0,20, 95% CI 0,07-0,55, p=0,002).

Conclusion

It is recommended to take into account the presence of iron-deficiency anemia in case of investigation of lipid metabolism characteristics in women of child-bearing age.

Key words

iron-deficiency anemia, hemoglobin, dyslipidemia, cholesterol.

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Introduction

In 1981 J.L.Sullivan proposed that levels of serum iron in women of child-bearing age lower comparing with men have protective action against atherogenesis [1]. Several studies in models of donors with atherosclerosis and hemochromatosis have been conducted, and their results are controversial [2-7]. Iron-deficiency anemia (IDA) could have become another model for testing J.L.Sullivan's hypothesis. The study of relation between IDA and known cardiovascular risk factors, first of all, such surrogate atherosclerosis signs like lipid metabolism characteristics appears to be possible in this case [8]. There are single evidences related to lipid metabolism characteristics and based on clinical observation in patients with IDA. The features of lipid metabolism characteristics in females of child-bearing age with IDA in relation to known cardiovascular risk factors are not studied enough in population level.

The objective of this study was to determine interrelation between lipid metabolism characteristics with IDA and other cardiovascular risk factors in women of child-bearing age

Materials and methods

This work has been performed as a part of the Countrywide Integrated Noncommunicable Diseases Intervention (CINDI) program. We conducted a complex epidemiological study of the dwellers of Muslumovo village (Chelyabinsk region) on the base of Chelyabinsk Regional Hospital №1 diagnostic center involving wide spectrum of professionals (physician, gynecologist, surgeon, neurologist, ophthalmologist, etc). Population involvement reached 93%. All patients signed informed consent. Patients underwent physical examination, laboratory tests (complete blood count, urine test, urea, creatinine, bilirubin, glucose, lipids' blood levels), spirometry, electrocardiography (ECG), abdominal and kidney echography, and additional laboratory and instrumental tests, if it was necessary.1242 females aged 18-82 years have been observed. Exclusion criteria were: acute posthemorrhagic anemia, anemia of chronic disease, megaloblastic anemia, cancer, thyroid gland disorders (hypothyroidism, hyperthyroidism), diabetes mellitus, severe hepatic disorders with clinical and laboratory signs of active process (hepatic depression, syndromes of cytolysis and cholestasis), any malabsorption syndrome, chronic alcoholism and drug addiction, active phase of kidney disorders and/or nephrotic syndrome, chronic kidney failure, acute myocardial infarction, infectious diseases (acute and exacerbations of chronic disorders), systemic connective tissue disorders, pregnancy. We excluded patients with non-iron deficiency anemia and patients with possible secondary disorders of lipid metabolism.

We selected medical records of 506 women according with inclusion/exclusion criteria. IDA diagnosis was established according with the WHO guidelines, if hemoglobin (Hb) blood levels were <120 g/L or if there was erythrocyte hypochromia (color index) and reduced concentration of serum iron (<12 mmol/L). IDA was detected in 26 female patients (average age 35.7±7.5 years), the control group included 480 women without IDA (average age 33.4±7.9 years). There were no significant differences of age between women with IDA and the control group (p=0.80). The majority of IDA cases were related to uterine bleeding (18 cases), less frequently they were caused by nasal (4 cases) and hemorrhoidal bleeding (4 cases).

Morphological composition of peripheral blood was investigated using standard laboratory techniques. Hb levels were evaluated using Sahli's hemoglobinometer, number of erythrocytes and leukocytes was estimated using cell-counting chamber, platelets were quantified using Fonio's method. Leukocyte count was performed using samples stained with Romanowsky method and visualized using light microscopy. Total cholesterol (TC), triglycerides (TG), high density lipids cholesterol (HDL Ch) levels were determined using reagents of "Human" company (Germany) and "Hitachi" machine (Japan). Serum concentration of iron was evaluated using reagents of "Human" company (Germany) and "Flexor E" (Netherlands) machine.

We developed a specific questionnaire that allowed us to estimate cardiovascular risk factors. Cardiovascular risk factors were estimated using WHO criteria (1995). Low physical activity (LPA) was described as staying in sitting position for more than 5 hours per day in case of less than 10 hours of physical activity per week or intensive physical activity less for less than 30-40 minutes per day. Character of alcohol consumption within the last year was estimated using J Merta's classification [10]. Burdened family history included sudden death, acute myocardial infarction, stroke, early development of arterial hypertension (AH) (before the age of 65 years in women and before 55 years in men) in the relatives of the first degree of kinship. AH was diagnosed if blood pressure (BP) levels were ≥ 140/90 mm Hg after two measurements. Body mass index (BMI) was quantified

using the following formula: BMI=body weight / (body height^2, m^2). BMI between 18 and 24.9 kg/m^2 was considered normal, excessive body weight started from BMI⩾25 kg/m^2.

Impairment of lipid metabolism and dyslipidemia type were diagnosed according with the guidelines of dyslipidemia diagnosis and management [8]: TC ⩾ 5.0 mmol/L, TG ⩾ 1.7 mmol/L, HDL Ch < 1.2 mmol/L, LDL Ch ⩾ 3 mmol/L. LDL Ch concentration was quantified using W.T. Friedewald's formula [11]: LDL Ch (mmol/L) = TC = HDL Ch – 0.45*TG. Atherogenic index (AI) was estimated using A.N. Klimov's formula [12]: AI = TC/HDL Ch. The presence of IIa, IIIb, III, and IV dyslipidemia types was considered as atherogenic impairment of lipid metabolism.

Results were analyzed using STATISTICA 6.0 software [13]. We chose statistical test after performing normality test. Results are present as M±σ, where M is average value, σ – root-mean square deviation in case of normal distribution, and as Me (25; 75), where Me is median, 25 and 75- 25th and 75th percentiles, respectively if the distribution was different from normal. If the distribution was normal, comparison of quantitative characteristics was performed using Student's τ-test, if the distribution was not normal, Mann-Whitney test was used. The odds ratio (OR) was quantified with 95% confidence interval (CI) using EpiInfo 5.16 software. To evaluate relation between the characteristics of lipid metabolism and risk factors we made multiple logistic regression analysis. P-value <0.05 was considered significant.

Results

Women with IDA had significantly lower TC, LDL CH, and AI levels comparing with the women of the control group (p=0,009, p=0,003, p=0,003, respectively) (Table 1).

There were no statistically significant differences in the structure of atherogenous dyslipidemias (AD) between two groups (x^2=0.75, p=0.73). Dyslipidemia, IIa type prevailed in both groups (Table 2).

The frequency of lipid metabolism abnormalities in the group of women with IDA and in the control group was 15.4% and 41.9% for dyslipidemia, IIa type and 19.2% and 47.9% for other AD, respectively. The chance to have IIa type dyslipidemia and other AD in women with IDA was significantly lower comparing with the women of the control group (OR=0,25, 95% CI – 0.07-0.79, p=0.07 for dyslipidemia IIa type and OR=0.26, 95% CI 0.08-0.74, p=0.04 for other AD types) (Table 3, 4).

Regression model of AD demonstrated that age, BMI and burdened family history were independent factors that significantly increased the probability of AD in women of child-bearing age. The presence of IDA was an independent factor that reduced significantly the chance to have AD in the studied population (Table 5).

