Moderate dietary salt restriction improves blood pressure and mental well-being in patients with primary aldosteronism: The salt CONNtrol trial

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Background. Primary aldosteronism (PA) is a frequent cause of hypertension. Aldosterone excess together with high dietary salt intake aggravates cardiovascular damage, despite guideline-recommended mineralocorticoid receptor antagonist (MRA) treatment.

Objectives. To investigate the antihypertensive impact of a moderate dietary salt restriction and associated physiological changes, including mental well-being.

Methods. A total of 41 patients with PA on a stable antihypertensive regimen—including MRA—followed a dietary salt restriction for 12 weeks with structured nutritional training and consolidation by a mobile health app. Salt intake and adherence were monitored every 4 weeks using 24-h urinary sodium excretion and nutrition protocols. Body composition was assessed by bioimpedance analysis and mental well-being by validated questionnaires.

Results. Dietary salt intake significantly decreased from 9.1 to 5.2 g/d at the end of the study. In parallel, systolic (130 vs. 121 mm Hg) and diastolic blood pressure (BP) (84 vs. 81 mm Hg) improved significantly. Patients' aptitude of estimating dietary salt content was refined significantly (underestimation by 2.4 vs. 1.4 g/d). Salt restriction entailed a significant weight loss of 1.4 kg, improvement in pulse pressure (46 vs. 40 mm Hg) and normalization of depressive symptoms (PHQD scale, $p < 0.05$). Salt restriction, cortisol after dexamethasone suppression test and dosage of renin-angiotensin-aldosterone-system (RAAS) blockers were independently associated with BP reduction.

Conclusion. A moderate restriction of dietary salt intake in patients with PA substantially reduces BP and depressive symptoms. Moreover, the findings underline that a sufficient RAAS blockade seems to augment the effects of salt restriction on BP and cardiovascular risk.

Keywords: aldosterone, cardiovascular risk, hypertension, mineralocorticoid receptor antagonist, salt restriction, salt sensitivity, sodium

Introduction

High dietary sodium intake is an important factor in the development and aggravation of arterial hypertension and cardiovascular disease. Sodium is mainly consumed as sodium chloride (salt) [1–4]. Therefore, reducing dietary salt

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intake to a maximum of 5 g/d is considered a safe non-pharmaceutical approach to lowering blood pressure (BP) in patients with hypertension and is an established recommendation in guidelines [5, 6]. Yet, the effect of the reduction in dietary sodium intake on BP levels depends on the population studied, with substantial differences reported between certain subgroups (−23/9 mm Hg in patients with resistant hypertension vs. −1.1/0.33 mm Hg in the general population) [7]. The huge BP response in resistant hypertension, while impressive, was registered under arbitrary conditions with provision of a pre-formulated high- and low-salt diet (corresponding to a sodium reduction by 80%). Any long-term maintenance of a comparable sodium reduction seems unrealistic. A less vigorous restriction would be expected to be more sustainable because of better compatibility with western dietary habits.

Aldosterone interferes with sodium homeostasis on multiple levels, including renal and central effects: Animal studies suggested that key neuronal structures involved in the regulation of salt appetite are the nucleus of the solitary tract in an intricate interplay with the central nucleus of the amygdala (CeA) [8–10]. In patients with aldosterone excess, such as primary aldosteronism (PA), salt appetite is impaired, which facilitates high dietary salt intake [11, 12].

Moreover, the detrimental cardiovascular effects of aldosterone are proposed to depend on high dietary sodium intake, even after initiation of PA-specific treatment [13]. Medically treated patients with PA have persistently elevated cardiovascular risk [14]. Unfortunately, for this subgroup, no risk reduction strategies exist which extend beyond mineralocorticoid receptor antagonist (MRA) treatment. In the view of the salt dependence of aldosterone-mediated cardiovascular damage [13], a moderate restriction of dietary salt intake holds promise to allow for relevant BP reduction, whereas at the same time, not risking patient adherence because of an inconveniently low prescribed dietary sodium intake.

