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EARLY DETECTION AND CONTROL OF RISK FACTORS FOR CARDIOVASCULAR DISEASES IN THE ARAL REGION: EXPERIENCE OF UZBEKISTAN

<i>Aim</i>	To analyze the results of screening of the population older than 40 years for early detection of risk factors for cardiovascular diseases in real clinical practice of family clinics in the Aral Sea region.
<i>Material and methods</i>	The results of screening of the population older than 40 years were analyzed for a total of 2,430 respondents from family clinics of the district (Republic of Uzbekistan, Republic of Karakalpakstan, Ellikkala district) according to the modified WHO PEN protocol. 1,020 of the respondents with blood pressure $\geq 140/90$ mm Hg were included in the study (mean age, 57.68 ± 8.06 years; women, 61.4%; men, 38.6%). Additionally, the following parameters were determined: salt-taste threshold using the R. Henkin method, echocardiography, ultrasonography of the brachiocephalic arteries, blood lipid spectrum, microalbuminuria, serum creatinine and uric acid. Statistical data are presented as mean \pm SD. The prevalence of signs in the study group was assessed using the Pearson's chi-square test, and the Pearson correlation coefficient was used.
<i>Results</i>	Among the patients with elevated blood pressure included in the study, 24 (2.4%) were younger than 40 years, 847 (81%) were 40–65 years old, and 169 (16.6%) were older than 65 years. Low cardiovascular risk was twice more common among women compared to men: 11.3% vs. 5.6% ($\chi^2=8.990$; $p=0.003$); almost 75% fewer patients with ischemic heart disease, 7.4% vs. 28.9% ($\chi^2=14.939$; $p=0.0001$); however, the incidence of type 2 diabetes mellitus was twice higher, 13.7% vs. 7.4% ($\chi^2=9.205$; $p=0.002$); the female group had significantly fewer cases of postinfarction atherosclerosis (PICS) ($\chi^2=5.313$; $p=0.021$). Among women, there were no tobacco users or regular alcohol drinkers whereas among men these risk factors were identified in 59.4% ($\chi^2=178.848$; $p=0.0001$) and 35% ($\chi^2=82.238$; $p=0.0001$), respectively. 85.6% of the respondents had a high salt-taste threshold, 96% had left ventricular hypertrophy, 76% had microalbuminuria, 21% had proteinuria, and 92% of both men and women had a common carotid artery intima-media thickening >0.9 mm.
<i>Conclusion</i>	The study showed a broad prevalence of cardiovascular risk factors in the population of hypertensive patients in the Aral region, a high salt-taste threshold, and significant damages to target organs, which differed from other regions of Uzbekistan. Among hypertensive men, there was a significant prevalence of tobacco and alcohol use, and a significantly more frequent detection of ischemic heart disease, PICS and hyperuricemia compared to women; in the female population, the prevalence of type 2 diabetes mellitus was significantly greater.
<i>Keywords</i>	Arterial hypertension; cardiovascular risk; Aral region; damage to target organs
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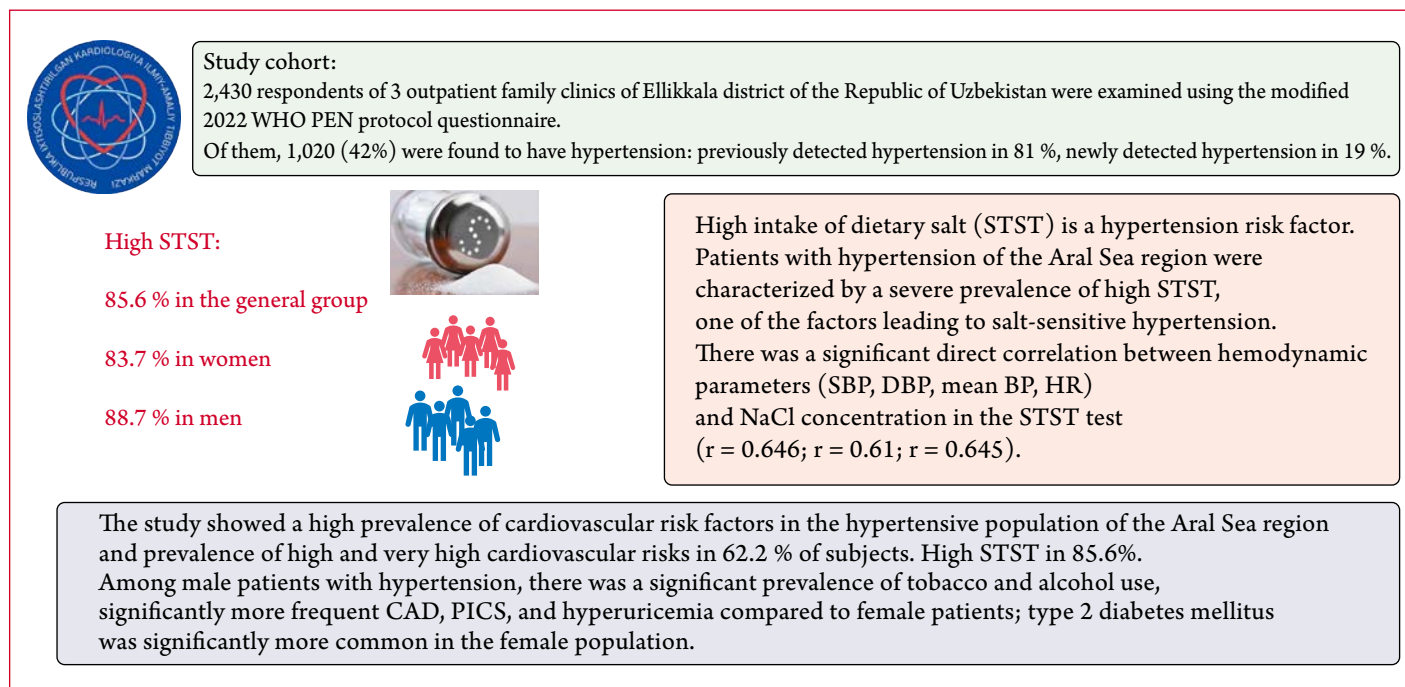
Introduction