Table 1. **Lipid metabolism characteristics in women with IDA and control group women, Me (25, 75)**

Characteristics	IDA, n=26		Control, n=480		p
	Me	(25; 75)	Me	(25; 75)	
TC, mmol/L	4.23	3.46-4.80	4.87	3.90-5.60	0.009*
TG, mmol/L	0.88	0.68-0.99	0.93	0.64-1.11	0.9
LDL CH, mmol/L	2.55	1.93-2.92	3.18	2.38-3.82	0.003*
HDL CH, mmol/L	1.28	1.14-1.48	1.27	1.10-1.47	0.8
AI	3.33	2.89-3.79	3.96	3.11-4.50	0.003*

Comment: * - p< 0,05.

Table 2. **The frequency of lipid metabolism disorders in women with IDA and women of the control group, absolute number and %**

Dyslipidemia type	IDA, n=26		Control, n=480	
	abs.number	%	abs. number.	%
IIa type	4	15.4	201	41.9
IIb type	0	0	18	3.7
III type	1	3.8	4	0.8
IV type	0	0	7	1.5
Total number o AD cases	5	19.2	230	47.9

Comment: abs.number – absolute number

Table 3. **The frequency of cardiovascular risk factors in women with IDA and in control group women, abs. number, %**

Risk factor	IDA, n=26		Control, n=480	
	abs.number	%	abs. number.	%
Burdened family history	10	38.5	174	36.3
AH	18	69.2	365	76.0
Increased body weight	14	53.9	294	61.3
AH	5	19.2	84	17.5
Excessive body weight	15	57.7	262	54.6

Comment: abs.number – absolute number

Table 4. **OR for cardiovascular risk factors in women with IDA and women of the control group**

Risk factor	OR	95% CI for OR	p
Burdened family history	1.10	0.45-2.63	0.82
AH	0.71	0.28-1.83	0.43
Increased body weight	0.74	0.31-1.74	0.45
AH	1.12	0.36-3.26	0.79
Excessive body weight	1.13	0.48-2.71	0.76

Table 5. **AD multiple regression analysis model (logistic regression)**

Risk factor	OR	95% CI for OR	p
Initial value	0.02	0.01-0.07	<0.0001*
Age	**1.07**	**1.04-1.11**	**<0.0001***
IDA	**0.22**	**0.08-0.60**	**0.004***
LPA	0.84	0.57-1.25	0.39
Alcohol consumption	0.80	0.51-1.25	0.32
Burdened family history	**1.52**	**1.03-2.24**	**0.034***
AH	0.73	0.43-1.25	0.25
BMI	**1.06**	**1.02-1.11**	**0.008***
Total significance of the model			<0.0001*

Comment: * - p< 0,05.

Discussion

For the first time we demonstrated that women of child-bearing age with IDA have significantly lower levels of the main atherogenic lipid fractions comparing with the control group women of the same age. We discovered for the first time that IDA could be an independent factor that reduced significantly the probability to develop AD. Our results support the hypothesis of J.L. Sullivan.

Single clinical studies demonstrated antiatherogenic shift in blood lipid spectrum in case of IDA [14-15]. The study of Zhelobov and coauthors demonstrated positive correlation between the number of erythrocytes and concentration of proatherogenic lipids in IDA and revealed the correlation between changed lipid spectrum and severity of anemia.

It has been demonstrated that the role of iron in atherogenesis is related to lipid peroxidation and inflammation [16-18]. Xanthine oxidase, mieloperoxidase, lipoxygenase have iron atoms, by this iron participates in enzymatic part of lipid peroxidation. OH-groups can be produced through non-enzymatic reaction between peroxides and metalloproteinases. Hydrogen peroxide's decomposition in Fenton's reaction in the presence of Fe^{2+} leads to formation of hydroxyl radical. Iron up-regulates tumor necrosis factor- α (TNF- α) expression. Pre-latent and latent iron deficiency decreases the activity of macrophages. From one side, it leads to impaired immune system activity associated with IDA, from another side, it can have a protective effect on atherogenesis.

We think that it is impossible to explain lower values of atherogenic lipid fractions and lower frequency of dyslipidemia just by the effect of iron. It is necessary to consider other factors like hemic hypoxia that leads to compensatory hemodynamic effects and requires further investigation. The mechanism of hipolipidemic effect in IDA is related to the action of enzymatic systems of erythrocytes' cytoplasm [19], hypoxia action [20], and possible reduction of liver synthetic function. Authors consider this phenomenon as a compensatory-adaptive reaction on hypoxia that leads to increased resistance of erythrocyte' membrane. Thus, reduction of cholesterol levels in IDA can be related to its mobilization for erythrocytes' survival in anemia. Antiatherogenic shifts in lipid spectrum can be present in blood malignancies.

Our results are very relevant for further theoretical and practical studies. It is recommended to take into account the presence of IDA while investigating lipid metabolism characteristics in women of child-birth age.

Conclusion

Women with IDA had significantly levels of TC, LDL Ch, and AI levels comparing with the women from the control group

The possibility to have IIa type of dyslipidemia and any AD in women with IDA was significantly lower comparing with the control group.

Important characteristics of lipid metabolism in women with IDA do not depend on the other cardiovascular risk factors.

Conflict of interest: None declared.

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Arterial hypertension and heart remodeling in athletes

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Summary

Objective

To investigate left ventricle's hemodynamic characteristics and morphofunctional condition in different types of athletes.

Materials and methods

This study included 231 athletes aged 18-32 years working in 8 different sport types: boxing, wrestling, weight lifting, track and field athletics (middle-distance running), cycle racing, bicycle motocross, yachting, and pentathlon. Analysis of the character of physical exercise was performed using J.H. Mitchell classification (2005) that classified sports according with the combination of dynamic and static loads. All athletes underwent examination, standard resting electrocardiogram, repeated blood pressure (BP) measurement, and transthoracic echocardiography. Athletes with high normal and elevated BP underwent 24-hours BP monitoring. Athletes with elevated BP underwent additional questioning of specific arterial hypertension (AH) risk factors.

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Results

Elevated BP was detected in 5.6% of examined athletes. Elevated BP was presented mostly in athletes specializing on static loads of high intensity combined with aerobic loads of moderate or high intensity. According with the results of echocardiography study, 19 men had mild increase of left ventricular myocardial mass, and 10 men had left ventricular hypertrophy. Specific AH risk factors in athletes include increased consumption of sodium, alcohol, caffeine and prohibited medications like erythropoietin, growth hormone and oral contraceptives in females.

Conclusion

Patterns of athletic heart development may be explained by the orientation of training and competition activity; normally they do not lead to abnormal systolic and diastolic function, but BP elevation in athletes increases the risk of myocardial hypertrophy and remodeling that may be a possible contraindication for sports requiring high intensity static loads.

Key words:

Arterial hypertension, myocardial remodeling, isokinetic and isometric exercise, athletic heart.

Introduction

Treatment and prevention of arterial hypertension (AH) is one of the most important healthcare objectives in developed countries. Increased AH prevalence goes along with proportional growth of morbidity and mortality due to myocardial infarction and brain stroke that are currently considered to be associated with AH. Distinct correlation between blood pressure (BP) levels and cardiovascular mortality risk indicate that BP reduction is the most effective method of cardiovascular mortality prevention not only in patients with elevated BP, but also in patients with normal BP. According with epidemiological studies, in the Russian Federation AH occurrence in persons above 15 years reaches 39.5%, that is equivalent to approximately 40 mln people suffering from AH. AH is detected more often in females comparing to males (40.4% and 37.2%, respectively) [1].