The antihypertensive activity of salt restriction efforts in patients with PA is still elusive. Therefore, we conducted a salt restriction trial in patients with medically managed PA. Our data close the knowledge gap and provide a simple non-pharmacologic therapeutic framework for the practicing clinician.

Methods

The authors declare that all supporting data are available within the article and its online Supporting Information section. A detailed description of methods is available in the online supplement.

Patient enrollment

A total of 44 patients with PA were recruited from the Munich center of the German Conn's Registry after having been diagnosed with PA based on the Endocrine Society Clinical Practice Guidelines [15]. All patients were on a stable regimen of antihypertensive medication for at least 4 weeks, including spironolactone at a mean dose of 50 mg/d or eplerenone at a mean dose of 80 mg/d. Three patients did not comply with the study protocol and were excluded from the analysis: Two patients changed their antihypertensive medication during the study, and one patient was lost to follow-up for personal reasons. The final study cohort consisted of 41 patients with PA (Fig. S1). All participants gave written informed consent. The study protocol was approved by the ethics committee of the University of Munich and registered as a clinical trial (ID DRKS00026030).

Study protocol

At the beginning and the end of the study, patients underwent standardized procedures such as BP measurement, bioelectrical impedance analysis, and assessment of duplicate measurement of 24-h urinary sodium excretion to estimate dietary salt intake. Adherence to the study protocol was monitored every 4 weeks by two consecutive determinations of 24-h urinary sodium excretion and nutrition protocols during the study. To facilitate the dietary approach to reduce salt intake, all patients received a personal structured nutritional training at the beginning of the study and were supported by a dietician (who also conceived and conducted the training) and a mobile health program [16, 17] throughout the study (see also Fig. S2 for a flowchart of the study protocol).

Blood pressure measurements and laboratory analysis

All measurements were performed under standardized conditions according to guideline recommendations (morning, room temperature at 18–21°C, 10 min of resting). During office visits, patients were subjected to three consecutive BP determinations in seated position on both arms simultaneously using a validated automatic oscillometric

device (Watch BP-Office, Microlife). The mean of the second and third reading was taken as final value for each arm [5]. In the initial office visit, the reading of the extremity displaying the higher value was taken as the initial BP value and compared to the reading of the same extremity at the end of the study period [18]. The measurement was attended by a study nurse or an investigator. To ensure appropriate BP cuff size, upper arm circumference was determined at each visit. Pulse pressure was calculated as the difference between systolic BP (SBP) and diastolic BP (DBP). The remaining conditions are described elsewhere [18].

Blood samples, including post dexamethasone cortisol, were obtained in a fasting state between 8.00 and 9.00 AM at the beginning and the end of the 12-week period. Samples were either directly analyzed or processed and stored at $-80°C$ until analysis. Aldosterone was measured by mass spectrometry (see Supporting Information section).

Assessment of dietary salt intake and salt taste thresholds

All participants collected two consecutive 24-h urine samples for measurements of urinary sodium excretion before each visit. Urinary sodium concentrations (in mmol/d) were used to estimate daily dietary salt intake. Moreover, patients were asked to keep a nutrition protocol on each day of urine collection, as published before [11]. The taste threshold for sodium chloride was assessed using a modified staircase method [11, 19].

Statistical analysis

Based on current literature [20], we assumed a difference of systolic BP of at least 5 mm Hg as relevant and, therefore, defined this as the primary endpoint of our study. We calculated a total sample size of 38 patients to be sufficient to detect a difference of 5 mm Hg SBP with a power of 0.9 and a type I error of $\alpha = 0.05$ after moderate salt restriction.

All numerical values are expressed as means if not mentioned otherwise. Data between groups were compared using a t-test or chi-square test for numerical or categorical variable, respectively. Within-group changes from baseline to follow-up were calculated by paired t-test. Spearman's Rank correlation coefficient was used to perform bivariate correlation analysis.

Stepwise multiple linear regression analysis was performed for multivariate analysis. Two-tailed probability values of <5% were considered statistically significant. Statistical analysis was performed using standard statistical software (IBM SPSS Statistics for Windows, Version 26. Armonk, NY: IBM Corp. and Prism 9.5, GraphPad Software Inc., San Diego, USA).

