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ПОСТПРАНДИАЛЬНАЯ ГИПОТЕНЗИЯ У ПОЖИЛЫХ ПАЦИЕНТОВ: ПАТОФИЗИОЛОГИЯ, ДИАГНОСТИКА И МЕРЫ ПРОФИЛАКТИКИ

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Postprandial Hypotension in Elderly Patients: Pathophysiology, Diagnosis and Prevention Measures

Резюме

Постпрандиальная гипотензия (ППГ) является важным, но недостаточно распознаваемым состоянием, возникающим в результате неадекватной компенсаторной реакции сердечно-сосудистой системы на индуцированное приемом пищи висцеральное скопление крови. ППГ признана важной клинической проблемой поскольку имеет высокую распространенность в популяции старшей возрастной группы и связана с развитием сердечно-сосудистых осложнений и гериатрических синдромов. Возможные патофизиологические механизмы ППГ: повышенный висцеральный кровоток; ослабление барорефлекторной функции из-за нарушений, связанных с возрастом или вегетативной дисфункцией; неадекватная активация симпатических нервов; нарушение регуляции вазоактивных кишечных пептидов; инсулин-опосредованная вазодилатация. Опрос о симптомах гипотонии после приема пищи и снижение систолического артериального давления (АД) на ≥20 мм рт. ст. через 15- 60 минут после еды имеет первостепенное значение для постановки диагноза ППГ. Одной из основных стратегий профилактики ППГ является снижение растяжения желудка (небольшие порции пищи и более частое питание), отдых лежа на спине после еды, употребление достаточного количества воды. Ходьба после приема пищи, по-видимому, также помогает восстановить АД после еды. Необходимо проявлять осторожность при назначении белковых добавок у пожилых людей, модифицировать диету путем замены высокопитательных подсластителей низкокалорийными (d-ксилоза, ксилит, эритрит, мальтоза, мальтодекстрин и тагатоза). Метформин или акарбоза модулируют сердечно-сосудистую реакцию у пациентов с сахарным диабетом, уменьшают постпрандиальную гипотензию. Таким образом, ППГ является достаточно распространенным и клинически значимым феноменом у пожилых больных. Повышение информированности врачей о патофизиологии и методах диагностики, профилактики позволит повысить эффективность и безопасность ведения гериатрических пациентов.

Ключевые слова: *постпрандиальная гипотензия, патофизиология, пожилой пациент, профилактика падений*

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Abstract

Postprandial hypotension (PPH) is an important but underrecognized condition resulting from an inadequate compensatory cardiovascular response to meal-induced visceral blood pooling. PPG is recognized as an important clinical problem because it has a high prevalence in the older age group and is associated with the development of cardiovascular complications and geriatric syndromes. Possible pathophysiological mechanisms of PPG: increased visceral blood flow; weakening of baroreflex function due to disorders associated with age or autonomic dysfunction; inappropriate

activation of sympathetic nerves; dysregulation of vasoactive intestinal peptides; insulin-mediated vasodilation. Ask about symptoms of postprandial hypotension and a decrease in systolic blood pressure (BP) of ≥20 mm Hg. Art. 15-60 minutes after eating is of paramount importance for making a diagnosis of PPG. One of the main strategies for preventing PPG is to reduce gastric distension (small meals and more frequent meals), resting on your back after eating, and drinking enough water. Walking after eating also appears to help restore blood pressure after eating. Caution should be exercised when prescribing protein supplements in the elderly, modifying the diet by replacing high-nutrient sweeteners with low-calorie sweeteners (d-xylose, xylitol, erythritol, maltose, maltodextrin, and tagatose). Metformin or acarbose modulates the cardiovascular response in patients with diabetes mellitus and reduces postprandial hypotension. Thus, PPG is a fairly common and clinically significant phenomenon in elderly patients. Increasing the awareness of doctors about pathophysiology and methods of diagnosis and prevention will improve the efficiency and safety of managing geriatric patients.

Key words: *postprandial hypotension, pathophysiology, elderly patient, prevention of falls*

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AH — arterial hypertension, BP — blood pressure, DBP — diastolic blood pressure, PPH — postprandial hypotension, SBP — systolic blood pressure, DM — diabetes mellitus, CVD — cardiovascular diseases, GLP-1 — glucagon-like peptide-1, GIP — glucose-dependent insulinotropic polypeptide

Introduction

Postprandial hypotension (PPH), a drop in systolic blood pressure (SBP) of at least 20 mm Hg after meals, is an important, but under-diagnosed condition, which is a result of an inadequate compensatory cardiovascular response to meal-induced visceral blood accumulation.

PPH is a recognised clinical issue due to its high incidence in elderly population [1, 2]. PPH affects 24–33 % of elderly people in care homes, 67 % of geriatric patients and about 50 % of people with unexplained syncope [3]. In inpatient patients, the incidence of PPH is 30.4 % [4]. A meta-analysis (2024) of the data from 3,021 subjects demonstrated that the PPH incidence in elderly people was 40.5 % [5]. PPH is most common in conditions associated with vegetative dysfunction. For example, in type 2 diabetes mellitus (DM) [6], the incidence of PPH is likely to be higher than that of orthostatic hypotension [7].

Some authors suggested a correlation between PPH and cardiovascular disease and mortality [8]. A prospective study in elderly population with AH showed that 83 % of patients admitted for PPH had cerebrovascular damages [9]. A prospective 36-month study demonstrated association between PPH and CVD development (adjusted risk factor: 11.18, 95 % confidence interval: 2.43–51.38, p = 0.002), which did not disappear even after consideration of other variables [4]. The maximum drop in postprandial blood pressure (BP) is an independent predictor of later falls, syncope, cardiovascular events (myocardial infarction and stroke), and general mortality [10, 11]. In a cohort study in 401 elderly patients with outpatient AH, 72.8 % of subjects had PPH, while falls after breakfast were the most powerful predictor of deaths in this cohort [10].

Methods of Literature Source Search

PubMed databases in Russian and English were used for a full-text search (automated search of documents, when a search is based not on document titles, but on their contents, both the entire contents and its part) with keywords (postprandial hypotension, elderly age, pathogenesis, risk factors of postprandial hypotension), with a 5-year period of time limitation (duplicate articles and non-full-text articles were excluded).

Pathophysiology of PPH

The pathophysiology of PPH is multifactorial and is understudied. PPH development points to an inadequate cardiovascular response to meals, which is a result of complex interactions between consumed nutrients and gastrointestinal tract. There are convincing evidences that gastrointestinal factors, such as meal composition, nutrient delivery rates to the small intestine (i.e. stomach emptying), nutrient absorption, are an integral part of the postprandial blood pressure response. Possible mechanisms of PPH (see Fig. 1):

1. Increased visceral blood flow
2. Reduced baroreflex function due to disorders associated with the age or vegetative dysfunction
3. Inadequate sympathetic nerve activation
4. Inadequate regulation of vasoactive intestinal peptides
5. Insulin-mediated vasodilation.

Healthy elderly people have more marked haemodynamic reactions to meals vs. healthy young people; higher, age-related noradrenaline levels are released, which causes a more marked haemodynamic reaction to meals, despite stable BP values (see Table 1).

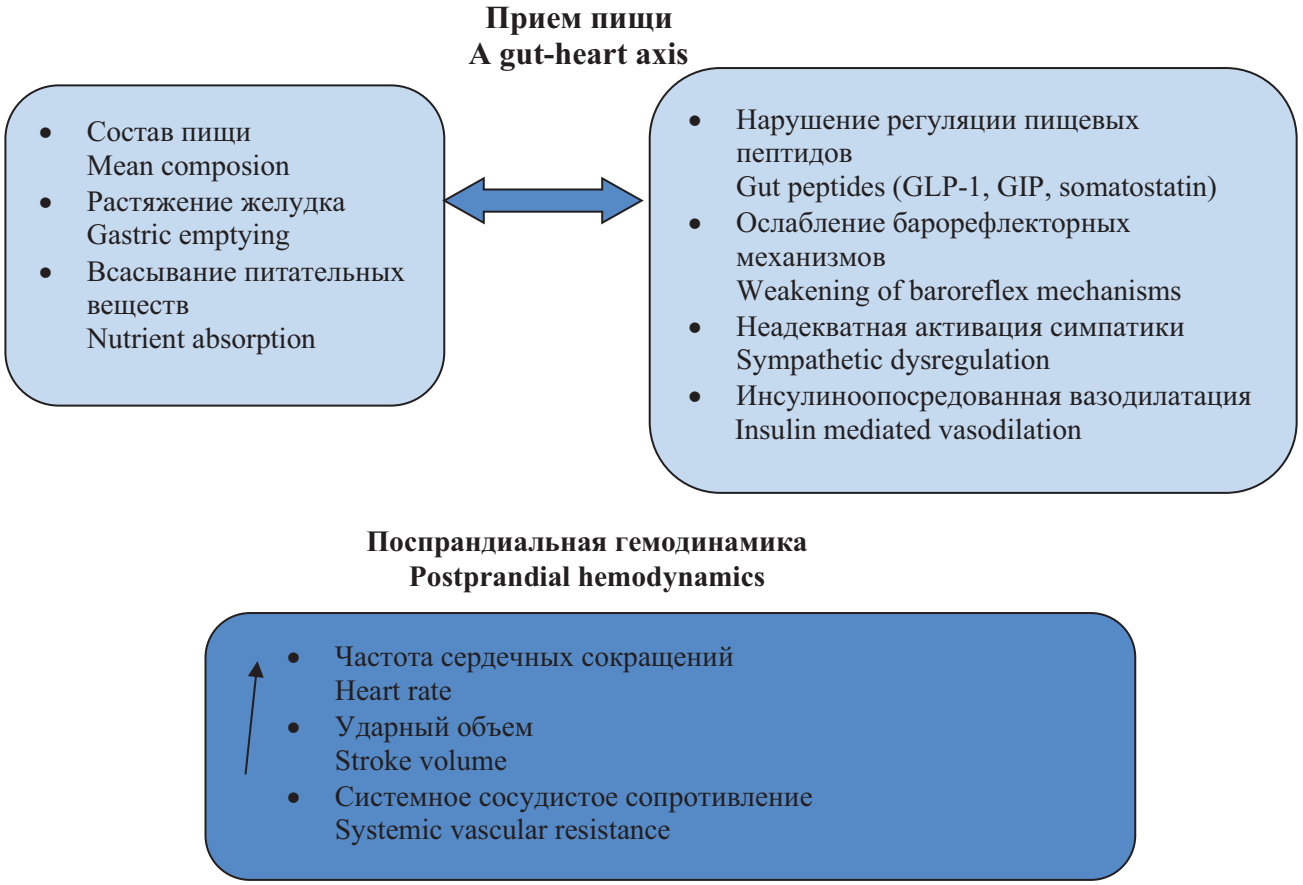

Figure 1. *Postprandial hemodynamic response (model)*
Abbreviations: GLP-1 — glucagon-like peptide 1, GIP — glucose-dependent insulinotropic polypeptide

Table 1. *Age-dependent physiological and pathophysiological postprandial reactions*

	Young healthy	Elderly healthy	PPG
Heart rate	↑	↑	↑↑
Arterial pressure	↔	↔ or ↓	↓↓
Norepinephrine in plasma	↔	↑	↔
Vascular response to norepinephrine	↑	↔ or ↓	↓↓

Abbreviations: PPG — postprandial hypotension, ↑ — increase, ↓ — decrease, ↔ — no change.

It has been demonstrated that carbohydrates, fats and proteins cause various haemodynamic reactions. For instance, in elderly people with AH, oral carbohydrates can reduce mean AH values faster than fats or proteins. In healthy elderly people, intraduodenal glucose administration reduced SBP and DBP more rapidly vs. low-calorie fat and protein, as well as led to a lower increase in flood flow in the superior mesenteric artery, which is an artificial indicator of visceral blood deposition as a response to intraduodenal protein [13]. Variable haemodynamic responses to macronutrients can be evidence of differences in neurohormonal profiles. For instance, fats vs. carbohydrates are a more potent stimulus for the secretion of two incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [14].

The rate of nutrient delivery to the small intestine is strictly controlled by gastric emptying, which is very individual [15]. There are evidences that stomach emptying is a major factor affecting response of the blood pressure to meals. For example, postprandial drop in SBP is higher when the stomach is emptied relatively more rapidly, thus reflecting a stronger association between nutrients in small intestine and visceral blood accumulation [16]. However, the association between intestinal emptying and postprandial BP is not linear; in healthy elderly people, BP reduction increased with a higher rate of intraduodenal glucose infusion

from 1 to 2 kcal/min, but did not differ between 2 and 3 kcal/min [17].

Nutrient absorption in the small intestine also affects the postprandial dynamics. Interventions, which inhibit the rate of carbohydrate absorption in the small intestine, such as intake of alpha-glucosidase inhibitors, acarbose, are associated with reduced visceral deposition of blood and less pronounced drop in SBP in healthy elderly people [13]. It has been demonstrated that exposure to glucose in the duodenum results in a more marked SBP reduction and more intensive blood flow in the superior mesenteric artery vs. iliac artery, together with more rapid glucose absorption, higher GIP release and lower GLP-1 secretion [17].

After meals, the blood flow in the superior mesenteric artery doubles; and in healthy young people with preserved baroreflex function, an increase in the visceral blood flow is associated with an increase in the heart rate, peripheral vascular resistance, systolic discharge, and cardiac output. In patients with PPH, these compensatory responses are inadequate, postprandial drop in BP is more prominent, when stomach emptying is faster [18], while distended stomach lowers PPH both in young and elderly subjects [19]. Usually, a drop in the system blood flow as a result of visceral vasodilation is compensated by a combination of an increase in cardiac output resulting from higher heart rate and/or systolic discharge, and a higher systemic vascular resistance [8]. Cardiovascular responses to meals involve numerous neurohormonal mechanisms. Stomach distension after meals triggers a gastrovascular reflex including stimulation of noradrenaline secretion, which boosts sympathetic neural activity. This response is often subsided in elderly people, especially those with PPH. Modulation of secretion or signalling of these intestinal peptides can significantly affect the blood pressure response to meals, bringing about potentially new targets for PPH therapy [9].

PPH pathophysiology includes sympathetic dysfunction associated with vegetative neuropathy (e.g. in Parkinson disease, DM and heart failure) and causing reduced baroreceptor reflex. These patients are unable to increase the heart rate in response to abrupt reduction in BP when visceral blood flow increases as a result of postprandial vasodilatation of gastrointestinal vessels [20].

Intestinal peptides, especially GLP-1, GIP and somatostatin, can significantly impact postprandial haemodynamic responses [21]. GLP-1 stimulates insulin secretion, inhibits glucagon secretion and slows down stomach emptying. It has been shown that GLP-1 infusion mitigates BP drop after oral or intraduodenal glucose administration.

Genetic susceptibility to postprandial BP dysregulation remains understudied. Although some scientists demonstrated correlation between polymorphism of beta-adrenergic receptor genes and orthostatic BP dysregulation in patients with AH [22], additional studies are required to characterise any PPH-associated genetic susceptibility.

Diagnosis of PPH

Asking about symptoms of hypotension after meals is vital for correct diagnosis of PPH. Some patients may have asymptomatic PPH; however, the most common signs and symptoms of PPH are motive weakness, dizziness, delirium, syncope, falls, angina, nausea and vision disorders; also, patients may be unable to stand or walk after meals [22]. There is evidence of transient ischaemic attacks in elderly patients, who had significantly reduced postprandial BP, with the symptoms disappearing when BP values return to normal. Cerebral symptoms ~~depend on or~~ depend on the characteristics of cerebral hypoperfusion [3].

PPH is preferably diagnosed with outpatient BP monitoring. Baseline BP and heart rate before meal (after a 5-minute rest) are measured; BP and heart rate are then measured every 10 minutes for about two hours. Diagnostic reduction in BP (a drop in SBP by ≥ 20 mm Hg) is usually diagnosed 15 minutes after meals in 15 % of patients with PPH and in 30–60 minutes in 70 % of patients. During tests, there were no limitations in food or caloric value; however, it might be preferable to use low-carb test food because of the impact from insulin-induced reactive hypoglycaemia. Intrasubject reproducibility of PPH is quite high, therefore, a single test is enough to diagnose this condition. Diagnostic procedures performed in the morning can be more efficient [22].

Risk factors of PPH

1. It has been demonstrated that delayed stomach emptying with moderately distended stomach causes a 200 % increase in the sympathetic nervous system activity [23]. This activation of sympathetic signalling can be efficient in the maintenance of postprandial BP. Abundant meals are highly likely to cause a drop in BP as compared to a light meal.

2. Fluid volume deficit in elderly can make patients susceptible to PPH.

3. BP response to sweeteners is usually unchanged in healthy young people; however, in elderly people, glucose causes the highest drop in postprandial BP, whereas response to sucrose is less pronounced [24].

4. The strategy, which becomes more common in prevention or therapy of malnutrition, weight loss and sarcopenia in elderly, involves consumption of high-energy, protein-rich supplements [18]. Oral protein or supplements rich in serum protein can lower BP to the point, where some elderly people face the risk of fall. The hypotensive effect of proteins is likely to be mediated by amino acids produced during digestion; it can explain the latent period and onset of changes in BP and heart rate after protein load. Consumption of 70 g of a serum protein drink is associated with a significant drop in BP in healthy elderly males; the majority of elderly subjects

had lower systolic BP (SBP) by 20 mm Hg or more, and the highest drop was observed 2–3 hours after the drink [25]. It is unclear whether the hypotensive effect of serum protein drinks is dose-dependent in elderly people, and whether serum doses below 70 g cause a significant drop in BP [25].

PPH prevention

It is worth noting that currently there is no efficient and safe PPH management strategy [6, 26]. Nevertheless, several methods were proposed to reduce the PPH risk:

1. One of the main therapeutic strategies is elimination of distended stomach in order to delay digestion products from entering the small intestine. Smaller portions were associated with a drop in postprandial BP by 11–20 mm Hg [23]. Therefore, it is advisable to regulate food intake in patients with PPH by consuming smaller portions at smaller intervals.

2. Symptomatic patients should also rest after meals lying flat on their backs, because standing or sitting tend to have additional hypotensive effect [9].

3. Sufficient hydration also facilitates protective stomach distension and delayed emptying: 350–480 mL of water increases BP by 20 mm Hg in patients with vegetative insufficiency [13].

4. In elderly people, who consumed 60 mg of caffeine (in tea or coffee) five times a day, SBP was 4 mm Hg higher without any impact on the baseline systolic BP [13]

5. Walking is likely to help to restore BP after meals. The mean blood pressure increased by 18 ± 4 mm Hg during exercises after the meal, but dropped 10 minutes later to the pre-exercise level [24]. It means that exercises after meals can be useful in preventing PPH.

6. Caution may be required when prescribing protein supplements in elderly people, and their haemodynamics should be monitored. Measures (e.g. standing position) should be recommended to reduce harmful effects of excessively reduced BP after meals. Diet modifications — replacing highly-nutritious sweeteners (glucose, fructose and sucrose) with low-calorie ones (d-xylose, xylitol, erythritol, maltose, maltodextrin, and tagatose) and calorie-free sweeteners — can be a simple, yet efficient PPH therapy.

7. Metformin modulates cardiovascular response to intraduodenal glucose in patients with DM2 and reduces postprandial hypotension. Mechanisms, by which metformin attenuates hypotension resulting from oral glucose, needs to be identified [27].

8. It has been demonstrated that delayed stomach emptying, e.g. consumption of food fibre or acarbose, slows down SBP drop after consumption of carbohydrate-rich food in healthy elderly people and DM2 patients [28]. Data from a meta-analysis (Wang B., 2021) show that acarbose attenuates drops in postprandial systolic and diastolic BP and is therefore efficient in PPH prevention. Acarbose inhibits enzymes, which are required to digest carbohydrates, reduces the amount of carbohydrate products to the duodenum and potentially delays stomach emptying. Moreover, inhibition of enzymes required for carbohydrate digestion in the stomach reduces release of intestinal peptides, such as vasoactive intestinal peptide, which mediates visceral vasodilation [29].

Conclusion

In spite of the common medical idea, the phenomenon of BP drops after meals is a common event, especially in elderly and old people. PPH is a clinically significant event associated with the risk of cardiovascular complications and geriatric syndromes (including the risk of fall, osteoporosis, sarcopenia). Epidemiological data show the low rate of PPH diagnosis in clinical practice; at the same time, the condition can be easily diagnosed, given the widespread introduction of outpatient blood pressure measurements. Awareness-building among medical professionals about pathophysiology and methods for diagnosis and prevention can boost efficiency and safety of geriatric patient management. Up-to-date knowledge of prevention and account of respective individual features of the patient make it possible to significantly enhance clinical efficiency and safety of antihypertensive therapy and to improve the quality of life for geriatric patients.

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ТРОМБОЗ ВОРОТНОЙ ВЕНЫ ПРИ ЦИРРОЗЕ ПЕЧЕНИ. ЧАСТЬ 2: ЛЕЧЕНИЕ, ПЕРВИЧНАЯ И ВТОРИЧНАЯ ПРОФИЛАКТИКА

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Portal Vein Thrombosis in Liver Cirrhosis. Part 2: Treatment, Primary and Secondary Prevention

Резюме

В большинстве случаев тромбоз воротной вены прогрессирует без лечения, спонтанная реканализация воротной вены развивается у 42 % больных циррозом печени. Существующие стратегии лечения включают назначение антикоагулянтов, проведение интервенционных мероприятий, таких как трансъюгулярное внутрипеченочное портосистемное шунтирование или эндоваскулярный фибринолиз. Антикоагулянтная терапия имеет определенные трудности у пациентов с циррозом печени из-за сложного профиля гемостаза, склонности как к геморрагиям, так и к гиперкоагуляции. Помимо традиционных антикоагулянтов (препараты гепарина, фондапаринукс, антагонисты витамина К) в последние годы при тромбозе воротной вены широко используются прямые оральные антикоагулянты. Ранее тромбоз воротной вены считался противопоказанием к выполнению трансъюгулярного внутрипеченочного портосистемного шунтирования, в настоящее время метод часто применяется с целью восстановление портального кровотока через шунт и предотвращения повторного тромбоза. Эндоваскулярный фибринолиз по-прежнему остается опцией специализированных центров для «сложных» больных. В случаях повышенного риска венозных тромбоэмболий пациентам с циррозом печени рекомендуется профилактика препаратами низкомолекулярного гепарина или прямыми оральными антикоагулянтами, однако дальнейшие исследования должны уточнить их эффективность в этом аспекте. В обзоре освещены данные об особенностях терапии, первичной и вторичной профилактики тромбоза воротной вены у больных циррозом печени. Несмотря на существующие клинические рекомендации по ведению больных цирротическим тромбозом воротной вены, выбор той или иной стратегии, прежде всего, зависит от индивидуализированной оценки рисков и преимуществ каждого из методов лечения.

Ключевые слова: *тромбоз воротной вены, цирроз печени, лечение, антикоагулянты, трансъюгулярное внутрипеченочное порто-системное шунтирование, профилактика*

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Abstract

In most cases, portal vein thrombosis progresses without treatment; spontaneous recanalization of portal vein develops in 42 % of patients with liver cirrhosis. Effective treatment strategies include administration of anticoagulants, interventional procedures such as transjugular intrahepatic porto-systemic shunt or endovascular fibrinolysis. Anticoagulant therapy has certain difficulties in patients with liver cirrhosis due to the complex profile of hemostasis, a tendency to both hemorrhages and hypercoagulation. In addition to traditional anticoagulants (heparin preparations, fondaparinux, vitamin K antagonists), direct oral anticoagulants have been widely used in recent years for portal vein thrombosis. Previously, portal vein thrombosis was considered a contraindication to performing transjugular intrahepatic porto-systemic shunt, currently the method is often used to restore portal blood flow through the shunt and prevent repeated thrombosis. Endovascular fibrinolysis is still an option for specialized centers for «difficult» patients. In cases of increased risk of venous thromboembolism, patients with liver cirrhosis are recommended to be prevented with low-molecular-weight heparin or direct oral anticoagulants, but further studies should clarify their effectiveness in this aspect. The review highlights data on the features of therapy, primary and secondary prevention of portal vein thrombosis in patients with liver cirrhosis. Despite the existing clinical recommendations for management of patients with cirrhotic portal vein thrombosis, the choice of a particular strategy primarily depends on an individualized assessment of risks and benefits of each treatment method.

Key words: *portal vein thrombosis, liver cirrhosis, treatment, anticoagulants, transjugular intrahepatic porto-systemic shunt, prevention*

Conflict of interests

Co-author of the article Yagoda A.V. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Yagoda A.V. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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APPT — activated partial thromboplastin time; CI — confidence interval; INR — international normalised ratio; LMH — low molecular heparin; UFH — unfractionated heparin; HR — hazards ratio; OR — odds ratio; PVT — portal vein thrombosis; TIPSS — transjugular intrahepatic porto-systemic shunt

Treatment

The natural course of portal vein thrombosis (PVT) in hepatic cirrhosis is variable; this heterogeneity makes PVT a unique condition among venous thromboses [1]. Spontaneous portal vein repatency is observed in 42 % of PVT cases [2-4]. Its incidence reaches 70 % in compensated cirrhosis or partial thrombosis [4], whereas in decompensated cirrhosis or in patients on the liver transplantation list, spontaneous repatency is significantly less frequent [5]. Predictors of spontaneous improvements in portal vein thrombosis are unknown.

In asymptomatic patients, who are not candidates for liver transplant and have thrombosis in their small intrahepatic branches of the portal vein or minimal occlusion (< 50 % of the vein lumen), follow-up is usually enough [6, 7].

At the same time, in 33–70 % of patients with hepatic cirrhosis, when left untreated, portal vein thrombosis progresses [3, 8]. According to clinical guidelines, a decision to initiate therapy is based on the extent of the thrombus, presence of symptoms, and need for a liver transplant [6, 7, 9, 10]. If bowel ischaemia is suspected, early anticoagulant therapy is initiated; it is also recommended to consult a surgeon and a specialist in intensive care and interventional radiology [7].

PVT development in cirrhosis impacts the possibility and outcomes of liver transplantation. Candidates for a transplant need to have at least a partially re-canalised portal vein to ensure portal blood flow to the transplant using end-to-end anastomosis, which reduces post-surgery morbidity and mortality. If the vein is not re-canalised, the purpose of PVT management is to prevent thrombus growing, especially to prevent mesenteric vein involvement [6, 7].

Therapy is also recommended in patients with chronic occlusive PVT or cavernous portal vein transformation to prevent repeated thrombosis and, to a lesser extent, to ensure vein re-patency, especially in hereditary thrombophilia, progressive thrombosis, bowel ischaemia caused by thrombotic involvement of the mesenteric vein, or in patients waiting for liver transplantation [10].

Possible therapies of the portal vein thrombosis in cirrhosis patients include anticoagulants, transjugular intrahepatic porto-systemic shunt, endovascular clot lysis.

PVT is associated with a high risk of varicose bleeding, that is why before initiation of anticoagulants, patients with cirrhosis should undergo endoscopic vein ligation and use β-adrenoreceptor blocking agents [9]. However, anticoagulation therapy should not be delayed until complete esophagus vein eradication and b-adrenoreceptor blocking [7].

Anticoagulants

Data from retrospective studies [2, 11-15] and some meta-analyses [3, 16-18] show that, in cirrhosis patients, anticoagulants are an efficient and safety therapy of portal vein thrombosis. They promote any degree of vein re-patency in 66.6–71.5 % of cases; complete re-patency

was observed in 40.8–53 % of patients; and the rate of thrombosis progression, despite the therapy, did not exceed 5.7–9 % [3, 16-18]. Anticoagulation therapy in PVT patients with liver cirrhosis was associated with a higher rate of vein re-patency (44.4 % vs. 20.0 %, P = 0.016) and with lower thrombosis progression rates (7.4 % vs. 30.0 %, P = 0.026) vs. no therapy[19]. According to a meta-analysis, unlike observation, anticoagulants showed a 4-fold increase in the probability of portal vein re-patency (odds ratio (OR) 4.44; 95 % confidence interval (CI) 3.11–6.32) and 3-fold reduction in the probability of cirrhotic PTV progression (OR 0.33; 95 % CI 0.18–0.62) [20].

Nevertheless, the rate of portal vein re-patency after coagulation therapy for PVT in cirrhotic patients is lower than in other venous thromboses [1]. According to E.G. Driever et al., it is associated with the fact that cirrhotic PVT manifested as thickening of the portal vein wall intima, similar to intima fibrosis, and a fibrin-rich blood clot was observed only in one third of cases. The authors believe that the lack or small amounts of fibrin is a cause of relatively low rates of portal vein re-patency in cirrhosis [21].

According to meta-analyses, anticoagulation therapy has a positive effect on the course and mortality rates in cirrhotic patients by reducing the risk of esophagus bleeding [3, 16] and improving overall survival rates [18, 22], which to some extent depend on successful portal vein re-patency.

Anticoagulation therapy is safe and has a comparable rate of haemorrhages as compared to the patients who did not have any therapy [3, 18, 23, 24]. A history of varicose bleeding, platelet count below $50x10^9$/L and low serum albumin are the key risk factors of bleeding in patients receiving anticoagulation therapy [25, 26]. Complications of severe cirrhosis were observed in cases where no portal vein re-patency was achieved [25]. A retrospective study demonstrated that anticoagulation therapy of PVT did not increase the rate of bleeding in cirrhotic patients (14.8 % vs. 24 %, P = 0.343), including major bleedings (3.7 % vs. 6 %, P = 0.665) and varicose haemorrhages (3.7 % vs. 16 %, P = 0.109) [19], as compared to no therapy. A meta-analysis showed that anticoagulants did not cause any increase in the risk of bleeding (OR 1.21; 95 % CI 0.75–1.97), including major bleedings (OR 0.98; 95 % CI 0.49–1.95) and varicose haemorrhages (OR 0.35; 95 % CI 0.12–1.01) [20].

The modern anticoagulation therapies include heparin preparations, fondaparinux, vitamin K antagonists and direct oral anticoagulants.

Heparins

First, heparin therapy includes injections of unfractionated and low molecular heparins. Once bound to antithrombin III, unfractionated heparin (UFH) neutralises factor Xa and thrombin. Heparin therapy requires activated partial thromboplastin time (APPT) monitoring: the therapeutic margin should be 1.5–2 times higher than the normal APPT value. Due to these limitations and possible complications (heparin-induced low platelet count, osteoporosis, etc.), UFH is currently less common than low molecular heparin (LMH). UFH can be prescribed in renal insufficiency and/or in suspected bowel ischaemia, as it can be easily discontinued; however, intravenous administration makes it impossible to use the preparation for a long time [10].

LMH neutralises mainly factor Xa. It is administered subcutaneously once or twice daily in a fixed dose for prevention or depending on the body weight — for therapeutic use. It does not require laboratory monitoring; still, laboratory tests are recommended in obese patients, patients with renal failure (glomerular filtration rate of less than 15 mL/min) and in pregnant women [27].