AH often starts in early age. Swift increase of number of children and adolescents with AH causes concerns. AH occurrence in school students is around 12-18% [2.3]. Epidemiological studies demonstrated that physical activity and cardiorespiratory training have inverse relation with BP levels and AH occurrence. These trends have been proved in randomized trial that demonstrated that physical activity can reduce BP in both people with normal and increased BP. In general, aerobic exercise lowers systolic BP (SBP) approximately by 2 mm Hg (up to 7 mm Hg) [4, 5]. At the same time, patients with AH demonstrate the most significant BP reduction. General prevalence of AH in physically active people is 50% lower than in general population [4]. But one study that included 467 adolescents making sports demonstrated that 57 young people (12.2%) had elevated BP, and 43 of them (79.6%) had persistently elevated BP for one year. Another important observation of this study was related to the fact that speed-power loads prevailed in the group of young athletes. Secondary AH occurrence in athletes is the same as in general population. Together with the characteristics of training, prevalence of isometric and speed-power loads possibly promoting BP increase, other risk factors could influence AH in athletes: increased alcohol consumption, illegal use of drugs (cocaine, etc), anabolic steroids, stimulators use (for example, in supplementaries increasing organism's energetic resources and body weight controllers), high stress levels, male gender (it occurs twice as more often in African race patients comparing with the European ones, and Asians have lower morbidity comparing with Europeans), several hereditary factors: family history of AH and cardiac diseases in males above 55 years and females above 65 years, diabetes mellitus or impaired glucose tolerance, smoking and chewing tobacco, obesity. Secondary AH causes in athletes include administration of oral contraceptives (women), growth hormone, erythropoietin, non-steroidal anti-inflammatory drugs [6, 7, 8]. Unlike isokinetic training, isometric exercises, called strength training, are characterized with increased peripheral vascular resistance and normal or slightly increased cardiac output. This increase of peripheral vascular resistance leads to development of transitional conditions with increased post-load and potential risk of hypertension [6, 7, 8]. It is worth to notice that AH induced by physical exercise, apart from myocardial remodeling, may lead to myocardial fibrosis that can further provoke development of malignant arrhythmias [9, 10, 11]. More than that, several researchers think that

high-intense aerobic training often causes elevation of blood levels of myocardial damage markers (troponin I and B-type natriuretic peptide) correlating with reduced right ventricular ejection fraction [12].

Speed-sthrength training is the dominating form of activity in such sports like weight lifting, wrestling, throwing sports, American football, rugby. Many sports like playing sports (football, lacrosse, basketball, hockey, field hockey) include significant loads aiming to develop endurance and strength exercises.

Long intensive physical exercise causes physiological adaptation of heart resulting in its structural and functional changes like physiological hypertrophy of myocardial walls and moderate dilatation of its cavities. These physiological changes depend on such factors like age, gender, constitution, sport's type, and normally they do not exceed reference values. Athletes develop different kinds of physiological heart adaptation depending on particular features of their sport's type.

Sportsmen training in cycling, mostly aerobic sports (long-distance running, skiing, and swimming) develop mostly left ventricle (LV) cavity's dilatation with proportional increase of its walls' thickness. It is caused by increased cardiac output during exercise, so LV overload by volume, and increased systemic BP. It leads to development of eccentric LV hypertrophy without changing ratio between LV wall thickness and its diameter.

Sports requiring static or isometric loads (weight lifting, wrestling, throwing sports) lead to development of concentric myocardial hypertrophy, increased LV wall thickness without changing its cavity size because of increased systemic BP and increased heart post-load during exercising.

Results of echocardiography (EchoCG) studies demonstrate that LV posterior wall thickness (LVPWT) in athletes is increased by 15-20% comparing with untrained people. LV end diastolic size (LVEDS) of the majority of athletes is 10% bigger comparing with untrained people, still remaining in the range of reference values.

At the same time, A. Pelliccia and coauthors identified LVEDS increase up to 60 mm in sportsmen (reference value – up to 70 mm) and enlarged interventricular septum thickness (IVST) (>12mm) that were not associated with the signs of dilatation cardiomyopathy (DC) [13, 14]. The study of Basavarajaiah and coauthors found out increased LVPWT up to 13mm (maximal value 16 mm) in 1.5% of observed athletes [15].

Another sign of the "athletic heart" is increased volume and mass of the right ventricle. Systolic and diastolic function of both ventricles remains normal during rest and physical exercise. Usually dimensions of ventricular cavities and walls come back to normal values with termination of intensive training. Reversibility of these changes is considered to be one of key signs of the "athletic heart".

At the same time, there is a small group of athletes with evident myocardial hypertrophy and/or dilatation of cardiac cavities who have phenotype similar with hypertrophic cardiomyopathy (HC) and DC. There is a crossing area between different cardiomyopathy types and "athletic heart", so-called "grey zone" consisted of sportsmen with evident EchoCG signs of LV hypertrophy (13-16mm) and/or dilatation of LV cavity (LVEDS 55-60 mm) [16, 17.18.19.20.21].

. It is possible that myocardial hypertrophy in athletes could be caused by increased BP.It has been proved by several studies demonstrating that sportsmen with hypertensive reaction to load have significantly higher LV myocardial mass comparing with the athletes with normotensive reaction.

It's possible to consider elevated BP in athletes as one of the forms of overloaded cardiovascular system's reaction that may lead to "athletic heart" remodeling. One of the key differences between "athletic heart" and myocardial hypertrophy in patients with cardiovascular disease is the absence of LV diastolic dysfunction in sportsmen with increased heart mass.

Materials and methods

This study included 231 athletes aged 18-32 years (average age 22 years) working in 8 different sport types: boxing, wrestling, weight lifting, track and field athletics (middle-distance running), cycle racing, bicycle motocross, yachting, and pentathlon and having qualification from I adult class to the master of sports.

Analysis of the character of physical exercise was performed using J.H. Mitchell classification (2005) [22] that classified sports according with the combination of dynamic and static loads (Table 1). The classification is based on peak static and dynamic load. Degree of dynamic component increase is determined by maximal oxygen uptake (max O_2) and degree of cardiac output increase; degree of static component increase is identified using the percentage of maximal voluntary contraction (MVC) increase.

