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Sodium sensitivity / sodium resistance in patients with arterial hypertension: effect on lipids profile, glucose level, clinical and anthropometric parameters

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The objective: **to determine the lipid metabolism, glucose level, individual clinical and anthropometric indicators depending on sodium sensitivity/sodium resistance and gender in patients with essential arterial hypertension (EAH).**
***Materials and methods*. 100 patients with stage II EAH and 60 practically healthy individuals of the control group took part in the study. All persons underwent a complex of clinical and laboratory examinations. Sodium sensitivity/sodium resistance was determined according to the method of M.H. Weinberger. Metabolism was analyzed according to the lipid profile (total cholesterol, high- and low-density lipoproteins – HDL-C, LDL-C, atherogenicity coefficient, triacylglycerols – TG), glucose, creatinine, cystatin-C, bilirubin and albuminuria in blood. Body mass index (BMI), waist circumference (WC), hip circumference (HC), their ratio (WC/HC) were also determined.**
***Results*. The course of EAH in sodium sensitivity patients is characterized by higher BMI and WC than in sodium resistance patients, regardless of gender – by 29.32–33.54% ($p < 0.001$) and 15.02–23.40% ($p < 0.001$), a higher ratio WC/HC, but only in men – by 8.51% ($p = 0.003$), which is probably greater than that in women of all study groups by 6.82–28.75% ($p \le 0.028$–0.001). At the same time, sodium sensitivity hypertensive men had marginally higher albuminuria – by 42.34% ($p = 0.05$) and higher blood levels of creatinine and cystatin-C than sodium resistance men – by 11.39% ($p = 0.022$) and 11. 88% ($p = 0.022$), which causes a lower estimated glomerular filtration rate, but probably only for cystatin-C – by 12.23% ($p = 0.044$), respectively.**
Probable differences, taking into account sodium sensitivity, were not found in the blood pressure levels, lipid and glucose concentrations in the patients. In the control group sodium sensitivity individuals have a higher TG level than sodium resistance individuals – by 58.50% ($p = 0.011$) with lower HDL cholesterol in both women and men – by 15.82% ($p = 0.004$) and 41.04% ($p = 0.004$), respectively.
***Conclusions*. Sodium sensitivity in EAH patients is associated with changes in certain anthropometric parameters (higher BMI, WC) regardless of gender and metabolic factors (greater albuminuria, higher levels of cystatin-C and blood creatinine, WC/HC), but only in men.**
Keywords: *sodium sensitivity, sodium resistance, arterial hypertension, lipids, anthropometry, cystatin-C, creatinine, albuminuria.*

Солечутливість / солерезистентність у хворих на артеріальну гіпертензію: вплив на жировий обмін, рівень глюкози, окремі клініко-антропометричні параметри

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Мета дослідження: визначення ліпідного обміну, рівня глюкози, окремих клініко-антропометричних показників залежно від солечутливості/солерезистентності та статі у хворих на есенціальну артеріальну гіпертензію (ЕАГ).
***Матеріали та методи*.** У дослідженні взяли участь 100 хворих на ЕАГ II стадії та 60 практично здорових осіб групи контролю. Усім обстеженим проведено комплекс клініко-лабораторних обстежень. Солечутливість/солерезистентність визначали за методикою M. H. Weinberger Метаболізм аналізували за ліпідним профілем (загальним холестеролом, ліпопротеїнами високої і низької щільностей – ХС ЛПВЩ, ХС ЛПНЩ, коефіцієнтом атерогенності, триацилгліцеролами – ТГ), вмістом у крові глюкози, креатиніну, цистатину-С, білірубіну та альбумінурією. Також визначали індекс маси тіла (ІМТ), обвід талії (ОТ), стегон (ОС), їх співвідношення (ОТ/ОС).
***Результати*.** Перебіг ЕАГ у солечутливих пацієнтів характеризується більшим ІМТ та ОТ, ніж у солерезистентних, незалежно від статі – на 29,32–33,54% ($p < 0,001$) та 15,02–23,40% ($p < 0,001$), вищим співвідношенням ОТ/ОС, але тільки у чоловіків – на 8,51% ($p = 0,003$), що вірогідно переважає такий у жінок усіх груп спостереження на 6,82–28,75% ($p \le 0,028$–$0,001$). Водночас у солечутливих гіпертензивних чоловіків виявлено пограничо більшу альбумінурію – на 42,34% ($p = 0,05$) та вищі рівні у крові креатиніну і цистатину-С, ніж у солерезистентних – на 11,39% ($p = 0,022$) і 11,88% ($p = 0,022$), що зумовлює нижчу розраховану швидкість клубочкової фільтрації, але вірогідно тільки за цистатином-С – на 12,23% ($p=0,044$) відповідно. Вірогідних відмінностей з урахуванням солечутливості у хворих за рівнями АТ, концентрацією в крові ліпідів та глюкози не виявлено. У групі контролю у солечутливих осіб вміст ТГ вище, ніж у солерезистентних – на 58,50% ($p = 0,011$) за нижчого ХС ЛПВЩ як у жінок, так і чоловіків – на 15,82% ($p = 0,004$) і 41,04% ($p = 0,004$) відповідно.
***Висновки*.** Солечутливість у хворих на ЕАГ асоціює зі змінами окремих антропометричних параметрів (вищими ІМТ, ОТ) незалежно від статі та метаболічних чинників (більшою альбумінурією, вищими рівнями цистатину-С і креатиніну крові, ОТ/ОС), але тільки у чоловіків.
Ключові слова: *солечутливість, солерезистентність, артеріальна гіпертензія, ліпіди, антропометрія, цистатин-С, креатинін, альбумінурія.*