Due to the need of parenteral administration, low molecular heparin reduces compliance and patient's quality of life, that is why it is used as initiation therapy and then patients switch to vitamin K antagonists or direct oral anticoagulants. However, with refractory abdominal dropsy, where periodic paracentesis is required, or because of challenges with long-term monitoring of the international normalised ratio (INR), LMH is more preferable than oral anticoagulants [27].

LMH is the most acceptable variant in any Child-Pugh liver cirrhosis, while unfractioned heparin can be a frontline therapy in acute kidney injury until their function normalises [28].

The major concerns about the use of LMH are associated with its efficacy and safety in cirrhotic patients, similar to patients without liver damage, given this cohort has lower antithrombin III activity. *In vitro* and *in vivo* studies showed that LMH is efficient and safe for patients with PVT and liver cirrhosis, despite lower levels of anti-Xa and antithrombin III [23, 24, 26, 29]. For instance, dalteparin and enoxaparin resulted in portal vein re-patency in 66.1 % and 78.5 % of PVT cases, respectively [29, 30]. The rate of complete or partial portal vein re-patency after nadroparin/warfarin therapy was higher vs. controls, both for cirrhotic PVT with acute varicose bleeding (67.4 % vs. 39.5 %, P = 0.009) [23] and without bleeding (62.5 % vs. 34.4 %, P = 0.024) [24]. In addition to anticoagulants (OR 4.189; 95 % CI 1.660–10.568; P = 0.002) predictors of therapy efficiency were low Child-Pugh scores (OR 0.692; 95 % CI 0.488–0.982; P = 0.039) and D-dimer values below 2.00 μg/mL (OR 3.600; 95 % CI 1.134–11.430; P = 0.030) [23, 24]. LMH (enoxaparin or dalteparin) facilitated portal vein re-patency in 61.5 % of patients with liver cirrhosis and PVT, the probability of which increased with a favourable Child-Pugh category and short duration of thrombosis [26].

Lower doses of LMH did not reduce its efficiency [31]. For instance, enoxaparin 1 mg/kg twice daily demonstrated similar results, but was associated with fewer complications (4-fold reduction in the risk of non-varicose bleeding) vs. 1.5 mg/kg daily [30]. At the same time,

it is assumed that the efficacy of a fixed dose of dalteparin is 2.6 times lower than when the preparation dose is based on the body weight [29].

Fondaparinux

Fondaparinux inhibits factor Xa by selectively binding to antithrombin III. Unlike heparin, it does not inhibit thrombin or platelet factor IV, which reduces the risk of heparin-induced low platelet count [32]. A fixed dose of the preparation is administered once daily without laboratory monitoring, so it is more convenient than LMH.

In a retrospective study of fondaparinux vs. LMH, fondaparinux demonstrated a higher probability of PVT elimination in patients with liver cirrhosis (77 % and 51 %; P = 0.001); however, it was associated with a higher number of bleedings (27 % and 13 %; P = 0.06) [33]. It is suggested that fondaparinux can be an agent of choice in cirrhotic patients with extremely low platelet count.

Vitamin K antagonists

Vitamin K antagonists impair carboxylation and reduce the activity of vitamin K-dependent blood clotting factors. Due to a narrow therapeutic window and drug-drug interactions, their administration required INR monitoring. The therapeutic range corresponds to INR 2.0–3.0 (target INR: 2.5) [9].

Determination of the therapeutic range of vitamin K antagonists in cirrhotic patients is challenging because of the initially longer prothrombin time. That is why the therapeutic range requires lower doses, therefore, patients can receive a low dose. On the other hand, because of higher values the normal INR is not suitable for cirrhotic patients, that is why a modified INR (liver INR) can be used as an alternative [9].

Vitamin K antagonists are recommended in cirrhotic patients with Child-Pugh class A; still, they should be used with caution, since initially modified INR can affect its target values [28].

Vitamin K antagonists used as maintenance therapy are efficient and safe [13], and their rates of re-patency and side effects are similar to those of LMH [2, 23, 24]. Unlike untreated patients, patients receiving warfarin had higher rates of portal vein re-patency (P = 0.011); thrombosis improved in 68.2 % and 25 % of cases, remained stable in 18.2 % and 37.5 % of cases, and progressed in 13.6 % and 37.5 % of cases, respectively [2]. In a randomised study, the rate of portal vein re-patency was twice as high with warfarin vs. controls (71.9 % vs. 34.4 %, P = 0.004); anticoagulation therapy was a predictor of re-patency (OR 2.776; 95 % CI 1.307–5.893; P = 0.008) and was not associated with a higher risk of bleeding [34].

Direct oral anticoagulants

Direct oral anticoagulants directly inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, edoxaban, betrixaban and apixaban) without antithrombin III involvement or impaired carboxylation of vitamin K-dependent blood clotting factors. In addition to fixed oral doses, their advantages include no need for laboratory monitoring and no impact on INR values [9].

Given a possible-drug-drug interaction, the concentration or efficacy of direct oral anticoagulants can be impacted by P-glucoprotein preparations, as well as medications modifying CYP3A4 activity [35].

Pharmacokinetics of direct oral anticoagulants in liver cirrhosis has been understudied. *In vitro* and *in vivo* studies show that the efficacy of preparations inhibiting factor Xa can be lower in cirrhotic patients; it is a result of impairments at various stages of drug metabolism (binding to plasma proteins, cytochrome p450 function, bile excretion and renal clearance) [36, 37].

Direct oral anticoagulants can be safely used in patients with Child-Pugh class A. In Child-Pugh class B or where creatinine clearance is below 30 mL/min, they should be used with caution because of possible accumulation, which requires dose reduction [28, 35], while rivaroxaban is contraindicated in class B cirrhosis patients [38]. Direct oral anticoagulants are not recommended in Child-Pugh class C or with creatinine clearance below 15 mL/min [28, 35].

Direct oral anticoagulants are safe and efficient in thromboembolic conditions in liver cirrhosis [39], including portal vein thrombosis. Edoxaban was more efficient in complete PVT elimination in cirrhosis patients vs. warfarin (70 % and 20 %), while thrombosis progression was less common (5 % and 47 %, respectively) [40]. Rivaroxaban was superior to warfarin in the rate of portal vein re-patency and was more efficient in thrombosis relapses [41]. In a prospective study by M.-H. Ai et al. of 6-month rivaroxaban or dabigatran therapy of chronic PVT in cirrhosis patients, a higher rate of complete/partial portal vein re-patency and better blood flow were observed vs. controls (P < 0.05), while the risk of haemorrhage was similar (P > 0.05) [42]. In non-cirrhotic PVT, direct oral anticoagulants were more efficient than vitamin K antagonists (OR 4.33; 95 % CI 2.4–7.83), while in cirrhotic thrombosis — more efficient than no therapy (OR 3.86; 95 % CI 1.49–10.03) or vitamin K antagonists (OR 30.99; 95 % CI 7.39–129.87) [20, 43]. According to a meta-analysis, direct oral anticoagulants and vitamin K antagonists were effective in PVT re-patency in 87.3 % and 44.1 % of cirrhotic patients with PVT; at the same time, direct oral anticoagulants were associated with a higher rate of vein re-patency (OR 1.67; 95 % CI 1.02–2.74) and a lower risk of thrombosis progression (OR 0.14; 95 % CI 0.03–0.57) [44].

The rate of bleeding when taking direct oral anticoagulants was similar or lower than with the use of traditional anticoagulants [20, 40, 41]. In retrospective studies [39, 45-47] and meta-analyses [20, 44, 48, 49], direct oral anticoagulants in liver cirrhosis had safety profiles similar to those of traditional anticoagulants; however,

the risk of bleeding was higher in progressive disease [46]. In cirrhotic PVT, direct oral anticoagulants were associated with a lower total risk of a major bleeding (OR 0.29; 95 % CI 0.08–1.01) vs. vitamin K antagonists, but they had a similar total risk of varicose bleeding (OR 1.29; 95 % CI 0.64–2.59) and death (OR 0.31; 95 % CI 0.01–9.578) [44].

Duration and predictors of successful therapy

The highest probability of the efficient anticoagulation therapy is observed if the period between PVT diagnosis and therapy initiation is less than six months [8, 31]; however, according to other data, early anticoagulation (within 1–2 weeks) is also associated with higher rates of portal vein re-patency [25]. Therefore, the optimal timing for anticoagulation therapy initiation is still unclear [37].

The mean time for portal vein re-patency is 5.5–8 months [8, 50]; however, there are reports on delayed response one year after therapy [50]. The therapy lasts at least half a year, and patients with superior mesenteric vein thrombosis and bowel ischaemia should be on life-long anticoagulation therapy [6, 9].

Other factors of good response to therapy are a mild hepatic disease, mild thrombosis, superior mesenteric vein thrombosis of less than 50 %, no history of bleeding associated with portal hypertension, and smaller spleen [13, 18, 51].

Therapy efficiency should be evaluated every 2–3 months with imaging [27].

Once therapy was discontinued after portal vein repotency, thrombosis relapses were observed in 27–56.6 % of cases 2–5 months later (median time to relapse: 4 months) [25, 26, 29]. The risk of thrombosis relapse after dalteparin therapy increased 3.1–3.9-fold if therapy was initiated 3–6 months after diagnosis [29]. According to the recommendations on thrombosis relapse prevention, therapy should continue for several more months after vein re-patency or until liver transplantation [9].

Transjugular intrahepatic porto-systemic shunt (TIPSS)

Earlier portal vein thrombosis was a contraindication to TIPSS. Current guidelines list the following indications for TIPSS in patients with hepatic cirrhosis and PVT: inadequate response or contraindications to anticoagulants; chronic PVT/portal cavernoma with severe sequelae of portal hypertension (recurring varicose bleeding or abdominal dropsy), refractory to drug therapy; chronic PVT preventing physiological anastomosis between the transplant and recipient's portal vein [6, 7, 10, 52]. Liver transplant candidates with progressive PVT with no response to anticoagulation therapy undergo TIPSS, which prevents thrombosis aggravation and complete portal vein occlusion [9].

The purpose of TIPSS is restoration of portal blood flow with the help of a shunt and prevention of thrombosis recurrence.

The most common indication for TIPSS in cirrhosis patients with PVT was not thrombosis itself, but therapy-resistant consequences of hypertension. Successful TIPSS was associated with clinical improvements of cirrhosis, low incidence of thrombosis recurrences and recurrent portal bleeding, reduced need for systemic anticoagulation, which was required only in prothrombotic condition [53, 54].

After TIPSS, re-patency rates varied from 70 to 100 % [53, 55, 56]. Meta-analyses showed that re-patency and complete re-patency after TIPSS was 81–84.4 % and 73–74.61 %, respectively; the probability of severe complications exceeds 10 % [55, 57, 58]. Unlike anticoagulants, TIPSS was more efficient in portal vein re-patency and prevention of bleeding relapses; it did not increase the risk of side effects, however, the survival rates did not improve as well [55, 59, 60]. If compared to the conservative therapy (endoscopic ligation of esophagus veins and propranolol), TIPSS was associated with better portal vein re-patency outcomes (95 % vs. 70 %; P = 0.03), thrombosis relapses (5 % vs. 33 %; P = 0.06), rate of recurrent varicose bleedings (15 % vs. 45 % one year later and 25 % vs. 50 % two years later, respectively; OR 0.28; 95 % CI 0.10–0.76; P = 0.008); however, patient survival rates were similar [61]. The group of successful TIPSS after chronic PVT had lower portal vein pressure (27.15 vs. 19.74 mm Hg, P < 0.001); mortality rates were comparable (12.9 % vs. 19.2 %; P > 0.05); while bleeding recurrences (14.7 % vs. 30.8 %; P = 0.017) were lower than in unsuccessful TIPSS procedures [56]. In patients with cirrhotic PVT with varicose bleeding, TIPSS more often resulted in complete portal vein re-patency (85.5 % vs. 19.6 %, P < 0.001) and lower rates of 5-year recurrent esophagus vein bleeding (31.0 % vs. 50.1 %; P = 0.017), than in endoscopic management and anticoagulants [62].

In patients with frequent PVT caused by hepatic cirrhosis, awaiting transplantation, TIPSS did not affect the rate of complications, outcomes, duration of transplantation or the need for blood preparations.

TIPSS is justified for PVT with cavernous transformation [63]; however, it is associated with lower technical success rates, which increase to 90 % (ranging from 75 % to 100 %) with the use of a modified transplant or transhepatic approach [64]. In this situation, portal vein re-patency is achieved with angioplasty/stenting and TIPSS insertion [65].

Technical complications with TIPSS emerge in advanced PVT because of the impossibility to puncture the intrahepatic branch of the portal vein, so the transcutaneous approach is used, which is more risky.

Unlike anticoagulants, endoscopic management or endovascular clot lysis, TIPSS can increase the risk of hepatic encephalopathy (rate: 25–32 %) [62, 66]; however, it was not confirmed in a number of studies [56, 61].

Endovascular clot lysis

Experience in using local or systemic clot lysis, also in combination with TIPSS or anticoagulants, in patients with cirrhosis-associated PVT is limited. In cirrhotic PVT, clot lysis usually results in partial portal vein repatency and is more efficient if combined with thrombectomy [53]. In PVT patients, clot lysis combined with anticoagulants had efficiency similar to anticoagulation therapy; however, it was associated with a higher risk of morbidity and mortality [67].

Similar to TIPPS, endovascular clot lysis improved PVT in cirrhotic patients (85 % and 70 %; P = 0.304); clot lysis was more often associated with dissolution of blood clots in superior mesenteric (P = 0.048) and splenic veins (P = 0.02) [66].

Current guidelines recommend that clot lysis in patients with persistent bowel ischaemia despite anticoagulants is performed in specialised clinics [7, 68].

Contraindications for clot lysis include recent stroke, GIT bleeding, recent orthopaedic, cerebral or spinal trauma and an intracranial tumour [53].

Primary PVT prevention in hepatic cirrhosis

Patients with hepatic cirrhosis and a high risk of venous thromboembolism are recommended to undergo prevention with LMH or direct oral anticoagulants with an acceptable safety profile, although their efficiency is unclear. For Child-Pugh class C cirrhosis, direct oral anticoagulants are not used for prevention of thrombotic complications [28].

This recommendation is based on a randomised study, which demonstrated that enoxaparin therapy in cirrhosis patients prevented PVT [69]. The enoxaparin group demonstrated lower rates of PVT (8.8 % vs. 27.7 %, P = 0.048) and hepatic decompensation (38.2 % vs. 83.0 %, P < 0.0001) vs. placebo; enoxaparin also reduced the risk of deaths without a higher risk of bleeding, which may be associated with a better barrier function of the bowel and reduced bacterial translocation [69].

Post-splenectomy initiation of antithrombin III concentrate or antithrombin III, danaparoid sodium and warfarin in patients with a high risk (antithrombin III activity of less than 70 % and splenic vein diameter of less than 10 mm) and a very high risk (splenic vein diameter of over 15 mm) of PVT resulted in reduction in the rate of thrombosis [70].

Unlike aspirin, warfarin was more efficient in prevention of PVT after laparoscopic splenectomy in cirrhosis patients (no thrombosis in 38.5 % and 12.8 % of cases, respectively, P = 0.010), and had a hepato- and nephroprotective effect [71].

Therapy of liver cirrhosis patients with direct oral anticoagulants had a good safety profile, absence of venous thrombosis and no high risk of bleeding, lower rates of ischaemic stroke in liver cirrhosis [48, 72-75].

At the same time, there is some evidence that thrombosis prevention with low molecular or unfractioned heparin did not reduce the risk of venous thromboembolism (OR 0.94; 95 % CI 0.23–3.71) in patients admitted with hepatic cirrhosis [76, 77] and mortality, but tended to increase the risk of bleeding when unfractioned heparin was used [76].

Secondary prevention of PVT after liver transplantation

Post-transplantation portal vein thrombosis, especially long-lasting, is a risk factor of recurrence in case of non-anatomical anastomosis [5]. In addition to presurgery thrombosis, risk factors of post-transplantation PVT include slow portal blood flow after reperfusion (< 1,300 mL/min or < 65 mL/min/100 g), partial thrombectomy, damaged vein intima during thrombectomy, inappropriate reconstruction of inflow to the portal vein, thrombophilic impairments in the recipient [27]. Patients with risk factors and without blood-clotting disorders, transplant dysfunction or low platelet count (< 30–50x10^9/L) within first 24 hours after surgery, have LMH therapy (1 mg/kg) for at least two months, if there are no complications, the therapy can then be prolonged based on individual considerations [78].

Conclusion

The article describes the therapy, possible measures for primary and secondary prevention of portal vein thrombosis in patients with liver cirrhosis. Despite the existing clinical recommendations for the management of cirrhosis patients with PVT, selection of a therapeutic strategy depends mostly on an individualised evaluation of risks and benefits of each therapy.

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ПРИНЯТИЕ МОБИЛЬНОГО ЗДРАВООХРАНЕНИЯ ПАЦИЕНТАМИ С СЕРДЕЧНО-СОСУДИСТЫМИ ЗАБОЛЕВАНИЯМИ: СТРУКТУРНАЯ МОДЕЛЬ ИСПОЛЬЗОВАНИЯ МЕДИЦИНСКИХ ПРИЛОЖЕНИЙ

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Acceptance of Mhealth by Patients with Cardiovascular Diseases: the Structural Model of Health Applications Use

Резюме

Многими исследователями отмечается проблема приверженности лечения лекарственными препаратами пациентов с сердечно-сосудистых заболеваний (ССЗ). Технологии мобильного здравоохранения (mHealth) могут оказывать существенное положительное влияние на изменение поведения пациентов, профилактику и предупреждение обострений сердечно-сосудистых заболеваний (ССЗ). Для внедрения в практику такого подхода прежде всего следует выяснить возможности использования mHealth для пациентов с ССЗ. **Цель.** Изучить принятие медицинских приложений пациентами с ССЗ, а также оценить отношение пациентов к личной ответственности за сохранение своего здоровья в контексте использования mHealth. **Материалы и методы.** Моделирование структурных уравнений методом частичных наименьших квадратов в программе «Smart-PLS» (производитель SmartPLS GmbH, Германия) использовали для реализации модели UTAUT (англ. the unified theory of acceptance and use of technology: Единая Теория Принятия и Использования Технологий), включающую 10 конструктов: «Использование приложений», «Намерение использовать приложения», «Ожидаемая производительность», «Социальное значение», «Поддерживающие условия», «Отношение к использованию приложений», «Тревога», «Роль пациента», «Роль профилактики» и «Значение информации». В исследование включили 437 пациентов с ССЗ, которые имели опыт использования медицинских приложений: 253 женщины и 184 мужчин, средний возраст 47,95±5,22 лет. **Результаты.** Конструкты «Ожидаемая производительность», «Социальное значение», «Поддерживающие условия» и «Значение информации» оказывали прямое положительное влияние на конструкт «Намерение использовать приложения», объясняя 59,3 % дисперсии этого конструкта. Положительное влияние конструкта «Намерение использовать приложения» и «Отношение к использованию приложений» объясняло 61,2 % дисперсии конструкта «Использование приложений». Конструкт «Тревога» косвенно, через «Отношение к использованию приложений», оказывала негативное влияние на конструкт «Использование приложений». 41,4 % дисперсии конструкта «Значение информации», то есть понимание необходимости медицинской грамотности, зависело от конструкта «Социальное значение» и понимания роли личной ответственности за здоровье и профилактику ССЗ. **Заключение**. Пациенты с ССЗ понимают значимость личного участия в сохранении своего здоровья и готовы использовать mHealth для профилактики заболевания и снижения модифицируемых факторов риска ССЗ. Барьером внедрения mHealth может быть страх пациентов перед самостоятельным использованием приложений. Принятие mHealth пациентами с ССЗ для повышения эффективности лечения будет возможно при наличии соответствующих технических условий, социальной поддержки, а также понятного и профессионального образа mHealth.

Ключевые слова: *сердечно-сосудистые заболевания; мобильное здравоохранение; UTAUT; PLS-SEM; профилактика; роль пациента; медицинская грамотность*

Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
Many researchers have noted the problem of adherence to drug treatment in patients with cardiovascular diseases (CVD). Mobile health (mHealth) technologies can have a significant positive impact on changing patient behavior, preventing and preventing exacerbations (recurrences) of cardiovascular diseases (CVD). To put this approach into practice, first of all, it is necessary to find out the possibilities of using mHealth for patients with CVD. **Aim.** To study the acceptance of medical applications by patients with CVD, and also to assess patients' attitudes towards personal responsibility for maintaining their health in the context of using mHealth. **Materials and Methods.** Partial least squares structural equation modeling in the Smart-PLS environment was used to implement the UTAUT model (the unified theory of acceptance and use of technology), which included 10 constructs: Use of Applications, Intention to Use, Performance Expectancy, Social Influence, Facilitating Conditions, Attitude towards the use of Applications, Anxiety, Patient's Role, Role of Prevention and Value of Information. The study included 437 patients with CVD who had experience using medical applications: female (253) and males (184), average age 47.95±5.22 years. **Results.** Constructs Performance Expectancy, Social Influence, Facilitating Conditions, and Value of Information had a direct positive effect on construct Intention to use of health Applications and explained 59,3 % of the variance this construct. The positive influence of the construct Intention to use of Applications and Attitude towards the use of Applications explained 61,2 % of the variance in the construct Use of Applications. The construct Anxiety indirectly, through Attitude towards the use of Applications, had a negative impact on the construct Use of Applications. 41,4 % of the variance of construct the Value of Information, that is, an understanding of the need for medical literacy, was determined by the Social Influence construct, as well as an understanding of the role of personal responsibility for health and CVD prevention. **Conclusion.** Patients with CVD understand the importance of personal participation in maintaining their health and are ready to use mHealth to prevent the disease and develop behavior aimed at reducing modifiable risk factors for CVD. One of the barriers to mHealth adoption may be patients' fear of using medical applications on their own. Acceptance of mHealth technologies by patients with CVD to improve the effectiveness of treatment will be possible if there are appropriate technical conditions and social support that creates a trusting, professional, understandable and attractive image of mHealth.

Key words: *cardiovascular diseases; mHealth; UTAUT; PLS-SEM; prevention; patient role; health literacy*

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The authors declare no conflict of interests

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Conformity with the principles of ethics
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mHealth — mobile health, PLS-SEM — Partial Least Squares Structural Equation Modelling, CVD — cardiovascular diseases, UTAUT — unified theory of acceptance and use of technology, IT — information technology

Introduction

Cardiovascular diseases (CVD), such as arterial hypertension, ischaemic heart disease and myocardial infarction, that are associated with the lifestyle, are the leading cause of deaths among employable population in any country. Prevention of exacerbations of these diseases and development of serious complications bears a significant component: reduction of mortality rates and incapacitation among employable population.

An economic analysis of the use of non-drug and drug therapies in patients with cardiovascular diseases (CVD) demonstrates the advantage of using non-drug

measures for improvement of health and survival rates in such patients [1]. Cardiologists believe that prevention [2] and innovative strategies in medical institutions and non-clinical settings [3] are the keys to solution of this problem.

However, despite convincing facts on the need for prevention, people with a high risk of CVD are exposed to modified risk factors and inadequate drug therapies. For instance, Kotseva K. et al. (2016) [4] found out that 48.6 % of CVD patients continued smoking, were barely active or inactive at all; 37.6 % were obese; in 42.7 % of patients, blood pressure was above 140/90 mm Hg; and 80.5 % of patients did not achieve the target low density lipoprotein cholesterol values, etc.

This situation is a result of health-related decision-making outside the healthcare facilities. This demonstrates the need to search for tools, which allow taking sound decisions at home. A majority of experts agree that mHealth (mobile health) technologies can become a driving force in health improvement for patients with CVD [5].

This opinion is supported by experts from the World Health Organisation (WHO), who define mHealth as "the medical practices and public health practices supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" [6]. The possibility of using mobile medical programs is supported by the public interest to such applications: in 2022, the estimated value of the global mobile health market was 8.9 billion US dollars; by 2030, it is expected to reach 72.10 US dollars, with an average annual rate of growth of 29.89 % over the period from 2022 to 2030 [7].

It is assumed that systems supporting clinical decision-making with the help of mHealth allow reducing the number of medical errors and boost both quality and efficiency of healthcare [8]. Medical applications modify users' behaviour: they reduce the risk of CVD development and exacerbations [9]. Moreover, studies by Donovan G. et al. (2022) showed that the automation of bilateral doctor/patient communication and drug medication monitoring can facilitate reflexive motivation to take medications and comply with therapy regimens [10].

Nevertheless, the actual use of such systems is currently limited [11]. One of the obstacles is a subjective attitude of users regarding both clinical and economic efficiency of mHealth in use. Not all people are ready to embrace information technology (IT). For instance, irrespective of age, users may face some challenges due to personal characteristics, lack of knowledge, technical resources, etc. [12].

In a majority of cases, introduction of innovations is resource-intensive, and the use of smart solutions requires active public participation. In other words, introduction and efficient use of such technologies require an evaluation of the possibility of their acceptance by the target groups: doctors, patients and other interested parties. It necessitates the study of the factors affecting intention to use communication technologies, especially in healthcare.

Thus, this study was conducted **to** evaluate the public attitude to health-related applications in general, as well as to analyse the public attitude to the personal responsibility for health and use of applications to prevent CVD.

Mobile healthcare, including CVD management, is discussed in a number of publications, e.g. Belenkov Yu.N. and Kozhevnikova M.V. (2022) [13], Simenyura S.S., Sizova Zh.M. (2021) [14], Arshed M. et al. (2023) [15], etc. This study differs, as its main perspective is the idea of personal role in health support, factors which are essential for CVD prevention and adequate awareness of the mobile healthcare use. To this end, the UTAUT model used has been updated with new healthcare-specific constructs, namely "Patient's role", "Role of prevention", and "Significance of information".

Materials and Methods

Justification of the model selection

There are wide array of models to study the acceptance of technologies. e.g. the Theory of Reasoned Action (TRA) the Theory of Planned Behavior (TPB), the Social Cognitive Theory (SCT), and the Extended Technology Acceptance Model (TAM2). However, these theories have significant limitations, and they are unable to describe the multidimensionality of technology acceptance by people. An attempt to create a single model combining various theories [16] resulted in the emergence of the unified theory of acceptance and use of technology (UTAUT), which was able to explain up to 77 % of differences in user intents and 52 % of dispersion in the use of technologies [17]. Later, in order to dismiss any doubts as to its ability to explain acceptance of technologies by some people, for the purpose of a more accurate explanation of user behaviour, the authors developed UTAUT2 [18], a model which explained up to 74 % of differences in user intents and 52 % of dispersion in the use of technologies [17]. The UTAUT2 model contains nine main constructions: intent to use and actual use of technologies, expected performance, expected effort, social significance, facilitating conditions, cost, hedonist motivation and habits, as well as three moderating variables:

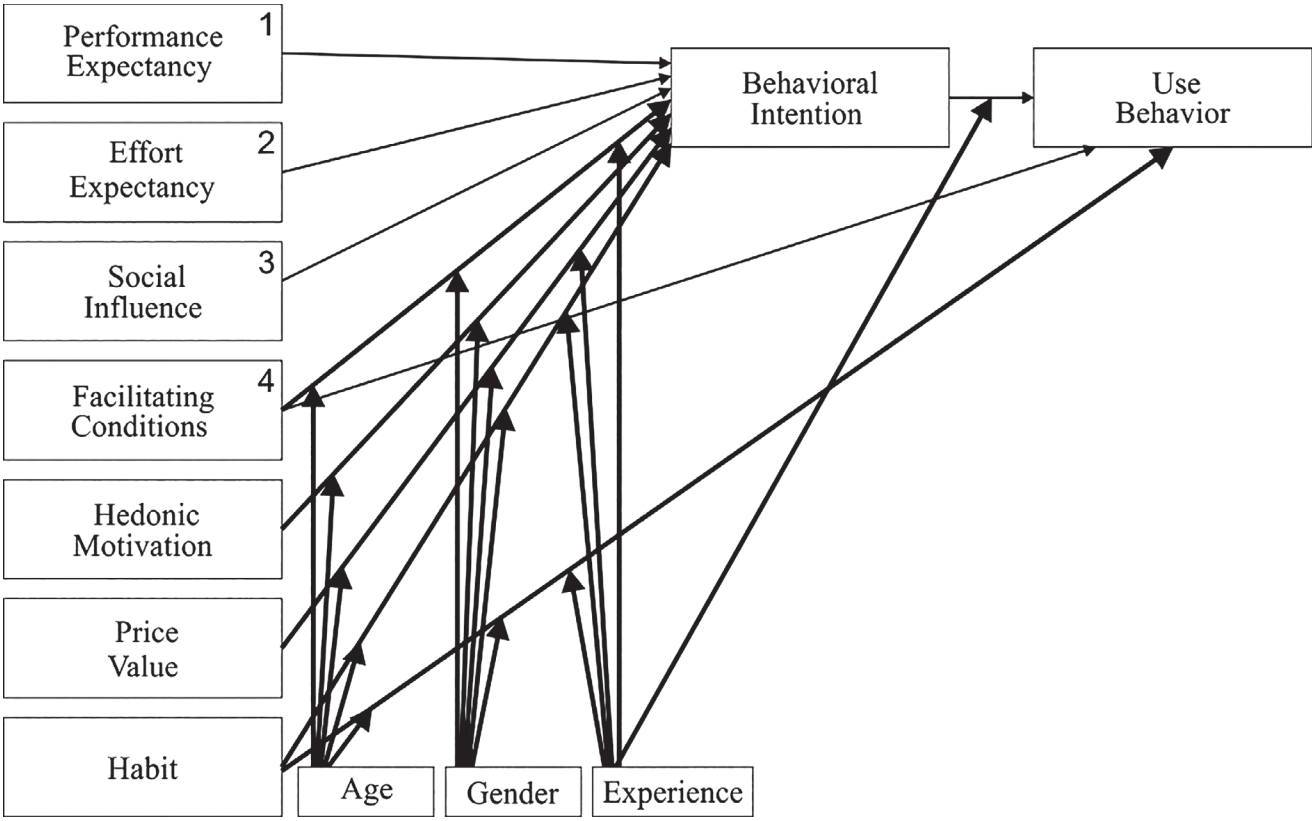

Figure 1. *Модель UTAUT 2. Source: Venkatesh, Thong and Xu, 2012.*
Note: 1. Moderated by age and gender. 2. Moderated by age, gender, and experience. 3. Moderated by age, gender, and experience. 4. Effect on use behavior is moderated by age and experience. 5. New relationships are shown as darker lines

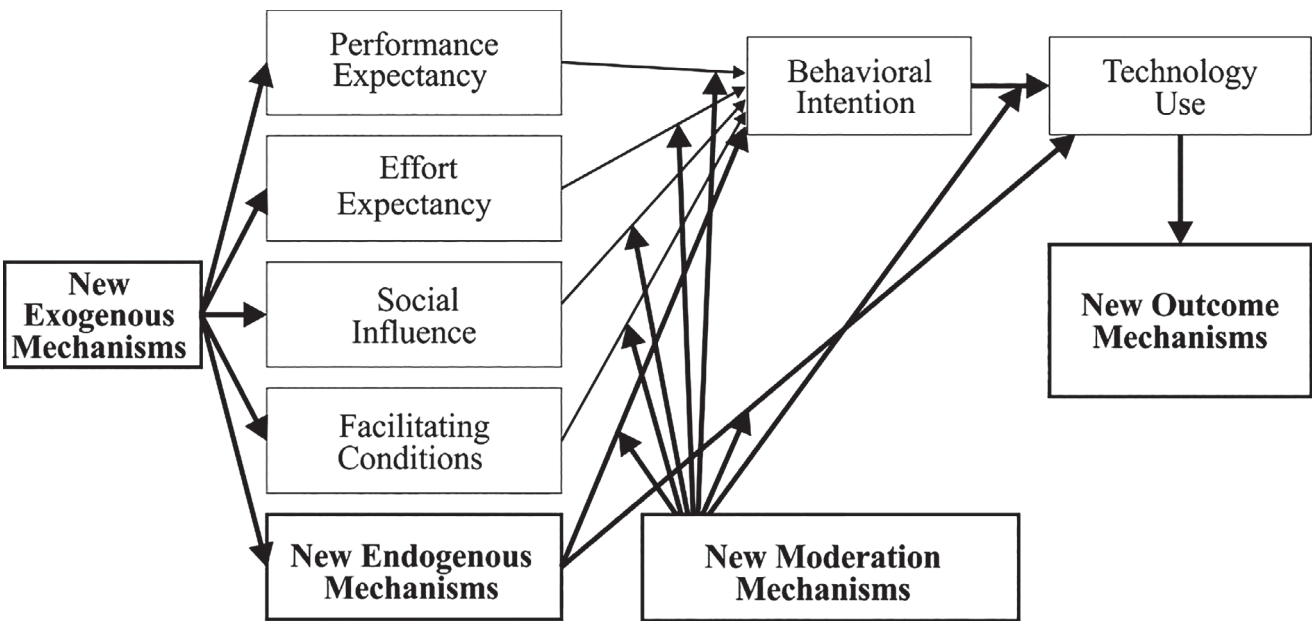

Figure 2. *Four types of UTAUT extensions: new endogenous and exogenous mechanisms, new outcome and moderation mechanisms. Source: Venkatesh, Thong and Xu, 2016*

sex, age and experience, which can impact the relations between constructs (Fig. 1).

