RESEARCH LETTER

Low-sodium dietary approach in the management of resistant and refractory hypertension: preliminary results

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Introduction Hypertension is one of the most prevalent health problems, affecting almost 25% of the population worldwide. Based on the current estimates from population studies, it has been reported that 11% to 15% of these patients have treatment-resistant hypertension and up to 5%, refractory hypertension.[1] The role of salt sensitivity in the development and management of hypertension and cardiovascular adverse effects has been widely investigated. However, the number of studies indicating effectiveness of a low-sodium diet in apparent treatment-resistant hypertension is limited. Recently published meta-analyses revealed that the reduction in blood pressure (BP) obtained with a low-sodium diet was dose dependent and greater in those with higher BP.[2] The only randomized study presenting the effects of dietary sodium reduction in patients with apparent treatment-resistant hypertension showed that a low-salt diet was an efficient strategy to overcome treatment resistance.[3]

Current sodium intake ranges from 3.5 to 5.5 g/d, which corresponds to 9 to 12 g of sodium chloride. The World Health Organization recommends dietary sodium intake of 2 g daily (5 g of salt) for adults as an essential part of hypertension and cardiovascular disease prevention. The recent 2017 American College of Cardiology / American Heart Association hypertension guidelines recommended an upper limit of 1500 mg/d for adults or a reduction of sodium intake by at least 1000 mg/d.[4]

There is evidence that excessive sodium intake compromises the function of the immune system, gut microbiota, circadian clock as well as cognitive function.[5] However, last decades brought lively discussion on potential adverse outcomes of very low sodium intake for the systemic hemodynamics and metabolic homeostasis. Several studies have indicated that both high (>6 g/d) and low (<3 g/d) intake of sodium might be associated with a higher risk of adverse effects.[6] On the other hand, it has been claimed that physiological requirement for sodium in humans might go below 1.0 g/d.[7] Hence, the aim of our study was to assess BP reduction in patients on a very low–sodium diet as a component of treatment of resistant and refractory hypertension. Most studies on the role of a low-sodium diet in hypertension treatment are burdened with imprecise evaluation of sodium intake, despite assessment of 24-hour sodium excretion.[8] Therefore, we decided to undertake strict control of sodium consumption as a basis of our study. We hereby present the design and preliminary results.

Patients and methods This was an interventional clinical trial approved by local ethics committee. It has been started in January 2019 in patients referred to the hospital due to apparent treatment-resistant hypertension. Candidates were considered eligible for the study if they were at least 18 years old and gave their written informed consent. Resistant hypertension was defined as systolic BP (SBP) greater than 140 mm Hg and diastolic BP (DBP) greater than 90 mm Hg during at least 2 outpatient measurements, despite 3 or more antihypertensive agents of different classes (including one diuretic) administered at maximum recommended or maximum tolerated doses. Otherwise, it was defined as well-controlled hypertension on 4 or more antihypertensive medications. Refractory hypertension was defined as uncontrolled BP (>140/90 mm Hg) on the treatment with 5 or more antihypertensive agents of different classes including a thiazide-like diuretic and a mineralocorticoid receptor antagonist

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administered at maximum recommended or maximum tolerated doses.

Prior to enrolment, all patients were thoroughly checked regarding pharmacotherapy compliance and potential factors contributing to BP increase (medications, chronic mental distress). At baseline, all patients were carefully examined to rule out pseudoresistance. Patients had hypertension of at least 1-year duration and had been put on antihypertensive therapy at least 8 weeks before the study initiation. None had been using any reduced sodium regimen.

The study was conducted in the hospital setting due to the risk of BP destabilization and in order to control the quality and quantity of meals provided to the participants. Baseline BP was a mean value from 3 measurements taken on day 1 (hospital admission). Endpoint BP was a mean value from 3 measurements taken on day 7.

The exclusion criteria were as follows: secondary hypertension, advanced hypertension-related complications, congestive heart failure (New York Heart Association class IV), chronic kidney disease (creatinine >3 mg/dl), liver failure, active malignancy, arrhythmia.