The Republic of Uzbekistan is a rapidly developing country, both economically and demographically. Since 1991, the country's population has increased 1.5-fold and is expected to exceed 36 million by the first half of 2023 (<https://stat.uz>). In line with positive demographic changes, morbidity, and mortality from non-communicable diseases (NCDs), including circulatory system diseases (CSDs),

have been rising. In 2019, CSDs caused 83.5% of all deaths in Uzbekistan (702.8 cases per 100,000 people). CSDs take the first place in overall mortality – 63.3% (583.2 cases per 100,000 people): mainly coronary artery disease (CAD), hypertension, and their complications (myocardial infarction, cerebral stroke, etc.). [1].

Identifying the most common risk factors and controlling the prevalence of NCDs are prerequisites for

Central Illustration. Early detection and control of cardiovascular risk factors in the Aral Sea region: the experience of Uzbekistan



developing appropriate, effective health care strategies and planning NCD prevention activities. For this purpose, a study on the prevalence of NCD risk factors based on the WHO STEPS approach was conducted in Uzbekistan in July-September 2019. It included 3 main steps: interviewing respondents to collect social, demographic, and behavioral data; conducting examinations, including measurement of height, weight, blood pressure (BP), heart rate, and assessment of biochemical parameters. The total sample size was 4,320 respondents and the study coverage was 88.3% of the respondents. According to the STEPS (2019) study, the detectability of cardiovascular disease (CVD) risk factors in the adult population of Uzbekistan was analyzed. It was found that:

- 16.5% of the population use various types of tobacco (smoking and smokeless) and 4.7% use alcohol;
- 16% of the population consumes less than five servings of fruits and/or vegetables a day, more than one-third (36.6%) always or often adds salt or salt sauce to foods before or during meals, and more than one-third (36.2%) always or often consumes processed foods high in salt;
- 26.1% of the population does not meet the WHO recommendations for physical activity necessary to maintain good health;
- 38% of residents aged 18–69 years, including those taking antihypertensive therapy in the previous month, have elevated BP ≥ 140 mm Hg and/or ≥ 90 mm Hg;
- 32.9% of the population is overweight, 23.5% is obese, and more than half of men (64.4%) and women (55.4%) have abdominal obesity.