There are various extensions of this model, which include new variables, e.g. attitude to the use of technologies, ease of use, perceivable risk and benefit, satisfaction, self-efficiency, etc. [19]. To account for all modifications made by researchers and not to set limits, the authors proposed to be guided by the four types of expended UTAUT studies described in publications, which include new endogenous and exogenous mechanisms, new mechanisms of moderation and result achievement (Fig. 2). The theory has been widely applied in the study of the use of information technology in healthcare [20], including introduction of mHealth, where additional constructs can include health consciousness and motivation, etc. [21]. Successful application of UTAUT in various areas and the possibility to add new essential constructs were the reasons for the use of this model in this study.

Selection of constructs and research hypotheses

In this study, the UTAUT model used both standard constructs (constructs 1–5) and additional constructs (constructs 6–10), introduced for the purposes of the study objective:

1. Construct **"Use of technologies"**: actual use of technologies. In this study, it means use of any health-related applications, the final construct of the model. Of note, the final construct in the UTAUT model is "Use of applications", so this model is unable to study potential users' interest in non-existing applications. Thus, in this study, the public opinion was evaluated in regard to the use of any health-related applications. This construct is defined by three questions (α = 0.79): 1) Use of applications to monitor health (I have experience in using applications for health monitoring). 2) Use of applications to receive health-related information (I'm using applications to receive information on health support, healthy lifestyle). 3) Use of applications to assess physical activity (I sometimes use applications to assess my physical activity).

2. Construct **"Intent to use applications"**: in the UTAUT model, the actual use of a technology is dependent on the intent to use applications, which also depends on other key constructs [17]. In this study, it is use of medical and recreational applications. This construct is defined by three questions: 1) Intent to use medical applications in the future (I'm planning to use medical applications in the future). 2) Intent to use medical applications more regularly to monitor health (I'm planning to use medical applications more regularly in the future). 3) Intent to use medical applications more often for prevention and therapy (I'm planning to use medical applications in the future for prevention and therapy).

3. Construct **"Expected performance"**: in this study, it is the importance of applications to prevent CVD. This construct is defined by three questions: 1) Benefit (I think that health applications can be beneficial in my daily life). Performance (Use of health applications will facilitate health support). 3) Enhancement of efficiency (Health applications will make prevention more efficient).

4. Construct **"Social significance"**: it is the extent, to which an individual perceives that other people think that he/she should use the application, public opinion on the use of the application. This construct is defined by three questions: 1) Attitude to the use of applications (The general public should use health application functionality as much as possible). 2) Social role of applications (Health applications are essential in the social role of health support). 3) Need in applications for communication (Efficient communication with medical institutions is impossible without special applications).

5. Construct **"Facilitating conditions"**: it is the extent, to which an individual thinks that there is an organisational and technical infrastructure to facilitate use of the system, adequate technical equipment, as well as sufficient knowledge to use applications and availability of support where necessary. This construct is defined by four questions: 1) Sufficiency of technical devices (I have sufficient technical resources to use applications). 2) Knowledge (I have knowledge required for the use of electronic applications). 3) Adequacy of knowledge (I have sufficient knowledge to use applications). 4) Help with the use (I have someone to help me if I have questions on the use of applications).

6. Construct **"Attitude to the use of applications"**: attitude to similar applications in general, desire to have medical applications, readiness to explore new applications and enjoy it. This construct is defined by four questions: 1) Unwillingness for the applications to stop working (I wish health application did not stop working). 2) The ability of applications to make life more interesting (Health applications make life more interesting). 3) Need in medical applications (Applications for prevention and therapy are necessary for the general public). 4) Enjoyment from exploring new applications (I like exploring new mobile and computer apps).

7. Construct **"Anxiety"**: the intent and actual use of applications can be impacted by the fear to use any applications, fear to make an error, lose information, and reluctance to accept any types of technologies. This construct is defined by four questions: 1) Fear to use

applications (There are applications which I'm afraid to use (for various reasons). 2) Fear to lose information (I'm afraid that during the use of some applications I may lose a lot of information if I press a wrong button). 3) Fear of an error (I don't dare to use some applications because of the fear to make an error, which I won't be able to undo). 4) Fear to use (I'm a bit afraid of any applications).

Also, the model was updated with three new constructs, which characterised the overall attitude of respondents to information support, CVD prevention and the patients' role in this matter:

8. Construct **"Patient's role"**: the role of the patient in CVD development, the need to engage the patient in CVD prevention and therapy, patient's readiness to act in case of a heart attack and their active participation in medical decision-making, i.e. implementation of one of the most important aspects of the patient-oriented approach. In this study, this construct in essential for understanding the possibility of engagement with CVD prevention and management. This construct is defined by four questions: 1) Overall role of the patient (The patient has an important role to play in CVD development). 2) Patient's engagement in prevention and therapy (The healthcare provider should try to engage the patient in CVD prevention and therapy). 3) The role of patient's knowledge (Each individual should be aware of CVD prevention and cardiovascular health). 4) An active position of the patient (Successful CVD prevention and therapy is impossible without active engagement of patients in medical decision-making).

9. Construct **"Role of prevention"**: understanding of the need to prevent CVD exacerbations (relapses), avoidance of CVD risk factors, cholesterol level monitoring, participation in prevention in general, as well as the impact of the lifestyle, including smoking and obesity, and irreversibility of cardiovascular disorders. This construct allows assessing the attitude to the need to modify patients' behaviour to mitigate modifiable risk factors of CVD. To determine this construct, answers to the following eight statements were used: 1) Everyone needs CVD prevention. 2) It is important to avoid any factor triggering CVD. 3) Damaged heart cannot be repaired. 4) Heart diseases are associated mainly with the person's lifestyle. 5) The lifestyle should facilitate CVD prevention. 6) Monitoring of cholesterol levels is essential for CVD prevention. 7) Diabetes prevention reduces cardiac problems. 8) Smoking promotes CVD.

10. Construct **"Significance of information":** understanding that professional medical information should be available, and understanding the role of medical literacy for CVD therapy and prevention. Assessment of the need in highly available medical information on measures to prevent CVD, the role of diet in CVD development, physical exercises, etc. This construct is defined by four questions: 1) Medical literacy (Medical literacy if crucial for prevention of cardiac disorders). 2) Information on prevention (Highly available professional information on measures to prevent CVD is required). 3) Information on the role of the diet (Reliable professional information should be available on the role of the diet in CVD). 4) Information on the role of physical exercises (Reliable professional information on physical exercises in prevention of CVD and exacerbations is essential).

Study hypotheses

The conceptual model of the study included testing of 17 hypotheses:

H1: The use of medical applications by CVD patients is positively impacted by the intent to use them

H2 (a, b): Construct "Expected performance" has positive impact on the intent of CVD patients to use applications (a) and the use of applications (b).

H3 (a, b): Construct "Social significance" has positive impact on the intent of CVD patients to use applications (a) and the use of applications (b).

H4 (a, b): Construct "Facilitating conditions" has positive impact on the intent of CVD patients to use medical applications (a) and the use of these applications (b).

H5 (a, b): Construct "Attitude to the use of applications" has positive impact on the intent of CVD patients to use applications (a) and the use of applications (b).

H6 (a, b): Construct "Anxiety" has negative impact on the intent of CVD patients to use applications (a) and the use of applications (b).

H7 (a, b): Construct "Significance of information" has positive impact on the intent of CVD patients to use applications (a) and the use of applications (b).

H8 (a, b): Construct "Role of prevention" has positive impact on the intent of CVD patients to use applications (a) and the use of applications (b).

H9 (a, b): Construct "Patient's role" has positive impact on the understanding of the need in available professional medical information (a) and preventive measures (b).

Data gathering

The study design corresponded to a cross-sectional observational sampling study. Data were collected from 15 December 2023 to 15 February 2024 using a questionnaire in Yandex Forms. This exploratory study used convenient sampling, where an electronic questionnaire was distributed like a "snowball" in social networks and

Table 1. Presence of arterial hypertension (AH), coronary heart disease (CHD), myocardial infarction (MI) and their combinations in male and female respondents

Cardiovascular diseases	Number of respondents, n (%)		
	Male	Female	Total
AH	160 (36,68)	214 (48,98)	374 (85,66)
AH + CHD	21 (4,74)	38 (8,68)	59 (13,43)
CHD + MI	3 (0,69)	1 (0,23)	4 (0,92)
Total	184 (42,11)	253 (57,89)	437 (100)

messengers: the authors of the article sent requests to their contacts (total: 120 people, including 67 men and 53 women), asking to send a link to the questionnaire to their 4–5 contacts of various ages and ask them to distribute the link as well. The request stated that of interest were subjects with a confirmed cardiovascular disease.

This study was approved by the Local Ethics Committee at the Siberian State Medical University of Russia (No. 9628 dated December 15, 2023). Participation in the study was voluntary, anonymous, non-interventional and did not involve any potentially dangerous or burdensome questions. Participants of the survey provided their informed consent typical for online surveys: the study objective was described in the chat inviting to participate, and its anonymous nature was mentioned; a person willing to participate could follow the link to complete the questionnaire. Users had two tiers to agree or refuse to take part: 1) they could not agree to take part in the survey in the chat, 2) they could refuse to send the electronic questionnaire to the researchers.

The questionnaire consisted of three parts:

- **Part 1**. Personal information (age, sex, education), experience in the use of any mobile applications and an idea of medicinal mobile applications, CVD status of the respondent.
- **Part 2**. Seven questions to implement the UTAUT model, i.e. to identify components of the following constructs: 1) "Use of applications", 2) "Intent to use applications", 3) "Attitude to the use of applications", 4) "Expected performance", 5) "Social significance", 6) "Facilitating conditions", and 7) "Anxiety". Questions defining UTAUT components were taken from published studies with a minor adjustment [17].
- **Part 3**. Three questions related to constructs of the study area: "Patient's role", "Role of prevention", and "Significance of information".

A 5-point Likert-type scale was used to evaluate the statements in parts 2 and 3 of the questionnaire; the total score for the model elements was calculated by adding up answers to respective questions [22, 23].

So that all questions and answers were adequately clear to respondents, the questionnaire was pre-tested in 17 subjects of various age and educational background; the questionnaire was then improved and modified.

In this study, of interest were respondents who had experience in the use of medical applications and who were diagnosed with one or several of the following CVDs: ischaemic heart disease (IHD), myocardial infarction (MI), arterial hypertension (AH) (Table 1).

All in all, 793 answers by respondents were received, including 437 answers of "a cardiovascular disease diagnosed by a healthcare provider". All respondents were cis-genders: 253 (57.89 %) women and 184 (42.11 %) men. 170 (38.90 %) respondents had secondary or vocational education, 267 (61.10 %) subjects had higher education. The mean age of respondents was 47.95 ± 5.22 years old, including 124 (28.38 %) respondents under 35 years of age, 170 (38.90 %) respondents — 35 to 55 years of age, and 143 (32.72 %) respondents — 56 to 71 years of age.

Since the survey was based on an electronic questionnaire on the Internet, the survey did not include users who did not use Internet technologies in their daily life.

Data analysis and software

The correlations were analysed using structural equation modelling with the use of partial least squares (PLS-SEM). PLS-SEM is widely used as a method to assess correlations between hidden (latent) variables [24] including in the use of UTAUT. Hidden variables cannot be measured directly, they are impacted by a number of measurable parameters, which are combined to form constructs. PLS-SEM does not require normally distributed data, because it is a non-parametric methodology, where a recommended measurement scale is ordinal, while the Likert-type scale is one of the most optimal.

The use of PLS-SEM allows quantifying correlations between constructs and identifying the most relevant parameters for the model, most significant

Table 2. *Cronbach's alpha (α) coefficient values for model constructs*

Constructs of model	α
Performance Expectancy	0,85
Attitude Towards the Use of applications	0,77
Social Influence	0,73
Facilitating Conditions	0,75
Behavioral Intention	0,83
Use Behavior	0,79
Anxiety	0,72
Role of Patient	0,81
Role of Prevention	0,87
Value of Information	0,75.

recommendations and suggestions. PLS-SEM is focused on identification of the key constructs and is recommended not for testing of existing theories, but for exploratory studies [25], which was an additional reason to select this approach.

Calculations for UTAUT under the PLS-SEM model were performed with 3.3.3.Smart PLS software. p-Values, which equalled to 0.0000 in SmartPLS, were presented as $p < 0.001$. The statistical significance threshold α was $p < 0.05$. Also, statistical data were processed in MS Excel 2010 and Statistica 8.0. Stat.Soft. Inc.

Hypothesis testing

To confirm or reject suggested hypotheses, the study includes analysis of 17 correlations. According to the rule of ten [24], which is a rough, but a simple method to determine the sample size, for meeting the representativity requirements, this study requires 170 valid results, which is smaller than the resulting sample size.

The internal consistency of the questionnaire scales in Statistica 8.0. StatSoft. Inc. was detemined using the Cronbach's alpha, where the values were above the recommended 0.7 (Table 2).

Results

Usually, the use of PLS-SEM includes two steps: assessment of measurement validity and reliability and then structural model interpretation [24].

Assessment of model measurements

First, we deleted parameters (questions in the questionnaire) with the factor weight of less than 0.60, i.e. one question in construct "Facilitating conditions". All other questions in the questionnaire had the factor weight of over 0.7 [26], in other words, they were significant for the model.

The reliability and confidence of the construction variables were assessed using composite reliability (CR) and average extracted dispersion (AVE) (Table 3). All CR values were above the recommended level of 0.700 and AVE 0.500, confirming convergent confidence Factor dispersion inflation for each indicator to evaluate multicollinearity was < 5.0 [27]. Discriminant validity was assessed using cross-loads and the heterotrait-monotrait ratio of correlations (HTMT) method. All factor weights exceeded their cross-loads, and HTMT was below 0.85, it being a sign of discriminant validity [27]. The obtained results demonstrated sufficient reliability and confidence of measurements. This fact allows continuing with the analysis of technology acceptability using the UTAUT model to test the suggested hypotheses.

Hypothesis testing

Hypothesis testing resulted in a structural model of patients' attitude to the use of medical applications for prevention, therapy and avoidance of CVD relapses (Fig. 3).

Correlations between elements were described with path coefficients (β) and the coefficient of determination (adjR2) as a predicative value of the model (Table 3, Fig. 3).

The resulting model is able to explain **59.3 %** of dispersion in intent to use medical applications and **61.2 %** of dispersion in the use of medical applications. Data analysis fully confirmed only 6 out of 17 hypotheses suggested in this study (Fig. 3):

H1: Construct "Intent to use applications" (medical applications) directly correlated with their use ($\beta = 0.51$, $p < 0.001$)

Table 3. *Average variance extracted (AVE), composite reliability (CR), and coefficient of determination (adjR2) of model constructs.*

Конструкты	AVE t / p	CR t / p	adjR²
Performance Expectancy	0,701 9,014/<0,001	0,813 17,365/<0,001	0,332
Attitude Towards the Use of applications	0,721 12,024/<0,001	0,837 15,249/<0,001	0,174
Social Influence	0,758 14,083/<0,001	0,862 22,271/<0,001	0,223
Facilitating Conditions	0,601 9,616/<0,001	0,816 17,936/<0,001	
Anxiety	0,73 16,45 /<0,001	0,892 36,960 /<0,001	
Behavioral Intention	0,750 10,599/<0,001	0,875 23,798/<0,001	0,593
Use Behavior	0,771 13,205 /<0,001	0,849 15,752/<0,001	0,612
Value of Information	0,775 11,433/<0,001	0,832 22,521/<0,001	0,41
Role of Patient	0,750 10,607/<0,001	0,857 15,303/<0,001	
Role of Prevention	0,698 7,021/<0,001	0,704 7,002/<0,001	

Note: t — t-test value, p — level of statistical significance

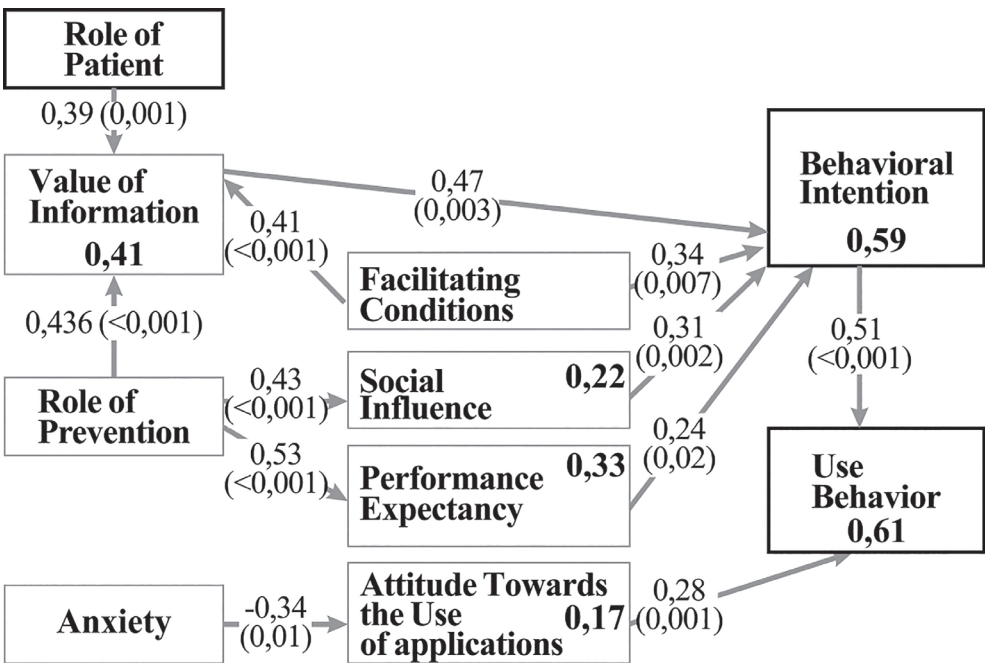

Figure 3. *Structural model of patients' attitudes towards the use of medical applications for the prevention, treatment and prevention of exacerbations (recurrences) of CVD*

Note: inside the rectangles is the coefficient of determination — adjR2, the arrows indicate the path coefficients β and the p values in parentheses

H2 (a): Construct "Expected performance" directly correlated with the intent to use medical applications (β = 0.24, p = 0.02), but not with their use.

H3 (a): Construct "Social significance" directly correlated with construct "Intent to use applications" (β = 0.31, p = 0.002), but not with the use of medical applications.

H4 (a, b): Construct "Facilitating conditions" directly correlated with construct "Intent to use applications" (β = 0.34, p = 0.007), but not with the use of medical applications.

H5 (b): Construct "Attitude to the use of applications" directly correlated with construct "Use of applications" (β = 0.28, p = 0.001), but not with construct "Intent to use applications".

H7 (a): Significance of professional medical information directly correlates with construct "Intent to use applications" (β = 0.47, p = 0.003), but not with the use of medical applications.

H9 (a): Understanding the patient's role in health support directly correlates with construct "Significance of information", i.e. with the understanding of the need in availability of professional medical information (β = 0.44, p < 0.001), but not with construct "Role of prevention".

Construct "Role of prevention" is cot directly associated with "Intent to use applications" and "Use of technologies". At the same time, construct "Role of prevention" directly correlates with construct "Intent to use applications" via construct "Significance of information" (β = 0.30, p < 0.001), "Social significance" (β = 0.29, p = 0.02) and "Expected performance" (β = 0.19, p = 0.03).

"Anxiety" was inversely associated only with "Attitude to the use of applications" (β = -0.34, p = 0.01) and, via it, with "Use of medical applications" (β = -0.12, p = 0.03).

All mentioned constructs had statistically significant indirect impact on "Use of technologies" via "Intent to use applications".

Discussion of Results

Results demonstrated that, on the one hand, the use of medical applications is impacted by construct "Intent to use applications" and, on the other hand, by construct "Attitude to the use of applications", i.e. the extent, to which the user is generally willing to use such information technologies and considers them essential for prevention and therapy of cardiovascular diseases.

Predictably, "Expected performance", i.e. the benefit of using mHealth, greatly impacted the intent to use the application. Expected performance can be a factor, which is more important for acceptance and rejection of mHealth, as in case of chatbots in healthcare [28]. Also, our data confirm the UTAUT theory, suggesting that a significant factor of intention to use or the actual use of applications is "Facilitating conditions". Acceptance and introduction of IT in healthcare is more likely, when patients have required resources and support [28].

For the implementation of the mHealth technologies, it is essential to take into account that one of the most important factors of the wide-scale implementation of information and communication technologies is anxiety associated with their use. It is assumed that a lot of people are still anxious when pushed to use computer technologies [29]. In this model, anxiety during the use of applications (construct "Anxiety") had negative indirect and minor impact on the use of medical applications via "Attitude to the use of applications". These results do not contradict other studies; moreover, they correspond to the statement that the attitude to acceptance of applications fully mediates the negative correlation between user's anxiety and the attitude to the use [30]. At the same time, it has been demonstrated that anxiety has negative impact on perceived usefulness and perceived easy to use, therefore, it can reduce in the interest in the use of IT [31]. It is highly likely that implementation of mHealth will require special measures to eliminate fear to use applications, so that patients have positive attitude to these technologies and willingness to explore them.

"Social significance" of information and communication technologies is also essential to ensure their acceptance. That is why wide use of medical applications will require proof of their social significance. It is assumed that these correlations can be impacted by the social and economic status of the population [32], which should be taken into account during development and promotion of applications. To form a favourable attitude to mobile healthcare, it is advisable to efficiently use influencers' opinion in order to eliminate obstacles in the use of applications; these should be close people and healthcare providers rather than famous persons.

The readiness of patients with cardiovascular disorders to use medical applications is impacted by availability of professional information on the measures to prevent CVD, the role of the diet and physical exercises in CVD development (construct "Significance of information"). Such correlations are discussed in other studies [33], where respondents are happy about information and communication technologies, if they can see that technologies are able to provide necessary and reliable information. Users feel they can trust and are in control when they are sure that services provided by mobile

health applications are reliable and meet their expectations [20].

The number one priority in the development of this structural model was to study respondents' opinion about the role of the patient in preservation of their own health and the role of prevention, which is one of the most pressing problems in healthcare. Surprisingly, constructs "Role of prevention" and "Patient's role" had only direct correlations with the intent to use applications via constructs "Significance of information" and "Facilitating conditions". The results show that the understanding of the role of prevention leads not only to the intent to use medical applications, but, what is most important, to understanding of the significance of professional medical information.

Of note, among the participating patients with cardiovascular diseases, there were no patients who fully denied the patient's role. It might have been associated with the fact that patients gave socially desired answers. However, on the plus side, patients with cardiovascular diseases think that this idea is correct, and they need some help in putting this idea into action. Results showed that the patients' understanding that successful prevention and management of cardiovascular diseases is impossible without their active involvement ensures acceptance of medical information. It means that patients need quality professional information, which should be provided to them. It can be one of the significant factors to attract patients to mobile healthcare. This idea is indirectly supported by studies, where the knowledge of health, health support and attitude to health were directly associated with intents to use innovative IT [34, 35]. On the other hand, such correlations are not always relevant. For example, Yang M. et al. (2024) [21] published data, where, according to the authors, specific behaviour of the Indonesians was responsible for a minor correlation between the intent to use m-Health and constructs "Conscious health" and "Motivation of health", i.e. readiness to take responsibility and undertake actions, which are beneficial for the health, or their motivation to engage into activities to facilitate good health.

Also, an important factor is that understanding of the role of cardiovascular disease prevention (indirectly) impacts the intent to use medical devices. It is clear that efficient measures to prevent cardiovascular recurrences are impossible without introduction of relevant IT (user applications); for example, to boost compliance of cardiovascular patients [13, 15]. Lack of full-scale comprehensive use of information and communication technologies in healthcare is inefficient not only medically, but also economically, because non-use of technologies results in low efficiency of healthcare [1].

Conclusions

Analysis of the structural model UTAUT of the use of mobile healthcare by patients with CVD allows making a number of general conclusions. CVD patients realise the significance of their personal involvement in preservation of their health and are ready to use mobile healthcare to prevent the disease and form habits focused on minimisation of the modifiable risk factors of CVD. One of the obstacles for the introduction of mHealth can be that patients fear to use medical applications on their own. Also, acceptance of mobile healthcare solutions by CVD patients for more efficient therapy will be possible if there are required technical conditions and social support, forming a trusted, clear and attractive image of mHealth. Therefore, some patients may require special training sessions to be able to use mobile applications.

An important task of the healthcare system is involvement of all populations in technological information processes. The practical value of this study is to study the factors impacting decisions to use applications and take an active part in support of own health, bringing about economic benefits for the society. On the other hand, the UTAUT model was updated with new healthcare-related constructs, which were tested for the significance for patient integration in the processes of CVD prevention and therapy using medical information technologies.

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Zagulova D.: research concept, questionnaire development, collection of material, analysis of material, statistical processing, construction and analysis of the model, approval of the final version of the article;

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QUESTIONNAIRE

The questionnaire consists of three parts:
Three variants of answers on the 5-point Likert-type scale and modified 5-point Likert-type scale were used to evaluate the statements in parts 2 and 3 of the questionnaire [Golubkov EP, 1998; Sandakov YaP et al., 2019].

Part 1. Personal information (age, sex, education), experience in the use of any mobile applications and CVD status of the respondent.

1. Choose your sex:
   - ☐ Male
   - ☐ Female
2. Choose your age group:
   - ☐ Below 35 years old
   - ☐ 35–55 years old
   - ☐ Over 55 years old.
3. Choose your education
   - ☐ Primary
   - ☐ Secondary
   - ☐ Vocational training
   - ☐ Incomplete higher
   - ☐ Higher
4. Have you had any EXPERIENCE IN USING any mobile applications to track your health? These are applications used to track your physical exercises, health status, calorie intake; they can remind you to take medications or drink water; you can use them to record blood pressure, blood glucose, etc. (e. g. Apple Health, Wellory, FatSecret, MyTherapy, Tide, Water Meter, Daylio, etc.):
   - ☐ Yes
   - ☐ No
5. Do you have any diagnosed cardiovascular disease? If yes, please specify:
   - ☐ _____

Part 2: Questions about the main constructs of the UTAUT model

1. Construct **"Use of applications"**:

1) I use a medical application **to track my health status**:
- ☐ Almost always
- ☐ Often
- ☐ Sometimes
- ☐ Rare
- ☐ Never

2) In my daily life, I use **information on the Internet** to support my health:
- ☐ Almost always
- ☐ Often
- ☐ Sometimes
- ☐ Rare
- ☐ Never

3) I use mobile applications **to record my physical activity**:
- ☐ Almost always
- ☐ Often
- ☐ Sometimes
- ☐ Rare
- ☐ Never

2. Construct **"Intent to use applications" (medical applications)**:

4) I am planning to use medical applications in the future:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

5) **I will be** using medical applications **to monitor my health status** more regularly in the future:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

6) In the future, **I will be using** medical applications **for prevention and therapy:**
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

3. Construct **"Expected performance"**:

7) I think that medical applications can **be beneficial** in my daily life:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

8) Using medical applications will **benefit my health**:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

9) Medical applications will ensure **more efficient preventive healthcare** more me:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

4. Construct **"Social significance"**

10) The public should use mobile health functionality as much as possible:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

11) Medical applications are essential for the social role in health support:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

12) Efficient cooperation with medical organisations is impossible without special web-based applications:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

5. Construct **"Facilitating conditions"**:

13) I have technical resources to use mobile applications:
- ☐ Completely wrong
- ☐ Partially wrong
- ☐ Neither true nor wrong
- ☐ Partially true
- ☐ Completely true

14) I have knowledge required for the use of mobile applications:
- ☐ Completely wrong
- ☐ Partially wrong
- ☐ Neither true nor wrong
- ☐ Partially true
- ☐ Completely true

15) I have sufficient knowledge to efficiently use mobile applications:
- ☐ Completely wrong
- ☐ Partially wrong
- ☐ Neither true nor wrong
- ☐ Partially true
- ☐ Completely true

16) I have someone to support me if I have questions about the use of mobile applications:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

6. Construct **"Attitude to the use of applications"**:

17) I would not like that mobile health applications stopped working:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

18) Mobile health applications make life more interesting:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

19) Mobile applications for prevention and therapy are essential for the public:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

20) I like exploring new mobile applications:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

7. Construct **"Anxiety"**:

21) There are mobile applications I don't dare to use (due to various reasons):
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

22) I fear that I can lose a lot of information if I do something wrong while using some applications:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

23) I don't dare to use some mobile applications because of the fear to make irreversible mistakes:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

24) I'm a bit afraid of any applications:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

Part 3. Three questions related to constructs of the study area: "Patient's role", "Role of prevention", and "Significance of information".