Results

Clinical and biochemical baseline characteristics of the cohort

Baseline characteristics of the cohort are found in Table 1. Patients were on a stable BP regimen for at least 4 weeks. Mean age was 50 years, and sex distribution was balanced. Patients were overweight with a mean BMI of 28.0 kg/m^2. BP was sufficiently controlled with mean values of 130/84 mm Hg, which required a defined daily dose (DDD) of 2.0 antihypertensives (see Table S1 for a detailed list of antihypertensive drug classes). All patients were on MRA treatment as evidenced by stimulated aldosterone and renin levels. Estimated dietary salt intake was 9.1 g/d according to 24-h urinary sodium excretion and 6.8 g/d according to nutrition protocols. Salt taste threshold was 32 mmol/L. As expected [11, 21, 22], male compared to female probands featured higher estimated dietary salt intake (178 vs. 139 mmol/d; $p = 0.016$), higher salt taste thresholds (36 vs. 27 mmol/L; $p = 0.030$), and larger body water content (51 vs. 35 l; $p < 0.001$).

Among the variables significantly associated with baseline 24-h urinary sodium excretion were parameters of the metabolic syndrome such as BMI ($r = 0.41$; $p = 0.009$) and fasting plasma glucose ($r = 0.39$; $p = 0.013$) as well as body water ($r = 0.37$; $p = 0.016$), and systolic BP ($r = 0.35$; $p = 0.025$).

#### Characteristics at the end of the study (12-week follow-up)

Patients achieved a significantly lower systolic BP (121 vs. 130 mm Hg at baseline, $p < 0.001$, Fig. 1A) and a mean diastolic BP (81 vs. 84 mm Hg at baseline, $p = 0.003$), respectively. Estimated salt intake was reduced effectively from 9.1 g/d at baseline to 5.2 g/d at the end of the 12-week study period ($p < 0.001$, Fig. 1B). After the intervention, estimated salt intake was still negatively correlated with body water and markers of the metabolic syndrome. In terms of safety endpoints, no

Table 1. *Clinical and biochemical parameters before and after salt restriction.*

Patient characteristics (n = 41)	Before low-salt diet	After low-salt diet	p
Age (years)	50 ± 8	–	–
Sex (f/m)	23/18	–	–
Diabetes mellitus (n)	4	–	–
Duration of hypertension (months)	118 ± 89	–	–
Weight (kg)	83.2 ± 18.4	81.8 ± 16.9	<0.001
BMI (kg/m^2)	28.0 ± 5.5	27.5 ± 5.0	<0.001
Body water (L)	42.2 ± 9.5	41.1 ± 8.9	0.005
Body fat (kg)	25.4 ± 10.5	24.9 ± 9.9	0.198
Office SBP (mm Hg)	130 ± 8	121 ± 9	<0.001
Office DBP (mm Hg)	84 ± 7	81 ± 8	0.003
Pulse pressure (mm Hg)	46 ± 7	40 ± 8	<0.001
DDD (n)	2.0 ± 1.7	2.0 ± 1.7	>0.999
DDD RAAS blocker (n)	1.2 ± 1.2	1.2 ± 1.2	>0.999
Plasma aldosterone (pg/mL)	194 ± 154	263 ± 180	0.009
Plasma renin (mU/L)	26.5 ± 35.4	49.7 ± 59.9	0.008
ACTH (pg/mL)	7.6 ± 5.8	9.6 ± 6.7	0.018
ACE (U/L)	36.3 ± 15.6	34.9 ± 15.2	0.135
Angiotensin II (pg/mL)	1.9 ± 6.5	1.6 ± 5.1	0.556
Cortisol after Dexa (mg/dL)	1.2 ± 0.5	–	–
Plasma metanephrines (pg/mL)	40.1 ± 8.6	38.4 ± 6.3	0.293
Plasma normetanephrines (pg/mL)	53.6 ± 10.1	57.1 ± 16.3	0.148
Serum sodium (mmol/L)	138 ± 2	138 ± 3	0.366
Serum potassium (mmol/L)	4.5 ± 0.3	4.5 ± 0.3	0.362
Serum osmolality (mosm/kg)	289 ± 5	287 ± 6	0.070
24-h urinary sodium (mmol/d)	156.1 ± 57.0	89.6 ± 34.8	<0.001
Reported salt intake (g/d)	6.8 ± 1.8	3.8 ± 1.5	<0.001
Estimated salt intake (g/d)	9.1 ± 2.7	5.2 ± 2.0	<0.001
Difference calculated-reported salt intake (g/d)	2.4 ± 2.2	1.4 ± 1.2	0.021
Salt taste threshold (mmol/L)	31 ± 13	21 ± 8	<0.001
GFR (mL/min/1.73 m^2)	99.2 ± 15.0	96.5 ± 13.6	0.123
HDL-C (mg/dL)	54 ± 18	54 ± 17	0.516
LDL-C (mg/dL)	125 ± 31	126 ± 30	0.694
Triglycerides (mg/dL)	143 ± 113	133 ± 102	0.065
Fasting plasma glucose (mg/dL)	97 ± 12	97 ± 15	0.770
24-h urinary potassium (mmol/d)	67.7 ± 18.4	64.9 ± 19.2	0.325
24-h urinary albumin (mg/d)	17.1 ± 27.0	11.6 ± 12.2	0.057
24-h urinary cortisol (μg/d)	79.7 ± 32.8	70.7 ± 31.8	0.056
GAD-7	4.0 ± 4.2	3.1 ± 3.6	0.002
PHQD	5.3 ± 6.2	4.3 ± 5.3	0.008