Table 1. **Classification of sports depending on combination of static and dynamic loads**

Characteristic of physical exercise	A. Low intensity dynamic exercise (<40% max O_2)	B. Moderate intensity dynamic exercise (40-70% max O_2)	C. High intensity dynamic exercise (>70% max O_2)
I. Low demand static exercise(<20% MVC)	Billiards, bowling, cricket, curling, golf, riflery	Baseball/softball, table tennis, volleyball	Badminton, cross-country skiing (classic technique), race walking, running (long distance), squash, orienteering, tennis
II. Moderate demand static exercise (20-50% MVC)	Archery, auto racing[1, 2], diving[2], motorcycling[1, 2], gymnastics[1, 2], karate[1, 2], judo[1, 2], equestrian[1, 2], yachting	American football, field events (jumping), figure skating (pair skating)[1], rugby[1], cross, running (sprint), synchronized swimming^	Basketball[1], ice hockey[1], biathlon, cross-country skiing (skating technique), lacross[1], running (middle and long distance), figure skating (single), swimming[2], handball, football[1]
III. High demand static exercise (>50% MVC)	Bobsledding/luge[1, 2], martial arts[1], field events (throwing), gymnastics[1, 2], sport climbing, water skiing[1, 2], weight lifting[1, 2], windsurfing[1, 2]	Body building[1, 2], downhill skiing[1, 2], skateboarding[1, 2], snowboarding[1, 2], wrestling[1, 2]	Boxing[1], canoe/kayaking, cycling[1, 2], decathlon, rowing, speed-skating[1, 2], triathlon[1, 2], mountain skiing, water polo

Comment: [1] - risk of injury, [2] - high risk of syncope

All observed athletes underwent standard ECG at rest, repeated BP measurement, transthoracic echocardiography using Aloka 3500 (Japan), Vivid 7 GE (USA), Philips IE 33 HP (Netherlands) apparatus and cardiac sector transducer with 3.5 mHz frequency in B- and M- modes, impulse-wave, color and tissue Doppler-echocardiography (TD-EchoCG). 24-hours BP monitoring (Astrocard® Holtersystem) was performed in all athletes with high normal and elevated BP.

Sportsmen with elevated BP including high normal BP underwent addtional questioning in order to evaluate specific AH risk factors.

Left ventricular myocardium mass (LVMM) was quantified using modified ASE formula: LVMM=0.8*[1.04*((EDS+IVST+LVPWT)^3-EDS^3)]+0.6. LV myocardial mass index (LVMMI) was estimated using body surface area (BSA) quantified with Dubois formula. Males with LVMMI >116g/m^2 and females with LVMMI> 109g/m^2 were considered to have LV myocardial hypertrophy (LVH).

LV diastolic function (DF) was evaluated using characteristics of trans-mitral flow (TMF) measured in impulse-wave mode of Doppler-EchoCG (peak velocity of early diastolic filling of LV – E, cm/sec, peak velocity of late diastolic filling – A, cm/sec, E-wave deceleration time (Dt, msec) were measured, then the E/A ratio was quantified), and mitral fibrous ring displacement (lateral part, interventricular septum, LV anterior and posterior walls) in impulse-wave TD-EchoCG mode. During TD-EchoCG we measured the following parameters of LV systolic and diastolic function: maximal velocity of main "peaks" of myocardial movements (Sa – systolic movement of myocardium, two diastolic movements: e and a, cm/sec), then we quantified the ratio of main peak velocities of early TMF, diastolic myocardial movement (E/e), and ratio of diastolic myocardial movements peaks (e/a).

Systolic myocardial stress (SMS, din/cm^2) was quantified using the following formula:

SMS=(SBP*LVESS/4*systolicLVPWT)*(1+systolicLVPWT/LVESS), where LVESS –left ventricular end systolic size.

Diastolic myocardial stress (DMS, din/cm^2) was quantified using the following formula:

DMS=(SBP*LVEDS/4*diastolicLVPWT)*(1+diastolicLVPWT/LVEDS), where LVEDS –left ventricular end diastolic size.

Statistical analysis of results was performed using Excel 2007 and STATISTICA 8.0 (StatSoft Inc., USA) software. Before choosing the method of data comparison we performed normality tests. To test the hypothesis of two average values equation in two groups we used Student's t-test or non-parametric Mann-Whitney test, to disprove the null hypothesis we applied Student's t-test. Probability of differences was quantified accurate within 0.0001. P-value <0.05 was considered significant.

Results and discussion

5.6%(13 persons) of 231 athletes involved in this study had elevated BP, increased BP was present mostly in sportsmen practicing static exercises of high demand combined with aerobic loads of moderate or high intensity.

According with the results of EchoCG study, sportsmen were divided into following groups: females without LVH (n=81), males without LVH (n=103), males with insignificant increase (border-line) of LVMMI (n=19), males with LVH (LVMMI 132-148 g/m^2,

n=10). Enlargement of one of LV walls during diastole (up to 1.2 cm) or LVMMI 116-131 g/m^2 were considered as border-line LVMM.

Results of comparative analysis of myocardial DF in relation to LVMMI are present in the Table 2.

TD-EchoCG results demonstrated no abnormal LV myocardium DF in all groups of athletes; this fact goes along with the majority of known studies [23, 24]. There were no statistically significant differences in DF char-

Table 2. **Morphofunctional condition of LV (according with TD-EchoCG results)**

Characteristic		Women with normal LVMMI, N=81	Men with normal LVMMI, N=103	Men with insignificantly increased (borderline) LVMMI, N=19	Men with LVH, N=10
MMI, g/m^2		76.5±15	92±16	106±12	139±16
Relative wall thickness (RWT)		0.38±0.06	0.40±0.05	0.46±0.04	0.43±0.04
Dt, msec		188±29	194±31	200±17	195±30
E/A		2.0±0.4	1.82±0.4	2.0±0.5	2.2±0.6
Lateral wall	Sa, cm/sec	12.9±2.5	12±2.5	11.3±3.5	10.1±2.8
	e, cm/sec	18±3.4	18±3.7	17±3.2	16±3.5
	E/e	5.1±0.8	4.9±1.2	5.1±1.1	5.5±1.2
	E/a	2.7±0.7	2.8±0.8	2.9±1.1	3.0±1.1
Interventricular septum (IVS)	Sa, cm/sec	9.3±1.9	9.2±1.2	8.9±1.4	8.6±1
	e, cm/sec	14.1±2.3	13.2±2.2	12.6±2.0	12.1±1.7
	E/e	6.7±1.3	6.6±1.3	6.3±1.6	6.9±1.8
	E/a	2.2±0.6	2.0±0.5	2.0±0.6	2.2±0.6
Anterior wall	Sa, cm/sec	11.9±2.7	11±2.4	10±2.4	9.7±2.1
	e, cm/sec	17.8±3.2	17.3±3.8	16.8±3.2	18.7±3.1
	E/e	5.3±0.9	5.2±1.2	4.8±1.3	4.5±0.7
	E/a	2.7±0.8	2.7±1	2.8±1.2	3.2±1
Posterior wall	Sa, cm/sec	9.5±0.9	9.7±1.5	9.3±1.25	9.3±1.7
	e, cm/sec	15±2.3	14±2.5	13.2±2.0	13.9±2.7
	E/e	6.3±1.2	6.1±1.2	6±1.5	6.1±1.6
	E/a	2.3±0.6	2.2±0.6	1.8±0.6	2.2±0.9