- 8.4% of the population has elevated blood glucose levels or take antidiabetic medication, 13.5% have abnormal fasting blood glucose. [1].

The results of the STEPS study allowed attaining a proper perspective on the current prevalence of CVD risk factors in the country's adult population and largely determined the approaches to NCD prevention in Uzbekistan for the coming years. The Decree No. 103 of the President of the Republic of Uzbekistan dated 26.01.2022 "On measures to prevent and improve the quality of treatment of cardiovascular diseases" (hereinafter Presidential Decree No. 103) was the cardinal solution to reduce the burden of cardiovascular morbidity and mortality. It provided for improving the quality of cardiological and cardiac surgery services provided to the population, expanding measures for prevention, early detection, and effective treatment of CVDs in the regions, creating favorable conditions for patients and flawless provision of essential drugs [2]. The organization of periodic medical examinations by primary health care institutions and the widespread promotion of healthy lifestyles are the main areas of CVD prevention. For this purpose, it is planned to drastically increase the role of medical teams working with the population in outpatient family clinics of primary health care in the prevention and early detection of CVDs.

According to Presidential Decree No.103, annual preventive examinations of the population aged 18 to 40 years with assessment of the health profile (nutrition, tobacco dependence, body mass index, BP, blood glucose and cholesterol, etc.) are organized since 2022; targeted screening examinations of the population aged over 40 years

are conducted at least once a year. Careful work on early detection of risk factors and patients with CVDs, increasing treatment coverage, targeted and timely application of high-tech interventions over the past 4 years (2019-2023) has reduced cardiovascular mortality by 10% in the second half of 2023 amounting to 53% (www.president.uz).

The expert team of the Republican Specialized Scientific and Practical Medical Center of Cardiology set out to analyze the results of screening of the population over the age of 40 for early detection of high BP and other cardiovascular risk factors in the real-world clinical practice of outpatient family clinics in the Aral Sea region.

Material and Methods

The study was conducted in Ellikkala district, Karakalpakstan. The results of screening of the population over the age of 40 (a total of 2,430 respondents) in outpatient family clinics of the district were analyzed according to the WHO's PEN protocol modified for Central Asia and Transcaucasia [3]. The study protocol was reviewed and approved by the ethics committee of the Republican Specialized Scientific and Practical Medical Center of Cardiology on December 10, 2022 (Protocol No.6). The screening was performed by the patronage nurses during home visits and in the pre-doctor service office in outpatient family clinics using a mobile application for cardiovascular risk assessment based on the PEN protocol. From the total number of respondents ($n=2430$), individuals with high systolic and diastolic BP ≥ 140 mm Hg and ≥ 90 mm Hg (SBP and DBP, respectively) were selected ($n=1020$) including both newly diagnosed patients and patients who had previously been diagnosed with hypertension but had not achieved BP control.

All included patients underwent BP measurement using the Korotkoff method, anthropometry, waist circumference measurement, electrocardiogram; 10 year risk of fatal and non-fatal cardiovascular complications was calculated using a mobile calculator based on the WHO's PEN protocol: green $<5\%$ and yellow $5\% < 10\%$, the two groups differed in frequency of examinations per year; they were attributed to the following groups: low risk; orange $10\% < 20\%$ – moderate risk; red $20\% < 30\%$ – high risk; dark-red $\geq 30\%$ – very high risk. To identify additional risk factors and target organ damage (TOD), we performed echocardiography according to generally accepted methods with determination of left ventricular mass index (LVMI), ultrasound examination of brachiocephalic arteries with determination of intima media thickness (IMT) of the common carotid artery; complete blood count and urinalysis, biochemical tests: creatinine (with estimation of glomerular filtration rate – eGFR), fasting blood glucose, serum uric acid; lipid profile and microalbuminuria (MAU). Given that the Aral