8. Construct **"Patient's role"**:

25) Patients themselves have an important role to play in development of cardiovascular diseases:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

26) Doctors should strive to **engage patients in prevention and therapy** of cardiovascular diseases:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

27) Each and every one should possess **knowledge on measures to prevent** cardiovascular diseases and support cardiovascular health:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

28) Successful prevention and therapy of cardiovascular diseases are impossible without **active engagement of patients** in medical decision-making:
- ☐ Completely agree
- ☐ Partially agree
- ☐ Neither agree nor disagree
- ☐ Partially disagree
- ☐ Completely disagree

9. Construct **"Role of prevention"**:

29) Each person **needs prevention** of cardiovascular diseases:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

30) It is essential that everyone avoids any factor, which causes cardiovascular diseases:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

31) A damaged heart cannot be repaired:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

32) Heart diseases are mostly associated with the person's lifestyle:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

33) **The lifestyle** should promote prevention of cardiovascular diseases:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

34) **Cholesterol levels should be monitored** in order to prevent cardiovascular diseases:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

35) Diabetes prevention reduces the risk of heart conditions:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

36) Smoking increases the risk of cardiovascular diseases:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

10. Construct **"Significance of information"**:

37) **Medical literacy** is **essential for prevention** of cardiovascular diseases:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

38) It is essential to ensure high availability of reliable professional **information on prevention of** cardiovascular diseases:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

39) It is essential to ensure availability of reliable professional **information on the role of diet** in the development of cardiovascular diseases:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

40) It is essential to ensure availability of reliable professional **information on the role of physical exercises** in prevention of cardiovascular diseases and prevention of relapses:
- ☐ Completely true
- ☐ Partially true
- ☐ Neither true nor wrong
- ☐ Partially wrong
- ☐ Completely wrong

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СТАТУС ВИТАМИНА D У ЖИТЕЛЕЙ РОССИЙСКОЙ ФЕДЕРАЦИИ, ЕГО ВОЗРАСТНЫЕ ОСОБЕННОСТИ И ВЗАИМОСВЯЗЬ С УРОВНЕМ ПАРАТИРЕОИДНОГО ГОРМОНА

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Vitamin D Status Among Residents of the Russian Federation and Its Relation with Age and Parathyroid Hormone

Резюме

Цель: оценить статус витамина D (25(OH)D) в различных регионах Российской Федерации (РФ), а также установить взаимосвязь между уровнем 25(OH)D, возрастом и уровнем паратиреоидного гормона (ПТГ). **Материалы и методы:** оценка статуса витамина D проводилась у жителей различных регионов РФ (Северно-Западного федерального округа (СЗФО), Центрального (ЦФО), Южного (ЮФО) и Дальневосточного (ДФО)) в период с 2012 по 2017 г. Всего в кросс-секционном исследовании проанализировано 115694 анонимных образцов, предоставленных независимой коммерческой лабораторией. Для определения уровня 25(OH)D использовался хемилюминесцентный иммуноанализ. **Результаты:** Выявлена повсеместная распространенность низких уровней 25(OH)D: дефицит (<20 нг/мл) — 33,16 %, недостаточность (≥20 и <30 нг/мл)- 37,11 %, которая значительно не отличалась в зависимости от региона проживания (ЮФО (76,3 %), ЦФО (69,2 %), СЗФО (67 %) и ДФО (63 %), p>0,05). В летние месяцы медиана уровня витамина D оказалась выше, чем в зимние (25,3 нг/мл [18,3; 33,5] vs 24 нг/мл [16,7; 32,5], p=0,006). Уровень 25(OH)D<30 нг/мл чаще всего встречался у участников младше 20 лет и старше 80 лет (75 % и 81 %, соответственно). Также в группе младше 20 лет количество участников с целевыми уровнями витамина D (>30 нг/мл) оказалось низким, что было сопоставимо с группой старше 80 лет (22,6 % и 18 %, соответственно, p=0,1). Подтверждена отрицательная обратная связь между уровнями витамина D и ПТГ (r=-0,11, p=0,002). Выявлена слабая положительная корреляция между возрастом участников и уровнями ПТГ (r=0,18, p=0,000). **Заключение:** Полученные данные свидетельствуют о широкой распространенности низких уровней 25(OH)D среди всех возрастных групп в РФ. Выявлены статистически значимые различия в статусе витамина D в зависимости от возраста и времени года. При этом географические факторы не оказали значимого влияния на уровни 25(OH)D. Отмечена высокая распространенность выраженного дефицита витамина D у лиц младше 20 лет и старше 80 лет. Установлена слабая положительная корреляция между возрастом и уровнем ПТГ, что вместе с высокой частотой низких концентраций витамина D в старшей возрастной группе, требует адекватной своевременной коррекции данного состояния и дальнейшего динамического наблюдения, с целью предотвращения потенциальных негативных влияний дефицита витамина D на костную ткань.

Ключевые слова: *витамин D, паратиреоидный гормон, статус витамина D, дефицит витамина D, распространенность, возраст*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Исследование представляет собой анализ анонимных образцов, которые были предоставлены добровольно без какой-либо идентифицирующей информации лицом, не принимающим никакого участия в этой работе. Основные положения Хельсинской декларации нарушены не были. В рамках данного исследования медицинское вмешательство участникам не проводилось, и участие не несло никаких потенциальных рисков, поэтому работа не считается исследованием на человеке и не требует заключения этического комитета.

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Для цитирования: Мармалюк Д.А., Рунова Г.Е., Глинкина И.В. и др. СТАТУС ВИТАМИНА D У ЖИТЕЛЕЙ РОССИЙСКОЙ ФЕДЕРАЦИИ, ЕГО ВОЗРАСТНЫЕ ОСОБЕННОСТИ И ВЗАИМОСВЯЗЬ С УРОВНЕМ ПАРАТИРЕОИДНОГО ГОРМОНА. Архивъ внутренней медицины. 2024; 14(4): 276-283. DOI: 10.20514/2226-6704-2024-14-4-276-283. EDN: ULGLRC

Abstract

Objective: to study the vitamin D (25(OH)D) status in various regions of the Russian Federation (RF), and to determine the relation between age, levels of 25(OH)D and parathyroid hormone (PTH). **Methods:** The vitamin D status was investigated in residents of various regions of the Russian Federation (Northwestern Federal District, Central Federal District, Southern Federal District and Far Eastern Federal District) between 2012 and 2017. In this cross-sectional study 115694 anonymous samples were analyzed. All samples were provided by an independent commercial laboratory. Serum levels of vitamin D (25(OH)D) were measured using chemiluminescent assay. **Results**: The prevalence of low levels of 25(OH)D was widespread in the Russian Federation: deficiency (<20 ng/ml) — 33,16 %, insufficiency (≥20 and <30 ng/ml) — 37,11 %, which did not significantly differ between various regions (Southern Federal District (76,3 %), Central Federal District (69,2 %), Northwestern Federal District (67 %) and Far Eastern Federal District (63 %), p>0,05). The median level of vitamin D was higher in the summertime than in the winter months (25,3 ng/ml [18,3; 33,5] vs 24 ng/ml [16,7; 32,5], p=0,006). Levels of 25(OH)D<30 ng/ml were most common in the age group younger than 20 years and in the age group older than 80 years (75 % and 81 %, respectively). Also in the age group younger than 20, the number of participants with vitamin D levels in target range (>30 ng/ml) was low, which was comparable to the age group over 80 years (22,6 % and 18 %, respectively, p=0,1). A negative inverse correlation between vitamin D and PTH levels was confirmed (r=-0,11, p=0,002). There was a weak positive correlation between the age of participants and PTH levels (r=0,18, p=0,000). **Conclusion:** The obtained data indicate the high prevalence of 25(OH)D deficiency among all age groups in the Russian Federation. Vitamin D levels were statistically differed depending on age and season. Geographic factors did not have a significant impact on vitamin D status in different regions of the Russian Federation. The highest prevalence of severe D deficiency was observed in age group younger 20 years and over 80 years. A weak positive correlation was established between age and PTH levels. Consideringthe high frequency of low vitamin D concentrations in the elderly age group, this condition rerequires adequate correction and further follow-up in order to prevent the negative effects of vitamin D deficiency on bones.

Key words: *vitamin D, parathyroid hormone, vitamin D status, vitamin D deficiency, prevalence, age*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The study is an analysis of anonymous samples that were provided voluntarily without any identifying information by a person not involved in any way with this work. The main provisions of the Helsinki Declaration were not violated. There were no medical interventions performed on participants in this study, and there were no potential risks associated with participation, so the work is not considered human research and does not require an ethics review

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FEFD — Far Eastern Federal District, PTH — parathyroid hormone, RF — Russian Federation, NWFD — North-Western Federal District, CFD — Central Federal District, SFD — Southern Federal District

Relevance

Low vitamin D concentrations are observed in the populations all over the world [1]. The precursor of the active vitamin D (25-hydroxyvitamin D, 25(OH) D) is synthesised in the liver induced by enzymes CYP2R1 and CYP27A1 from vitamin D3, which forms in the skin exposed to UV radiation, and can also enter the body with food. Exposure to the sun, which directly impacts the synthesis of endogenous vitamin D, depends on the geographical latitude and climate in the place of residence. In the regions lying above 40° of the north latitude, exposure to the sun in winter is inadequate for the body to have a sufficient amount of vitamin D [2]. Therefore, a major part of the population in the Northern Hemisphere is at risk of vitamin D deficiency. Data of epidemiological studies confirm that fact: the incidence of vitamin D deficiency (25(OH)D < 20 ng/mL) in Europe varies from 30 % to 60 % [3].

In addition to geographical factors, vitamin D status can be impacted by lifestyle, skin colour, clothes, less time spent in the sun, and a wide use of sunscreens [4]. In the Middle East, vitamin D deficiency can be as high as 90 %, despite a lot of sun during the year, because of their lifestyle [5].

Without timely correction of low vitamin D concentrations, levels of parathyroid hormone (PTH) rise to compensate the deficit, causing more intense bone resorption [6]. Also, severe vitamin D deficiency usually has direct negative impact on bones, impairing calcium phosphate deposition in new bone tissue and causing

osteoid mineralisation defects. All these factors can compromise the quality of the bone tissue and increase the risk of fractures, especially in elderly [7].

The Russian Federation (RF) is located between 77° and 41° of northern latitude; the climate, number of sunny days in a year and UV index differ. In addition to climatic factors, regions of Russia differ in culture and traditions of their populations. Therefore, vitamin D status of the RF citizens can vary depending on the region. Due to geographic factors, a major part of the population in Russia is at risk of vitamin D deficiency, this fact being confirmed by study results. For example, in a study by P. Lips et al. (2019), vitamin D deficiency was observed in 39.7 % of samples, while low vitamin D levels were diagnosed in 36.5 % [3]. A study by E.A. Pigarova et al. (2020) also demonstrated a high incidence of low vitamin D concentrations in Russia: 84.3 % of subjects had 25(OH)D < 30 ng/mL [8].

Since the vitamin D status depends on geographic and demographic factors, as well as quality of life, dynamic monitoring of vitamin D levels in various regions of Russia is required to prevent its deficiency and potentially negative impact of low levels of 25(OH)D on the bone tissue.

The objective of this study was to evaluate the extent of vitamin D deficiency and insufficiency among the population of the Russian Federation depending on geographic factors and age, as well as to analyse the correlation between 25(OH)D levels, PTH values and age.

Materials and Methods

The study enrolled 115,694 anonymous samples provided by the independent laboratory INVITRO. The samples were collected over the period from 2012 to 2017 in the regions of Russia located between 43° and 59° of northern latitude: central region (CFD) — 61,772 (53.4 %) participants; north-western region (NWFD) — 10,003 (8.7 %) participants, southern region (SFD) — 18,288 (15.8 %) participants, and Far Eastern region (FEFD) — 25,631 (22.1 %) participants. The study included specimens from patients aged 18 and above years old (the median age was 45 [33; 58] years old): the under 20 years old group included 5,553 (4.8 %) people; 20–39 years old — 39,105 (33.8 %) people; 49–59 years old — 44,658 (38.6 %) people; 60–79 years old — 24,411 (21.1 %) people; and over 80 years old — 1,967 (1.7 %) people. This study did not require any inclusion/exclusion criteria to be met.

Serum 25(OH)D levels were measured by a chemilumescent analysis (Architect 8000, Abbot, USA). The results were evaluated in accordance with the clinical guidelines for the diagnosis, management and prevention of vitamin D deficiency in adults (2016), where an adequate 25(OH)D level was 30–60 ng/mL, 25(OH)D of less than 20 ng/mL is deficiency, while 25(OH)D levels of 20–30 ng/mL is vitamin D insufficiency [9]. In addition to vitamin D levels, blood creatinine, calcium and PTH levels were measured (reference range: 1.6–6.9 pmol/L). The correlation between PTH and vitamin D levels was analysed only for samples, where calcium and creatinine levels were within the reference range (reference calcium values depending on the age: 12–60 years old — 2.1–2.55 mmol/L, 60–90 years old — 2.2–2.55 mmol/L; creatine: 50–98 μmol/L for women and 64–111 μmol/L for men).

Statistical Analysis

Statistical data processing was performed using STATISTICA6.0 package (StatSoftInc., 2001, USA). Data are presented as the median (Me) and quartiles [Q1;Q3]. Quantitative differences between two independent groups were identified using the Mann-Whitney test. The Kruskal-Wallis test was used to identify quantitative differences between three and more independent groups. Frequency differences in groups were evaluated using χ^2. The Spearman's test was used to evaluate the correlation. The level of statistical significance was 0.05.

Results

The median age of participants was 45 [33; 58] years old. The median 25(OH)D concentration for all samples was 23.9 ng/mL [17.0; 31.6]. Vitamin D insufficiency was observed in 42,934 (37.11 %) samples. Vitamin D deficiency (< 20 ng/mL) was diagnosed in 38,364 (33.16 %) participants, including 4,211 (3.6 %) cases of severe deficit. Thus, 70 % of participants had 25(OH)D levels below 30 ng/mL. Target vitamin D levels (30–60 ng/mL) were recorded only in 31,237 (27 %) of participants (Fig. 1).

Given varying daylight duration and number of sunny days in a year, vitamin D status has been evaluated for different federal districts of Russia (Fig. 2). Vitamin D

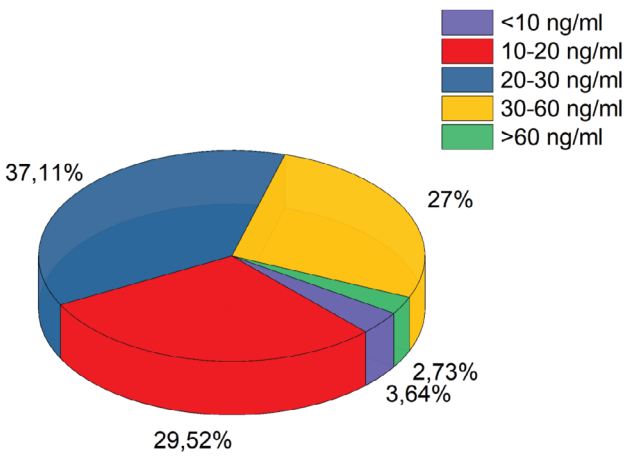

Figure 1. *Vitamin D status from 2012 to 2017 in Russian Federation*

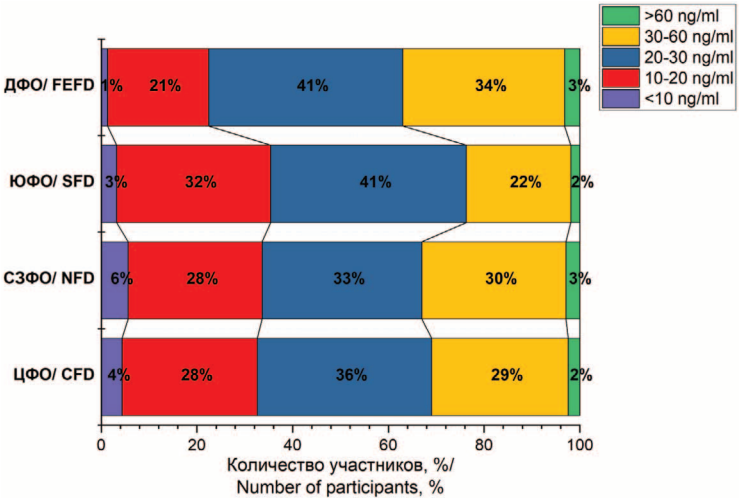

Figure 2. *Vitamin D status among residents of different regions of Russian Federation*

Note. CFD — Central Federal District, NFD — Northwestern Federal District, SFD — Southern Federal District, FEFD — Far Eastern Federal District

deficiency and insufficiency are a common condition among the citizens of Russia, irrespective of a region of their residence: CFD — 33 % and 36.2 %, NWFD — 33.6 % and 33.4 %, SFD — 35.4 % and 40.9 %. There were no significant differences in the number of participants with adequate vitamin D levels in the CFD, NWFD, SFD and FEFD ($p > 0.05$).

The incidence of severe vitamin D deficiency (< 10 ng/mL) was higher in the NWFD — 5.6 % ($p < 0.05$ for all) vs. other federal districts of Russia.

Low vitamin D levels were usually observed during winter. 35 % of samples collected during winter had vitamin D deficiency; it is higher than during summer (30 %) ($p = 0.006$). The data for the CFD demonstrated this trend: in winter, the median vitamin D levels were lower and made 24 ng/mL [16.7; 32.5], while in summer, they were 25.3 ng/mL [18.3; 33.5] ($p = 0.006$). Of note, in the NWFD this trend was not observed: vitamin D levels were similar in winter (24.5 ng/mL [17.2; 33.0]) and summer (26 ng/mL [18.5; 33.9]), $p = 0.244$ (Fig. 3).

The 25(OH)D status was analysed in various age groups (Fig. 4). It has been shown that vitamin D deficiency and severe vitamin D deficiency were most common in participants under 20 years of age — 42 % and 7.7 % vs. other age groups: 20–39 years of age (31.5 % and 3.9 %) and 40–59 years of age (32 % and 3.7 %), $p = 0.000$ for all. At the same time, the number of participants with the target vitamin D levels in the group of under 20 years old was also low and comparable with the group of over 80 years of age (22.6 % and 18 %, respectively, $p = 0.1$). Vitamin D concentrations below 30 ng/mL were predictably common in patients over 80 years old (79 %). Adequate 25(OH)D concentrations were observed in 29.1 % of participants in the age group 20–39 years old, which is statistically higher than in all other age groups ($p = 0.000$ for all).

PTH levels at various vitamin D concentrations were evaluated. At the vitamin D level of below 30 ng/mL, the median PTH value was 5.1 pmol/L [3.9; 6.6], while at the target vitamin D value, the median PTH was 4.7 pmol/L [3.7;6.1], which is statistically lower ($p = 0.002$) (Fig. 5).

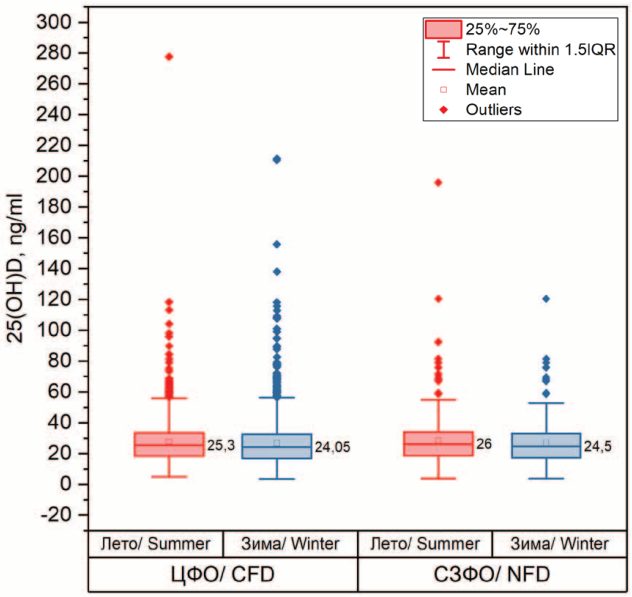

Figure 3. *Vitamin D levels during summertime and winter in the Central and Northwestern regions*

Note. 25(OH)D — vitamin D, NFD — Northwestern Federal District, CFD — Central Federal District

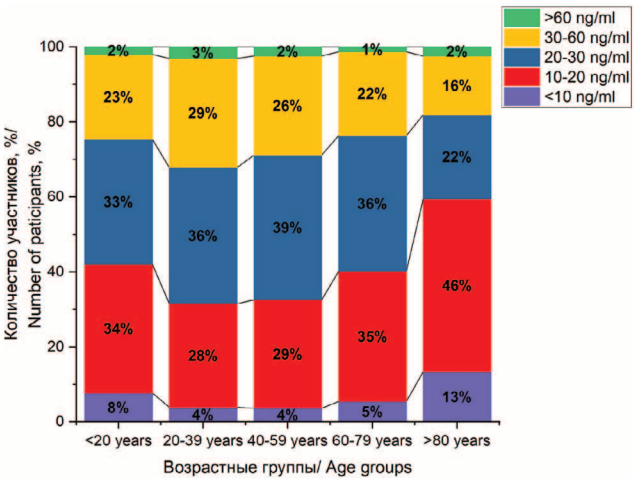

Figure 4. *Vitamin D levels in different age groups*

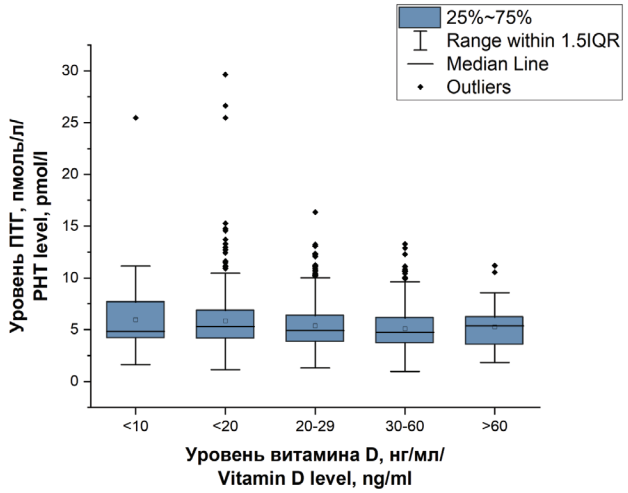

Figure 5. *The relation between PTH and vitamin D levels*

Note. PTH — parathyroid hormone, <10 ng/ml — severy vitamin D deficiency, <20 ng/ml — vitamin D defiency, 20-29 ng/ml — vitamin D insufficiency, 30-60 ng/ml — optimal levels, >60 ng/ml — above target range

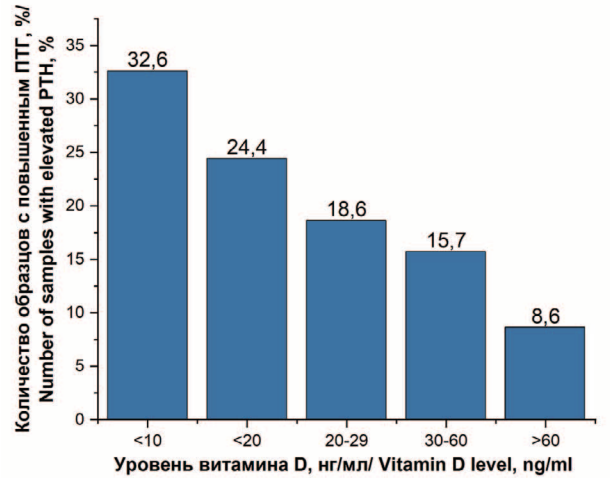

Figure 6. *The number of samples with eveleted PTH levels depending on vitamin D levels*

Note. PTH — parathyroid hormone, <10 ng/ml — severy vitamin D deficiency, <20 ng/ml — vitamin D defiency, 20-29 ng/ml — vitamin D insufficiency, 30-60 ng/ml — optimal levels, >60 ng/ml — above target range

Among samples with the vitamin D levels of 30–60 ng/mL, higher PTH levels (reference range used in the laboratory: 1.6–6.9 pmol/L) were observed in 15.7 % of samples, whereas with the severe vitamin D deficiency — in 32.6 %; where the 25(OH)D concentration was below 20 ng/mL — in 24.4 % and only in 8.6 % of participants — at the vitamin D levels of above 60 ng/mL (p = 0.000 for all) (Fig. 6).

A weak negative reverse correlation between the vitamin D level and PTH (r = -0.11, p = 0.002) was confirmed. A weak direct correlation between the age and PTH levels (r = 0.18, p = 0.000) was observed. There was no correlation between the age and the vitamin D level (r = -0.015, p > 0.05).

Samples with the vitamin D level of 30–60 ng/mL and PTH exceeding the upper reference limit were analysed separately. The median age in the high PTH group was 64 years old [56;70], whereas in the group with the target PTH group, it was 56 years old [47;63], (p = 0.000).

Discussion

This study analysed the 25(OH)D status of 115,694 samples from various regions of Russia, and this number is higher than in any similar study in the Russian Federation. Vitamin D insufficiency was recorded in 37.11 % of samples, while deficiency was observed in 33.16 %. Only 27 % of participants had the 25(OH)D level of over 30 ng/mL. The data confirm the high incidence of low vitamin D levels in Russia, which corresponds to other Russian studies [8, 10-14]. A study by Smirnova D. et al. (2022) in 30,040 participants showed that in 2013–2018 the vitamin D deficiency rates were 39.7 %, while the target 25(OH)D levels (> 30 ng/mL) were recorded only in 23.8 % of participants [10].

More strict inclusion criteria can affect the results. E.g. [8] evaluating in 2020 the 25(OH)D status of 500 volunteers living in the regions of Russia located between 45° and 70° north longitude showed that the mean vitamin D level was 20.9 ng/mL. Vitamin D deficiency was observed in 56.4 % of participants, while insufficiency was recorded in 27.9 %. However, in this study we did not have information on any vitamin D preparations taken, comorbidities and reasons to test 25(OH)D levels. At the same time, Pigarova E.A. et al. (2020) did not include participants taking vitamin D preparations, and that could have caused lower 25(OH)D values [8].

An evaluation of the 25(OH)D status of people residing in various regions of Russia showed a high incidence of vitamin D deficiency and insufficiency, even in the areas with a larger number of sunny days and warmer climate. For instance, in the SFD, the adequate vitamin D level was observed only in 21.8 % of samples, while deficiency and insufficiency were observed in 76.3 %. A high incidence of low 25(OH)D levels was also observed in other southern regions of the Russian Federation. In 2013–2015, vitamin D deficiency and insufficiency were recorded in 82 % of the citizens of Rostov-on-Don [11]. In their article Pigarova E.A. et al. [8] describe that the 25(OH)D level below 30 ng/mL among the population of the same region was recorded even in a larger number of cases (92.86 %), while the target vitamin D levels were observed only in 7.14 %.

The incidence of vitamin D deficiency in Moscow (55° north latitude) was 32 %, in Saint-Petersburg (59° north latitude) — 34 %, which was higher than in other countries in the same geographical region. For instance, in Sweden (58° north latitude), 25(OH)D levels of below 20 ng/mL were recorded in 17 % of the population [15]

and in Denmark (56° north latitude) — in 23.6 % [16]. These differences in the incidence of low vitamin D concentrations can be associated with differences in the diet. In Russia, food is usually not supplemented with vitamin D, and people eat little fatty fish [17], while in the Nordic countries, food supplementation with vitamin D is a common practice, and the populations in these countries each more fish and seafood [18].

In this article, the geographical distribution is not the major factor impacting the differences in the vitamin D status. At the same time, in a study by Smirnova D.V. et al. (2022) [10], an analysis of the correlation between mean vitamin D values and the latitude revealed a non-linear dependence. In women, the highest 25(OH)D concentrations were observed in mid-latitudes, while the lowest concentrations were recorded in southern and northern regions. In men, the vitamin D concentrations were roughly at the same level (25 ng/mL) in southern and mid-latitudes, with a sharp drop in values in regions located to the north of latitude 69°.

Elderly people are especially susceptible to vitamin D deficiency because of the reduced time spent under the sun, reduced synthetic function of the skin and reduced glomerular filtration rate [19]. As expected, vitamin D deficiency (81 %) and severe vitamin D deficiency (18 %) were recorded in subjects over 60 years of age. In another Russian study analysing the vitamin D status in the Irkutsk Region, the mean vitamin D level in the group of people over 70 years of age was lower than in people of other ages and made 15.13 ± 2.24 ng/mL [13]. In elderly people, low vitamin D levels often cause phosphoric-calcium exchange impairments, as well as contribute to sarcopenia. Sarcopenia in patients is associated with senile asthenia, an increased risk of falls, fractures, thus reducing the quality and length of life. In 2022, in Russia over 33 million of people were people aged 60 and over years old [20]; and this study shows that a majority of them have vitamin D deficiency. This condition requires adequate and timely correction in order to prevent possible negative impact by vitamin D deficiency.

High rates of vitamin D deficiency and severe vitamin D deficiency in people under 20 years of age is of particular interest. In a study by Pigarova E.A. et al. (2020), an analysis of the vitamin D status in 18–50 years olds showed a similar pattern: vitamin D deficiency was observed in 72.2 % of samples collected from people aged 18–25 years old, i.e. higher than in other age groups [8]. It can be assumed that this pattern is a result of a higher demand in vitamin D in this age group. According to Rosstat data for 2022, there are 7 million people aged 15–19 years old [20]. This study shows that vitamin D deficiency is recorded in 42 % of people under 20 years old, i.e. in approximately 3 million young people. Bone mass acquisition starts in childhood and adolescence and peaks at the age of 20–30 years old; therefore, correction of vitamin D deficiency in this age group is crucial for the prevention of poorer bone tissue quality and age-related fractures.

This study confirmed the impact of the sunlight on vitamin D concentrations. 25(OH)D levels were statistically higher during summer than during winter.

Given that a number of articles [21, 22] discuss the significance of vitamin D status accounting when setting reference PTH range, this study evaluated the association between PTH levels and various 25(OH)D values.

Median PTH at the target vitamin D levels was lower than at 25(OH)D < 30 ng/mL. However, the median PTH value at severe vitamin D deficiency was comparable with median PTH at vitamin D levels of 30–60 ng/mL, which can be a result of a small sample size selected for analysis.