Table 3. **Morphofunctional condition of LV (according with TD-EchoCG results)**

Characteristic		Men with normal LVMM, (n=103)	Men with LVH and border-line LVMM (n=29)	p-value
MMI, g/m^2		92±16	117±20	0.0001
SMS		190±36	236±32	0.0001
DMS		177±31	224±29	0.0001
RWT		0.40±0.05	0.45±0.04	0.0001
Dt, msec		194±33	198±22	0.607
E/A		1.8±0.4	2.1±0.5	0.006
Lateral wall	s, cm/sec	11.5±2.5	10.9±3.3	0.346
	e, cm/sec	17.7±3.7	13.3±3.3	0.115
	E/e	4.9±1.2	5.2±1.1	0.387
	e/a	2.7±0.8	2.9±1.1	0.356
IVS	s, cm/sec	9.2±1.2	8.8±1.2	0.204
	e, cm/sec	13.2±2.2	12.4±2.1	0.189
	E/e	6.6±1.3	6.3±2.1	0.470
	e/a	2.1±0.5	2.2±0.9	0.531
Anterior wall	s, cm/sec	11.2±2.4	10.0±2.3	0.064
	e, cm/sec	17.3±3.8	17.5±3.2	0.804
	E/e	5.2±1.2	4.8±1.6	0.351
	e/a	2.7±1.0	3.1±1.1	0.276
Posterior wall	s, cm/sec	9.7±1.5	9.3±1.4	0.263
	e, cm/sec	14±2.5	13.5±2.3	0.154
	E/e	6.1±1.2	6.0±2.0	0.853
	e/a	2.2±0.6	2.1±0.8	0.698
Shortening of anterior-posterior dimensions	%	31.2±4.1	30.6±5.4	0.543
Ejection fraction (EF) (Simpson)	%	60.9±4.7	58.3±5.1	0.013
Cardiac output	L	4.6±1.2	4.8±1.3	0.288

acteristics between the groups. But Sa and diastolic e peak in the lateral area of mitral valve fibrous ring (MVFR), IVS, and to less extent – posterior wall, tended to decrease with the growth of myocardial mass.

In order to perform more obvious comparative analysis, we divided the athletes into two groups: males without LVH (n=103) and males with insignificant increase of LVMM and LVH (n=29). The results of this comparative analysis are demonstrated in Table 3.

Correlation analysis did not reveal correlation between LVMM characteristics and E/A peaks ratio (r=0.022, p=0.741). There were no significant differences in parameters characterizing LV DF. We identified weak but statistically significant correlation of LVMM characteristics and Sa velocity of MVFR lateral part (r=-0.174, p=0.013). Comparative analysis of LV EF measured using Simpson's approach demonstrated that this value was significantly lower in athletes with increased LVMM. Sa values in sportsmen with borderline LVH did not differ significantly from the same value in the group of patients with normal LVMM.

According with the results of Vinereanu D et al., 2001 [24], average systolic speed of fibrous ring movements less than 9 cm/sec should be considered as the most significant criteria of pathological LVH (sensitivity 87%, specificity 97%). In our study the average systolic speed of mitral valve fibrous ring movements in athletes with LVH was 10.1±2.8 cm/sec that can be possibly caused by initial steps of hypertensive LV myocardial remodeling. Other parameters of LV myocardium DF function in the group of sportsmen with LVH were normal.

7 out of 13 athletes with elevated BP verified with 24h BP monitoring had border-line LVH or LVH that allowed prescribing them antihypertensive therapy with angiotensin converting enzyme (ACE) inhibitor enalapril (5 mg/day). Evaluation of 3-month therapy efficacy is present at Figure 1.

According with the results of our previous studies that had been performed in 47 boat racing athletes (aged 17-19 years) high normal BP was detected in 8.5% of cases, and AH 1 stage was found in 25.6% of cases. Apart from it, these sportsmen with elevated BP had LVMMI=89.07 g/m^2 comparing with 74.6 g/m^2 in sportsmen with normal BP [25]. At the same time, there was no correlation between LVMM and the level of physical functionality in athletes with elevated BP (r = 0.17).

Results of our current study suggest that athletes with AH, apart from particular exercise program, had

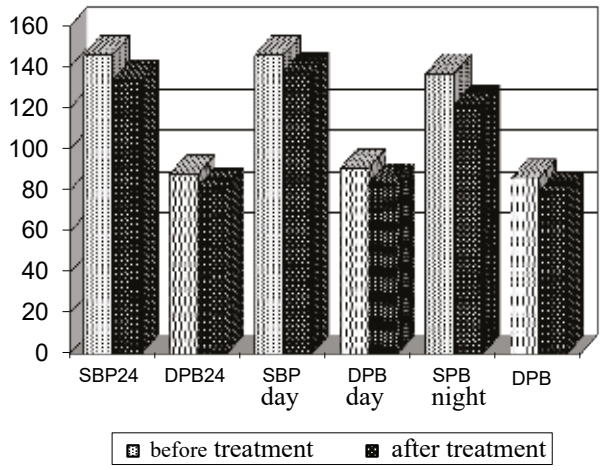

Figure 1. Dynamics of BP parameters in athletes before and after treatment

more isometric and speed-strength loads that could have influenced AH development, and myocardial hypertrophy in sportsmen with AH could be caused by increased post-load. The presence of elevated BP and increased LVMM evaluated as target organ lesion allowed us using ACE inhibitor enalapril as the drug of choice. Results of 3-month treatment have led to significant reduction of 24h-BP monitoring parameters, but they did not favour regression of myocardial hypertrophy.

Standard criteria of the Russian Society of Cardiology (RSC) should be used for estimation of BP levels and AH stage in athletes; apart from it, RSC guidelines discuss the tactics of observation of sportsmen with elevated BP [26].

Before starting training and competition activity athletes should undergo routine BP measurement, and in case of elevated BP (>140/90 mm Hg) it is reasonable to measure "not-office" BP in order to exclude white coat hypertension. Sportsmen with BP in the range of 120-139/80-89 mm Hg are advised to change the lifestyle and minimize possible AH risk factors without changing physical activity. In case of resistant BP elevation it is recommended to perform EchoCG for differential diagnostics of athletic heart and LVH. The presence of LVH is an indication for restriction of physical training and possible pharmacological correction.

The presence of AH 1 stage in case of no target organs' lesions like LVH or concomitant cardiac disorders do not restrict training and competition activity of sportsmen, but it is recommended to measure BP every 2-4 month to control the influence of physical exercise on BP.

Athletes with more severe AH (II-III stage), even if they have no evident target organs' lesions like LVH,

should be kept away from static exercises of high intensity (IIIA, IIIB, IIIC classes of sports) unless lifestyle change or pharmacological treatment would help to normalize BP levels.

When prescribing antihypertensive therapy it is necessary to take into account the fact that athletes belonging to registered pool of international federation or participating in international competitions can receive medications only according with the rules of their international federation.

Talking about young athletes, American Academy of Pediatrics recommends to admit children and adolescents with AH to training and competitions if the absence of target organs lesions or concomitant cardiac pathology is proved; it is advised to perform control ECG every two months. Sports with high static (isometric) loads are not recommended to young athletes with severe AH, even if there are no evidences of target organs' lesions [27].