Note: Shown are means ± SD.
Abbreviations: ACE, Angiotensin-converting enzyme; ACTH, Adrenocorticotropic homone; BMI, Body mass index; DBP, diastolic blood pressure; DDD, Defined daily dose; Dexa, dexamethasone; GAD-7, Generalized Anxiety Disorder 7-item; GFR, Glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; PHQD, Patient Health Questionnaire, German Version; RAAS, Renin-angiotensin-aldosterone system; SBP, systolic blood pressure.
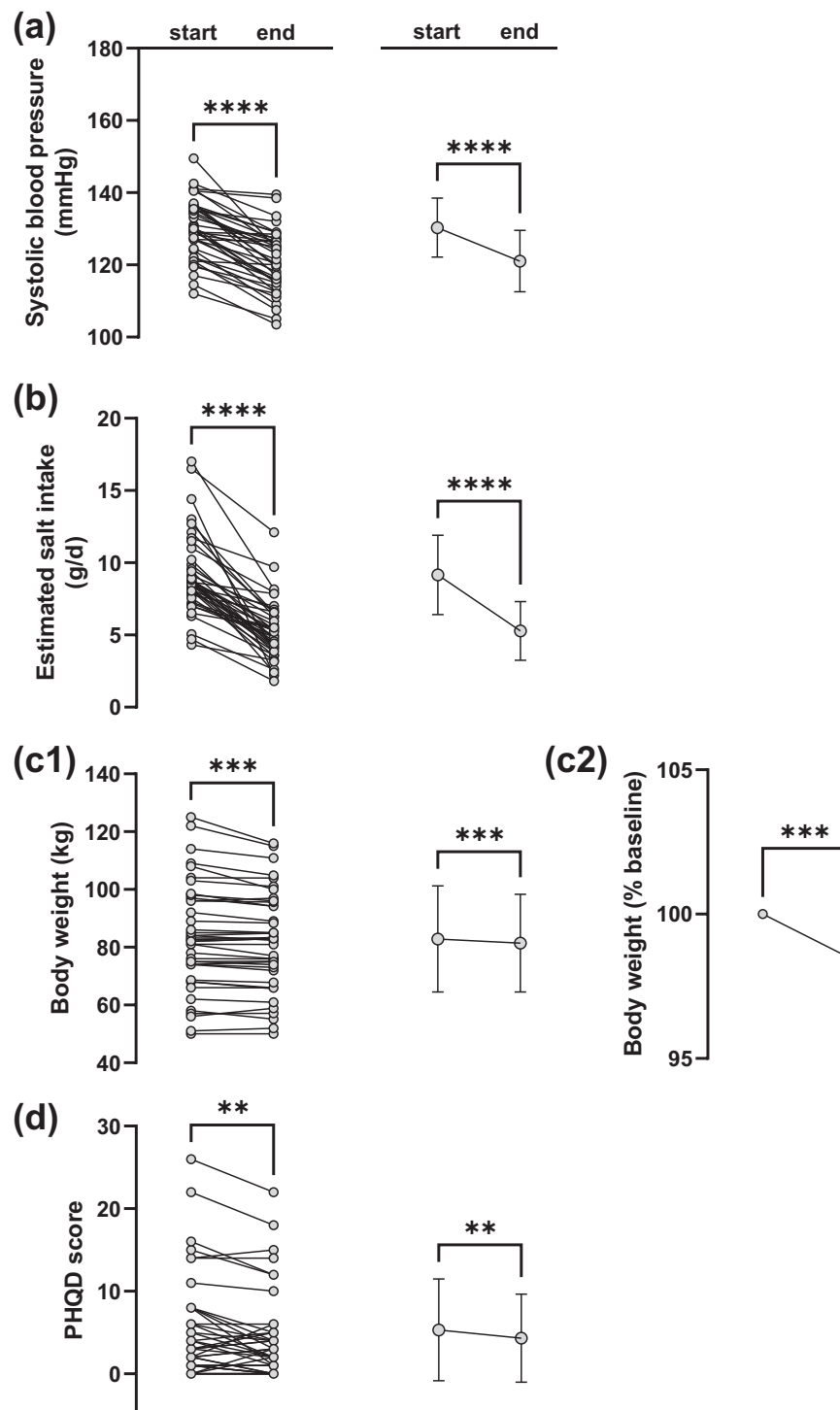
Fig. 1 *Left column, time course of patient-specific individual values for systolic blood pressure (a), salt intake (b), absolute body weight (c1), relative body weight (c2, in % of baseline value), and PQHD score (d) over the course of the trial. Right column, mean ± SD values for (a)–(d). ****p < 0.0001, ***p < 0.001, **p < 0.01. Paired t-test.*