The age can also impact the association between PTH and vitamin D levels [23, 24], that is why age-related changes in PTH and 25(OH)D levels were analysed. A weak negative reverse correlation between PTH and vitamin D levels was confirmed. A weak direct correlation between the age and PTH levels was observed. Also for the samples with the target sufficient vitamin D levels, but with higher PTH concentrations, participants were older than for the samples with target PTH and 25(OH) D values. Y. Jiang et al. (2020) demonstrated that, with ageing, parathyroid glands express less vitamin D receptor, 1-alfa-hydroxylase(CYP27B1) and 24-hydroxylase (CYP24A1), and it results in reduced synthesis of the active form of vitamin D ($1,25(OH)_2D$) and higher PTH levels in elderly people [25].

A high incidence of lower vitamin D levels not only in elderly, but also in young people (under 20 years of age) can signify a U-shape correlation between vitamin D levels and age of participants.

This is a large-scale cross-sectional study; however, there were a number of limitations: anthropometric information, including sex and body weight, was missing; comorbidities were unknown; there was no information on medications or biologically active supplements containing vitamin D, which could impact 25(OH)D concentration.

Conclusion

We analysed 115,694 samples collected in 2012–2017. The incidence of vitamin D insufficiency and deficiency was 37.11 % and 33.16 %, respectively. There are statistically significant differences in the vitamin D status depending on age and time of year. At the same time, geographic factors did not have any impact on vitamin D levels. A high incidence of vitamin D deficiency in participants under 20 years of age and over 80 years of age was observed. Since the bone mass is actively acquired up to 30 years of age, correction of 25(OH)D deficiency in young people is essential for normal bone mineralisation in order to prevent fractures. A weak direct correlation

between the age and PTH levels was established. Given the low vitamin D levels in elderly people and an increase in PTH levels with ageing, this group of patients needs adequate and timely correction of low vitamin D levels and follow-up.

Вклад авторов:

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Мармалюк Д.А.: анализ и интерпретация данных, написание статьи

Рунова Г.Е.: разработка концепции и идеи статьи, анализ и интерпретация данных, внесение правки с целью повышения научной ценности статьи

Глинкина И.В.: анализ содержания рукописи, проверка критически важного интеллектуального материала

Фадеев В.В.: разработка концепции, редактирование и окончательное утверждение рукописи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Marmalyuk D.A.: participation in data analysis, interpretation of results, writing of the manuscript

Runova G.E.: development of the concept and design of the study, data analysis, interpretation of results, verification of critical intellectual content

Glinkina I.V.: verification of critical intellectual content

Fadeyev V.V.: development of the concept of the study, final approval of the manuscript for publication

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РАЗРАБОТКА И ВАЛИДАЦИЯ ОПРОСНИКА ДЛЯ ОЦЕНКИ УРОВНЯ ПОТРЕБЛЕНИЯ СОЛИ У ВЗРОСЛОГО НАСЕЛЕНИЯ МОСКВЫ И МОСКОВСКОЙ ОБЛАСТИ ПРИ ПОМОЩИ МЕТОДОВ МАШИННОГО ОБУЧЕНИЯ

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Development and Validation of a Questionnaire to Assess the Level of Salt Intake in the Adult Population of the Russian Federation Using Machine Learning Methods

Резюме

Цель: разработать и валидировать инструмент для оценки уровня потребления соли у взрослого населения РФ. **Материал и методы.** Респонденты заполняли пищевые дневники, где учитывался тип приема пищи, ее объем и факт дополнительного досаливания блюда. Для статистической обработки полученных данных использовали язык R, версия — 4.2.1, среда разработки RStudio (пакеты ggplot2, ggpubr, dplyr, tidyverse, gtsummary, rstatix). **Результаты.** Всего в исследование был включен 271 респондент, медианный возраст которых составил 52 [20; 70] года. Было установлено, что основными факторами высокого потребления натрия является досаливание, потребление соленых продуктов, меньший уровень потребления кондитерских изделий, для низкого уровня потребления соли характерно более высокое потребление молочных продуктов. Тест согласованности Коэна составил $\kappa = 0{,}48$ 95 % ДИ (0,08; 0,08), значения альфы Кронбаха $\alpha = 0{,}8$. При пороговом значении ≥12 баллов по данным опросника, опросник имеет чувствительность 85 % по сравнению с медианной оценкой по данным 3-дневного пищевого дневника. При пороговом показателе <12 баллов опросник имеет специфичность 74 % с медианной оценкой по данным 3-дневного пищевого дневника. **Заключение:** Опросник СОЛЬ может быть использован для определения оценки уровня потребления соли.

Ключевые слова: *потребление соли, пищевой опросник, потребление натрия, машинное обучение*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Purpose: To develop and validate a tool to assess salt intake in the adult population of the Russian Federation. **Material and Methods:** Respondents filled out food diaries, where the type of food intake, its volume, and the fact of additional salting of the dish were taken into account. R language, version 4.2.1, RStudio development environment (packages ggplot2, ggpubr, dplyr, tidyverse, gtsummary, rstatix) were used for statistical processing of the obtained data. **Results:** A total of 271 respondents were included in the study, with a median age of 52 [20; 70] years. It was found that the main factors for high sodium intake were pre-salting, consumption of salty foods, lower intake in confectionery, low salt intake was characterized by higher consumption of dairy products. Cohen's consistency test was $\kappa = 0.48$ 95 % CI (0.08; 0.08), Cronbach's alpha values $\alpha = 0.8$. At a threshold score of ≥12 points on the questionnaire, the questionnaire had a sensitivity of 85 % compared with the median score from the 3-day food diary data. At a threshold score <12 points, the questionnaire has a specificity of 74 % compared with the median score from a 3-day food diary. **Conclusion:** The SOLE questionnaire can be used to determine the estimated level of salt intake by the population, but for wider application in the territory of the Russian Federation additional validation by regions is required.

Key words: *salt consumption, food questionnaire, sodium consumption, machine learning*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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Conformity with the principles of ethics

The study was approved by the local ethics committee of the State Budgetary Healthcare Institution «City Clinical Hospital No. 4 DZM» (Pavlovsk Hospital, protocol No. 44 of September 20, 2020). All participants signed the Informed Consent

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24hDR — 24-hour diet recall, CCF — chronic heart failure, XGBoost — eXtreme Gradient Boosting, BMI — body mass index, NHANES — National Health and Nutrition Examination Survey, RSA — Republic of South Africa

Introduction

Since the 1960s, attempts have been made to study dietary behaviours using diet questionnaires [1]. First questionnaires to study sodium intake were developed in the 1980s [2]. In 1982 Pietinen et al. developed a questionnaire to classify salt intake levels. The questionnaire consisted of five questions about salting and self-assessed salt consumption, as well as the frequency of eating the seven products containing the highest amounts of salt. The questionnaire was completed by 1,471 people aged 14 to 65 years old, who also underwent daily urinalysis in order to assess the amount of sodium in urine. The resulting data were used to develop a questionnaire called the Salt Index. The correlation between the 24-hour sodium extraction with urine and salt intake was weak: r = 0.18 in men and r = 0.20 in women ($p < 0.001$). This analysis used validation based on 24-hour urine collection, which for a long time was a golden standard for the study of sodium consumption. However, taking into account the recent data on the sodium exchange physiology [4], it is essential to understand that natriuresis is not constant and can change under the impact of a number of factors, for instance, differences in the respondent's diet during the week and on weekends [5]. Besides, sodium deposits can be released as a result of a long-lasting low-salt diet, as seen in study MARS520 [6].

Therefore, it is advisable to validate the questionnaire with the help of a diet diary. The study of sodium intake using the SALT questionnaire [8] is optimal, because it allows to take into account only one nutrient and variability in sodium consumption during several days.

Therefore, the purpose of our study was to develop and validate a tool for the assessment of salt intake by the adult population in Russia.

Materials and Methods

The first step was to develop a database of 7,641 products with the known salt content per 100 g of product. Data were sourced from guidelines edited by I. M. Skurikhin, Yu. B. Bulanov, E. V. Novikov [9–12], as well as the data on nutrients and sodium intake from open official sources provided by the manufacturers of products and fast food certified in Russia. Products were grouped by types into categories, which were used to compile a diet diary. The study design is presented in Figure 1. The diary recorded the meal type, extent and fact of additional salting of food. Extent of additional salting was based on 0.1 g of salt per one additional salting [13]. Products containing less than 50 mg of sodium per serving were excluded from analysis. The response rate took into account the intake during the last week and excluded two weekdays and one weekend [14], since the mean salt intake on weekends can increase by 8–14 % vs. weekdays [15]. Meals during festive periods were disregarded. Respondents completed their diaries strictly on a same day basis. During the observation and diary completion, all respondents did not adhere to any special or low-salt diets. Servings were measured by weighing

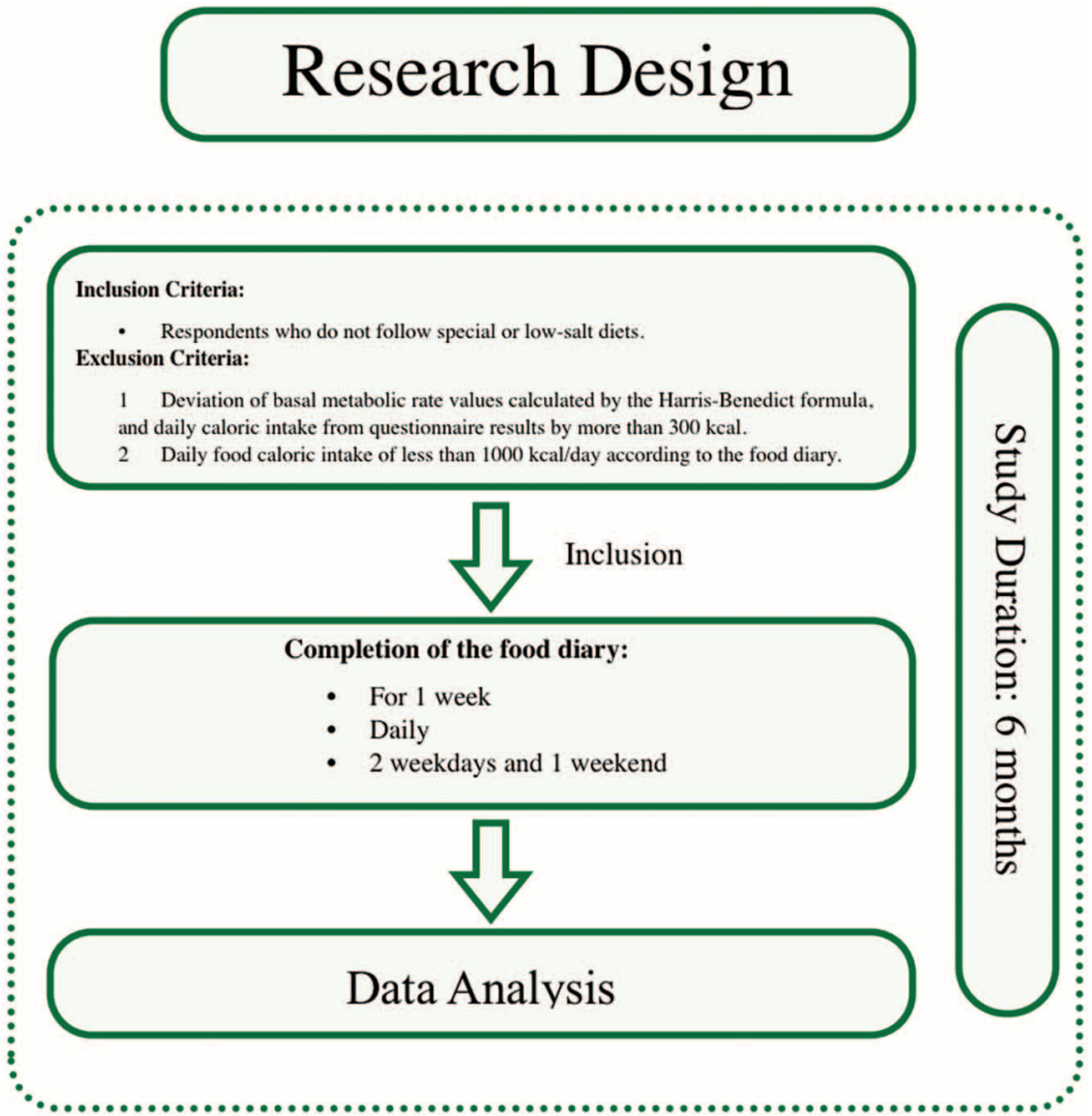

Figure 1. *Study Design*

the product or by package label (if any), or using an atlas of pictures of servings and food [14]. Subjects could were interviewed with the help of 24-hour diet recall, once per season. The data were collected using the weekday/weekend days ratio of 2 : 1 (patient follow-up/diary completion duration is not specified).

Development of the salt intake questionnaire

The purpose of the questionnaire was to have a tool to assess the median level of salt intake by respondents during the week. Therefore, immediately after questionnaire completion, the respondent was offered to complete a questionnaire of consumption of certain product groups or foods during the same period of time.

Products and foods were grouped by the content of sodium; the information on the content of salt was taken from the developed product and food database. All products were divided, taking into account categories and mean salt content in products and foods (e.g. Fish and seafood, etc.). All in all, there were 35 product categories.

Respondents were asked the following question: How often do you consume this type of products during the week? Depending on the frequency of consumption, responses were marked as "Never" — 0, "1–3 times a week" — 1, "4–6 times a week" — 2, "Once daily" — 3, "Twice daily" — 4, "More than three times daily" — 5. Additional salting was reported separately: an affirmative response added one more point.

Salt consumption rates used for data analysis

In order to validate the questionnaire result, it was compared to the median sodium intake calculated on the basis of the sum of three 24-hour diet diary results, which included information on salt consumption for each subject during two weekdays and one weekend day.

Salt intake by respondents was calculated using the formula:

$$z = median \sum_{d_1}^{d_3}$$

Where z is the median sum of salt consumption during three days, d is the day in the diet diary.

Analysis of the data obtained during various days of the week demonstrated a certain degree of variability in salt-containing product consumption; the median range for the sample was 4.2 [2.3; 7.3] g. Therefore, we used the median salt consumption to minimise individual variability of salt intake by each respondent. All patients who reported low salt consumption or special diets were excluded from the study and were disregarded in the analysis.

Machine learning was used to determine the product category and additional salting affecting salt consumption rates. We divided the sample into the teaching and test ones, then it was subjected to V-fold cross-check. The following algorithms were used: K mean method, random forest and eXtreme Gradient Boosting (XGBoost). Model optimality was evaluated using RMSE criteria and R^2.

The sample size for the study was calculated with the formula based on the Bland–Altman limits of agreement [16]. According to the literature and pilot testing results, it was assumed that the expected mean difference between the questionnaire and 24-hour diet diary would be about 5 points per one gram of salt, which was partially based on the expected difference between the diet diary and questionnaire. Given some uncertainty in our estimates, possible mean difference and standard deviation, the coefficient of variation was 10 %, which ensured an acceptable degree of certainty that the estimated limits of agreement would be sufficiently reliable to confirm questionnaire results, with the 80 % power of the study. It corresponded to the minimal sampling size of 162 respondents for the evaluation of the lower Bland–Altman limit for the salt intake level. Taking into account possible exclusion of respondents due to partial compliance with the study protocol, the sampling size was to be 50 % larger than the calculated value and would be at least 243 people. This sampling size was adequate for an accurate evaluation of the Bland–Altman limits of agreement.

Statistics

Statistical processing of the data was performed using language R, v. 4.2.1, with the RStudio development framework. Normality of distribution was determined with the help of Shapiro-Wilk test and Kolmogorov-Smirnov test. Quantitative measures are presented as the mean value (M) ± standard deviation (S) or median, 25th and 75th percentile. When several groups were compared, Kruskal-Wallis test or analysis of variance were used. For comparison of the groups, the Student's t-test was used for normal distribution, while the Wilcoxon's test was used for non-normal distribution. Categorial variables were compared using Yates corrected χ2; if the number of subjects in a group was below 5, then Fisher's ratio test was used, followed by a post hoc analysis adjusted for multiple comparisons (Holm's method). The relationships between variables were studied using Spearman's rank correlation or Pearson correlation coefficient, depending on data distribution. Polynomial logistic regression was

used to test the association between categorial dependant variables with several categories. The Cronbach's alpha was calculated to determine the correspondence of data in the questionnaire. Questionnaire coherence was tested using the Cohen's kappa. The degree of difference between sodium intake estimates was visually assessed with the Bland–Altman plot. The zero hypothesis was discarded with the level of significance below 0.05.

Results

Clinical characteristics of the study group

Patient enrolment run from September 2021 till January 2023 in Moscow and Moscow region. The general cohort included 271 respondents: 220 (81 %) women and 51 (19 %) men. The mean age was 52 [20;70] years old. On average, women were younger than men (44.8 ± 26.2 years for women vs. 50.7 ± 25.1 years for men). Respondents below 30 years of age did not have any chronic conditions, whereas those over 30 years of age had various chronic diseases. The following diseases were diagnosed: chronic cardiac failure (CCF) was observed in 123 (45.4 %) subjects; 122 (45 %) patients were diagnosed with hypertension; 47 (17.3 %) had a history of myocardial infarction; atrial fibrillation and diabetes mellitus were diagnosed in 73 (26.9 %) and 39 (14.4 %) subjects, respectively. Lung diseases included bronchial asthma (13 (4.8 %) subjects) and chronic obstructive pulmonary disease (17 (6.3 %) subjects). Quite a lot of patients over 30 years of age had chronic kidney disease (99 (36.5 %) respondents). Joint diseases were least numerous: 8 (3 %) patients (Table 1).

Salt intake variability in the groups

Based on the data distribution and study objectives, the following age groups were used: 18–40 years old, 41–70 years old, 71–80 years old and 80+ years old. It ensured a more detailed evaluation of various age categories and their impact on salt and calorie intake, as well as variability. Despite the fact that these age groups may not completely correspond to the generally recognised approaches used by the WHO, this distribution was chosen for a more accurate analysis of specific characteristics and consumer habits in each group in this study.

Table 2 shows salt and calorie intake and their variability in various age categories. There were no statistically significant differences in salt consumption in the age groups; the median average intake for three days was about 6 g. Also, calorie intake in the groups is not statistically different, unlike the expected basic metabolism, the mean value of which in all groups is below calorie intake. Body mass index is statistically lower in 18–40 years old group, then the median values are practically the same. Salt intake variability for three days recorded in the diet diary is not statistically different in the groups. The widest range in salt intake is observed in the groups of 18–40 and 41–70 years old, where variability varies from 20 to 50 %; the same trend is reported for

Table 1. *Clinical characteristics of the group*

Category	Value
Women	220 (81 %)
Men	51 (19 %)
Average age	52 [20;70] years
Average age of women	44.8±26.2 years
Average age of men	50.7±25.1 years
Chronic heart failure	123 (45.4 %)
Hypertensive disease	122 (45 %)
Myocardial infarction	47 (17.3 %)
Atrial fibrillation	73 (26.9 %)
Diabetes mellitus	39 (14.4 %)
Bronchial asthma	13 (4.8 %)
Chronic obstructive pulmonary disease	17 (6.3 %)
Chronic kidney disease	99 (36.5 %)
Joint diseases	8 (3 %)

Table 2. *Salt intake, calorie consumption, and intake variability by age using a diary*

Variables	All patients N=271 Me(IQR)	18 — 40 years n = 131 Me(IQR)	41 — 70 years n = 70 Me(IQR)	71 — 80 years n = 46 Me(IQR)	over 80 years n = 18 Me(IQR)	p-value
Average salt intake, g	6,2 (4,8; 8,5)	6,1 (4,7, 8,7)	6,4 (4,9, 8,4)	6,4 (4,7; 8,5)	6,0 (4,9, 8,1)	>0,9
Average calorie intake, calories	2119 (1765, 2604)	2095 (1725, 2592)	2178 (1819, 2650)	2120 (1846, 2526)	2080 (1703, 2623)	0,8
Salt intake to calorie ratio, mg/cal	2,93 (2,20; 3,76)	2,94 (2,19, 3,86)	2,89 (2,23, 3,60)	2,83 (2,15, 4,28)	3,04 (2,25, 3,29)	>0,9
Basal metabolism, calories	1434 (1378, 1501)	1434 (1380, 1540)*	1434 (1408, 1502)*	1434 (1400, 1434)**	1434 (1259, 1434)**	0,032
BMI, kg/m²	23,2 (21,4; 25,1)	21,7 (19,7; 23,2)*	23,2 (23,2; 27,3)**	23,2 (23,2, 27,2)**	23,2 (23,2, 28,9)**	<0,001
Salt intake variability (%)	37 (27, 56)	37 (24, 58)	37 (29, 54)	39 (30, 57)	31 (16, 39)	0,2
Caloric intake variability (%)	24 (14, 34)	24 (16, 34)	22 (13, 34)	21 (16, 35)	20 (12, 34)	0,7
Gender						0,3
Female, n (%)	220 (81 %)	111 (85 %)	52 (74 %)	36 (78 %)	15 (83 %)	
Male, n (%)	51 (19 %)	20 (15 %)	18 (26 %)	10 (22 %)	3 (17 %)	

Notes: Data are presented as median and interquartile range (Me [IQR]) and n (%).
The p for trend is presented in the last column. Values for specific comparisons: *p <0.05 ** p <0.01 *** p <0.001

calorie intake. It appears that these variables are interrelated, and the higher the overall calorie intake with food, the higher the sodium intake; and this is especially true for younger subjects. Of note, despite its statistical insignificance, the ratio between salt and calorie intake is the highest in the age group of 80+ years old, it being a result of higher consumption of home-cooked preserves containing high amounts of salt and not so many calories.

Internal consistency check of the questionnaire

To test the consistency of the developed questionnaire, the internal consistency criterion was calculated; the Cronbach's alpha was 0.8, i.e. evidencing a high degree of consistency in questions.

Questionnaire size reduction

Figure 2 shows five most commonly chosen products/product categories, distributed by the rate of consumption during the week. Figures indicate the median salt content in each product category, based on the diet diary per meal and taking into account the amount consumed. Products with extremely high median salt content were consumed not often; however, they could contain huge amounts of salt (e.g. Fish, the median value per meal was 5.3 g, i.e. the dietary reference intake per day). Also, it is important to take into account products containing moderate amount of sodium (about 1 g per meal, but taken quite often, i.e. at least once daily (e.g. bread, 0.6 g per meal, but three timely daily, i.e. 1.8 g per day from a single product)). Therefore, there is certain variability in consumption of products with high and moderate amounts of salt. That is why sodium intake should be considered on the weekly basis to reduce the degree of error.

When testing the degree of correlation between questions, several product categories were identified, which were highly correlated ($r > 0.3$). A number of categories with a high degree of correlation are mutually associated with products containing high amounts of sodium (e.g. fast food and pizza, etc.), therefore, some categories were combined in one category to reduce the number of questions. Of note, the pattern of high sodium intake is not observed in all categories. For instance, dairy products, soups (the median value is 0.4 and 0.7 g of salt per meal, respectively) are not associated with a high salt content. Thus, it is impossible to just combine these categories, because salt intake in this respondent category could differ. That is why we conducted an additional analysis using machine-aided cognition in order to identify product categories, which corresponded to the pattern of salt intake by respondents best of all.

Cluster analysis

To identify the main product categories in the questionnaire, which impacted the salt intake levels in patients, a cluster analysis with k-mean values was performed. Analysis of the scree plot showed that

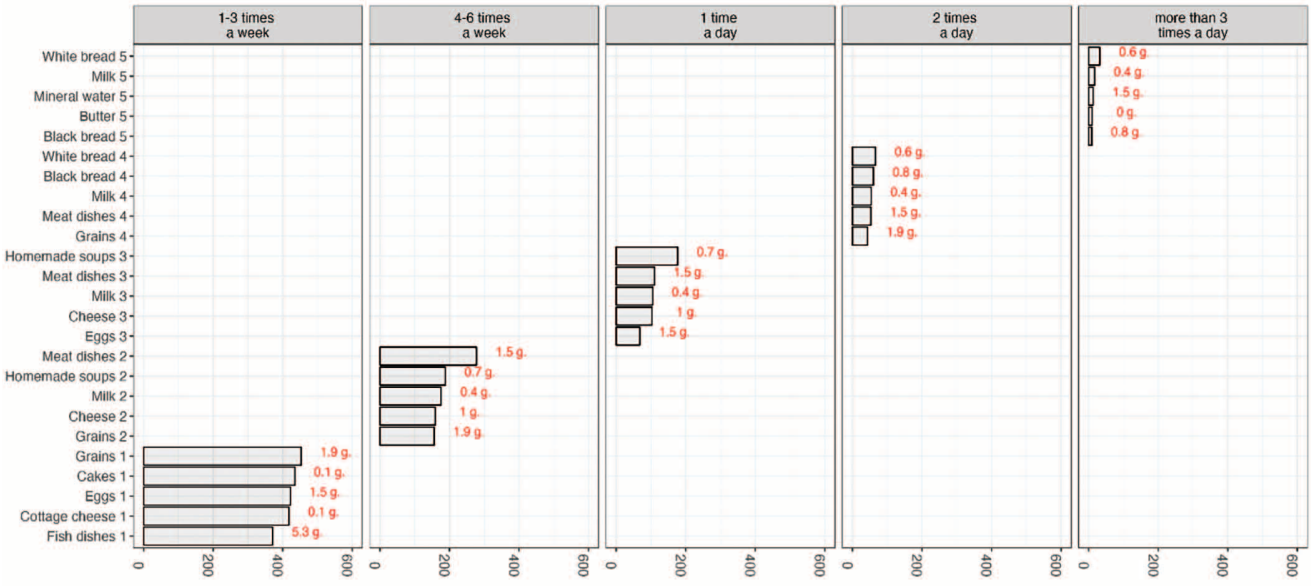

Figure 2. *Frequency of food consumption (numbers indicate the frequency of food consumption by respondents: 1 — 1-3 times a week, 2 — 4-6 times a week, 3 — once a day, 4 — twice a day, 5 — more than 3 times a day)*

the optimal number of clusters is three. The median intake in cluster 1 was 4.1 [2.9;5.1] g, in cluster 2 — 8.7 [7.6;10.6] g, and in cluster 3 — 17 [15.5;19.7] g ($p < 0.0001$). To identify the most important product categories in each cluster, a post hoc analysis was performed between each group, which identified products with statistically significant impact on salt intake values. Figure 3 shows the differences between clusters (A) and product groups (B), with statistically significant impact on salt intake by respondents. Figures in Figure 3 show the mean frequency of intake (points). In other words, the main factors of high sodium intake are additional salting, consumption of salty products, lower consumption of confectionery (see "cakes" in the plot); lower salt consumption values are associated with higher dairy product consumption. Therefore, the ratio of the frequency of this or that product consumption can be used to predict median salt consumption.

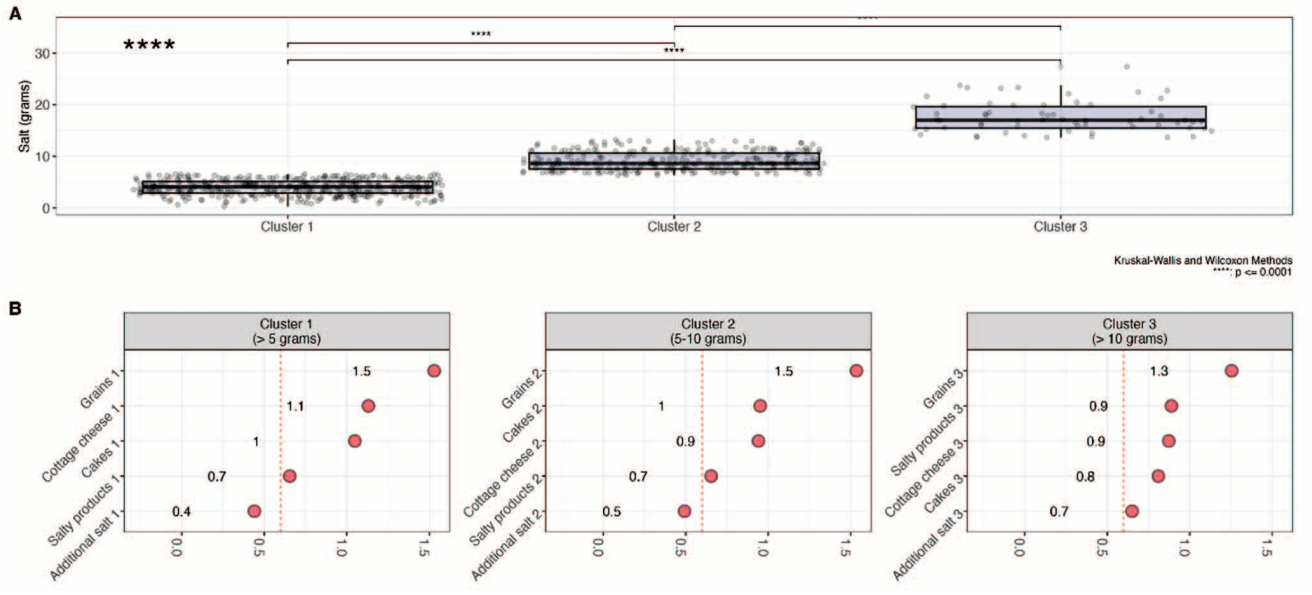

Figure 3. *Comparative analysis of salt consumption in different clusters of respondents and the contribution of individual product categories*

Algorithms of machine-aided learning

To select an optimal number of predictors, step-by-step linear regression plots were developed until an optimal model was identified. It resulted in a model with the following characteristics: R^2 = 0.06 (McFadden), p < 0.0001, and an optimal number of coefficients for forecasting. Table 3 shows the resulting optimal predictors. If compared with cluster analysis results, it is obvious that the majority of statistically significant predictors overlap. Also, the sign of the coefficient β can be evaluated, which allows assessing the product category as increasing (positive coefficient β) or reducing salt intake (if coefficient β is negative).

Since it might be possible that the results did not have any linear dependence between variables, a method based on decision trees with a regression module was used. In Figure 4 (A), the resulting predictors are ranked depending on their degree of impact (incidence in clusters) on predicted salt intake. Figure 4 (B) shows first clusters of the resulting decision tree.