Sea region is characterized by unfavorable climate and saline soil and water, all subjects were tested to determine salt taste sensitivity threshold (STST) according to the method by R. Henkin [4]. by applying NaCl solution drop by drop in increasing concentration to the anterior third of the tongue. NaCl solution was prepared by diluting dietary salt in distilled water in concentrations from 0.0025% to 5.12%, with a 2-fold increase in each subsequent sample. Salt taste sensitivity threshold was taken to be the lowest concentration of NaCl solution at which the subject felt salty taste for the first time. Subjects were divided into the groups of low STST $\leq 0.08\%$, medium STST = 0.16%, and high STST $\geq 0.32\%$.

The study did not include patients with hypertension supervised in the outpatient family clinics and having disability due to CVDs. The study was limited by the fact that, according to the study protocol, only persons with hypertension were examined rather than the entire population over the age of 40 who underwent primary screening.

The results were statistically processed in Statistica 6.0. The main characteristics are presented as means (M) and standard deviations (SD). Pearson's χ^2 method was used to evaluate the incidence of signs in the study group. Pearson's correlation criterion was used to determine the presence or absence of a linear correlation between two quantitative indicators and to assess its statistical significance. For all types of analyses, p -values < 0.05 were considered statistically significant.

Results

After screening, 1020 patients with BP $\geq 140/90$ mm Hg were included in the study, representing 42% of the sample population ($n=2,430$): women – $n=626$ (61.4%), men – $n=394$ (38.6%). Of those, 194 patients were newly diagnosed with hypertension (19%), 826 (81%) had previously been diagnosed with hypertension, but BP was not controlled, although many were on antihypertensive therapy (AHT). The clinical characteristics of the patients are shown in Table 1.

Among those included in the study, 24 patients (2.4%) with high BP were younger than 40 years, 847 (81%) were aged 40–65 years, and 169 (16.6%) were older than 65 years. Although there were more women among them, there was no statistically significant difference in such clinical parameters as age, duration of hypertension, BP level and degree of hypertension, HR, BMI, and WC, hypodynamia, aggravated family history of CVDs, blood lipid profile, and fasting blood glucose. At the same time, low cardiovascular risk was 2 times more common in women than in men: 11.3% versus 5.6% ($\chi^2 = 8.990$; $p = 0.003$); almost 4 times less had CAD: 7.4% versus 28.9% ($\chi^2=14.939$; $p=0.0001$);

but twice as many patients with type 2 DM: 13.7% versus 7.4% ($\chi^2=9.205$; $p=0.002$); there was a slight prevalence of obesity: 49% versus 42%; post-infarction atherosclerosis was significantly less common ($\chi^2=5.313$; $p=0.021$); there were no tobacco users and no regular alcohol users consuming more than the WHO recommended amount, whereas these risk factors were present in 59.4% ($\chi^2=178.848$; $p=0.0001$) and 35% ($\chi^2=82.238$; $p=0.0001$) of male patients, respectively, which is much higher than the rates reported in the Uzbek population in the STEPS study. Other risk factors not included in the PEN protocol and markers of hypertension-related TOD were further investigated (Table 2).

As shown in Table 2, the patients with hypertension from the Aral Sea region were characterized by a pronounced prevalence of high STST (85.6% of the general group, 83.7% of women, 88.7% of men), which required on average more than 0.32% NaCl concentration for threshold estimation. There was a direct correlation between hemodynamic parameters (SBP, DBP, mean BP, HR) and NaCl concentration in the STST test ($r = 0.646$; $r = 0.610$; $r = 0.645$; $r = 0.642$, respectively). The dietary questionnaire based on the PEN protocol also showed that 68% of subjects added more salt to food and/or ate pickles, with a slight difference between women and men: 61.2% and 72.6%, respectively, which was significantly higher than similar rates in the Uzbek population in the 2019 STEPS study.