compensatory increase in sympathetic nervous system activity as assessed by plasma levels of meta- and normetanephrines was notable, and lipid levels were likewise unchanged [23]. No orthostatic side effects were reported.

Body composition

Even though none of the participants reported changes in lifestyle habits apart from sodium restriction, patients experienced a weight loss of 1.4 kg (Fig. 1C), which translated into a BMI reduction from 28.0 to 27.5 kg/m^2 ($p < 0.001$). The weight loss was mainly driven by a loss in total body water of 1.1 kg as determined by body impedance. Body fat remained stable ($p = 0.198$).

Physiological adaptations

In response to the salt reduction, aldosterone concentrations rose significantly. This increase in aldosterone was paralleled by significantly stimulated renin and ACTH levels. Plasma cortisol, however, was unchanged, whereas 24 h urinary cortisol excretion showed a trend for reduction ($p = 0.056$). Serum sodium, osmolality, and potassium as well as 24 h urinary potassium excretion remained unchanged.

We observed a linear correlation between changes in aldosterone and changes in plasma renin concentration ($r = 0.443$, $p = 0.004$). This could not be demonstrated for aldosterone and ACTH ($r = 0.136$, $p = 0.396$), indicating that after dietary salt restriction aldosterone secretion was still primarily renin dependent.

No significant correlation was observed between changes in ACTH and changes in 24 h urinary cortisol excretion ($r = 0.045$, $p = 0.780$).

Male patients showed more pronounced endocrine changes: Salt restriction stimulated renin release more so in males (68 vs. 30 mU/L at baseline, $p < 0.01$; females: 36 vs. 23 mU/L at baseline, $p < 0.05$) and aldosterone concentrations only increased significantly in the male subcohort (235 vs. 152 pg/mL at baseline, $p < 0.05$).

Although 24 h urinary cortisol levels were unchanged in females, we saw a significant decrease in male patients (75 vs. 93 μg at baseline, $p < 0.05$). Concentrations of ACTH increased numerically in both sexes; however, it only in the

male patients was the difference significant (12 vs. 10 pg/mL at baseline, $p < 0.05$).