Table 3. *The impact of various food categories on salt intake: results of regression analysis*

Values	Coefficient (Beta)	Statistic	p-value
(Intercept)	6,83	13,41	p <= 0,0001
Adding salt	1,13	3,5	p <= 0,001
Cottage cheese	-0,6	-2,93	p <= 0,01
Fast food	0,89	3,32	p <= 0,001
Salty products	0,32	1,49	Not significant
Cakes	-0,42	-2,07	p <= 0,05
Lard	0,4	1,87	Not significant
Condensed milk	-0,6	-2,38	p <= 0,05
Groats	-0,44	-2,37	p <= 0,05
Canned foods	0,7	2,06	p <= 0,05
Meat dishes	0,27	1,54	Not significant
Powdered milk	1,36	1,5	Not significant

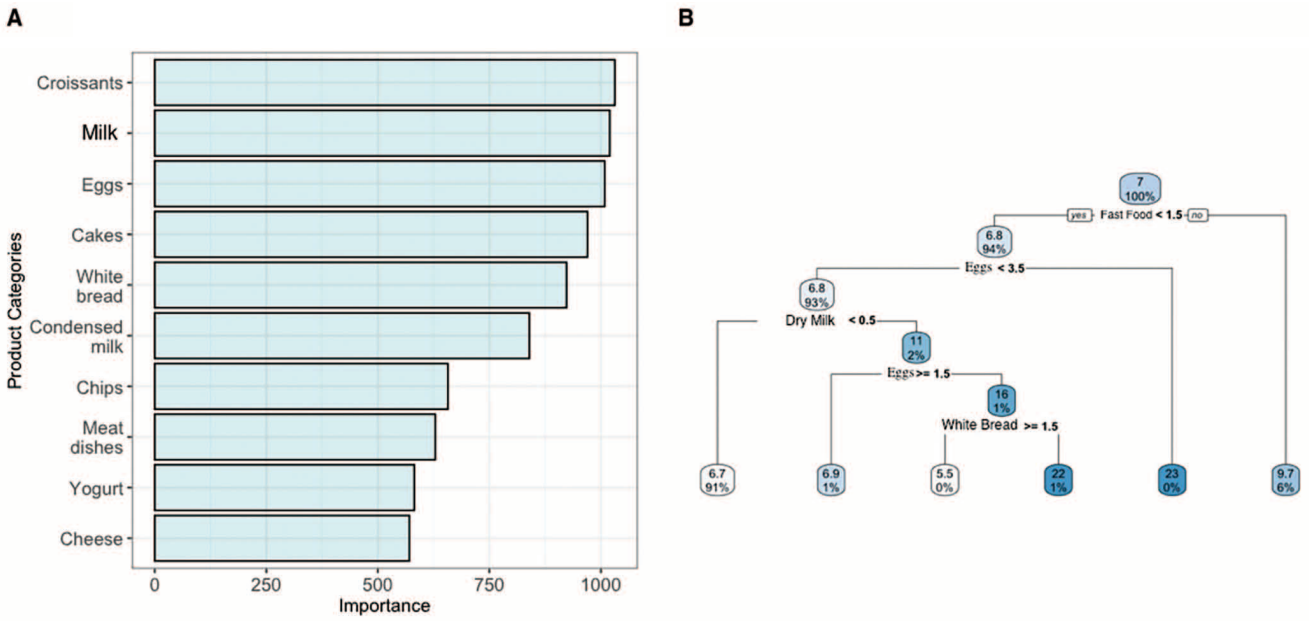

Figure 4. *Decision trees. A — frequency of product categories in the node, B — pruned tree*

Note. The decision tree divides the data starting with the condition "Fast food < 1.5" at the root node, where 97 % of the samples fall into this branch. Then, the data is further split by the condition "Eggs < 3.5", and subsequently by "Powdered milk < 0.5". Each node shows the number of samples and the percentage of the total that meet the conditions. The terminal leaves, such as "6.7 (91 %)", represent data groups that cannot be further split. Nodes with zero values indicate the absence of samples meeting those conditions

Therefore, it is apparent that one of the main clusters is Fast Food consumption: if eaten more than once per week, salt intake is 9.7 g, and the share of such respondents is 6 %. At the same time, the level of correlation of the resulting model in a test sample was r = 0.42, p = 0.0001.

The most significant clusters in the two machine-aided learning models (random forest and XGBoost) were identified based on the results of test sample handling. The random forest model demonstrated a coefficient of correlation r = 0.42 with the confidence level of p < 0.0001, while XGBoost had a coefficient of correlation r = 0.36 and the confidence level of p < 0.0001. Although the forest model yielded better results in the test sample, a number of product categories overlap in these models.

We analysed product categories, which were most commonly used by various machine-aided learning algorithms to predict salt intake by respondents. Product categories used at least two times in predicting salt intake levels by various algorithms were divided into those with positive and negative impact on salt consumption. For example, the "Cakes" category reduced salt consumption, while "Fast food" category increased salt intake. The majority of algorithms used the "Cakes" category to predict salt intake by respondents. Only two algorithms used such categories as "Horse radish", "Brown bread", "Frankfurters", "Lard", "Preserves", and "Yoghurt". Therefore, the weight of these categories is much lower.

Increasing the questionnaire efficiency

We have optimised the questionnaire to make it more easy-to-use and efficient for routine use. First, we reduced the number of product categories to 10 to make the questionnaire more compact and easy-to-complete. We separated the following categories: *"Dairy products", "Confectionary", "Eggs", "Baked goods", "Fast food", "Home-cooked meals", "Fish and seafood", "Meat/poultry and meat/poultry products", "Salty products/pickles/ mineral water", "Additional salting"*. We then optimised the frequency of responses for product consumption, by combining related categories. It allowed to specify what product categories impact salt intake and what product categories increase or reduce salt consumption. For instance, fast food products increase salt intake, while dairy products reduce it. Knowing these categories allowed us either to calculate coefficients for each category or apply inversion of points for a product category reducing the median salt intake levels during the day. Ignoring coefficients and point inversion, the correlation between points and salt intake was positive and statistically significant; however, the correlation was weak ($r = 0.14$, $p = 0.0279$).

We chose to use the point inversion method as it offered the highest clarity for users. As a result, the correlation between the highest salt consumption by the respondent during the week and the total points was $r = 0.61$, $p < 0.0001$.

To test the association between the points resulting from questionnaire modifications, sodium intake levels were presented as "less than 5 g", "5 to 10 g", and "more than 10 g", and a polynomial logistic regression model was developed. The resulting model has AIC = 191.9, OR = 2.38 [1.66;3.42] for intake of over 10 g; p = 0.00001 and OR = 1.6 [1.14;2.24] for intake of 5 to 10 g; p = 0.0001. Thus, the points in the questionnaire have statistically significant association with salt consumption by respondents and allow determining the points for various salt consumption levels: "less than 5 g" — 5.5 [4.25;6], "5 to 10 g" — 12.5 [10;14], "more than 10 g — 17 [15;18].

The resulting questionnaire titled ***SALT*** is presented in Appendix 1.

Testing validity and reliability of the SALT questionnaire

A Bland–Altman plot was generated to test the differences in the results obtained with the questionnaire and salt consumption values logged in respondents' diet diaries (Fig. 5). To bring all changes to a single scale, a preliminary unifactor regression analysis was performed, with the dependent variable being salt and the predictor being points in the questionnaire ($R^2 = 0.12$, $p < 0.0001$). A relevant model was generated, which was then used to calculate predicted salt consumption in grams, depending on the points.

The bias is presented as the difference between sodium consumption in the SALT questionnaire and the median salt consumption over three days logged in diet diaries. The mean difference was 0 ± 4.36 at 95 % CI (-0.45; 0.45). Thus, satisfactory variability was observed between the optimised questionnaire results and actual salt intake, with a slight underestimate of sodium consumption. The plot shows that 95 % of the values were within the limits of agreement, although nine respondents were outside the limits of the two standard deviations in the mean difference, it being a result of extremely high salt intake in this group of respondents (21–27 g/day).

The Cohen's kappa before an increase in the questionnaire efficiency was κ = 0.004 at 95 % CI (0.004; 0.004), after: κ = 0.48 at 95 % CI (0.08; 0.08), evidencing an average agreement and significant increase in agreement vs. the first variant. At the same time, the Cronbach's alpha dropped to α = 0.38 vs. the previous variant (α = 0.8).

Weekly Salt Questionnaire (SALT Questionnaire)

Patient's Full Name: _____

Date of Survey: "__" _____ 20_

	Never	Several times a week	Every day	More than once a day
Dairy Products[1]	0	2	1	1
Confectionery[2]	0	2	1	1
Eggs and Egg Dishes	0	2	3	4
Bakery Products[3]	0	2	3	4
Fast Food[4]	0	2	3	4
Home-Cooked Food[5]	0	2	1	1
Fish and Fish Dishes	0	2	3	4
Meat/Chicken and Meat/Chicken Dishes[6]	0	2	3	4
Salty Products[7] / Pickles[7] / Mineral Water[8]	0	2	3	4
Adding Salt	2			

Note:

1. **Dairy Products:** cottage cheese, sour cream, milk of all kinds (excluding dry and condensed milk), including milk fruit juice, milkshakes, kefir, ryazhenka, cream, acidophilin, koumiss, yogurt (including yogurt drinks), butter, margarine.
2. **Confectionery:** cakes, muffins, pies, donuts, sweet buns, condensed milk, curd snacks, ice cream, wafers, croissants, bagels, cookies, lightly salted crackers, rusks, flatbreads, etc.
3. **Bakery Products:** white bread, black bread, gray bread, grain bread, pancakes.
4. **Fast Food:** chips, popcorn, regular crackers (salted), pizza, nuggets, burgers, French fries, rolls, sushi, etc.
5. **Home-Cooked Food:** food prepared at home, including homemade or restaurant soups, porridges, etc.
6. **Meat/Chicken and Meat/Chicken Dishes:** boiled sausage, smoked sausage, dry-cured sausage, bacon, salami, jerky, sausages, lard, pâté; meat/chicken dishes — steaks, minced meat, cutlets, meatballs, stews, lasagna, dumplings, etc.
7. **Salty Products:** all types of cheese, all types of semi-finished products, all types of canned goods, salted and pickled products (cucumbers, cabbage, including sauerkraut, olives, etc.), canned soups or soups made from dehydrated mixes, including kharcho soup, sauerkraut soup, salted nuts and seeds (including sunflower seeds), horseradish and salad dressings, including mayonnaise, soy sauce, ketchup, mustard, seasonings, tartar sauce, etc.
8. **Mineral Water:** Essentuki, Borjomi, Narzan, Dilijan, etc.

Result Interpretation

Salt Consumption Level	Number of Points
<5 grams/day	<7 points
6 — 10 grams/day	7 — 15 points
> 10 grams/day	> 16 points

Appendix 1. *Salinity questionnaire weekly*

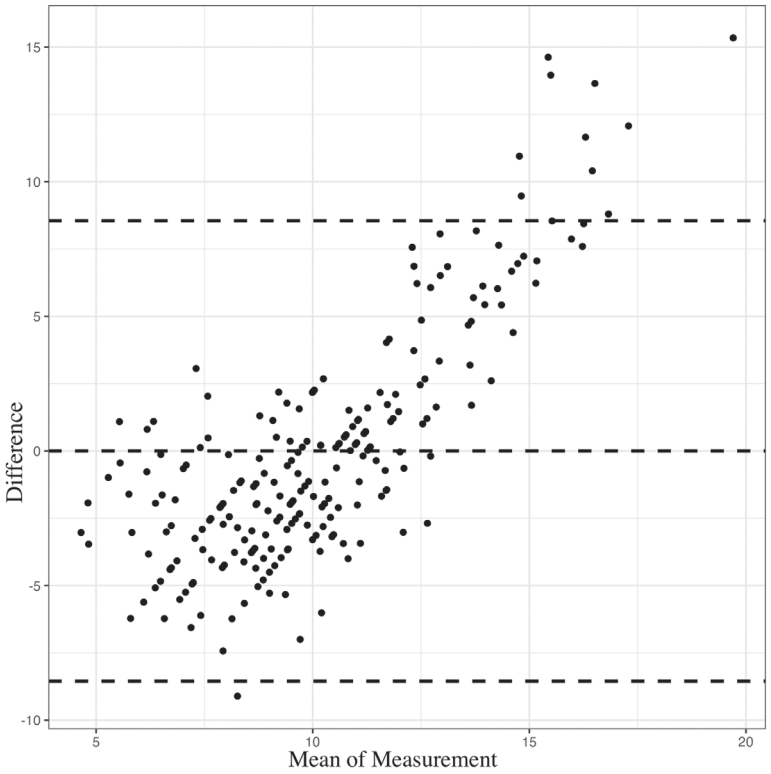

Figure 5. *Bland-Altman plot of the systematic error (mean difference) between predicted sodium estimates from the SOL questionnaire and median dietary sodium intake from three days of questionnaire data*

Note. The dotted line in the centre represents the mean difference between the two measurement methods. This value shows the systematic error, that is, the average amount by which one method differs from the other. The upper and lower dashed lines represent the limits of the 95 % confidence interval for the mean difference. These lines show the range within which 95 % of all differences between the two methods will lie

Sensitivity and specificity of the SALT questionnaire

At the threshold value of ≥ 12 points (corresponding to 7 g of salt per day) in the questionnaire, the sensitivity of the questionnaire is 85 % vs. the median estimate based on the three-day diet diary. At the threshold value of < 12 points, the specificity of the questionnaire is 74 % vs. the median estimate based on the three-day diet diary.

Discussion

The results of this study demonstrate that the *SALT* questionnaire can be a reliable tool for the assessment of the median sodium intake during the week. Some studies assessed eating habits in order to evaluate the daily salt intake. Mittelmark M. B. et al. [17] found out that 6 % of respondents did not use additional salt, although they stated otherwise. That is why salt consumption evaluation requires through statistical processing. In 1982, Pietinen et al. [2] used an approach based on statistical models to select products for the questionnaire. However, identification of the frequency of product consumption can be challenging. In this questionnaire, we used the questionnaire by Charlton K.E. et al. [18], developed in the Republic of South Africa (RSA) and validated in three RSA populations. The assessment of salt intake was based on the mean daily consumption, taking into account coefficients used for the frequency of consumption. However, the authors noted that the coefficients limit the use of the questionnaire and simplified it before counting the points. The accuracy of the questionnaire was tested using the correlation with the sodium urine levels (r = 0.171) and diet diary (r = 0.684). The correlation with the questionnaire was higher, which can be attributed to the lack of sodium depot understanding in 2008. During data processing, we concluded that the number of gradations of possible answers on the frequency of sodium intake during the week was superfluous and could add to the errors in respondents' replies.

In this study, the salt intake variability was 4.2 [2.3; 7.3] g/day, whereas other authors mention fluctuations from 897 to 1,403 mg/day [19]. We used the median value instead of the mean salt consumption in order to reduce the impact from outliers and bring the results closer to the central trend for the respondent. In a study by Charlton K.E. et al. [18], only eight products with high sodium content (such as popcorn, meat, fish, etc.) significantly

correlated with the sodium urine levels, which can be associated with sodium excretion peaks. In a study by Sasaki S. et al. [20], the correlation between sodium excretion was low (r = 0.14 for men and r = 0.23 for women). Any attempts to increase the correlation between the questionnaire and sodium excretion did not yield any results. In a study by McLean R. M. [21], the correlation between the questionnaire and sodium excretion was low (r = 0.257 for the population, r = 0.039 for men and r = 0.171 for women). A systematic review [22] demonstrated that the satisfactory association between 24-hour sodium excretion and sodium intake levels was possible only with repeated daily urine tests. The most relevant (in terms of the rate of correlation between sodium intake and 24-hour sodium excretion) are the results of 7-day urine collection, as evidenced by the results of a study by Day N.E. et al. [23], where the correlation was $r = 0.47$, and it was lower than with nitrogen $r = 0.81$. This result is likely to be associated with sodium excretion peaks and sodium depots.

Studies, where patients are interviewed using the national product databases, show a higher linear correlation between questionnaire results and interview results. E.g. the Sodium Screener questionnaire containing 26 questions and validated in a study by Tangney C. [24] demonstrated the correlation r = 0.83 for men and r = 0.85 for women ($p < 0.001$) with the NHANES product database. However, of note, all validation methods have bias, and currently none of them is absolutely reliable [25].

According to the guidelines for the development of diet questionnaires for the population, all questionnaires must be verified in a sample of the population, in which they are planned to be used [13]. Our questionnaire was compared to the 24-hour diet diary, which is considered one of the most accurate methods. We decided to gather information for three days, because this period of time was used in other studies of sodium intake. For the assessment of sodium intake, we included common products and foods, as well as processed products containing higher amounts of sodium. However, the use of questionnaires validated in other countries is limited by the lack of national food, typically consumed by the study population. Therefore, our questionnaire is the only questionnaire in Russia to assess the sodium intake levels.

We used a machine-aided learning method to assess the accuracy of the SALT questionnaire; it allowed us to increase the sample size and check the results multiple times (10 random samples generated with the help of a V-fold cross-check, equivalent to 7,000 patients). This method helped in identifying the most important product categories to assess sodium intake. We also used diet diaries to check the questionnaire results, because it allows to assess consumption during a longer period of time (days and weeks) and is independent of sodium depots [26] and sodium excretion peaks [27]. In this study, we used an eating behaviour pattern for the first time to develop a questionnaire, and this is an innovative approach.

Conclusions

This study demonstrated that the SALT questionnaire can be an acceptable tool for the assessment of sodium intake in Russia. We identified product categories, which correspond to the typical patterns of salt consumption in Russia, and the questionnaire demonstrates acceptable agreement with the data from the diet diary.

Study limitations

This questionnaire shows the categorial rate of salt intake in Moscow and Moscow Region and does not take into account diets in other regions of Russia. Additional validation is required in order to use this questionnaire in other regions of Russia.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Драгунов Д.О.: разработка концепции и дизайна исследования, определение его цели и задачи, а также методов сбора, анализа и интерпретации данных; статистическая обработка данных и машинное обучение; участие в сборе данных, их анализ и формирование выводов; написание рукописи, обоснование выводы и представление их в контексте предыдущих исследований

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Dragunov D.O.: The author makes a significant contribution to the concept and design of the study, defining its goals and objectives, as well as methods of data collection, analysis and interpretation. He actively participates in data collection, their analysis and formation of conclusions, as well as in writing the manuscript, justifying his conclusions and presenting them in the context of previous studies

Sokolova A.V.: The author plays a role in the conception and design of the study, defining its goals and objectives, as well as methods of data collection, analysis and interpretation. He is actively involved in the collection of data, their analysis and formation of conclusions, as well as in the writing of the manuscript

Arutjunov G.P.: The author plays a role in creating the concept and design of the study, defining its goals, objectives, and methods of data collection, analysis, and interpretation

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СТЕПЕНИ ТЯЖЕСТИ ПОСТКОВИДНОГО СИНДРОМА У РЕКОНВАЛЕСЦЕНТОВ COVID-19 И ИХ АССОЦИАЦИИ С ОСНОВНЫМИ ФАКТОРАМИ РИСКА ХРОНИЧЕСКИХ НЕИНФЕКЦИОННЫХ ЗАБОЛЕВАНИЙ

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Severity of Postcovid Syndrome in Convalescent Covid-19 and Their Association with the Main Risk Factors for Chronic Non-Communicable Diseases

Резюме

Цель исследования: оценить влияние основных факторов риска (ФР) хронических неинфекционных заболеваний (ХНИЗ) на степень тяжести постковидного синдрома (ПКС) у реконвалесцентов COVID-19. **Материалы и методы:** в обсервационное одномоментное исследование было включено 270 человек (из них 48,1% мужчин, средний возраст 53,2±13,2 года), являющихся реконвалесцентами COVID-19. Пациенты были разделены на 3 группы в соответствии со степенью тяжести ПКС. В группу 1 вошли 79 человек с отсутствием ПКС, в группу 2 — 97 пациентов с легкой степенью тяжести ПКС, в группу 3 — 94 пациента со средней степенью тяжести ПКС. Всем пациентам было проведено стандартное общеклиническое и лабораторное обследование, антропометрия, эхокардиография (ЭхоКГ), оценивались данные анамнеза. Лица без ПКС были моложе, чем пациенты, страдающие ПКС (p=0,003). У пациентов, имеющих ПКС, в сравнении с лицами, у которых ПКС не развился, статистически значимо был выше уровень глюкозы и IgG в сыворотке крови, значения систолического артериального давления (САД) и диастолического артериального давления (ДАД), показатели индекса массы тела (ИМТ), окружности талии (ОТ) и индексов- триглицеридглюкозного индекса (ТГИ)/ОТ, ТГИ /ИМТ, индекса накопления липидов (LAP), индекса висцерального ожирения (VAI), количество пациентов, страдающих ожирением, и лиц, имеющих диастолическую дисфункцию левого желудочка (ДД ЛЖ). Пациенты со средней степенью тяжести ПКС чаще имели сердечно-сосудистые заболевания (ССЗ) до развития новой коронавирусной инфекции (НКИ). **Результаты:** Показатели объема форсированного выдоха за 1 первую секунду ($ОФВ_1$), форсированной жизненной емкости легких (ФЖЭЛ) были ниже при легкой и средней степени тяжести ПКС, по сравнению с лицами без него. Обнаружена прямая связь между наличием ПКС и уровнем глюкозы (r =3,138, p=0,000), ДД ЛЖ (r =2,876, p=0,008) в общей группе. У женщин данная ассоциация была выявлена только с наличием ДД ЛЖ (r=4,457, p=0,008), а у мужчин — с уровнем глюкозы (r =4,343, p=0,000), ОТ (r =1,068, p=0,060) и наличием ДД ЛЖ (r =3,377, p=0,033). Шанс наличия ПКС средней степени тяжести у мужчин и женщин был ассоциирован с уровнем глюкозы (r =1,537, p=0,001), VAI (r =1,256, p=0,005), САД (r =0,977, p=0,027), ССЗ до COVID-19 (r =0,465, p=0,036). А в группе мужчин данная ассоциация сохранялась только с уровнем глюкозы (r =2,357, p=0,004), индексом VAI (r =1,430, p=0,020) и наличием предшествующих ССЗ (r =0,160, p=0,014). **Заключение:** наличие ПКС у реконвалесцентов COVID-19 независимо от других факторов связано с уровнем глюкозы и наличием ДД ЛЖ. ПКС средней степени тяжести ассоциирован с повышением уровня глюкозы, САД, индекса VAI и наличием ССЗ до заболевания НКИ, при этом у мужчин ПКС средней степени тяжести в большей степени ассоциирован с кардиометаболическими факторами риска (ФР).

Ключевые слова: *COVID-19, постковидный синдром, степень тяжести постковидного синдрома, реконвалесценты COVID-19, новая коронавирусная инфекция, ожирение*

Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
The purpose of the study is to assess the impact of the main risk factors (RF) of chronic non-communicable diseases on the severity of the post-COVID-19 syndrome (PCS) in COVID-19 convalescents. **Materials and methods:** 270 persons (48.1% of them men, mean age 53.2±13.2 years) were included in the one-time observational study and are COVID-19 convalescents. The patients were divided into three groups according to the severity of the PCS. Group 1 included 79 people with no PCS, group 2 included 97 patients with light PCS, group 3 included 94 patients with moderate PCS. All patients were given standard general clinical and laboratory examination, anthropometry, echocardiography, and anamnesis data were evaluated. Persons without PCS were younger than patients with PCS (p=0,003). In patients with PCS compared to persons who did not develop PCS, statistically significantly higher levels of glucose and IgG in the blood serum, systolic blood pressure and diastolic blood pressure, body mass index (BMI) waist circumference (WC) and indexes: triglyceride-glucose index (TyG /WC), TyG /BMI, lipid accumulation product (LAP), visceral adiposity index (VAI), number of obese patients and persons with diastolic left ventricular dysfunction. Patients with moderate PCS were more likely to have cardiovascular disease before developing a new coronavirus infection. **Results:** The forced expiratory volume in 1 s (FEV1), forced vital lung capacity (FVC) scores were lower for mild to moderate PCS compared to persons without PCS. There is a direct relationship between the presence of PCS and glucose level (r =3,138, p=0,000), diastolic left ventricular dysfunction (r =2,876, p=0,008) in the general group. In women, this association was detected only with the presence of diastolic left ventricular dysfunction (r=4,457, p=0,008). In men with glucose (r =4,343, p=0,000), WC (r =1,068, p=0,060) и diastolic left ventricular dysfunction (r =3,377, p=0,033). The chance of having a moderate PCS in men and women was associated with glucose level (r =1.537, p=0.001), VAI (r =1.256, p=0.005), САД (r =0.977, p=0.027), CVD before COVID-19 (r=0.460.036). In the group of men this association was preserved only with the level of glucose (r =2,357, p=0,004), the index VAI (r =1,430, p=0,020) and the presence of preceding CVD (r =0,160, p=0,014). **Conclusion:** the presence of PCS in convalescents COVID-19 independently of other factors is due to the level of glucose and the presence of diastolic left ventricular dysfunction. PCS of moderate severity is associated with an increase in glucose, systolic blood pressure, VAI index, and the presence of CVD prior to COVID disease, with PCS of moderate severity more associated with cardio-metabolic risk factors in men.

Key words: *COVID-19, post-COVID-19 syndrome, severity of the post-COVID-19 syndrome, convalescents COVID-19, new coronavirus infection, obesity*

Conflict of interests
The authors declare no conflict of interests

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Conformity with the principles of ethics
All patients gave their informed consent to participate in the study. The study was approved by the Ethics Committee of Research Institute of Therapy and Preventive Medicine — branch of the Federal State Budgetary Scientific Institution «Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences», Novosibirsk (protocol No. 71 of November 10, 2020)

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AH — arterial hypertension, WHO — World Health Organisation, DBP — diastolic blood pressure, LV DD — left ventricle diastolic dysfunction, IHD — ischaemic heart disease, BMI —body mass index, IRI — insulin resistance index, NCVI — novel coronavirus infection, TC — thigh circumference, WC — waist circumference, FEV_1 — forced expiratory volume per 1 second, PCS — post-COVID syndrome, PCR — polymerase chain reaction, RNA — ribonucleic acid, SBP — systolic blood pressure, GFR — glomerular filtration rate, CVD — cardiovascular disease, TGI — triglyceride glucose index, TG — triglycerides, FVC — forced vital capacity, RF — risk factors, CNCD — chronic non-communicable diseases, HDL cholesterol — high density lipoprotein cholesterol, echoCG — echocardiography, AIP — Atherogenic Index of Plasma, COVID-19 — Coronavirus Disease 2019, HADS — Hospital Anxiety and Depression Scale, LAP — lipid accumulation product, MFI-20 — Multidimensional Fatigue Inventory, SARS-CoV-2 — Severe Acute Respiratory Syndrome-related Coronavirus 2, VAI — visceral adiposity index

Introduction

Currently, the medical community has to deal with the consequences of the novel coronavirus infection (NCVI) more often. The main focus is on the condition of patients with persisting symptoms, which last for a long period of time and significantly worsen the quality of patients' life, reducing their capacity to work. This condition is called post-COVID syndrome (PCS). According to the World Health Organisation (WHO), PCS affects patients with a history of suspected or confirmed severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), usually 3 months after the onset, with development of symptoms, which last for at least two months and cannot be attributed to any other alternative diagnosis [1]. The relevance of the studies of PCS is due to significantly growing numbers of patients with this condition all over the world. At the moment, it is quite challenging to accurately determine the incidence of PCS because of the lack of standardised diagnostic criteria. The global incidence of PCS varies from 4.7 % to 80 % [2]. There are no official statistical data on the incidence of PCS in Russia. A wide array of manifestations of PCS in post-COVID patients [3, 4] necessitates more thorough and comprehensive studies of this problem. Despite the growing number of studies in this area [5, 6], there are still uncertainties about the factors affecting the severity of PCS (age, gender-related differences, comorbidities, etc.); also, of interest is finding causes of newly developed diseases or aggravation of existing symptoms during this period, identification of groups of a high risk of more severe PCS.

Given that chronic non-communicable diseases (CNCD) are the main cause of disability and premature mortality [7], the study of the main risk factors (RF) of their development (high blood pressure, hypercholesterolaemia, hyperglycaemia, smoking, overweight or obesity) as part of PCS studies is essential for resolution of problems and consequences of PCS.

Materials and Methods

This is a cross-sectional, observational study. The study was conducted at the Scientific Research Institute of Therapy and Preventive Medicine, a branch of the Federal Budgetary Scientific Institution Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Science. The study enrolled 270 subjects (48.1 % were male subjects) aged 18 to 84 years old (53.00 [43.00;64.00]), who were COVID-19 convalescents. Inclusion criteria: COVID-19 confirmed with a positive test for SARS-CoV-2 RNA by polymerase chain reaction (PCR) during the disease and/or presence of anti-SARS-CoV-2 IgG antibodies and at least two months after NCVI recovery. Exclusion criteria were acute infectious diseases and decompensated chronic diseases.

All patients provided their informed consent for participation in the study. The study was conducted as part of the budget section, Reg. No. 122031700115-7, and with a grant from the President of Russia and a grant from the Government of the Novosibirsk Region, Application No. 39423 (2024), approved by the Ethics Committee at the Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Science (Novosibirsk).

All patients were divided into three groups, depending on PCS severity, using certain criteria: presence of at least one sign, which developed during or after COVID-19 infection (verified by lab test results) and persisting over four weeks after onset of the disease; provided that it cannot be explained by any other causes [8]. Group 1 included 79 subjects without PCS; group 2 — 97 patients with mild PCS (non-life-threatening arrhythmias, development/aggravation of arterial hypertension (AH), changes in spirography without any impact on the quality of life, chronic cough, prediabetes, abdominal pain, mild neurological symptoms, subclinical anxiety/depression); group 3 — 94 patients with moderate PCS (ischaemic heart disease (IHD), atrial fibrillation, cardiac insufficiency, obstructive and interstitial lung disease, diabetes mellitus (DM), cerebrovascular event, anosmia, marked anxiety/depression, hair loss).

During the study, demographics (sex, age), medical history, chronic and newly diagnosed diseases (DM2, cardiovascular diseases (CVD), including IHD, AH, history of myocardial infarction, cerebrovascular event) were taken into account. Patients underwent anthropometry, including measurements of height, weight, waist circumference (WC) and thigh circumference (TC), and their blood pressure was measured. Body mass index (BMI) was calculated using the formula: BMI (kg/m2) = Weight (kg)/Height2 (m2); waist/thigh ratio (WC/TC) = WC (cm)/TC (cm). Fasting blood serum samples were taken after 8–14-hour night fasting. Thermo Fisher Scientific kits (Finland) and Konelab Prime 30i biochemical analyser (Thermo Fisher Scientific, Finland) were used to measure total cholesterol, triglycerides (TG) and high density lipoprotein cholesterol (HDL cholesterol) by direct enzymatic methods. Low density lipoprotein cholesterol levels were calculated using the Friedewald formula. Glomerular filtration rate (GFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology

Collaboration, 2011 modification) formula. Since the subjects were of child-bearing age, data of the sex hormones (oestradiol, testosterone) were used to standardise the regression models.