Among the TOD markers, a high incidence of MAU (76% of cases) and proteinuria (21%), with no significant difference between women and men, should be mentioned, while $GFR < 60 \text{ mL/min/1.73 m}^2$, reflecting the onset of chronic kidney disease, was detected in almost a quarter of the subjects: 24.1% (women 22.2%, men 27.2%). Hyperuricemia was detected in 13% of subjects and was more prevalent in men: 23.3% versus 6.4% ($\chi^2=60.243$; $p=0.0001$).

Common carotid artery IMT (mean 1.22 mm) exceeded the threshold ($< 0.9 \text{ mm}$) in 92% of cases with no statistical difference between women and men, indicating the presence of vascular remodeling. Left ventricular hypertrophy (LVH) was detected in 96.3% of patients with hypertension according to LVMI, and the frequency of LVH was similar in women and men.

Discussion

The study showed the relevance of annual screening in the adult population with identification and control of cardiovascular risk factors using the modified WHO PEN protocol and a mobile calculator based on the protocol questionnaire. Cardiovascular risk is assessed by patronage nurses both at home and in the pre-doctor service offices, which unloads the family physicians, simplifies the routing

Table 1. Clinical characteristics of the Aral Sea region residents with high BP (PEN protocol)

Parameters	General group, n = 1020
Age, years	57.68 ± 8.06
Duration of hypertension, years	7.88 ± 3.35
Body mass index, kg/m²	29.86 ± 5.28
Waist circumference, cm	104.59 ± 11.61
Obesity, n (%)	471 (46.2)
Systolic BP, mm Hg	168.9 ± 17.56
Diastolic BP, mm Hg	99.3 ± 10.03
Hypertension grade:	
Grade 1, n (%)	160 (15.7)
Grade 2, n (%)	557 (54.6)
Grade 3, n (%)	303 (29.7)
HR, bpm	84.1 ± 7.2
TC, mg/dL	201.14 ± 36.26
TG, mg/dL	236.85 ± 54.32
LDL-C, mg/dL	112.23 ± 23.47
HDL-C, mg/dL	41.65 ± 6.03
Fasting plasma glucose, mmol/L	5.72 ± 1.88
CAD, n (%)	160 (15.7)
DM type 2, n (%)	115 (11.3)
CVA, n (%)	5 (0.49)
PICS, n (%)	12 (1.17)
Burdened family history, N (%)	489 (47.9)
Hypodynamia, n (%)	689 (67.5)
Consumption of 4 servings of vegetables and fruits, n (%)	120 (11.8)
Tobacco use (smoking and smokeless), n (%)	243 (23)
Alcohol use, n (%)	138 (13.5)
Cardiovascular risk (PEN protocol):	
Low, n (%)	93 (9.1)
Medium, n (%)	293 (28.7)
High, n (%)	375 (37)
Very High, n (%)	259 (25.2)

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CAD, coronary artery disease; DM, diabetes mellitus; CVA, acute cerebrovascular accident; PICS, postinfarction atherosclerosis; PEN, package of essential noncommunicable (disease interventions).

of patients at high and very high risk, and allows conducting targeted diagnostic examination and treatment.