In conclusion it is worth to notice that AH prevalence in athletes is enough low and is 50% less than in general population, but it increases significantly with age. At the same time, it does not mean that the problem AH is not relevant for the athletic population, since 8% of sudden cardiac death cases of sportsmen younger than 35 years are caused by non-differentiated myocardial hypertrophy (according with autopsy results), and in fact it is the only proved cause of sudden death in this population. Major epidemiologic studies demonstrated that LVMH is an independent risk factor of cardiovascular disease development. According with the results of the Framingham study, LVMM increase by 50 g/m^2 correlates with 2.21 and 1.73 times increase of 4-years risk of cardiovascular disease in females and males, respectively, LVH is an independent risk factor for heart failure, coronary heart disease (CHD), ventricular arrhythmias and sudden death. LVH presence is responsible for 5-fold increase of congestive heart failure risk. The presence of concomitant CHD increases three times the risk of lethality, and myocardial infarction increases this risk four times. CHD is the main cause of sudden death of sportsmen above 35 years old; it is very likely that development of coronary atherosclerosis in athletes is caused by the presence of LVH and AH that had not been diagnosed in time. Whereas the only morphological substrate for the main cause of sudden death in athletes above 35 years old is CHD, it is impossible to exclude such direct cause of it like malignant arrhythmias possibly caused by myocardial fibrosis; it requires further studies of electric remodeling of sportive heart [9, 10, 11]. Taking into account all the mentioned above facts, it is necessary to control precisely BP in athletes including children and adolescents especially in sports requiring intense speed-strength and isometric loads. Diagnostic procedures should include EchoCG diagnostics and stress tests. Sportive activity can be allowed only in case of well-controlled BP and low risk of cardiovascular complications. Nowadays there is a hypothesis that moderate aerobic loads after intensive speed-strength training may be one of approaches for AH prevention in athletes.

The question of AH pharmacological therapy in athletes is the subject of further investigation, since there are not enough evidences. According with several researchers [28], it is more relevant to prescribe ACE inhibitors, angiotensin-1 receptor blockers and dihydropyridine calcium channel blockers, because the use of other drugs like diuretics and beta-blockers is restricted by the World Anti-Doping Agency.

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CLINICAL SEMINAR

Chronic mesenteric ischemia.
What should the general practitioner know?

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Summary

This review article observes the problems of chronic mesenteric ischemia. It is difficult for general practitioners to diagnose this condition correctly due to lack of specific symptoms. This article discusses the questions of etiology, classification of this condition made by several authors, clinical manifestations depending on localization of vascular lesions and covers the issues of chronic mesenteric ischemia. Aortic angiography, abdominal aorta and mesenteric arteries duplex scanning, computer angiography and magnetic resonance angiography, spiral computer tomography can be used for the diagnostics of visceral artery stenosis. Chronic mesenteric ischemia can be treated conservatively and surgically, considering both urgent and planned operations. The tactics of conservative treatment depends on clinical manifestations' intensity, disease's functional class and should include lipid-lowering therapy.

Key words

Chronic mesenteric ischemia, ischemic gastropathy, ischemic pancreatopathy, ischemic hepatopathy.

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Chronic mesenteric ischemia (CMI) is a collective term including different aclinical syndromes and digestive organs' disorders caused by impaired blood supply of abdominal aorta and its unpaired visceral branches inadequate to provide normal tissue functioning due to insufficient oxygen delivery that leads to ischemia development, cell damage and necrosis.

There are more than 20 terms describing this pathology: "angina abdominalis", "chronic mesenteric arteries' obliteration", "mesenteric arterial insufficiency", "chronic mesenteric ischemia", and "abdominal ischemic syndrome". The following codes are included in the International Classification of Diseases: I70.0 – abdominal aorta atherosclerosis, I71.4 abdominal aorta aneurism, I74.0 – abdominal aorta embolism and thrombosis, I77.4 – the syndrome of celiac trunk compression, K55 – intestinal vascular disorders.

The frequency of CMI occurrence is high enough. For example, the study of A.V.Pokrovsky (188) revealed that the lesions of abdominal aorta's unpaired visceral branches appear in 75.5% of autopsies of patients with atherosclerosis of coronary arteries and brain arteries and with arterial hypertension (AH). Atherosclerosis of unpaired visceral branches of abdominal aorta can be detected in 54% of patients undergoing angiography: 45% of general population have isolated celiac trunk atherosclerosis, 18.4% of patients have atherosclerosis of upper mesenteric artery, 1.2% of patients have atherosclerosis of gastroduodenal artery, common hepatic artery atherosclerosis occurs in 1% of cases, splenic artery – in 1% of cases, inferior mesenteric artery – in 15.4% of cases. 66.3% of patients having occluding lesions of unpaired visceral branches of abdominal aorta verified with angiography develop asymptomatic course of this pathology, CMI is diagnosed in 3.2% of patients undergoing in-patient treatment of chronic pancreatitis [2]. Difficult diagnostics of CMI could be explained by the lack of specific symptoms. In general, clinical manifestations of CMI are related to other gastroduodenal zone disorders like gastroduodenitis, hepatitis, pancreatitis, etc. Mesenteric ischemia is detected the most frequently only in case of development of acute mesenterial circulation disturbance that is intestinal infarction.

Etiology

Acute ischemia of gastrointestinal organs could be caused by thrombosis, embolism, and trauma. Chronic ischemia is caused by intravascular lesions (inherited, acquired) and extravascular compression of visceral arteries. Intravascular lesions occur more frequently than extravascular ones (62-90% of cases comparing with 10-38% of cases, respectively). Atherosclerosis occurring in 52.2-88.3% of cases is the most important cause of acquired intravascular lesions of visceral arteries, the second most frequent cause is Takayasu's arteritis (22-31% of cases). The most common congenital diseases leading to CMI are fibromuscular dysplasia, hypoplasia, visceral arteries; development anomalies, and angiodysplasia. The most frequent cause of extravascular compression is arcuate ligament of diaphragm or its medial crux (40.8-72.5% of cases) [3].

Classification

There is no common classification of mesenteric ischemia. O.Sh.Oinotkinova and Yu.V.Nemytina (2001) had developed a pathogenetic classification of CME [9].

1. Forms:
- ✓ celiac;
- ✓ mesenteric;
- ✓ celiac-mesenteric

2. Stages of disease:
- ✓ compensated;
- ✓ subcompensated;
- ✓ decompensated;

3. Clinicopathologic variants:

Visceralgia:

abdominal ischemic visceralgia (AIV):
- ✓ stable abdominal visceralgia;
- ✓ progressive abdominal visceralgia;
- ✓ abdominal ischemic visceropathy (AIVP).

Gastroduodenopathy:
- ✓ atrophy;
- ✓ erosions;
- ✓ ulcers (gastric, duodenal).

Hepatopathy:

✓ hepatocellular insufficiency with impairment of protein-synthetic function;

✓ hepatocellular insufficiency with impairment of absorbing and excretory function;

Pancreatopathy:
- ✓ algesic;
- ✓ latent;

with impaired exocrine secretion

with impaired endocrine function

Enterocolopathy:
- ✓ proximal entropathy;
- ✓ terminal colonopathy.

Complications:

✓ gastrorrhaggia, perforation;

✓ hepatocellular insufficiency (hepatic coma);

✓ pancreatic insufficiency, diabetes mellitus, pancreonecrosis;

✓ bowel gangrene;

The classification of L.B. Lazebnik and L.A. Zvenigorodskaya (2003) reflects clinical forms and functional classes of CMI [7].

Ischemic gastroduodenopathies

- atrophic gastritis, atrophic duodenitis;
- erosive gastritis, erosive duodenitis (acute, chronic);
- ischemic stomach ulcer, ischemic duodenal ulcer;

Complications:

- chronic ischemic gastric ulcer, chronic ischemic duodenal ulcer;
- acute gastrorrhaggia;
- penetrating stomach ulcer, penetrating duodenal ulcer;
- perforated stomach ulcer, perforated duodenal ulcer;.

Ischemic lesions of pancreas (ischemic pancreatopathies):

- acute ischemic pancreatitis;
- chronic ischemic pancreatitis;
- pancreatic lipomatosis.