Very low–salt meals containing 20 mmol (0.46 g) of sodium per day were prepared by the diet kitchen of the hospital. Throughout the study, all participants were maintained on a constant number of calories calculated for individual needs. One or two antihypertensive agents were administered starting on day 2 (β-adrenergic receptor antagonist and/or calcium channel blocker). When SBP exceeded 160 mm Hg and/or DBP exceeded 110 mm Hg, a thiazide diuretic was added to therapy. Participants with SBP exceeding 170 mm Hg and/or DBP exceeding 110 mm Hg on triple therapy were excluded from the study. On the morning of day 1 and 6 of a low-salt diet, patients began a 24-hour urine collection for the assessment of metanephrine and normetanephrine. At baseline and after 7 days of the intervention, blood samples were taken to assess serum concentrations of sodium, potassium, insulin, glucose, and uric acid. Insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR) as fasting insulin (mIU/ml) multiplied by fasting glucose (mg/dl) and divided by 405.

Statistical analysis Statistical analyses were performed using Statistica, 13.0 PL (StatSoft, Kraków, Poland). Normality was verified using the Shapiro–Wilk test. Continuous variables were expressed as means (SD) or medians (interquartile ranges [IQRs]), as appropriate. Depending on the normality of the variables, differences between the independent groups were investigated using the Mann–Whitney test or the *t* test. The difference between 2 dependent groups was analyzed using the Wilcoxon signed rank test or the *t* test. *P* values of less than 0.05 were considered significant.

Results We included 23 patients, and 20 completed the study. Three patients were withdrawn due to intolerance of a low-sodium diet. Six patients (30%) met the criteria for refractory hypertension. Baseline clinical and demographic parameters did not differ in resistant and refractory hypertension groups.

The mean (SD) baseline BP of the whole study population was 158 (19.7)/93.5 (13.2) mm Hg; the median (IQR) number of antihypertensive agents was 5 (4–6). After 7 days of a low-sodium diet, the mean (SD) SBP and DBP decreased by 22.8 (13.7) mm Hg (P <0.001) and 13.8 (11.2) mm Hg (P <0.001), respectively. BP reduction was greater in patients with refractory hypertension compared with those with resistant hypertension. However, the mean (SD) difference was not statistically significant (ΔSBP, 26.7 [8.2] vs 21.1 [15.5] mm Hg; P = 0.4; and ΔDBP, 14.2 [11.1] vs 13.6 [11.6] mm Hg; P = 0.9). Only one patient from the resistant hypertension group did not exhibit BP reduction in the observation period. **TABLE 1** shows a comparison of SBP, DBP, and laboratory results at baseline and after 7 days of a low-sodium diet. After cessation of the in-hospital observation, the study participants were discharged with a median (IQR) of 2 (2–3) antihypertensive agents. BP control seemed satisfactory in those who continued to follow a low-sodium diet.

Discussion A considerable number of studies indicate frequent occurrence of pseudo-resistant hypertension cases associated with inaccurate BP measurements, white-coat effect, inadequate or undertreatment, and medication noncompliance. In a recent prospective clinical trial, full antihypertensive medication adherence rate was 40%,[9] which corresponds to 50% to 68% nonadherence rates in patients with treatment-resistant hypertension shown in previous reports.[10] Notwithstanding, there is a substantial number of hypertensive patients with truly treatment-resistant and refractory hypertension who need more intensive BP-lowering therapy in order to reduce the risk of adverse cardiovascular outcomes. Carotid baroreceptor pacing and catheter ablation of renal sympathetic nerves have been investigated as procedures interrupting the sympathetic contribution. However, the efficacy of the above procedures for treatment-resistant hypertension has not been sufficiently confirmed.[4]

Healthcare practitioners are facing the challenge of improving BP control thereby enhancing cardiovascular outcome in patients on multidrug antihypertensive therapy with no additional pharmacological options. On that account, it is essential to implement all nonpharmacological methods available. A low-sodium diet has been shown to essentially decrease BP in patients with mild-to-moderate hypertension.