Arterial hypertension (AH) has become the leading cause of premature death on the planet, affecting 1.28 billion adults between the ages of 30 and 79. Most patients (2/3) live in low- and middle-income countries [1]. But almost 50% of them do not know about this disease. Whereas essential AH (EAH) insidiously affects target organs (vessels, heart, brain, kidneys, etc), regardless of whether a person is aware of the AH or not, becoming one of the leading causes of death worldwide [2, 3].

Hypertension and chronic kidney disease (CKD) are linked tightly, since AH can lead to nephron function deterioration and progressive CKD can contribute to the worsening of hypertension [4]. The pathophysiology of CKD comorbid with hypertension is complex and includes the various factors interaction: a decrease in the functioning nephrons number, sodium retention and fluid volume increase, sympathetic nervous system stimulation, RAAS system activation, oxidative stress, endothelial dysfunction, metabolic changes, genetic factors etc [5–7].

All these factors affect patients in different ways, depending on their individual sensitivity to sodium, which determines the volume-dependent mechanisms of blood pressure (BP) elevation activity. Therefore, preclinical or early clinical diagnosis of EAH, as well as the search for risk factors of CKD appearance linked to hypertension, depending on sodium sensitivity, is important. In view of the above, it was considered to investigate some metabolic disorders depending on salt sensitivity.

The objective: to investigate the lipids' metabolism, glucose level and some clinical and anthropometric data depending on sodium-sensitive (SS) / sodium-resistance (SR) and gender in EAH patients.

MATERIALS AND METHODS

EAH patients were selected in accordance with the guidelines and recommendations of the National Ukrainian and European Societies of Cardiology and Hypertension (ESC, ESH 2018, 2023) [8, 9]. The research protocol was approved by the Bioethics commission at the Bukovinian State Medical University (Protocol №2 from 19.10.2023). 100 patients with Hypertension-mediated organ damage (IInd stage), 1st-3rd degrees of arterial blood pressure (BP) elevation, moderate, high, or very high cardiovascular risk were screened and selected for the study. Inclusion and exclusion criteria are listed in the former publication [10, 11]. The patients age ranged from 45 to 70 years (59.87 ± 7.98 years on average), 21.0% of them were men, 79.0% were women. The control group consisted of 60 practically healthy people (22 men (36.67%), 38 women (63.33%)), aged 44.39 ± 5.92 years ($p < 0.001$). The groups did not differ by sex. All participants signed an informed consent to participate in the study.

Comprehensive examination included: general clinical tests, anthropometric (waist and hip circumference (WC, HC), waist-to-hip ratio (WHR)), body mass index, (BMI), laboratory tests (general blood and urine tests, urine protein, fasting plasma glucose, serum creatinine, cystatin-C, bilirubin, lipid spectrum), instrumental (12-lead ECG, Echocardiogram, office blood pressure (BP), ultrasound of the kidneys), as well as consultations of an ophthalmologist and a neurologist, if necessary.

Obesity was identified by BMI increase ≥ 30 kg/m^2, BMI ≤ 24.9 kg/m^2 was considered normal, and BMI 25–29.9 kg/m^2 was considered overwight [8, 9]. The lipid panel was studied using colorimetry after serum content of total cholesterol (TC), triacylglycerols (TG) and high-density lipoprotein cholesterol (HDL-C). Serum low-density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald equation, atherogenicity index (AI) – according to Klimov's equation [6, 10].