Additionally, the atherogenic index of plasma (AIP) was calculated using the formula: logarithm to base 10 (LOG10) [fasting TG (mmol/L) / fasting HDL cholesterol (mmol/L)] [9]. AIP < 0.11 was a predictor of a low cardiovascular risk; AIP 0.11–0.21 predicted a moderate cardiovascular risk, while API > 0.21 was a predictor of a high cardiovascular risk [10]. Also, insulin resistance (IR) index was calculated: triglyceride glucose index (TGI) = Ln [TG (mg/dL) × fasting plasma glucose (mg/dL) / 2], its derivatives: TGI /WC = TGI multiplied by WC; TGI /BMI = TGI multiplied by BMI) [11-13]. Besides, the following indices were evaluated on the basis of lipid and anthropometric parameters: lipid accumulation product (LAP) — formula for men: (WC (cm) — 65) multiplied by TG (mmol/L); for women: (WC — 58) x TG); and visceral adiposity index (VAI) — visceral adiposity index (formula for men: [WC/(39.68 + 1.88 × BMI)] × (TG/1.03) × (1.31/ HDL cholesterol)]; for women [WC/(36.58 + 1.89 × BMI)] × (TG/0.81) × (1.52/ HDL cholesterol)], where TG and HDL cholesterol are in mmol/L)] [14]. Instrumental methods included echocardiography (echoCG) and spirometry. The left ventricle diastolic dysfunction (LV DD) status was evaluated using echoCG: grade I LV DD was diagnosed if the ratio between LV filling rate at early diastole and atrial systole (E/A) was ≤ 0.8, while LV filling rate at early diastole (E) was ≤50 cm/s; grade II LV DD was diagnosed if two criteria out of three were present: 1) the ratio between LV filling rate at early diastole and average rate of LV elevation at early diastole (E/e′ > 14), 2) indexed left atrial volume (> 34 mL/m2), 3) highest tricuspid regurgitation rate > 2.8 m/s [15]. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) [16]. Pre-diabetes was diagnosed in accordance with the current clinical guidelines of the Russian Association of Endocrinologists (Type 2 Diabetes Mellitus in Adults, 2022). Cardiovascular pathologies were diagnosed in accordance with the current Russian guidelines. Asthenia was diagnosed on the basis of the Multidimensional Fatigue Inventory (MFI-20) results [17].

In the study subjects, CVDs (IHD, AH, chronic cardiac insufficiency) before NCVI were recorded in 161 subjects (59.6 %), bronchopulmonary disorders (chronic obstructive pulmonary disease, bronchial asthma) were diagnosed in 58 patients (21.5 %). The subjects did not demonstrate any significant differences in severity of the acute COVID-19 period and PCS manifestations; at the same time, all patients with severe acute COVID-19 period had PCS (Fig. 1).

The median age of the patients was 53.00 [43.00;64.00] (Table 1). All patients were divided into three groups, depending on PCS severity. Group 1 included 79 (29.3 %) subjects without PCS (45 (34.6 %) men, 34 (24.3 %) women); group 2 — 97 (49 (37.7 %) men, 48 (34.3 %) women) patients with mild PCS; group 3 — 94 patients with moderate PCS (36 (27.7 %) men, 58 (41.4 %) women). The characteristics of groups are presented in Table 1.

Statistical processing of results was performed in SPSS application package (v. 20.0). Statistical evaluations included a descriptive analysis of numerical characteristics. Normality of distribution was tested using the Kolmogorov–Smirnov test. Given that the distribution of a majority of data was other than normal, they were presented as median and quartiles (Me [Q1; Q3]).

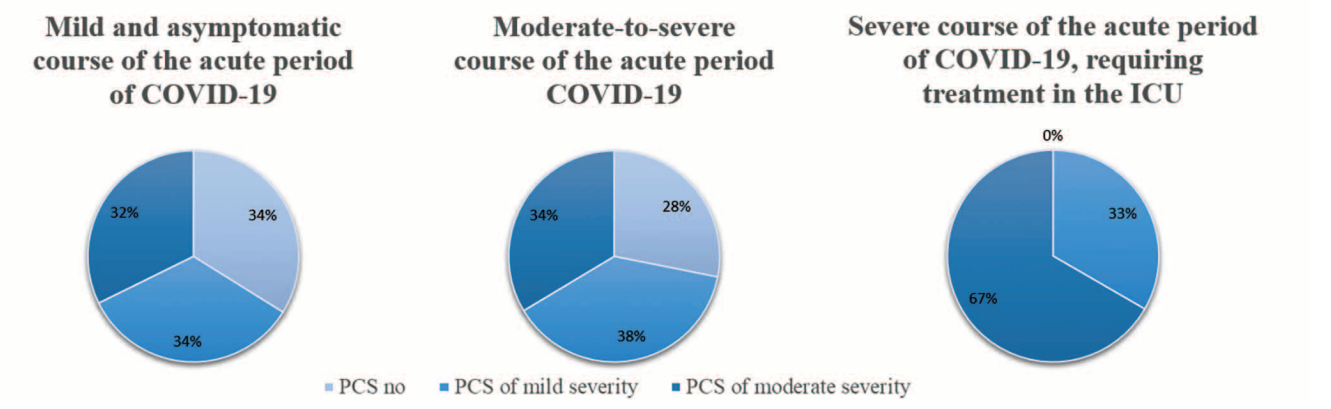

Figure 1. *Proportion of reported cases of PCS in COVID-19 convalescents, according to the course of the acute period of coronavirus infection*

Table 1. Characteristics of patients included in the study

Parameter	PCS no n=79 (29,3 %)	PCS of mild severity n=97 (35,9 %)	e PCS of moderate severity n=94 (34,8 %)	p
Age, years	46,0 [39,0;61,0]	56,0 [47,0;64,5]	55,5 [43,8;66,0]	**p — 0,003** **p_{1-2} — 0,002** p_{2-3} — 0,936 **p_{1-3} — 0,007**
Men, n (%)	45 (57,0 %)	49 (50,5 %)	36 (38,3 %)	p_{1-2} — 0,394 p_{2-3} — 0,089 **p_{1-3} — 0,014**
IgM, mg/dL	73,50 [37,25;256,25]	87,00 [44,75;297,25]	112,00 [40,25;180,00]	**p — 0,559** p_{1-2} — 0,302 p_{2-3} — 0,891 p_{1-3} — 0,398
IgM, mg/dL	1192,00 [367,00;1377,00]	1308,00 [773,00;1361,50]	1336,50 [1103,25;1390,25]	**p — 0,080** p_{1-2} — 0,402 p_{2-3} — 0,104 **p_{1-3} — 0,039**
SAD, mm Hg	121,25 [112,50;130,63]	128,00 [120,00;138,25]	125,00 [113,63;135,00]	**p — 0,005** **p_{1-2} — 0,001** **p_{2-3} — 0,024** p_{1-3} — 0,422
DAD, mm Hg	80,00 [70,75;85,00]	82,50 [79,75;88,00]	80,00 [70,75;87,13]	**p — 0,022** **p_{1-2} — 0,010** **p_{2-3} — 0,033** p_{1-3} — 0,734
WC, cm	92,00 [83,00;100,00]	101,00 [88,75;110,00]	100,00 [87,50;109,00]	**p — 0,002** **p_{1-2} — 0,001** p_{2-3} — 0,385 **p_{1-3} — 0,009**
BMI, kg/m	26,71 [23,75;30,53]	29,42 [25,85;34,66]	28,73 [24,76;32,36]	**p — 0,004** **p_{1-2} — 0,001** p_{2-3} — 0,169 **p_{1-3} — 0,043**

Note: SAD — systolic blood pressure, DAD — dyastolic blood pressure, WC — Waist circumference, BMI — body mass index

Standard characteristics for evaluation of statistical hypotheses were used: Mann–Whitney test for group comparison, univariate and multifactor logistic regression analysis for evaluation of the odds ratio. The Pearson's chi-squared test was used to compare frequencies in groups. The significance level for hypothesis testing was $p < 0.05$.

Results

52 (53.6 %) de novo cases of pre-diabetes were diagnosed in subjects with mild PCS, 12 (12.8 %) cases of pre-diabetes and 34 (36.2 %) cases of diabetes in patients with moderate PCS. Also, patients with moderate PCS had CVD, asthenia and hair loss de novo in 17 %, 37.2 % and 4.3 % of cases, respectively. The number of obese patients was statistically (2-fold) higher in the group of patients with mild PCS vs. patients without PCS. More patients with moderate PCS had CVD before COVID-19 vs. patients with mild PCS (Table 2).

No differences in lipid values were observed between the groups. In patients with mild PCS and moderate PCS, serum glucose levels were statistically higher (1.09 and 1.10 times higher, respectively) vs. patients without PCS (Table 3).

IR calculation showed that patients with mild and moderate PCS had higher values vs. patients without PCS: TGI (1.02 times higher), TGI/WC (1.13 and 1.10 times higher, respectively), TGI/BMI (1.09 and 1.05 times higher, respectively), and LAP (1.30 and 1.27 times higher, respectively) (Fig. 2). The visceral adiposity index (VAI) was statistically higher (1.15 times) in patients with moderate PCS vs. subjects without PCS ($p < 0.0001$). No statistically significant differences were observed in TG/HDL cholesterol ratio.

Table 2. *Incidence of risk factors for chronic non-communicable diseases in patients with PCS of various degrees of severity*

Parameter		PCS no n=79 (29,3 %)	PCS of mild severity n=97 (35,9 %)	PCS of moderate severity n=94 (34,8 %)	p
Smoking, *n (%)*		32 (40,5 %)	30 (30,9 %)	32 (34,0 %)	p_{1-2} — 0,186 p_{2-3} — 0,646 p_{1-3} — 0,380
Obesity, *n (%)*		22 (27,8 %)	46 (47,4 %)	36 (38,3 %)	**p_{1-2} — 0,008** p_{2-3} — 0,202 p_{1-3} — 0,148
CVD before COVID-19, *n (%)*		38 (48,1 %)	69 (71,1 %)	54 (57,4 %)	**p_{1-2} — 0,002** **p_{2-3} — 0,048** p_{1-3} — 0,220
Bronchopulmonary diseases before COVID-19, *n (%)*		9 (11,4 %)	10 (10,3 %)	9 (9,6 %)	p_{1-2} — 0,818 p_{2-3} — 0,865 p_{1-3} — 0,696
Hypertension, n (%)		38 (48,1 %)	73 (75,3 %)	56 (59,6 %)	**p_{1-2} — 0,0001** p_{2-3} — 0,605 **p_{1-3} — 0,004**
Prediabetes, *n (%)*			52 (53,6 %)	12 (12,8 %)	**p_{2-3} < 0,0001**
Anxiety disorder, *n (%)*	Subclinical stage	-	10 (10,3 %)	10 (10,6 %)	p_{2-3} — 0,808
	Severe stage	-	-	10 (10,6 %)	
Depression, *n (%)*	Subclinical stage	-	15 (15,5 %)	10 (10,6 %)	p_{2-3} — 0,457
	Severe stage	-	-	7 (7,4 %)	
Asthenia, *n (%)*		-	15 (15.5 %)	7 (7,4 %)	p_{2-3} — 0,083
Alopecia, *n (%)*		-	-	35 (37,5 %)	

Note: AH — arterial hypertension, PCS — postcovid syndrome, COVID-19 — Coronavirus Disease 2019, CVD — cardiovascular disease

As for the respiratory system, FEV_1 was lower in mild and moderate PCS vs. subjects without PCS (group 1 — 3.51 [2.71;4.20] L/s, group 2 — 3.03 [2.46;3.81] L/s, group 3 — 3.05 [2.50;3.62] L/s, p_{1-2} — 0.029 and p_{1-3} — 0.002 respectively). The same trend was observed for FVC (group 1 — 4.17 [3.48;5.22] L, group 2 — 3.76 [3.09;4.85] L, group 3 — 3.74 [2.98;4.48] L, p_{1-2} — 0.039, p_{1-3} — 0.002). No differences in the Tiffeneau index were observed. EchoCG results show that LV DD was statistically more often diagnosed in subjects with various degrees of PCS vs. subjects without PCS (group 1 — 24 (30.4 %), group 2 — 61 (62.9 %), group 3 — 59 (62.8 %), respectively, p_{1-2} — 0.000, p_{1-3} — 0.000); however, no statistically significant differences were recorded in LC ejection fraction and estimated pulmonary artery pressure.

Later, cardiometabolic parameters were included in the univariate logistic regression analysis, which demonstrated that the probability of PCS in COVID-19 convalescents was 0.97 higher if they had obesity; 0.96 times higher for an increase in WC by 1 cm; 3 times higher for an increase in glucose levels by 1 mmol/L; 0.92 times higher for an increase in BMI by 1 kg/m2; 0.97 times higher for an increase in DBP by 10 mm Hg; 2.5 times higher for diagnosed AH; and 3.5 times higher for diagnosed LV DD (Table 4). Besides, there was an association between PCS in COVID-19 convalescents with high IR index values (TGI, TGI/WC, TGI/BMI). When the multifactor logistic regression model includes such parameters as WC, glucose, TGI, DBP, DD, the probability of having PCS in COVID-19 convalescents is impacted by higher glucose levels (Exp (B) = 3.138; 95 % CI 1.797–5.478; p = 0.000) and LV DD (Exp (B) = 2.876; 95 % CI 1.315–6.292; p = 0.008).

The model of the multifactor logistic regression analysis of the probability of PCS in men and women (with age and sex hormone standardisation) included the following parameters: age, glucose, testosterone, oestradiol, DBP, TGI/BMI, WC, LV DD). In men, the probability of PCS was associated with higher glucose levels (Exp (B) = 4.343; 95 % CI 1.945–9.696; p = 0.000), WC (Exp (B) = 1.068; 95 % CI 0.997–1.143; p = 0.060) and LV DD (Exp (B) = 3.377; 95 % CI 1.106–10.313; p = 0.033). In women, this association was observed only with LV DD (Exp (B) = 4.457; 95 % CI 1.212–16.386; p = 0.024).

The unifactor logistic regression analysis demonstrated that the probability of moderate PCS was higher with higher glucose levels, VAI, SBP and was lower with

Table 3. *Clinical and biochemical values in patients with PCS*

Parameter	PCS no n=79 (29,3 %)	PCS of mild severity n=97 (35,9 %)	PCS of moderate severity n=94 (34,8 %)	p
ALT, Ed/*l*	20,00 [14,00;28,00]	23,00 [16,00;31,00]	20,00 [14,75;27,00]	p — 0,165 p_{1-2} — 0,106 p_{2-3} — 0,102 p_{1-3} — 0,902
AST, Ed/*l*	20,00 [17,00;26,00]	21,00 [18,00;28,00]	20,00 [16,00;24,25]	p — 0,381 p_{1-2} — 0,492 p_{2-3} — 0,155 p_{1-3} — 0,587
TC, mmol/l	196,80 [180,30;239,90]	209,70 [179,00;242,30]	204,85 [167,10;234,95]	p — 0,549 p_{1-2} — 0,825 p_{2-3} — 0,313 p_{1-3} — 0,402
Glucose, mmol/l	5,80 [5,40;6,10]	6,40 [5,70;6,90]	6,35 [5,70;7,60]	**p — 0,0001** **p_{1-2} — 0,0001** p_{2-3} — 0,346 **p_{1-3} — 0,0001**
TG, mmol/l	114,50 [74,50;170,30]	120,00 [90,20;172,95]	125,15 [80,23;219,08]	p — 0,383 p_{1-2} — 0,243 p_{2-3} — 0,760 p_{1-3} — 0,218
Uric acid, mmol/l	348,00 [281,00;410,00]	362,00 [282,00;418,00]	343,00 [294,25;415,50]	p — 0,857 p_{1-2} — 0,616 p_{2-3} — 0,675 p_{1-3} — 0,857
LDL-C, mmol/l	127,60 [104,50;159,85]	132,90 [100,55;159,27]	131,78 [90,35;157,44]	p — 0,860 p_{1-2} — 0,948 p_{2-3} — 0,634 p_{1-3} — 0,641
HDL-C, mmol/l	51,60 [39,80;63,70]	48,80 [41,25;63,80]	49,60 [36,97;56,52]	p — 0,163 p_{1-2} — 0,910 p_{2-3} — 0,108 p_{1-3} — 0,096
GFR, ml/min	84,00 [71,00;94,00]	78,00 [69,00;89,50]	78,50 [67,00;90,00]	p — 0,187 p_{1-2} — 0,106 p_{2-3} — 0,905 p_{1-3} — 0,110
Fibrinogen, g/l	3,77 [3,10;4,50]	3,55 [2,88;4,00]	3,55 [2,77;4,00]	p — 0,141 p_{1-2} — 0,055 p_{2-3} — 0,955 p_{1-3} — 0,108

Note: ALT — alanine aminotransferase, AST — aspartate aminotransferase, TG — triglycerides, LDL-C — Low-density lipoprotein cholesterol, HDL-C — high-density lipoprotein cholesterol, GFR — glomerular filtration rate

existing CVD (Table 5). This association persisted when the multifactorial logistic regression model included these parameters (glucose, VAI, CBP, CVD before COVID-19).

When the multifactor logistic regression analysis was performed in men, the probability of moderate PCS was 2.4 times higher with an increase in glucose levels by 1 mm, 1.4 times higher with an increase in VAI, and was 6.3 times lower in case CVD was diagnosed before COVID-19. In women, this analysis did not reveal any association with the above parameters (Table 6).

Discussion

The NCVI pandemic of 2021 established that it was necessary to make every effort to identify prognostic risk factors of complications and sequels of COVID-19, which have a direct impact on the long-term functional status and quality of patients' life.

One of the RF in question is visceral obesity, which impacts CVD development and anti-inflammatory status [18-20]. In this study, over a half (159 (58.9 %), men 43.4 %) of NCVI convalescents with PCS were obese.

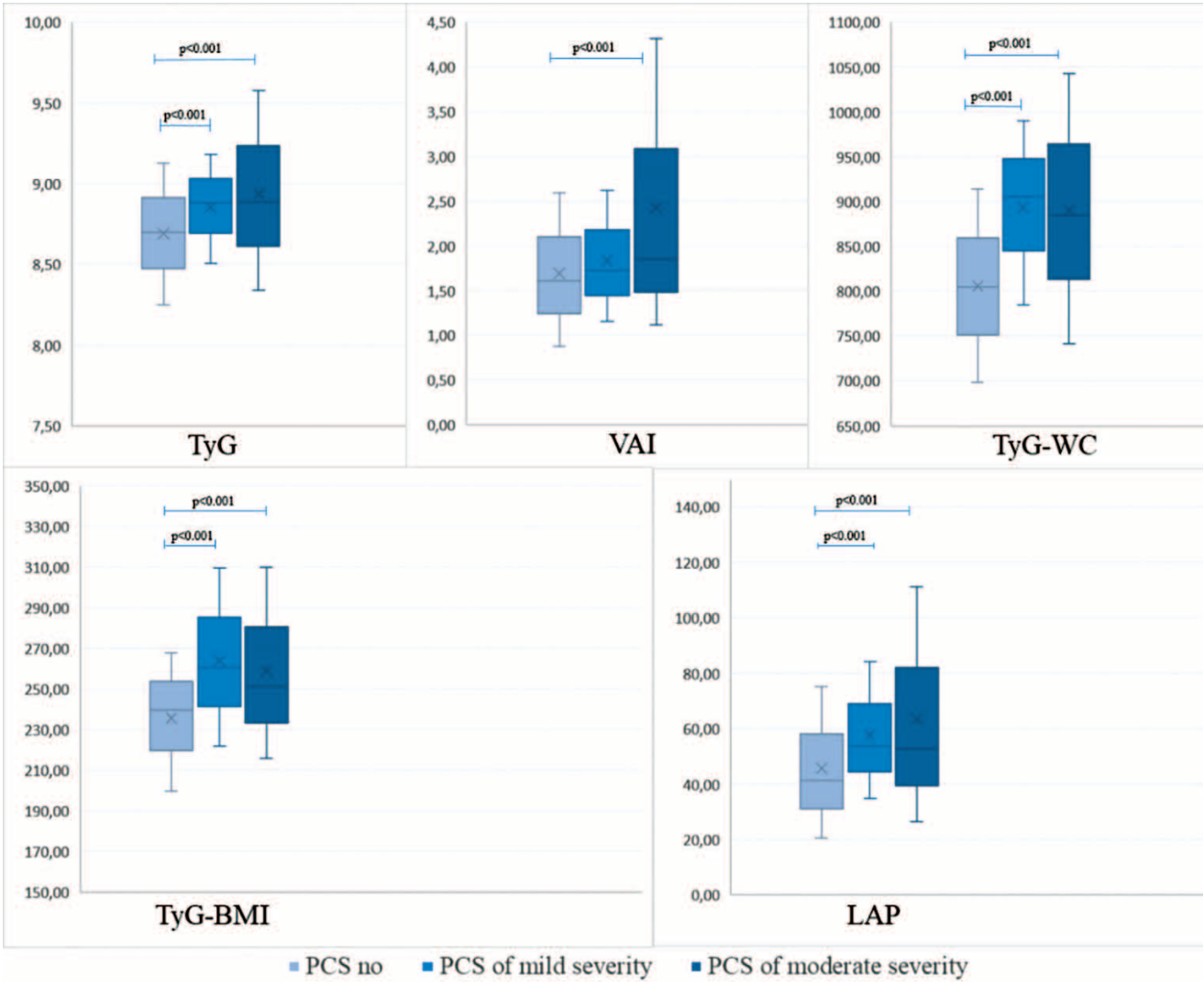

Figure 2. *Median and Quartiles of insulin resistance index in COVID-19 convalescents depending on the presence or absence of PCS of different severity*

Note: PCS — postcovid syndrome, TyG — triglycerides glucose index, TyG-WC — triglyceride glucose-waist circumference, TyG-BMI — triglyceride glucose-body mass index, LAP — lipid accumulation product, VAI — visceral adiposity index

Other authors provide similar information. According to the data from COVID-NET, a US surveillance network, 90 % of patients admitted to hospitals with confirmed NCVI had underlying conditions, and obesity accounted for 48.3 % of cases [21]. According to the AKTIV register, in 27.7 % of cases followed up for 6 months after hospitalisation, patients had obesity. The study results indicate that this risk factor is observed in patients with diseases de novo (AH, IHD, MI and DM) [22]. One of the mechanisms, of how obesity impacts the course and prognosis of NCVI, is detectable high levels of angiotensin converting enzyme-2 expression in visceral adipose tissue, which increases SARS-CoV-2 tropism to adipocytes and creates a virus depot in these cells [23]. Immunological and metabolic disorders typical for obese patients create conditions for chronic inflammation in the body, facilitating higher susceptibility to infections and defining the course of post-infectious changes [24]. In their study, S.H. Loosen et al. (2022) suggested that dyslipidemia, obesity and elderly age are a significant risk factor of PCS [25]. In this study, it was established that more severe PCS is directly associated with higher VAI values, which, in turn, are independently associated with new cases of IHD, type2 DM, AH [26,27]. It is worth mentioning that AKTIV and AKTIV 2 studies demonstrated that obesity in COVID-19 convalescents with PCS was associated with onset of such diseases as AH, DM1 and DM2, IHD, atrial fibrillation, arthritis, stroke, bronchial asthma, cancer, chronic cardiac insufficiency, myocardial infarction, chronic kidney disease, which aggravate PCS; during the three post-COVID months, obesity in patients over 60 years of age increased the probability of death (OR = 2.23; 95 % CI 1.05–4.72; p = 0.032) [28]. Therefore, the data obtained and the study results make

Table 4. Logistic regression analysis of the chance of availability PCS (standardized by age and gender)

Parameter	Univariate analysis			Multivariate analysis		
	Exp B	95,0 % C.I.	p	Exp B	95,0 % C.I.	p
Age	-	-	-	0,985	0,956-1,015	0,326
Gender	-	-	-	**3,602**	**1,735-7,478**	**0,001**
Obesity	**1,027**	**1,050-3,398**	**0,034**	-	-	-
WC	**1,042**	**1,020-1,065**	**0,0001**	1,019	0,992-1,048	0,171
Glucose	**3,038**	**1,924-4,798**	**0,0001**	**3,138**	**1,797-5,478**	**0,0001**
BMI	**1,088**	**1,031-1,148**	**0,002**	-	-	-
TyG	**1,663**	**1,042-2,655**	**0,033**	0,603	0,320-1,133	0,116
TyG/WS	**1,004**	**1,002-1,006**	**0,0001**	-	-	-
TyG/BMI	**1,009**	**1,004-1,014**	**0,001**	-	-	-
LAP	**1,007**	**1,001-1,014**	**0,033**	-	-	-
VAI	1,055	0,925-1,204	0,423	-	-	-
DAD	**1,033**	**1,002-1,064**	**0,034**	1,012	0,977-1,049	0,492
AH	**2,491**	**1,322-4,693**	**0,005**	-	-	-
DD LV	**3,538**	**1,778-7,041**	**0,0001**	**2,876**	**1,315-6,292**	**0,008**
CVD before COVID-19	1,435	0,773-2,663	0,252	-	-	-
FEV_1	0,952	0,636-1,424	0,812	-	-	-
FVC	1,017	0,727-1,424	0,919	-	-	-
Pulmonary pressure	1,007	0,964-1,053	0,749	-	-	-

Note: AH — arterial hypertension, DAD — diastolic blood pressure, DD LV — Left ventricular diastolic dysfunction, BMI — body mass index, WC — Waist circumference, TyG — triglycerides glucose index, TyG-BMI — triglyceride glucose-body mass index, TyG-WC — triglyceride glucose-waist circumference, FVC — forced vital capacity LAP — lipid accumulation product, VAI — visceral adiposity index

Table 5. Logistic regression analysis of the chance of availability PCS of moderate severity in persons with PCS (standardized by gender and age)

Parameter	Univariate analysis			Multivariate analysis		
	Exp B	95,0 % C.I.	p	Exp B	95,0 % C.I.	p
Age	-	-	-	0,995	0,966-1,025	0,733
Gender	-	-	-	**2,510**	**1,242-5,072**	**0,010**
Obesity	0,706	0,394-1,265	0,242	-	-	-
WS	0,999	0,979-1,020	0,917	-	-	-
Glucose	**1,537**	**1,183-1,998**	**0,001**	**1,736**	**1,268-2,378**	**0,001**
VAI	**1,256**	**1,070-1,474**	**0,005**	**1,224**	**1,015-1,475**	**0,034**
SAD	**0,977**	**0,956-0,997**	**0,027**	**0,975**	**0,951-0,999**	**0,043**
DAD	0,972	0,941-1,004	0,086	-	-	-
CVD before COVID-19	**0,465**	**0,227-0,951**	**0,036**	**0,365**	**0,157-0,846**	**0,019**

Note: DAD — diastolic blood pressure, WC — Waist circumference, SAD — systolic blood pressure , CVD — cardiovascular disease, VAI — visceral adiposity index

Table 6. Logistic regression analysis of the of the chance of availability PCS of moderate severity in men and women with PCS (standardized by age and sex hormones)

Parameter	Men			Women		
	Exp B	95,0 % C.I.	p	Exp B	95,0 % C.I.	p
Age	0,996	0,954-1,039	0,842	1,003	0,959-1,050	0,887
Glucose	**2,357**	**1,319-4,211**	**0,004**	1,443	0,916-2,241	0,115
Testosterone	1,002	0,959-1,047	0,926	-	-	-
Estradiol	-	-	-	1,332	0,202-8,786	0,776
SAD	0,995	0,950-1,041	0,823	0,970	0,939-1,003	0,073
VAI	**1,430**	**1,057-1,934**	**0,020**	1,085	0,871-1,351	0,467
CVD before COVID-19	**0,160**	**0,037-0,687**	**0,014**	0,506	0,165-1,555	0,235

Note: SAD — systolic blood pressure , CVD — cardiovascular disease, VAI — visceral adiposity index

it possible to suggest that the role of obesity in a higher probability of a poor outcome in NCVI convalescents with PCS is crucial.

Also, another risk factor of PCS is hyperglycaemia. It was established that PCS of a various degree of severity in COVID-19 convalescents is independently associated with glucose levels. Researchers report that higher glucose levels in the post-COVID period can smooth out or transform to DM, which can aggravate PCS [29,30]. It can be assumed that there are several causes of these findings: glucocorticosteroid therapy during the acute period and recovery; long-lasting pro-inflammatory status (including higher cytokine levels) after the infectious period; direct impact of SARS-CoV-2 and antivirals on β-cells of the pancreas and liver, impacting fasting glucose levels [31].

It is known that impaired diastolic functions of the myocardium usually precede a drop in the pumping ability of the LV and are a risk factor of a cardiac pathology [32]. According to Chistyakova MV et al. (2021), patients with moderate and severe NCVI develop LV diastolic impairment 98 [92;103] days after the diagnosis [33]. This study showed that LV DD was associated with PCS in COVID-19 convalescents irrespective of other factors. A systematic review by Ramadan M.S. et al. 3–6 months after the acute COVID-19 period showed a relatively high percent (40 %) of impaired LV diastolic function [34]. There are reports on various mechanisms of myocardial involvement in COVID-19: effects of the virus on cardiomyocytes via angiotensin converting enzyme-2 receptors with resulting fibrosis, that can manifest as impaired LV diastolic function [35-37], myocardial inflammation, vasculitis, thrombosis or sequels of hypoxia and haemodynamic instability [38]. LV DD is likely to be an early marker of intracardiac changes due to past NCVI; LV DD in COVID-19 convalescents can be a key to a comprehensive assessment of cardiac changes, which will help identify risks and develop a targeted approach to therapy.