Our findings showed a high prevalence of hypertension as one of the main cardiovascular risk factors in the adult population of the Aral Sea region. Hypertension was detected in 42%, although we did not adhere strictly to the criteria of the epidemiological study. The prevalence of hypertension in the Aral Sea region is consistent with the results of the PURE [5] and ESSE-RF [6] studies conducted in the Russian Federation, and slightly higher than the STEPS results for Uzbekistan. Eighty-one percent

Table 2. Additional determination of risk factors and markers of target organ damage in examined patients with hypertension

Parameters	General group
NaCl concentration (R. Henken)	0.57 ± 0.55 [median 0.32]
STST grading:	
Low, n (%)	13 (1.3)
Medium, n (%)	134 (13.1)
High, n (%)	873 (85.6)
Creatinine, µmol/L	89.38 ± 27.8
GFR < 60 mL/min/1.73 m ² , n (%)	246 (24.1)
Uric acid, mg/dL	321.19 ± 90.41
Hyperuricemia, n (%)	140 (13.8)
Albuminuria, mg/L	192.96 ± 130.31
Normoalbuminuria, n (%)	31 (3)
Microalbuminuria, n (%)	775 (76)
Proteinuria, n (%)	214 (21)
IMT, mm	
right	1.23 ± 0.21
left	1.22 ± 0.21
LVMI, g/m ²	172.22 ± 44.03

STST, salt taste sensitivity threshold; GFR, glomerular filtration rate; IMT, intima-media thickness of the common carotid artery; LVMI, left ventricular mass index.

of the subjects had previously been diagnosed with hypertension, but their BP was not controlled at the time of screening, and only 19% of the subjects were diagnosed with hypertension for the first time. The study [7] recorded a global BP control rate in patients with hypertension in 2019, which averaged 23 (20-27) % in female patients and 18 (16-21) % in male patients; this rate was within 10% in low- and moderate-income countries and over 50% in Canada, South Korea, and Iceland. It should be noted that two thirds of patients with hypertension in our study, who did not control their BP, mentioned in the questionnaire that they regularly took antihypertensive therapy (AHT), from monotherapy to triple combination therapy, but the lack of routine medical control, possibly inadequate doses and regimen, did not provide proper BP control. According to the results of the examination, hypertension of grade 2 and 3 prevailed, which, together with other risk factors, determined a high frequency of high and very high cardiovascular risk (62.2% in total) and, accordingly, the need for monitoring of such patients by both family physicians and cardiologists. The revealed high frequency of cardiovascular risk factors (hypodynamia, obesity, increased consumption of dietary salt, insufficient consumption of fruits and vegetables) suggests that the time was right for Presidential Decree No. 103, which prescribes the organization of Healthy Eating and Lifestyle offices in every outpatient family clinic.

According to the latest data, more than 3 million people live in the ecologically unfavorable Aral Sea region of Uzbekistan (<https://stat.uz>). The drying up of the Aral

Sea in Karakalpakstan and the Khorezm region often leads to salt and dust storms, which cause the deterioration of the ecological situation and negatively affect human health. The Aral Sea disaster has seriously affected the health of the local population. The number of cases of high BP has increased sixty-fold in the past twenty years, and the rates of urolithiasis and liver disease have increased seven times [8]. Given the drying of the Aral Sea and the formation of a large saline layer, the migration of salt particles with sandstorms and their contamination of soil and water can be expected, leading to increased salt consumption by the local population. The significance of high dietary salt intake as a cardiovascular risk has been demonstrated in many epidemiological and original studies [9–11]. In particular, BP increases with age more often in people who consume more dietary salt according to the INTERSALT study. In healthy people aged 25–55 years, an increase in dietary salt intake by every 10 mmol (0.6 g) increases SBP by 0.9 mm Hg. Reducing the amount of daily dietary salt intake by 6 g (100 mmol) reduces the risk of cardiovascular death by 16% and the risk of stroke by 23% [10].

In our study, we applied a screening method for determining STST according to R. Henkin. Needless to say, more accurate quantitative methods, such as Kharchenko's test [11] and determination of 24-hour NaCl excretion, are recommended for the diagnosis of salt-sensitive hypertension. However, our previous studies showed a positive correlation ($r=0.309$, $p=0.001$) of the mean BP increase during oral salt load according to the method by V.I. Kharchenko with NaCl concentration during the STST test according to the Henkin method, which allows considering patients with high STST as patients with salt-sensitive hypertension [12]. Our studies on salt-sensitive hypertension in the Toshkent population showed a significant predominance of patients with high STST compared to medium and low STST both in the general group ($n = 296$) and when divided by sex: 61.9% versus 21.2% and 16.9%, respectively ($\chi^2=104.905$; $p=0.000$) [12]. In contrast, the analysis of 148 healthy subjects showed a predominance of low STST compared to medium and high STST:

40.6% versus 35.1% and 24.3%, respectively ($\chi^2 = 17.065$; $p = 0.000$) [13]. This study showed that high STST was predominant in patients with hypertension in the Aral Sea region due to a decrease in medium and low STST (85.6% versus 13.1% and 1.3%, respectively, $\chi^2 = 1912.0$; $p = 0.000$), which characterizes the high prevalence of salt-sensitive hypertension in this part of Uzbekistan.

The high incidence of LVH, increased IMT and MAU determining TOD due to hypertension was shown in our previous work when we studied the peculiarities of development of hypertension complications in the Aral

Sea region [14]. However, differences in the incidence of these TOD markers can be observed when compared with the indicators of hypertensive patients in the population of Toshkent. In particular, the examination of 219 patients with hypertension (60% of female and 40% of male patients), almost one third of whom had grade 3 hypertension, as in our study, LVH was diagnosed in 75% of male patients and 84.4% of female patients [15]. Our results showed severe LVH and a high prevalence (96.3%) in patients with hypertension in the Aral Sea region, regardless of sex. The study showed that LVEF measured by electrocardiography was significantly associated with poor adherence to antihypertensive treatment before stroke in patients with a history of acute stroke. Poor adherence to antihypertensive treatment was independently associated with the presence of albuminuria [7]. According to the data of this study, the lack of adequate BP control in patients with hypertension from the Aral Sea region was accompanied by a high frequency of MAU (76% of cases) and proteinuria (21% of cases).

The study showed a high prevalence of cardiovascular risk factors in the hypertensive population of the Aral Sea region and prevalence of high and very high cardiovascular risk (a total of 62.2% of subjects). Among male patients with hypertension, there was a significant prevalence of tobacco and alcohol use, according to the STEPS criteria, significantly more frequent CAD, PICS, and hyperuricemia compared to female patients; and type 2 diabetes mellitus was significantly more common in the female population. Apparently, insufficient treatment coverage and ineffective BP control in Aral Sea region patients with hypertension, along with the environmental impact of climate, drinking water and soil pollution, leads to severe TOD (heart, blood vessels, kidneys), which requires physicians to improve their knowledge in choosing hypertension treatment regimens, using fixed drug combinations and careful outpatient monitoring.

The results of our study showed the importance of routine screening of the population over the age of 40 based on the modified PEN protocol with the calculation of cardiovascular risk using the mobile application to simplify

the work of patronage nurses, and to restore the functions of pre-doctor service offices, which have lost their relevance in the last 15–20 years. Introduction of the Henkin method of determining STST into clinical practice of outpatient family clinics with the possibility of conducting the test in the pre-doctor service offices will not require additional financial costs and will make it possible to prevent the negative impact of increased dietary salt consumption as a marker of unfavorable cardiovascular prognosis in the population. Further studies are needed to identify additional factors influencing the prognosis of patients with hypertension in the Aral Sea region, considering the current environmental situation and the impact of unfavorable factors on the incidence of NCDs and especially CVDs.

Conclusion

The study showed a high prevalence of cardiovascular risk factors among hypertensive population of the Aral Sea region and prevalence of high and very high cardiovascular risks in 62.2% of the study population, which was significantly higher in the male population.

A large prevalence of high salt taste sensitivity threshold in the study population was revealed – in 85.6% of cases, both among male and female patients. A direct correlation of sodium chloride concentration in the salt taste sensitivity test and blood pressure was noted.

Among male patients with hypertension, there was a significant prevalence of tobacco and alcohol use, significantly more frequent CAD, PICS, and hyperuricemia compared to female patients; type 2 diabetes mellitus was significantly more common in the female population.

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