Complications:

- secretory and incretory pancreatic insufficiency;
- diabetes mellitus;
- pancreatic cyst;
- pancreatic sclerosis;
- pancreatonecrosis.

Ischemic lesions of liver (ischemic hepatopathies):

- acute ischemic hepatitis;
- chronic ischemic hepatitis;
- non-alcoholic steatohepatitis;

Complications:

- hepatic fibrosis;
- liver cirrhosis;
- hepatocellular insufficiency;
- hepatic coma.

Ischemic lesions of intestine (enterocolopathies):

- ischemic enteropathies (mesenteric ischemia);
- ischemic enteropathy with the syndrome of impaired absorption;
- chronic ischemic ulcers of small intestine;
- ischemic colopathies with mucous membrane atrophy;
- ischemic colitis;
- schemic ulcers of large intestine;

Complications:

- large intestinal strictures;
- acute intestinal obstruction;
- acute enterorrhagia;
- intestinal infarction;
- bowel gangrene;
- fecal peritonitis.

Functional classes

✓ Functional class I (FC I) – no evident clinical symptoms. These patients have no impaired blood supply at rest and develop abdominal pain only after stress testing.

✓ Functional class II (FC II) – signs of impaired blood supply at rest and their aggravation after stress testing, evident clinical symptoms: pain and indigestion syndromes, weight loss, impaired pancreatic function, impaired secretory and absorptive function of intestine;

✓ class III (FC III) – patients with constant pain syndrome, weight loss and dystrophic changes of digestive organs.

Blood supply of digestive organs is provided by three unpaired visceral branches of abdominal aorta: celiac trunk (CT), superior and inferior mesenteric arteries (SMA and IMA). Three independent arterial pools mentioned above are tightly linked between each other with collateral vessels. The most important collateral vessels are celiacomesenteric and intermesenteric anastomoses. Straight intermesenteric anastomosis is also known as Riolan's arcade normally present in 2/3 parts of population. Marginal artery of Drummond is an important vessel connecting superior and inferior mesenteric arteries. Left colic branch of middle colic artery from the system of superior mesenteric artery makes anastomosis with left colic artery from the system of inferior mesenteric artery at the splenic flexure of the colon. This so-called Triffitt point is a critical segment of large intestine. 5% of people have open-loop blood supply at this point, which predisposes splenic flexure of the colon to ischemia in case of any decrease of perfusion pressure in the system of mesenteric arteries.

Localization of ischemic damage of digestive organs depends on visceral artery responsible for their blood supply. CT lesions result in damage of the organs of the upper part of abdominal cavity: liver, pancreas, stomach, duodenum and spleen. SMA occlusion or stenosis lead to abnormal function of small

intestine, and IMA lesions cause large intestine's (LI) ischemia. At the same time, well-developed system of collateral vessels between visceral arteries provides long-term functional compensation in case of impaired main blood supply; due to this lesions of visceral branches of abdominal aorta do not always lead to the development of chronic ischemic symptoms in digestive organs. Clinical symptoms manifest in the most evident way in case of lesions of 2-3 visceral arteries [4, 6].

According with the opinion of M.V. Tarbaeva (A.V. Vishnevsky Institute of Surgery), in case of atherosclerotic lesions of visceral arteries, atherosclerotic plaques are the most likely to be found in the proximal segment of the artery within the distance of 1-2 cm. Normally this process spreads from the aortic wall. Usually IMA is involved, TC lesions occur less frequently. Isolated lesions of single visceral arteries are not typical for Takayasu's arteriitis, normally both abdominal aorta and several visceral branches are involved. Arteries' lesions are usually more extensive. Takayasu's arteriitis is characterized with good collateral blood supply and big diameter of involved vessels, in particular, Riolan's arcade. In case of extravascular compression of celiac trunk with falciform ligament of diaphragm stenosis leads to abnormal laminar blood flow and facilitates thromb formation and embolism development. Thus, acute visceral ischemia can be a possible consequence of CMI syndrome.

Clinical syndromes of CMI

Gastroduodenal (erosive and ulcerous) syndrome appears in 46.2% of cases and is the most frequent clinical form of CMI of digestive organs, according with the results of the study that had been hold in Central Research Institute of Gastroenterology.

Erosive and ulcerous lesions of gastroduodenal zone in CMI are characterized by disease manifestation as a bleeding episode, lack of seasonal disease exacerbations, atypical clinical symptoms, high frequency of concomitant cardiovascular diseases, relapses, big dimensions of ulcers, low efficacy of antiulcerant therapy [5].

The frequency of ischemic pancreatopathy in CMI is 33.9% [6]. The main feature of pancreatic circulation is the lack of its own major arteries. Blood supply of pancreas is provided by the branches of common hepatic artery, SMA and lienal artery. The frequency of development of pancreonecrosis and ischemic pancreatopaties in CME is determined by these anatomic features.

Ischemic pancreatopathy can manifest as acute ischemic pancreatitis and fatal ischemic chronic pancreatitis. V.T. Ivashkin and coauthors [3] investigated clinical features of chronic pancreatitis with evident atherosclerotic lesions of mesenteric vessels and found out the following characteristics of this pathologic condition: older age of patients, less evident pain syndrome, high frequency of coronary heart disease (CHD) and AH, combination of chronic pancreatitis and erosive changes of gastroduodenal zone resistant to pharmacological treatment.

It is also necessary to take into account the fact that pancreatic ischemia appears very rarely as a single ischemic lesion and more frequently is combined with ischemic lesions of other abdominal cavity organs.

According with the results of L.A.Zvenigorodskaya and coauthors [2], ischemic lesions of intestine have the third position between the other forms of CME.

Ischemic colitis (IC) is characterized with restricted lesions of large intestine combined with the development of ischemia, inflammatory edema of mucosa, ulcers, bleeding, and fibrous strictures of colon, IC manifests more frequently in elderly and old patients with CHD, AH and diffused atherosclerosis.

IC development is characterized with impaired blood supply in the systems of CT, SMA an IMA. Typical feature of colon blood supply is the presence of collateral vessels connecting it with SMA and Riolan's arcade – parallel or marginal vessel passing along its mesenteric edge. IMA constriction causes segmentary ischemic lesions in the area of colon's splenic flexure, its ileocecal and rectosigmoid parts. Rectum blood supply is mediated by superior and inferior rectal arteries. Due to the presence of numerous intramural anastomoses between them rectum is rarely involved in CMI development. Mucosal lesions of large intestine are also inhomogenous because colon's free edge receives less blood supply than its mesenteric edge [2].

L.A. Zvenigorodskaya and coauthors notice that microscopic IC is more common than traditionally described IC forms. Microscopic ischemic signs (superficial epithelial necrosis, reduction of goblet cells' number, local lymphocyte infiltration, abnormal microcirculation with the development of stasis, thrombosis and plasmorrhagia in lamina propria of large intestinal mucosa) appear before macroscopic changes. Typical symptoms of microscopic ischemic colitits include postprandial abdominal pain mostly in left ileac region, constipation, abdominal discomfort, and flatulence. Abdominal palpation results in pain

and spasm in sigmoid colon, blind intestine is dilated, the psoas sign is positive [2, 3].