WC was considered as increased for men (M) > 102 cm, for women (W) > 88 cm; WHR increased in W > 0.85 U, in M > 0.95 U. All examined participants had objective signs of Hypertension-mediated organ damage (EAH IInd stage) [8, 9]. Compensated DM type 2 (T2DM) was found in 29% of EAH patients.

CKD was diagnosed in 43 EAH patients according to the US National Kidney Association recommendations (KDIGO 2024) [12]. Glomerular filtration rate (GFR) was estimated (eGFR) using the CKD-EPI equation based on Cystatin-C (cys) and creatinine (cr) serum values (depending on gender) [13]. There were 35 women (44.30%) and 8 men (38.10%) among EAH patients with CKD. A decrease in GFR was defined as ≤ 60 ml/min/1.73 m^2, for ≥ 3 months with or without other signs of kidney damage, according to the KDIGO recommendations (2024) [12].

SS/SR in EAH patients was determined according to Weinberger method (1996) [14]: a high-salt diet (15 g salt/day is equal to 249 mmol sodium/day) administered for 5 days, then restrict salt consumption (2 g/day – 50 mmol sodium/day) for another 5 days. BP was monitored during this period (provided office BP measurement on the last day of the high-salt diet and the last day of the low-salt diet).

Individuals who showed a ≥ 10% difference in the average office BP values under high and low sodium loads were considered «sodium sensitive" (SS), as well as those who showed BP decreased ≥ 10 mmHg, when switching from a high-salt to a low-salt diet (when comparing two BP measurements – on the 5th and 10th days of different salt diets). Individuals with BP decrease ≤ 5 mmHg were assigned to the "sodium resistant" (SR) group, and an intermediate decrease in blood pressure of 6–9 mmHg interpreted as "undetermined" (those who did not demonstrate a clear SS). In our study, 54% of EAH patients were found to be SS, 30% were SR, and the rest (16%) were "undetermined" (but not definitely SS, therefore they were included in SR group).

The statistical analysis carried out by the variation statistics methods using the Statistica v.7.0 software (StatSoft Inc., USA). The differences between groups for independent samples were verified using the unpaired Student's t-test (if the data distribution were close to normal according to the Kolmogorov-Smirnov tests and the Shapiro-Wilk W-test), or the Wilcoxon-Mann-Whitney U-test (for an uneven data distribution). Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

BMI in SS individuals exceeded that in SR subjects, both in controls and EAH, as in women as in men: in the control group – by 18.31% ($p = 0.05$) and 32.78% ($p < 0.001$) in women and men as well, in the study group – by 29.32% and 33.54% ($p < 0.001$), respectively (Table 1). It should be noted that the BMI in EAH women prevailed over that in women of the control group regardless of SS – by 21.30% ($p = 0.002$) and 10.67% ($p = 0.004$). WC was greater in SS than in SR patients – by 15.02% and 23.40% ($p < 0.001$), higher in men than in women – by 11.17% ($p = 0.001$). The WHR also prevailed in SS patients, but only in men – by 8.51% ($p = 0.003$) and was

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significantly higher than in women in all observed groups by 6.82–28.75% ($p \le 0.028–0.001$) respectively.

There were no significant differences in BP values, blood creatinine, Cystatin-C and albuminuria depending on SS/SR in EAH patients, although these parameters were higher than in the control group ($p < 0.001$) (Table 1). However, the presence of SS increases the risk of severe EAH course (SBP/DBP ≥ 160/100 mmHg) more than 2 times (OR = 2.19; OR 95%CI: 1.0–5.05; p = 0.049).

Some parameters of lipids' metabolism were depended on the SS/SR status, but only in the control group (Table 2): the TG level was higher in SS than in the SR subjects – by 58.50% ($p_1 = 0.011$), and HDL-C, on the contrary, was lower in women – by 15.82% ($p_1 = 0.004$), in men – by 41.04% ($p_1 = 0.004$), which led to an increase in the AI, but reliably only in men – by 45.90% ($p_1 = 0.005$). In addition, in men of both groups, the HDL-C level was lower than in women by 16.54–40.60% ($p_W \le 0.042–0.039$), which led to a correspondingly higher AI – by 31.75–57.52% ($p_W \le 0.048–0.006$), but did not have a clear dependence on the salt sensitivity status.