In our study, the reduction of sodium intake to 20 mmol/d resulted in a significant decrease

TABLE 1 The comparison of systolic and diastolic blood pressure and laboratory results at baseline and after 7 days of low-sodium diet

Variable	All (n = 20)			Resistant HT (n = 14)			Refractory HT (n = 6)			*P* value[b]
	Baseline	After 7 days	*P* value[a]	Baseline	After 7 days	*P* value	Baseline	After 7 days	*P* value	
SBP, mm Hg	158 (19.7)	135.3 (18.7)	<0.001	157.5 (19.3)	136.4 (20.6)	<0.001	159.2 (22.5)	132.5 (14.8)	<0.001	0.67
DBP, mm Hg	93.5 (13.2)	79.8 (12.2)	<0.001	91.4 (12.5)	77.9 (13.1)	<0.001	98.3 (14.7)	84.2 (9.2)	0.03	0.30
Metanephrine, µg/24h	20.9 (12.8)	28.3 (22.5)	0.25	20.8 (13.7)	25.4 (24.9)	0.59	21.3 (11.1)	36.6 (12.0)	0.02	0.35
Normetanephrine, µg/24h	57.5 (33.5)	61.3 (36.6)	0.73	53.3 (31.2)	50.5 (28.0)	0.80	69.2 (40.7)	91.6 (43.8)	0.47	0.03
Insulin, µU/ml	9.5 (5.3)	13.7 (9.3)	0.04	9.6 (5.8)	15.1 (10.9)	0.052	9.4 (4.5)	10.5 (3.1)	0.60	0.33
Glucose, mg/dl	106.8 (31.2)	106.3 (31.9)	0.90	107.3 (34.0)	109.5 (36.3)	0.63	105.5 (26.3)	98.8 (18.3)	0.12	0.50
HOMA-IR	1.9 (1.6–2.7)	3.6 (1.7–4.8)	0.39	1.9 (1.6–2.6)	2.5 (1.7–6.7)	0.27	2.1 (1.6–2.8)	2.4 (1.7–3.1)	0.92	0.30
Potassium, mmol/l	4.1 (0.3)	4.1 (0.3)	0.74	4.1 (0.3)	4.2 (0.3)	0.82	4.1 (0.2)	4.0 (0.2)	0.03	0.09
Sodium, mmol/l	140.4 (1.8)	140 (2.0)	0.36	140.8 (1.8)	140 (2.0)	0.13	139.3 (1.4)	140 (1.7)	0.24	0.94
Uric acid, mg/dl	6.3 (1.5)	6.4 (1.3)	0.62	6.2 (1.5)	6.5 (1.3)	0.33	6.1 (1.5)	6.1 (1.5)	0.21	0.64

Data are presented as mean (SD) or median (interquartile range).

a *P* values were calculated with the Wilcoxon signed-rank test, *t* test, or the Mann–Whitney test, as appropriate. *P* values <0.05 were considered significant.

b Comparison between the resistant HT group and the refractory HT group at day 7.

SI conversion factors: to convert glucose to mmol/l, multiply by 0.0555; uric acid to mmol/l, by 0.0595.

Abbreviations: DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment–insulin resistance; HT, hypertension; SBP, systolic blood pressure

in SBP and DBP, which approached the target values recommended for hypertensive patients by the American College of Cardiology/American Heart Association guidelines.[4] Only one patient failed to achieve BP reduction. It is estimated that 60% of hypertensive patients are salt sensitive, which means they respond with BP changes proportionate to reduction or increase of salt intake. The reduction in BP observed in this study was greater than that previously reported in less carefully selected hypertensive patients. This is in line with the study by Pimenta et al,[3] and seems to suggest that patients with resistant and refractory hypertension are highly salt sensitive.

According to a meta-analysis by Mozaffarian et al,[11] there is a linear dose-response relationship between sodium intake and BP. As sodium restriction to 20 mmol/d proved highly effective in BP lowering in patients with resistant and refractory hypertension, such a reduction of sodium intake in these 2 groups seems advisable.

In the present study, reduction of sodium intake caused increases in serum insulin and HOMA-IR as well as a nonsignificant increase of urinary fractioned metanephrines (statistically significant in refractory hypertension patients), which is consistent with previous reports.[12,13] However, clinical significance of these findings remains to be elucidated. It seems plausible that beneficial effects of BP reduction outweigh the negative impact of sympathetic nervous system activation observed on a low-sodium diet.

This study presents preliminary results of an ongoing study indicating a beneficial effect of very low–sodium intake in patients with treatment resistant and refractory hypertension. The main limitations of the current analysis are a low number of participants and short duration of dietary treatment; both should be eliminated by a gradual increase in the number of participants.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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