Conclusion

PCS in COVID-19 convalescents is independently associated with glucose levels and LV DD. Moderate PCS is associated with higher glucose levels, SBP, VAI and pre-existing CVD. As far as gender differences are concerned, severe PCS in men is associated with cardiometabolic risk factors (visceral obesity, pre-existing CVD, glucose levels). No such associations were observed in women. Men with cardiometabolic risk factors, particularly with visceral obesity, are likely to be at high risk of moderate PCS.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Карасева А.А.: сбор, анализ, интерпретация данных, написание рукописи

Афанасьева А.Д.: разработка концепции и дизайна рукописи, проверка критически важного интеллектуального содержания

Гарбузова Е.В.: проверка критически важного интеллектуального содержания

Кузнецов А.А.: анализ и интерпретация данных функциональных методов исследования

Палехина Ю.Ю: проведение ультразвукового исследования, анализ и интерпретация полученных данных

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СИСТЕМНЫЙ АМИЛОИДОЗ С ПОРАЖЕНИЕМ СЕРДЦА: ОСОБЕННОСТИ ТЕЧЕНИЯ И ТРУДНОСТИ ДИАГНОСТИКИ

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Systemic Amyloidosis with Cardiac Involvement: Features of Course and Diagnostic Difficulties

Резюме

Разнообразие клинических форм амилоидоза связано с различиями амилоидогенных белков-предшественников. Вовлечение сердца характерно для AL- и ATTR-амилоидоза, при этом поражение сердца развивается у подавляющего большинства больных с AL-амилоидозом и у 50 — 60 % пациентов с ATTR-амилоидозом. ATTR- (транстиретиновый) амилоидоз — один из вариантов системного амилоидоза; белком-предшественником является транстиретин при наличии мутаций в его молекуле (семейные формы) или возрастных нарушениях секреции его тетрамеров. До недавнего времени считалось, что на территории России транстиретиновый амилоидоз не встречается. Однако внедрение в практику методов молекулярно-генетической диагностики мутаций транстиретина продемонстрировало встречаемость ATTR-амилоидоза в России с частотой, близкой к среднеевропейской для не эндемичных зон. В статье представлено клиническое наблюдение системного амилоидоза у пациентки среднего возраста. Заболевание дебютировало в возрасте 54 лет карпальным туннельным синдром. В последующем доминирующим проявлением заболевания стала рефрактерная к лечению хроническая сердечная недостаточность. Выявленные в динамике неоднородность структуры и значительное утолщение миокарда при сохранной фракции выброса в сочетании с новыми симптомами (диарея, ортостатическая артериальная гипотензия, периорбитальная пурпура, протеинурия) были расценены как инфильтративное поражение сердца в рамках системного амилоидоза. Развившаяся асистолия послужила причиной летального исхода. По результатам аутопсии диагноз системного амилоидоза был подтвержден. В статье обсуждаются вопросы дифференциальной диагностики AL- и ATTR-амилоидоза, основанной на анализе анамнестических и клинических данных. Дебют заболевания с синдрома карпального канала, прогрессирующая дистальная невропатия в сочетании с автономной дисфункцией, доминирующее поражение сердца, отсутствие амилоидоза почек по данным аутопсии, длительность заболевания с момента клинической манифестации до летального исхода 43 месяца в большей степени указывает на ATTR-амилоидоз. В статье также обсуждаются современные подходы к диагностике амилоидного поражения сердца в клинической практике, указывается на возникающие при этом трудности, подчеркивается важность ранней диагностики амилоидоза сердца, что позволяет реализовать возможности современных методов лечения амилоидоза.

Ключевые слова: *системный амилоидоз, ATTR-амилоидоз, амилоидоз сердца, хроническая сердечная недостаточность, полиневропатия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The diversity of clinical forms of amyloidosis is related to differences in amyloidogenic precursor proteins. Cardiac involvement is characteristic of AL- and ATTR-amyloidosis, with cardiac involvement developing in the vast majority of patients with AL-amyloidosis and in 50-60 % of patients with ATTR-amyloidosis. ATTR- (transthyretin) amyloidosis is one of the types of systemic amyloidosis, the precursor protein of which is transthyretin in the presence of mutations in its molecule (familial forms) or age-related disorders of its tetrameric secretion. Until recently, it was believed that transthyretin amyloidosis did not occur in Russia. However, the introduction of molecular genetic diagnostic methods for transthyretin mutations has demonstrated the occurrence of ATTR amyloidosis in Russia with a frequency close to the European average for non-endemic areas. The article presents the case report of systemic amyloidosis in a middle-aged woman. The disease presented at the age of 54 years with carpal tunnel syndrome. Subsequently, chronic heart failure refractory to treatment became the dominant manifestation of the disease. Heterogeneity of structure and significant myocardial thickening with preserved ejection fraction detected in dynamics in combination with new symptoms (diarrhea, orthostatic arterial hypotension, periorbital purpura, proteinuria) were considered as an infiltrative heart lesion within the framework of systemic amyloidosis. The result was a fatal asystole. Autopsy findings confirmed the diagnosis of systemic amyloidosis. The article discusses the issues of differential diagnosis of AL- and ATTR- amyloidosis based on the analysis of anamnestic and clinical data. The onset of the disease with carpal tunnel syndrome, the progressive distal neuropathy combined with autonomic dysfunction, the dominant cardiac involvement, the absence of renal amyloidosis according to autopsy data, and the duration of the disease from the time of clinical manifestation to death of 43 months are more indicative of ATTR amyloidosis. The article also discusses modern approaches to diagnostics of amyloid heart lesion in clinical practice, points out the difficulties arising in this case, emphasizes the importance of early diagnosis of cardiac amyloidosis, which allows to realize the possibilities of modern methods of amyloidosis treatment.

Key words: *systemic amyloidosis, ATTR-amyloidosis, cardiac amyloidosis, chronic heart failure, neuropathy*

Conflict of interests

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BP — blood pressure, BMI — body mass index, EDD — end-diastolic dimension, LV — left ventricle, IVS — interventricular septum, PH — postural hypotension, RV — right ventricle, PASYS — pulmonary artery systolic pressure, EF — ejection fraction, CCF — chronic cardiac failure, ECG — electrocardiography/electrocardiogram, echoCG — echocardiography, NTproBNP — N-terminal pro B-type natriuretic peptide

Systemic amyloidosis is a group of diseases caused by extracellular deposits of insoluble fibrillar protein masses — amyloid, having a common physical (crystal-like) structure. A regular structure of amyloid fibrils ensures homogeneous behaviour when stained for morphological examinations, in particular congophilic properties, where the colour changes to apple-green in polarised light. Diverse clinical forms of amyloidosis are caused by differences in amyloid precursor proteins, the number of which currently exceeds thirty [1, 2].

The most common form of systemic amyloidosis in therapeutic practice is AA-amyloidosis, where the precursor protein is acute phase protein of chronic inflammation SAA, and AL (AH)-amyloidosis, where the precursor protein is light (L) or heavy (H) immunoglobulin chains in plasma cell dyscrasia, including multiple myeloma. ATTR-(transthyretin) amyloidosis is also a systemic form of amyloidosis; the precursor protein is transthyretin (a protein transporting thyroxine and retinol) with mutations in its molecule (family form) or age-related abnormalities in secretion of its tetramers [1, 2].

Until quite recently, it was believed that transthyretin amyloidosis does not affect the citizens of Russia. However, after the introduction of routine molecular genetic methods to diagnose transthyretin mutations, staff at E. M. Tareev clinic demonstrated cases of ATTR-amyloidosis in Russia, with the incidence close to the Central European rates for non-endemic regions (8 % vs. 10 %, respectively). Taking into account the time from first signs of the disease to diagnosis (median: 69 months), the authors conclude that in Russia ATTR-amyloidosis is under-diagnosed [3]. The presented case study can illustrate this observation.

Patient P., 58 years old, ethnicity: Russian, first noticed the signs of weakness, rapid fatigability, shortness of breath when walking at a moderate speed in November 2021, after the past coronavirus infection. During the next 4 months, exercise tolerance reduced, shortness of breath started appearing after walking 50–100 m and at

night; the patient noticed palpitations, swelling of her feet and shins, episodes of hypotension. An examination in the central district hospital in March 2022 showed pulmonary hypertension: pulmonary artery systolic pressure (PASYS) of 60 mm Hg, tricuspid regurgitation, D-dimer elevation to 900 ng/mL (normal range: 0–550 ng/mL). The patient was diagnosed with pulmonary embolism of small branches and prescribed rivaroxaban 20 mg, bisoprolol 2.5 mg, spironolactone 25 mg, torasemide 5 mg. The therapy was ineffective, and in May 2022 the patient was admitted to the Regional Clinical Hospital (Saratov). History taking showed that, prior to coronavirus infection, the patient did not have any cardiovascular disease; in 1995 she underwent cholecystectomy; in 2019 the patient underwent surgery for carpal tunnel syndrome (on the left); birth: 1, menopause from 56 years. Her father died at the age of 74 years old from a heart disease (no details are known); her mother was diagnosed with DM2 at the age of 82 years old. Upon admission, the patient had symptoms of congestion in the two circulations: shin swelling, positive hepatojugular reflux, bubbling rales in the lower sections of the lungs. Heart tones are muffled; heart rate is 72 bpm, blood pressure is 120/70 mm Hg. Computed tomography showed interstitial changes in the lungs, signs of venous stasis, bilateral hydrothorax. Echocardiography (echoCG) showed the following results: left ventricle ejection fraction (LV EF) — 66 %, left ventricular mass index (LVMI) — 97 g/m^2 (M-mode), PASYS — 55 mm Hg. Holter ECG monitoring recorded rare supraventricular and single polymorphous premature ventricular complexes. Duplex Doppler ultrasound of veins in the lower extremities did not show any pathologies. Laboratory test results, including troponins, creatine phosphokinase MB, C-reactive protein, D-dimer, total protein, were normal; N-terminal pro B-type natriuretic peptide (NTproBNP): 156.4 pg/mL. For more details, please refer to Table 1.

In the absence of clinical and instrumental signs of pulmonary embolism, myocarditis, ischaemic heart disease, which could cause chronic cardiac failure (CCF), unspecified cardiomyopathy was diagnosed. The therapy with perindopril 4 mg, bisoprolol 2.5 mg, spironolactone 100 mg, torasemide 5 mg yielded positive results. In August 2022, the patient was admitted to the Regional Clinical Hospital again. With the regular therapy for

Table 1. *Dynamics of complete blood count and the biochemical blood test*

Parameters / Date	May 2022	August 2022	March — April 2023
Red blood cells RBC, 10^{12}/L	4,3	5	4,0
White blood cells WBC, 10^9/L	6,6	10,6	9,2
Hemoglobin HGB, g/L	131	151	124
Platelets PLT, 10^9/L	294	341	323
Red blood cell sedimentation rate, millimeters/hour	13	15	18
Blood serum protein, g/L	60,3	61,7	53,8
Serum albumin, g/L	37	38,1	37,7
Creatinine, μmol/L	72,4	87,1	101
C-reactive protein, mg/L	1,9	17,32	21,7
Cortisol, nmol/L N 150-660	study not performed	study not performed	659
NTproBNP, пг/мл	156,4	study not performed	2259,9
ALT, units per liter	18,3	19,8	11,3
AST, units per liter	27	21,4	16,3
Glucose, mmol/L	4,5	6,0	5,4
Cholesterol, mmol/L	5,4	5,0	4,1
Sodium, mmol/L	141,9	135,2	134,1
Potassium, mmol/L	3,95	4,3	4,5
Calcium, mmol/L	1,22	1,24	1,22

Note. ALT — alanine aminotransferase, AST — aspartate aminotransferase

2.5 months, the patient did not have peripheral oedema; she did not have shortness of breath at rest, but it appeared with moderate exercise; however, one month before hospitalisation, the patient noted aggravation of shortness of breath (when walking 100 m), as well as chill feet, burning sensation in her fingers and toes, pain in calf muscles during walking. It is worth mentioning that lower pain and tactile sensitivity (like "gloves" and "socks"), paresthesia were observed for the past three years, but were less pronounced. Laboratory and instrumental test results are presented in Tables 1 and 2. Repeated echoCG showed that LVMI had increased from 97 to 122 g/m^2 (M-mode) and the anterior wall of the right ventricle (RV) slightly thickened to 0.55 cm. The neurologist diagnosed dysmetabolic sensory and motor polyneuropathy. The patient was discharged with recommendations to continue ACE inhibitors, diuretics, b-blockers. The neurologist recommended taking alpha-lipoic acid, gabapentin, vitamins B, bencyclane. After discharge in September 2022, the patient noted diarrhoea (3–4 times a day). Symptomatic therapy with Smecta, loperamide was inefficient. In November, the patient was diagnosed with chronic gastritis, chronic gallstone pancreatitis, dolichosigmoid, sigmoid diverticles, haemorrhoids in outpatient settings.

In January 2023, progressive CCF was observed, and the diuretic therapy was updated: spironolactone 200 mg and torasemide 40 mg were added. In April 2023, the patient was admitted to the Regional Clinical Hospital with shortness of breath with minimal exercise, shin swelling, blackouts when standing up from horizontal position, weight loss (30 kg in one year), burning sensation in her fingers, progressive weakness, loose stool (2–4 times a day). Examination revealed a new symptom — periorbital skin purpura (Fig. 1).

BP in prone position was 120–110/85mm Hg; when the patient stood up, systolic BP dropped to 85 mm Hg, diastolic BP — to 60 mm Hg. Non-rhythm pulse of 68–75 bpm. Holter ECG monitoring showed transient grade 2 atrioventricular block, type 1 and 2.

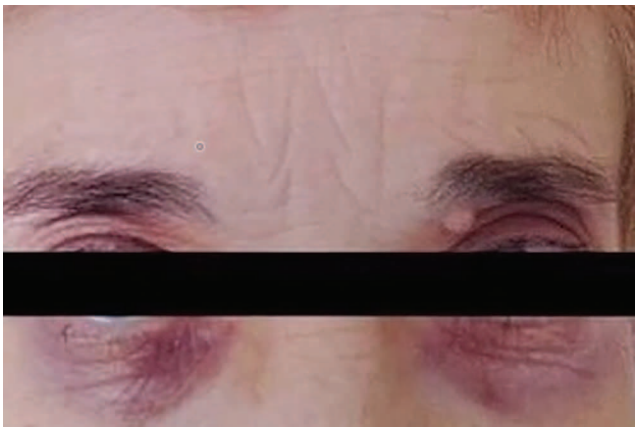

Figure 1. *Periorbital cutaneous purpura (the «raccoon eye» symptom)*

Laboratory test results demonstrated a clinically significant rise in NTproBNP values to 2259.9 pg/mL, moderate hypoproteinemia with normal blood albumin (Table 1), proteinuria (1.0 g/L).

Negative echoCG changes were observed: LVMI increased to 201 g/m^2 (M-mode), LV posterior wall thickness reached 1.8 cm, interventricular septum thickness — 2.0 cm, RV anterior wall thickness — 0.83 cm, right and left atria dimensions reached 4.46 and 4.05 cm, respectively. Thicker interventricular septum and ventricle and atria walls were not associated with ECG signs of myocardial hypertrophy and were interpreted as possible infiltrative heart damage. Also, during examination, reduction in LV end-diastolic dimension (EDD) from 5.1 to 3.9 cm, non-homogeneous myocardium structure, preserved EF (68.7 %) with progressive CCF (Table 2) were of interest.

Table 2. *Dynamics of echocardiography indicators*

Parameters / Date	May 2022	August 2022	March — April 2023
Left ventricular mass index, g/m^2	97	122	201
Ejection fraction left ventricular, %	66	62	68
Systolic pressure in the pulmonary artery, mm Hg	55	44	58
Left ventricular end diastolic size, mm	5,1	4,9	3,9
Thickness of left ventricular posterior wall, cm	1,0	1,1	1,8
Thickness of the interventricular septum, cm	1,0	1,1	2,0
Thickness of right ventricular anterior wall, cm	0,5	0,55	0,83
Left atrium, cm	3,7	3,8	4,05

EchoCG signs of restrictive cardiomyopathy and high grainy myocardium reflectivity were additional information pointing out to possible heart amyloidosis. In our observation, low ECG complex voltage (an additional sign) was absent. However, of note, currently low-voltage ECG is not a reliable sign, because it is recorded only in 20 % of ATTR cases and 29 % of AL-amyloidosis cases [3].

Restrictive cardiomyopathy with non-homogeneous myocardium structure and preserved EF with refractory CCF, combined with bilateral carpal tunnel, postural hypotension (PH), motor diarrhoea with weight loss, renal impairment (proteinuria), periorbital skin purpura (raccoon eyes) underlied a conclusion on systemic amyloidosis. To rule out AL-amyloidosis with multiple myeloma, blood and urine M-gradient was examined (result: negative), and a sternal puncture was performed: normocellular bone marrow, plasmatization — 1 %. However, no blood and urine tests were performed for the presence of free light immunoglobulin chains, therefore, it was impossible to reliable rule out AL-amyloidosis, including together with multiple myeloma. No amyloid was found in rectum mucous biopsy material. Given significant proteinuria, a renal biopsy was scheduled. On day 2 of hospitalisation to the nephrology unit, when the patient was standing up in the morning, she suddenly collapsed with cardiac arrest; ECG results showed asystole. Resuscitation was inefficient; the patient was pronounced dead.

Final clinical diagnosis.

Primary disease. Primary amyloidosis with involvement of the heart, GIT, somatic and sympathetic nervous system, kidneys (chronic renal disease, stage C3A2). Relative mitral and tricuspid incompetence with regurgitation, grade 3. Pulmonary hypertension, stage 2.

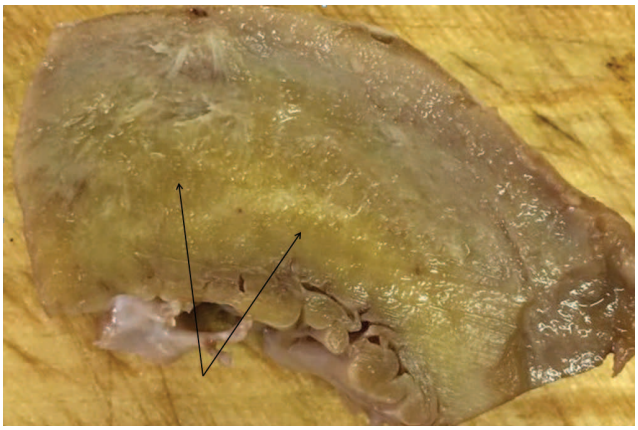

Figure 2. *Heart. Multiple yellowish layers (deposits of amyloid masses)*

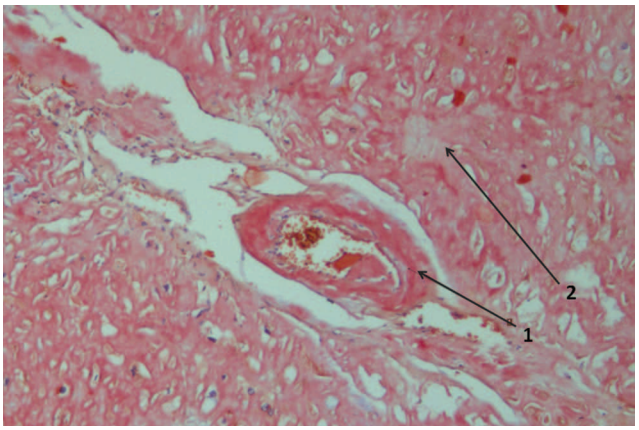

Figure 3. *Myocardium*
Note. 1 — deposits of amyloid masses in the wall of small myocardial artery; 2 — deposits of amyloid masses in myocardium. Congo red stain; magnification ×20

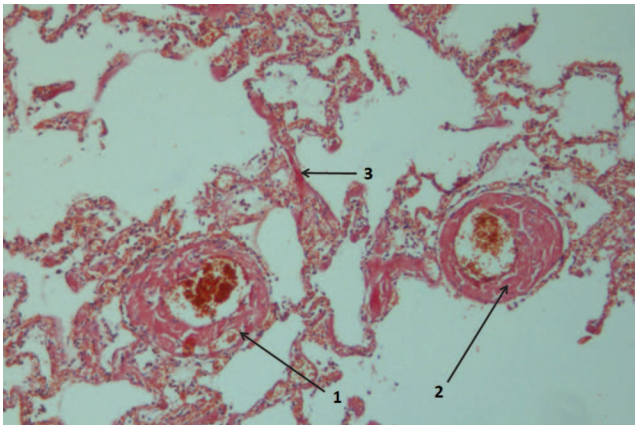

Figure 4. *Lung*
Note. 1,2 — deposits of amyloid masses in the walls of small arteries; 3 — amyloid deposits in the interalveolar septum. Congo red stain; magnification ×20

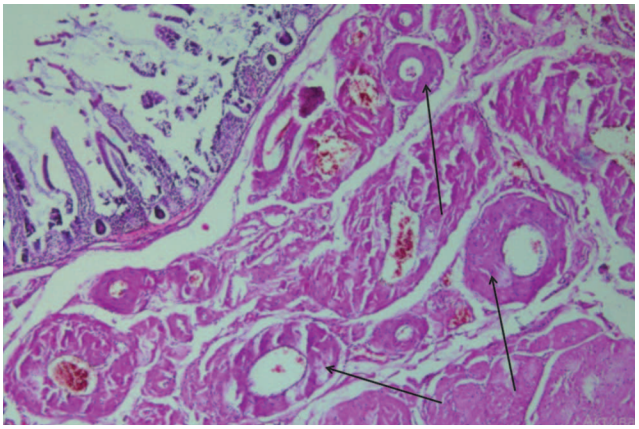

Figure 5. *Small intestine*
Note. Arrows indicate deposits of amyloid masses in many vessels of submucosa. Hematoxylin and eosin stain; magnification ×20

Primary disease complications. CCF with preserved left ventricle ejection fraction, functional class 4 (NYHA). Ascites, bilateral hydrothorax. Transient stage II atrioventricular block, type 1 and 2. Asystole on April 20, 2023. Condition after resuscitation on April 20, 2023.

Comorbidities. Dorsopathy, cervical osteochondrosis. Chronic gallstone pancreatitis. Chronic gastritis. Dolichosigmoid. Sigmoid diverticles. Haemorrhoids.

Postmortem diagnosis.

Primary disease. Primary amyloidosis, involving mostly the heart, with areas of complete replacement of myocardial tissue with amyloid masses in the posterior wall of the left ventricle; with involvement of the atria, valves, coronary and intramural artery walls; with involvement of vessels and walls of pulmonary alveoli, submucosal and muscular GIT layers, mesostenium, extraorganic arteries and renal veins.

Thus, postmortem examination confirmed the diagnosis of systemic amyloidosis. Severe heart damage seen on postmortem data is of utmost interest. Figure 2 shows a gross specimen with areas of complete replacement of the myocardium with amyloid masses. Also, a slide of the heart tissue shows an area of total replacement of the myocardium with amyloid masses, amyloid deposits in myocardial artery walls (Fig. 3). The systemic nature of the damage is illustrated with slides of the lung and small intestine tissue (Fig. 4 and 5, respectively). Kidney damage manifested as amyloid deposits in walls of extraorganic renal arteries and veins; however, no amyloid was found in renal parenchyma. The structure of the renal tissue showed some CCH-associated changes: acute dystrophy-like changes and necrosis of individual tubule cells, interstitial tissue sclerosis of 30 %.

Amyloid was verified using Congo red and dichroism in polarised light. Amyloidosis typing was not performed due to technical reasons.

Discussion

In this case study, the possibility of timely clinical diagnosis of amyloidosis and differential diagnosis of the type of amyloidosis require unconditional discussion. The absence of chronic inflammatory diseases, cancer, involvement mostly of the heart and nervous system rule out secondary AA-amyloidosis. Therefore, the differential diagnosis should include the concept of AL- and ATTR-amyloidosis.

In this patient, the disease started with a neurological pathology — progressive distal symmetric polyneuropathy, which included carpal tunnel syndrome. Over a long time the nervous system pathology was treated as a comorbidity; however, in the absence of diabetes mellitus, excessive alcohol consumption, absence of occupational stress for the wrist, genesis of this pathology was unclear and could be a reason for a deeper examination at the earlier stages of the disease. According to the literature, nervous system involvement is observed in 17 % to 35 % of AL-amyloidosis patients and almost in all patients with various hereditary amyloid polyneuropathies, including ATTR; while bilateral carpal tunnel syndrome is typical for ATTR-amyloidosis [3-5].

In AL-amyloidosis and especially in ATTR-amyloidosis, PH is a common event; this is a circulatory insufficiency, where vessels are no longer able to maintain normal blood pressure during orthostatic loads. Usually, this symptom is associated with dysfunctional sympathetic nervous system (amyloidosis of vessel nerve plexus); it manifests as sickness and blackout during orthostasis with an abrupt rise in BP. In severe cases, postural hypotension is associated with syncope, sometimes it causes an acute cerebrovascular accident. This sign is one of the most important factors of unfavourable prognosis [3, 4]. In this case study, during hospital admission in April 2023, PH was one of the symptoms to assume amyloidosis in this patient. PH was underestimated in the prehospital phase.

An autonomous dysfunction manifests not only as PH. Intestinal wall infiltration with amyloid involvement of intestinal nerve plexus presents as motor diarrhoea with secondary malabsorption, which results in weight loss. True malabsorption is significantly rarer (4–5 %) in amyloidosis [3]. When discussing the causes of significant weight loss, seen in this case study during the last year of the patient's life, impaired muscle trophism in patients with peripheral amyloid polyneuropathy should be taken into account as well.

According to the literature, kidney damage (proteinuria and renal insufficiency) is observed in 80–90 % of AL-amyloidosis patients and only in 20–23 % of patients with ATTR-amyloidosis; and often it is diagnosed after the heart and peripheral nervous system have been damaged [4]. This sequence of symptoms was observed in this clinical case: proteinuria was diagnosed just several weeks before death, during hospitalisation in April 2023. The cause of proteinuria is another topic for discussion. According to postmortem study results, the patient did not have amyloid damage to her renal parenchyma, but had amyloid deposits in extraorganic renal vessels, which is another argument for ATTR-amyloidosis. Proteinuria was likely to be a result of renal congestion because of progressive CCF, confirmed by morphological changes in renal parenchyma

in the form of protein degeneration and necrosis of tubule cells and interstitial tissue sclerosis.

Heart damage develops in a majority of patients with AL-amyloidosis and in 50–60 % of patients with ATTR-amyloidosis. In the clinical presentation of ATTR-amyloidosis, heart damage can be the most important symptom [3,4,6]. Patients with ATTR are known to have significantly thicker myocardium (median value: 17 mm, interquartile range: 16–18 mm) vs. AL patients (median value: 15 mm, interquartile range: 13–16.5 mm) [7]. The association between the life expectancy after first signs of the disease and the amyloid type has been confirmed. In AL-amyloidosis, the median survival rate with the natural course is less than 12 months. If left untreated, usually it takes ATTR-anyloidosis 5–15 years to progress to the terminal damage to the heart or nervous system; the median survival rate is 57 months [8]. In this case study, myocardial involvement was prevailing; myocardium was 20 mm thick, disease duration from onset of clinical symptoms (carpal tunnel syndrome) to death was 43 months.

When discussing differential diagnosis of AL- and ATTR-amyloidosis, a possible observation is that in this case study, the clinical data together with postmortem examination results are a very strong evidence of ATTR-amyloidosis. This conclusion is based mostly on the presence of some signs typical for ATTR-amyloidosis and unusual for AL-amyloidosis, such as bilateral carpal tunnel syndrome, absence of renal involvement and life expectancy of 43 months after onset of the disease. It is worth noting that pronounced cardiomyopathy, where the myocardium was 20 mm thick, is also typical for ATTR-amyloidosis. PH is reported in both forms of amyloidosis and is, therefore, irrelevant. Periorbital skin purpura, which was observed at the end stage of the disease and which is most typical for AL-amyloidosisa, cannot be the primary differentiating symptom.

In this case study, it is only at the late stage when echoCG showed a myocardium pathology typical for amyloidosis: high grainy myocardium reflectivity, significantly thicker myocardium, restrictive impairment of the LV diastolic function with preserved EF, dilated atria. Interestingly, in the presence of refractory CCF and systemic pathology, dynamic echoCG is advisable (in this case, the interval between echoCG examinations was 8 months). Of note, the role of echoCG in the diagnosis and evaluation of cardiac amyloidosis prognosis is much higher with the emergence of highly informative modes of tissue Doppler examinations (strain, strain rate and speckle-tracking) [3]. The use of strain and strain rate methods in patients with systemic amyloidosis demonstrates that despite prevalence of diastolic cardiac insufficiency in amyloid cardiomyopathy and relatively late reduction in LV ejection fraction, the most early sign of heart involvement is reduced global LV longitudinal strain [9].

At present, the diagnosis of heart amyloidosis includes two important stages: suspicion phase and definite diagnosis phase. Myocardial amyloidosis should be suspected when the left ventricle wall is at least 12 mm thick in combination with red flags of amyloidosis: at least one extracardiac (polyneuropathy, bilateral carpal tunnel syndrome, standalone dysfunction, macroglossia, skin bruising, proteinuria, renal insufficiency) and cardiac signs (cardiac failure with disproportionately high NT-proBNP levels, unexplained right-side heart failure with preserved ventricle and valve ejection fraction, idiopathic pericardial effusion, persistently high troponin levels, disproportionately low QRS voltage or early conduction abnormalities) [5].

The definite diagnosis phase is based on detection of diagnostic criteria of amyloidosis, which can be both invasive and non-invasive. Invasive diagnostic criteria (detection of amyloid fibrils in cardiac tissue or non-cardiac amyloid together with the typical signs on echoCG or heart MRI) can be used in any form of heart amyloidosis, whereas non-invasive criteria are used only for ATTR [5]. Non-invasive criteria include heart MRI with delayed Gd contrasting, which allows diagnosing heart amyloidosis in 47 % of patients, even with normal myocardium wall thickness [6]. Also, heart amyloidosis can be diagnosed using scintigraphy with 99mTc-pyrophosphate and 99mTc-3,3-diphospho-1,2-propanodicarboxylic acid (99mTc-DPD). Intensive imaging agent accumulation in the myocardium together with unspecified myocardium thickness is an indication of highly probable ATTR-amyloidosis, if AL-amyloidosis has been ruled out [4]. The diagnostic algorithm also includes amyloid typing, which is essential for specific therapy.

In this case study, the full algorithm for amyloidosis diagnosis was not implemented. The diagnostic experience in this observation was limited to suspicion of this pathology. On the one hand, the untimely diagnosis of heart amyloidosis was due to the late onset of cardiac symptoms. On the other hand, non-cardiac signs of the disease, a wide array of clinical manifestations were evaluated only at the advance stage of the disease, and no active timely diagnostic search was performed. Besides, diagnostic challenges can be associated with inadequate awareness of doctors of the signs of ATTR-amyloidosis, the distinctive feature of which is renal non-involvement in 80 % of cases.

Conclusion

Nowadays, clinicians are able to timely diagnose amyloidosis with heart damage. Despite the advancements and better availability of instrumental methods of examination, timely initiation of diagnostic search is still very relevant.

The totality of clinical symptoms, primarily a combination of progressive neuropathy and signs of unspecified cardiopathy and progressive CCF, allows suspecting amyloidosis and initiating diagnosis verification, including amyloidosis typing. Only early diagnosis can ensure that the new therapies are efficient. The recent years have been remarkable for significant success in the therapy of both AL- and ATTR-amyloidosis, which is a result of clinical introduction of proteasome inhibitor bortezomib in the therapy of AL-amyloidosis, primarily as part of multiple myeloma patient care [4], as well as transthyretin stabilisers, particularly tafamidis. Efficacy and safety of tafamidis in polyneuropathy progression inhibition have been confirmed, especially at early stages, as well as for better survival rates in patients with hereditary myocardial ATTR-amyloidosis [10]. It imposes specific requirements to early diagnosis of myocardial amyloidosis, where the key factor is adequate doctor awareness of this pathology.

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Волошинова Е.В.: разработка концепции и дизайна, обоснование и написание рукописи, анализ и интерпретация данных; согласие автора быть ответственным за все аспекты работы.

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Voloshinova E.V.: conceptualization and design, justification and writing of the manuscript, analysis and interpretation of data; author's agreement to be responsible for all aspects of the work.

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