Diagnostics

CMI diagnostics is based on detalization of patient's complaints, history taking, physical examination and instrumental/laboratory tests. Patient's history details reveal the presence of cardiovascular diseases, obliterating endarteritis, metabolic syndrome, diabetes mellitus and allow selecting risk groups for possible abdominal aorta atherosclerosis development (78% sensitivity). Postprandial abdominal pain is the main symptom in the majority of patients. Pain features may be different; initially it is discomfort in epigastrium, it changes to dull pain when circulatory lesions start to be more severe. Intestinal dysfunction is the second frequent sign of abdominal ischemia manifesting as abnormal secretory and absorptive function of small intestine (flatulence; unstable, frequent, watery stool) and evacuative function of large intestine with persistent constipation. Progressing weight loss is the third frequent symptom of CMI, and it is related both to patients' refusal to take food because of pain and impaired secretory and absorptive function of small intestine, which becomes particularly evident in the late stage of the disease [2, 3].

During auscultation systolic murmur can be heard in the projection of abdominal aorta's visceral branches. In case of TC stenosis murmur's epicenter is localized 2-4 cm below xiphoid process, in case of SMA lesions it can be found 2-3 cm below the previous position. Murmur indicates possible arterial lesions (the frequency of its detection is around 14-92.6%), but its absence does not allow excluding ischemia. Additional diagnostic tests should be directed on estimation of digestive organs' functional condition, detection of atherogenic dyslipidemia, abnormal blood rheological characteristics.

The following techniques can be used for the diagnostics of visceral arteries' stenosis [4, 11, 12]:

- aortoangiography;
- color Doppler ultrasonography of abdominal aorta and its visceral branches;
- computer angiography, magnetic resonance angiography, spiral computer tomography;

Treatment

CMI treatment is based on conservative and surgical techniques. It is possible to use planned surgery: reconstructive surgery eliminating occlusion and restoring circulation (endoscopic resection of plaques, vascular grafting), creation of vascular bypasses around a diseased artery – vascular bypass operations, percutaneous endovascular angioplasty, laser recanalization. Urgent surgical interventions in acute mesenteric ischemia usually result in bowel resection [12].

Conservative treatment tactics depends on severity of CMI clinical manifestations, thus its FC, and should include hypolipidemic therapy. Clinical guidelines and published articles shed almost no light on treatment of atherosclerotic lesions of unpaired visceral branches of aorta. Nevertheless, experts think that statins are indicated to patients with atherosclerosis of abdominal aorta and its branches (Class and level of evidence IIaC) [10].

Dozens of randomized clinical trials that have proved the efficacy of statins and their role in cardiovascular risk reduction have been conducted within the last 15 years.

According with the guidelines [1, 8, 10], dyslipidemic therapy of visceral branches' atherosclerotic lesions does not differ from the therapy of patients with high cardiovascular risk. But it is necessary to take into account the fact that more frequent control of drugs' safety is required in case of abnormal hepatic and pancreatic function common for TC atherosclerosis, and also in case of elevated blood levels of liver enzymes.

The most rational strategy considers prescription of the last generation statins like atorvastatin and rosuvastatin with well-proved impact on prognosis and good patients' tolerability. Results of numerous clinical studies demonstrate that statins significantly reduce CVD morbidity and mortality if being used for primary and secondary prevention. In clinical studies statins slowed down progression and even caused regression of coronary arteries' atherosclerosis [10].

The MIRACL and SPARCL studies have proved the efficacy of atorvastatin in acute cardiovascular catastrophes (unstable angina and stroke). The REVERSAL study of atorvastatin and the ASTEROID study of rosuvastatin demonstrated the important ability of statins not only to modify lipid blood spectrum (reduce the low density lipoproteins' (LDL) levels) but also to have direct impact on atherosclerotic plaques, stabilizing and reducing the volume of atheroma.

Statins were presented as the first line drugs for atherosclerosis treatment in the last European Guidelines on cardiovascular disease prevention in clinical practice (2016) [15].

It is necessary to reach target levels of LDL in order to reach the desired effect during statins' therapy.

Table 1. **LDL cholesterol target levels (mmol/L) depending on risk category**

Lipid parameters	In population (low risk)	Patients with moderate risk	Patients with high risk	Patients with very high risk
TCh	⩽5.5	⩽5.0	⩽4.5	⩽4.0
LDL cholesterol	⩽3.5	⩽3.0	⩽2.5	⩽1.8
HDL cholesterol	males.>1.0 females.>1.2	males>1.0 females.>1.2	males >1.0 females >1.2	males >1.0 females>1.2
TG	⩽1.7	<1.7	<1.7	<1.7

Patients belonging to the very high risk group have LDL cholesterol target levels <1.8 mmol/L (< ~70 mg/dL), if this value is impossible to reach it is recommended to reduce LDL cholesterol levels by 50% of its initial levels. The patients of the high risk group have LDL cholesterol target levels <3.0 mmol/L (<~100mg/dL). The patients of the moderate risk group have LDL cholesterol target levels <3.0 mmol/L (<~115 mg/dL).

LDL cholesterol target levels depending on risk category are present in Table 1.

It is necessary to evaluate the blood levels of lipids, aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), creatine-phosphokinase (CPK). 4-6 weeks after the start of the therapy it is necessary to evaluate treatment's safety and tolerability (repeat blood tests for ALT, AST and CPK) and the presence of muscular symptoms. For dose titration it's necessary pay attention at first on treatment's safety and tolerability, at second – on reaching target level of lipids. If transaminases' activity levels are elevated more than 3 times above the reference levels and/or CPK levels are 4 times higher than normal ones and if they are elevated less than 10 times in respect to reference values, it is necessary to cancel statin therapy or reduce their dose, to repeat blood test in 4-6 weeks, and to perform the monitoring of patient's condition and kidney function. Apart from this, it's necessary to exclude other causes of elevated enzymes' levels and evaluate all bilirubin fractions. Elevated levels of conjugated bilirubin are more significant than ALT and AST activity, if there is no biliary tracts' obstruction. If AST/ALT levels are ⩽ 3 values of upper reference level, it is possible to continue the treatment with regular (after each 4-6 weeks) control of enzymes' blood concentration. If there are the signs of active hepatic lesions, hyperbilirubinemia or CPK levels elevation more than 10 times above upper reference level, statins therapy should be cancelled in order to find out the cause of abnormal blood tests.

Several options are possible for patients intolerant to one statin drug: change of one statin for another, reduction of initial dose, taking statins once for 2 days or twice for a week, ezetimibe prescription and maximal lifestyle change. Combined use of statins and ezetimibe can be considered as a variant of treatment for patients with severe hypercholesterolemia who are intolerant to high doses of statins or haven't reached the target levels of LDL cholesterol. If these drugs are not effective, PCSK9 inhibitors prescription can be discussed [15].

Chronic liver diseases, non-alcoholic steatohepatitis or steatohepatosis with normal levels of liver enzymes are not considered to be contraindications for therapy with statins.

Statins are indicated to both young and elderly patients with verified CVD. From safety point of view, it's necessary to prescribe statins to elderly patients starting from the minimal dose with consequent monitoring of patient's condition. If statins are indicated for patients above 75 years, it is necessary to evaluate the correlation between risk and benefits. It is better to take into account the fact that elderly women of asthenic constitution receiving many drugs have elevated risk of myopathy, rhabdomyolisis and DM development in case of treatment with statins [15].

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Sources in Russian with transliteration:

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