Cardiovascular endpoint surrogate parameters

Besides BP, albuminuria was reduced from 18 to 12 mg/d ($p = 0.057$). Specifically, the number of patients with microalbuminuria decreased from five at baseline to two patients at the end of the intervention. In addition, pulse pressure as an indicator of arterial stiffness [24] and the rate-pressure product as a marker for myocardial workload—which may predict ischemic coronary events [25]—were both significantly reduced after the dietary intervention (both: $p < 0.001$).

Scoring systems related to psychological well-being, depression, and anxiety

Despite specific treatment for PA at the beginning of the study, patients still showed pathological scores for depression (PHQD scale), which normalized at the end of the intervention (4.3 vs. 5.3 at baseline, $p = 0.008$, Fig. 1D). Likewise, we observed a significant reduction of scores on the Generalized Anxiety Disorder 7-item scale (GAD-7, $p = 0.002$).

Separate multivariate regression analyses were performed to adjust for confounders. PHQD score reduction was independently correlated with the extent of renin-angiotensin-aldosterone-system (RAAS) blocker drug load ($r = 0.337$, $p = 0.049$, Table S2). Moreover, the reduction on the GAD-7 score was independently correlated with the rise in aldosterone levels at follow-up ($r = -0.494$, $p = 0.002$, Table S3).

Health literacy

We noticed a reduced discrepancy between objective (estimated) and subjective (reported) salt intake, from an initial delta of 2.4 g/d to a final difference of 1.4 g/d. Importantly, salt taste threshold improved significantly from 32 to 21 mmol/L [11]. In addition, participants reported high levels of satisfaction with the achievements of their participation in this trial (median 10/10 points, with higher numbers indicating greater satisfaction) and median 10/10 motivation to continue salt restriction efforts after the end of the study.

Prediction of blood pressure response

In a multivariate model, male patients with a low body surface area, minimal autonomous cortisol secretion, high DDD of RAAS blockers, and a high

Table 2. *Unified multivariate linear regression model to predict systolic blood pressure (SBP) reduction by salt restriction.*

	Regression coefficient	Standard error	Standardized coefficient r	p
Constant	46.734	14.765		0.003
Sex (1 = male, 2 = female)	−7.395	1.853	−0.651	<0.001
Age	0.040	0.097	0.055	0.683
Body surface area	−16.676	4.466	−0.693	<0.001
Cortisol after DST	−6.184	1.489	−0.552	<0.001
Presence of diabetes mellitus (1 = yes, 2 = no)	3.626	2.886	0.193	0.218
DDD RAAS blockers	2.130	0.645	0.433	0.002
Delta salt excretion	0.881	0.378	0.363	0.026

Abbreviations: DDD, defined daily doses; DST, 1 mg overnight dexamethasone suppression test; RAAS, renin-angiotensin-aldosterone system.

reduction in salt intake experienced the greatest reduction in BP. The presence of diabetes mellitus or age did not play a significant role in this analysis (Table 2).

Discussion

The aim of our study was to investigate moderate salt restriction as an antihypertensive strategy in patients with PA. We report the following main findings: First, dietary salt restriction in patients with PA is feasible and results in a strong and clinically relevant reduction of BP with parallel improvements in surrogate markers of cardiovascular risk. Second, we were able to identify several independent factors which mediate the degree of BP reduction by salt restriction in patients with PA. Third, we noted a normalization of depressive symptoms and amelioration of anxiety scores in addition to BP control.

During the study, our cohort experienced a reduction in SBP of 9 mm Hg with a reduction in sodium intake by about 60 mmol, which translates to −7 mm Hg per 50 mmol. This is a greater effect than observed in trials on patients with essential hypertension, which showed a reduction of −2.8 mm Hg [3] and −1.9 mm Hg [23] of SBP, respectively, per 50 mmol of daily sodium reduction. Altogether, these results suggest a greater dependence of hypertension on dietary salt status in PA than in essential hypertension. The achieved effect equates to one additional fully dosed antihypertensive drug [26]. Additional support for the notion of salt-dependent hypertension in aldosterone excess comes from a study on a mouse model with increased aldosterone synthase expres-

sion in which low salt restored the elevated BP of mutant mice on high-salt diet to levels of control mice [27]. Amelioration of night time BP by a short-term severe salt restriction was also reported in a small study on eight patients with unilateral PA before surgery [28].