Several studies have demonstrated BP response to dietary sodium intake in the general population [15, 16]. This has led to debates about whether sodium sensitivity and resistance are distinct phenotypes or merely the extremes of a Gaussian distribution of random BP responses to dietary sodium. Some studies have shown that salt sensitivity is a long-term reproducible and stable trait in the general population [16, 17]. The GenSalt Study, which involved 487 Chinese adults undergoing repeated low-sodium (1.180 mg/day) and high-sodium (7.081 mg/day) interventions 4.5 years apart, found significant correlations between initial and repeated BP responses [17]. He J et al [18] identified three distinct subgroups with high sensitivity, moderate sensitivity, and resistance to sodium intake, each with different risks for developing hypertension. These findings reinforce the importance of recognizing sodium sensitivity and resistance as clinical phenotypes for future interventions.

In a retrospective cohort study involving 156 hypertensive patients, SS was associated with a threefold increase in cardiovascular disease risk (Rel Risk 3.05; 95%CI: 1.34–6.89) [19]. Weinberger MH et al in another cohort study, which included 596 participants with normal or elevated blood pressure, found that SS was associated with an increased risk of all-cause mortality (OR=1.73; 95%CI: 1.02–2.94) [20].

Several cross-sectional studies have indicated that high SS is more prevalent in individuals with hypertension compared to those with normal BP [16, 18, 21]. However, it remains unclear whether salt sensitivity precedes the onset of EAH. He J et al in GenSalt study found that individuals with high SS had a significantly elevated hypertension risk developing, regardless of their baseline BP and other established risk factors [22]. Besides, the GenSalt study offered robust evidence that SS is an independent risk factor for EAH. Moreover, the GenSalt study has demonstrated the evidence that SR individuals are at a higher risk for developing hypertension com-

Table 1

Some clinical, biochemical and anthropometric parameters depending on Sodium sensitivity / Sodium resistance and gender

Parameters		Control, n = 60		Patients, n = 100	
		Sodium-sensitive, n = 12	Sodium-resistance, n = 48	Sodium-sensitive, n = 54	Sodium-resistance, n = 46
BMI, kg/m²	W	28.69 ± 2.54	24.25 ± 1.62 $p_1 = 0.05$	34.80 ± 1.58 p = 0.002	26,91±0,92 p = 0.004 $p_1 < 0.001$
	M	33.86±0.49	25.50 ± 0.54 $p_1 < 0.001$	35.95 ± 1.61	26,92±0,77 $p_1 < 0.001$
SBP, mmHg		118.32±1.19	115.83±2.50	155.68 ± 6.18 p < 0.001	149.13 ± 4.61 p < 0.001
DBP, mmHg		76.67±2.76	75.83±2.50	95.81 ± 3.0 p < 0.001	92.17 ± 2.69 p < 0.001
WC, cm	W	86.50 ± 3.87	76.73 ± 3.65	106.05 ± 3.38 p < 0.001	92.20±3.01 $p,p_1 < 0.001$
	M	108.50 ± 0.83 $p_W < 0.001$	93.33 ± 2.93 $p_1;p_W < 0.001$	117.90 ± 4.76 p = 0.035 $p_W = 0.001$	95.54±2.35 $p_1 < 0.001$
WHR, U	W	0.80 ± 0.03	0.78 ± 0.02	0.90 ± 0.02 p = 0.007	0.88±0.02 p < 0.001
	M	1.03 ± 0.03 $p_W = 0.028$	0.92 ± 0.02 $p_W < 0.001$	1.02 ± 0.02 $p_W < 0.001$	0.94±0.015 $p_1,p_W = 0.003$
Total bilirubin, μM/l		18,0 ± 1,50	14.34 ± 2.53	14.04 ± 3.52	13.59 ± 2.92
Serum Creatinin, μmol/l		68,83 ± 3,28	66.11 ± 1.26	78.74 ± 5.09 p = 0.05	78.78 ± 3.64 p < 0.001
Serum Cystatin-C, mg/l		0.88 ± 0,02	0.85 ± 0.025	1.01 ± 0.07 p = 0.05	1.01 ± 0.045 p < 0.001
Urea Albumin, mg/l		0.83 ± 0,24	0.87 ± 0.30	24.70 ± 4.91 p < 0.001	20.97 ± 2.73 p < 0.001

Note. W – women; M – men; WC – waist circumference; BMI – body mass index; SBP / DBP – systolic / diastolic blood pressure; WHR – Waist-to Hip Ratio; p – probability of differences with corresponding control group depending on sodium sensitivity / Sodium-resistance; p1 – probability of differences with sodium sensitivity subjects within every group; pW – probability of differences between men and women within every group according to particular data.

Table 2

Lipids' metabolism data and glucose level depending on salt sensitivity / salt resistance and gender

Parameters		Control, n = 60		Patients, n = 100	
		Sodium-sensitive, n = 12	Sodium-resistance, n = 48	Sodium-sensitive, n = 54	Sodium-resistance, n = 46
Serum glucose, mmol/l		5.45 ± 0.20	5.02 ± 0.23	7.66 ± 1.23 p = 0.025	7.16 ± 1.20 p = 0.004
TC, mmol/l		5.42 ± 0.28	5.58 ± 0.33	5.56 ± 0.44	5.74 ± 0.46
TG, mmol/l		2.33 ± 0.25	1.47 ± 0.24 p_1 = 0.011	2.10 ± 0.36	1.82 ± 0.32
LDL-C, mmol/l	W	4.0 ± 0.29	3.74 ± 0.29	4.0 ± 0.36	4.38 ± 0.36 p = 0.045
	M	3.71 ± 0.17	4.33 ± 0.26	4.39 ± 0.50	3.99 ± 0.42
HDL-C, mmol/l	W	1.33 ± 0.09	1.58 ± 0.15 p_1 = 0.004	1.28 ± 0.17	1.33 ± 0.12 p = 0.011
	M	0.79 ± 0.01 p_W = 0.042	1.34 ± 0.14 p_1 = 0.004	1.12 ± 0.10 p = 0.044	1.11 ± 0.08 p_W = 0.039
AI, U	W	3.39 ± 0.43	2.54 ± 0.31	3.37 ± 0.37	3.61 ± 0.42 p = 0.002
		5.34 ± 0.10 p_W = 0.048	3.66 ± 0.46 p_1 = 0.005 p_W = 0.024	4.44 ± 0.60 p_W = 0.006	3.80 ± 0.40

Note. p – probability of differences with corresponding control group depending on sodium sensitivity / Sodium-resistance; p1 – probability of differences with sodium sensitivity subjects within every group; pW – probability of differences between men and women within every group according to particular data; TC – total cholesterol; TG – triacylglycerols; HDL-C – cholesterol of high-density lipoprotein; LDL-C – cholesterol of low-density lipoprotein; AI – atherogenicity index; W – women; M – men.

pared to those with moderate SS. This finding challenges the conventional belief that normotensive individuals who are resistant to sodium are at a lower risk for EAH [22].

Among potential mechanisms of SR hypertension have been suggested metabolomic and lipidomic profile changes (insulin resistance, obesity, hormones abnormalities), signaling pathways disturbances including sodium and water transporters, endothelial dysfunction, elevated systemic vascular resistance, microbiome influence, genetic predisposition, etc [23–34]. Apart from these mechanisms there are some supportive co-factors of SS and EAH risk such as sex, age, race, baseline BP, physical activity, smoking, alcohol intake, potassium and sodium consumption, eGFR, immune disorders, etc [22, 35–38]. Our study conforms these results: EAH individuals with SS or SR were at an increased risk for EAH, dyslipidemia and glucose level changes without statistically reliable differences between them. But at the same time, SS patients had higher BMI and WC than SR individuals, regardless of gender, by 15.02–33.54%, moreover, men had greater albuminuria by 42.34% and higher serum creatinine and cystatin-C levels, accompanied by lower eGFR – by 12.23%, respectively.

Further research is needed to understand the underlying mechanisms of sodium-sensitive and sodium-resistant in EAH for improving hypertension management and prevention. Genomics research in identifying individuals predisposed to SS or SR hypertension will be crucial for prevention and treatment of hypertension.

CONCLUSIONS

The EAH course in salt-sensitive patients is featured by a higher than in salt-resistant persons BMI and WC, regardless of gender – by 15.02–33.54%, WHR, albuminuria and serum creatinine and Cystatin-C values but only in men – by 8.51%, 42.34% and 11.39% and 11.88%, respectively, that causes a lower eGFR – by 12.23%.

BP values, serum lipids profile and glucose concentrations did not differ significantly depending on salt sensitivity. This indicates an equal possibility of having high blood pressure, dyslipidemic manifestations and glucose level regardless of salt sensitivity status.

Prospects for further research: it is necessary to study the associations of SS/SR with clinical and laboratory data in EAH patients depending on genetic factors.

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