In-line with these findings, we observed a statistical signal for improvement of albuminuria ($p = 0.057$) and a significant decrease in pulse pressure as a marker of arterial stiffness, which was again more pronounced than in patients with essential hypertension [29]. It is worth noting that these effects were achieved on top of already well-controlled BP by PA-directed specific treatment at baseline (130/84 mm Hg). In total, our study achieved a dietary sodium restriction by 50 mmol, which is a comparatively modest and very patient-friendly reduction. Nevertheless and according to current literature, this reduction can be expected to translate into a cardiovascular risk reduction by more than 10% [20]. Further cardiovascular risk benefit may derive from a potential regression of left ventricular hypertrophy in patients with PA independently of BP levels [30].

Of note, our cohort also experienced a loss of body water with associated weight loss, which is well in accordance with other studies on salt restriction [31, 32]. Reductions in body weight will mathematically lead to reductions in calculated body surface area. We were able to demonstrate that salt restriction was more efficacious in patients with a lower body surface area. Excess sodium is proposed to be stored in the interstitial fluid as well as in bone and skin [33, 34]. Subjects with a larger body surface area can be expected to harbor

increased size of all body compartments, including the sites of sodium storage. It is conceivable that larger sodium stores are harder to deplete in the same time frame as it may be for patients with smaller body surface areas. Our finding may, therefore, suggest an increased washout latency of stored sodium in subjects with a larger body surface area. In addition, the effect of maintained salt restriction efforts after the 12-week intervention may be even stronger due to the reduced body surface area.

At baseline, dietary sodium intake in our patients was substantially above the WHO recommendations, although patients already had a long history of hypertension (Table 1). As expected, women displayed significantly lower estimated salt intake at baseline when compared to men. All these findings fit with our previous results [11] and are in-line with survey data from Germany [21]. In our study, both sexes reduced their estimated salt intake by a comparable absolute amount, indicating that males and females were similarly adherent to the dietary regimen. Interestingly, despite starting from a comparable level of systolic and diastolic BP at baseline, male sex was associated with a significantly better BP reduction to salt restriction (ΔSBP females vs. males: 8 vs. 11 mm Hg, $p = 0.039$) as further evidenced by a greater ΔSBP/Δsalt net effect in men (Table S4). These data are well in-line with numerous models for experimental hypertension in which male animals consistently developed more pronounced hypertension in response to salt loading (summarized in [35]). More recently, female salt resistance was attributed to a greater salt-dependent induction of macula densa NOS1β to mitigate tubuloglomerular feedback [36].

We could demonstrate that the BP response to salt restriction was inversely correlated with post dexamethasone cortisol levels, which could argue for a role of subclinical cortisol excess in sodium regulation. This interpretation aligns well with the findings of Connell et al. [37] on glucocorticoids and salt excretion. As another clue for the role of glucocorticoids in the response to dietary salt restriction, we observed that ACTH levels increased significantly throughout the course of the study. One additional independent mediator of the BP response to sodium restriction was the total drug load (DDD) of RAAS blocking agents. This finding corroborates results from experimental animals [38] as well as a cohort of patients with

nephropathy [31], which demonstrates that RAAS-directed drug treatment can augment the BP lowering effects of sodium restriction, that is, render subjects salt sensitive. A possible mechanism may be a protective blunting of tubuloglomerular feedback [39]. Our results, therefore, may indicate that patients in whom dietary salt restriction is considered should undergo prior evaluation for uptitration of RAAS blockers. This could be a helpful tool for clinicians to increase the effect of this dietary intervention [39].

An association of psychiatric disorders such as anxiety and depression with plasma aldosterone, particularly in patients with PA, is established [40]. Depressive symptoms respond better to adrenalectomy than to MRA treatment, so there is an unmet need in the medically treated population with PA [41]. Our probands experienced a significant improvement in scoring systems for anxiety and depression. Importantly, PHQD scores normalized throughout the course of the dietary intervention, in-line with an antidepressant effect. This antidepressant effect occurred although significant reactive increases in plasma aldosterone and may, accordingly, suggest central MR desensitization. Further evidence is provided by the multivariate regression which showed that the RAAS blocker dose correlated with the degree of PHQD change, that is, the antidepressant effect. Conversely, patients with refractory major depressive disorders show increased signs of central MR activation [42]. Thus, central modulation of MR signal transduction by salt restriction may be involved in the observed antidepressant activity. Even if these effects cannot be mechanistically resolved due to the study design, they can be viewed as catalysts promoting long-term adoption of salt restriction by an increased well-being.

Finally, patients in our study were able to estimate their dietary salt intake more accurately at the final evaluation. Thus, the intervention may have endowed patients with greater health literacy in assessing discretionary salt in processed foods. To the best of our knowledge, this is the first description of a successful dietary empowerment in patients with PA. Positive collateral effects of this empowerment on psychological well-being are likely and are probably reflected in the self-reported satisfaction with participation in the trial.

We acknowledge the limitation that, due to the exploratory nature of the study, a control group is

missing and, thus, patients could not be randomized to an alternative intervention. However, we used a run-in phase of 4 weeks to ensure BP stability under the concurrent antihypertensive treatments. At the same time, we cannot fully exclude distortion effects on BP levels, but this seems rather unlikely given that lifestyle changes were monitored and did not reveal changes in potential lifestyle and nutrition-related confounders such as physical activity (PAQ-50+ score [43] median 11,888 vs. 12,768 kcal at baseline, $p = 0.112$), glucose metabolism, and lipid profile as well as 24 h urinary potassium excretion (Table 1).

The strengths of our study include a structured and detailed patient phenotyping with a hitherto neglected focus on mental health and meticulous methodological accuracy, especially with the key variables of BP and salt excretion within the context of the German Conn's Registry. Finally, the combination of nutritional education and continuous self-supervision using a mobile health app is both innovative and applicable to other forms of arterial hypertension. Counseling was effective even under remote conditions, making it a possible blueprint intervention for future pandemic situations in settings with established telehealth infrastructures.

Conclusion

Our study provides an example of how a non-pharmacologic and sustainable intervention like moderate dietary salt restriction can significantly reduce BP in PA to a degree comparable to a full dose of an additional antihypertensive medication. BP was reduced even in subjects with well-controlled BP at baseline, so the effect can be expected to be even greater in patients with sub-optimal disease control. Our results further confirm the clinically relevant fact that BP response to salt restriction and, hence, salt sensitivity, can be enhanced by RAAS blockers. Salt restriction was further associated with a normalization of depressive symptoms in terms of mental well-being and with a reduction of pulse pressure in terms of cardiovascular risk. Finally, we observed that salt restriction mediates the BP response independently of additional competing factors, underlining that dietary salt is a variable which should be targeted in all patients with PA. Appropriate education, counseling, and self-monitoring increased patients' awareness of dietary salt consumption. Therefore, this strategy represents a cost-effective,

low-threshold measure which at the same time reduces BP and pill burden and empowers patients to take responsibility for their own health. The absence of detectable adverse effects suggests an extension of the findings to other forms of arterial hypertension, which should be addressed in future trials.

Author contributions

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Conflict of interest statement

The authors declare no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1: Patient screening, recruitment and dropouts until final cohort.

Figure S2: Flow chart of all data points acquired at the 4 study visits and at additional timepoints.

Table S1: Defined daily doses (DDD) for various drug subclasses before and after salt restriction. By study protocol, patients were required to keep their medication unchanged throughout the study.

Table S2: Multivariate linear regression model to predict changes in PHQD score.

Table S3: Multivariate linear regression model to predict changes in GAD-7 score.

Table S4: Gender differences in baseline and final values for blood pressure and salt intake as well as blood pressure response per salt reduction. ∎