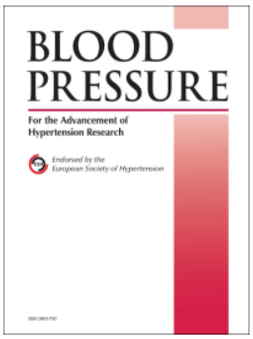

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# Blood Pressure Stability and Plasma Aldosterone Reduction: The Effects of a Sodium and Bicarbonate-Rich Water - A Randomized Controlled Intervention Study

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## ABSTRACT

**Objective:** Hypertension is a recognized risk factor for cardiovascular disease (CVD), and dietary sodium intake has been linked to its development. However, mineral water high in bicarbonate and sodium does not appear to have adverse effects on blood pressure.
This study examines the effects of consuming a mineral water high in bicarbonate and sodium (HBS) compared to a low bicarbonate and sodium (LBS) mineral water on blood pressure and related factors.
**Methods:** A randomized controlled intervention was conducted with 94 healthy participants, consuming 1,500 – 2,000 mL daily of either mineral water high in bicarbonate and sodium (HBS water, n = 49) or low in bicarbonate and sodium (LBS water, n = 45). Blood pressure, anthropometrics, and urinary calcium and sodium excretion were assessed at baseline and after 28 days. 3-day food protocols were assessed to evaluate possible dietary changes.
**Results:** Blood pressure changes did not differ between the groups. Both normotensive and hypertensive subjects showed similar changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) in response to the different test waters. Serum aldosterone decreased significantly in both groups, with a greater reduction in the HBS group. Urinary calcium excretion significantly decreased ($p = 0.002$) and sodium excretion increased in the HBS group. Multiple linear regression analyses indicated no association between urinary sodium excretion and systolic blood pressure increase in the HBS group ($B = 0.046$, $p = 0.170$). Changes in urinary sodium excretion did not correlate with changes in serum aldosterone in the same group ($r = -0.146$, $p = 0.350$).
**Conclusions:** The study revealed no significant differences in blood pressure changes between individuals consuming HBS water and LBS water. Notably, the additional sodium intake from the test water was effectively excreted.
**Trial registration:** This trial was registered in the German Clinical Trials Register (DRKS00025341, https://drks.de/search/en).

## PLAIN LANGUAGE SUMMARY

**What is the context?** High blood pressure is a risk factor for heart diseases, one of the leading causes of illness and death worldwide. Too much sodium in the diet has been linked to the development of high blood pressure. However, some high-sodium mineral waters appear to have a different effect on blood pressure. Researchers have demonstrated that mineral waters high in both sodium and bicarbonate may not have harmful effects on blood pressure.
**What is the study about?** In this study, 94 healthy participants between the ages 30 to 65 were divided into two groups. One group drank high-bicarbonate, high-sodium mineral water, and the other group drank low-bicarbonate, low-sodium mineral water for four weeks. Blood pressure was measured before and at the end of the study. The participants were asked not to change their usual diet and physical activity during the study.
**What are the results?** Blood pressure did not change differently between the two groups. Consumption of high-sodium, high-bicarbonate mineral water increased sodium intake, but sodium was effectively excreted in the urine. Moreover, aldosterone, a blood pressure regulating hormone, decreased with mineral water consumption. Its reduction is good for maintaining stable blood pressure.

## ARTICLE HISTORY

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Bicarbonate; sodium; mineral water; blood pressure; aldosterone

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## 1. Introduction

Hypertension is widely recognized as a major risk factor for cardiovascular disease (CVD), which is a leading cause of morbidity and mortality worldwide [1]. Notably, a high dietary sodium intake has been associated with the development of hypertension [2–6].

However, several studies have shown that the effect of a high-sodium mineral water on blood pressure seems to differ from the effect of dietary sodium intake [7–12]. The mineral content of high-sodium mineral waters varies widely. In some mineral waters, a high sodium content is accompanied by a significant amount of bicarbonate, while others have low amounts of bicarbonate. It has been observed that sodium bicarbonate and sodium chloride have different effects on blood pressure, depending on their anions [10, 12]. Studies focusing on mineral waters rich in both bicarbonate and sodium have shown no adverse effects on blood pressure [7–9]. In some cases, they have even shown a beneficial effect on systolic blood pressure (SBP) [10–12].

Several explanations have been proposed to support these findings. One underlying mechanism involves the renin-angiotensin-aldosterone system (RAAS). Acute consumption studies have shown that bicarbonate- and sodium-rich mineral waters affect this pathway, leading to a decrease in serum aldosterone and a subsequent increase in urinary sodium excretion [13, 14]. However, such effects have mainly been observed in acute studies, and the evidence from chronic studies remains inconclusive [8, 10, 12, 14]. Another potential mechanism relates to the improvement of acid-base balance due to the bicarbonate content of the water [15]. This in turn may reduce urinary calcium excretion [12, 16]. A recent meta-analysis of randomized controlled studies (RCTs) concluded that improved calcium status, achieved through calcium supplementation, has a beneficial effect on blood pressure [17]. This raises the question of whether the reduction in urinary calcium excretion may also have a beneficial effect on blood pressure and/or serum aldosterone. In addition, subgroup analyses of blood pressure changes have not been reported in previous trials.

Therefore, this intervention study was conducted to investigate the subchronical effects of consuming mineral water high in sodium and very high in bicarbonate, compared with mineral water low in bicarbonate and sodium, on blood pressure and related parameters. In addition, subgroup analyses (blood pressure status, blood pressure changes, sex, age) were performed to examine differences in changes in blood pressure and serum aldosterone and for different baseline blood pressures to provide a more complete understanding of the potential effects of these mineral waters in different subpopulations.

## 2. Materials and methods

### Study design

This parallel-group randomized controlled intervention study was conducted between June 2021 and May 2022 at the Institute of Food Science and Human Nutrition, Leibniz University Hanover, Germany. A total of 94 healthy participants without chronic diseases, aged between 30 and 65 years, were recruited from the general population of Hanover and Hildesheim. The main inclusion criteria were an omnivorous diet and a BMI between 20.0 and 29.9 $kg/m^2$. Individuals with manifest cardiovascular diseases, renal diseases and/or medically treated hypertension were excluded.

### Ethical approval

The study protocol was approved by the Ethics Committee of the Medical Chamber of Lower Saxony (Hanover, Germany) (Bo/24/2021) and was conducted in accordance with the ethical standards described in the Declaration of Helsinki. All participants gave informed consent. This trial was registered in the German Clinical Trials Register (DRKS00025341).

### Procedure

The intervention consisted of an initial assessment at baseline ($t_0$) and a final assessment after 4 weeks of mineral water consumption ($t_{28}$). Participants were randomly assigned by an independent researcher to one of two intervention groups using stratified randomization according to the covariates sex and age (in descending order). Participants in the high bicarbonate and sodium group (HBS) consumed a mineral water very high in bicarbonate (4,368 mg/L) and high in sodium (1,708 mg/L), while those in the low bicarbonate and sodium group (LBS) consumed a mineral water low in bicarbonate (228 mg/L) and low in sodium (8.4 mg/L) (Table 1). Throughout the four-week intervention period, participants were advised to drink a minimum of 1,500 mL and a maximum of 2,000 mL of the provided test water daily. Participants should maintain their drinking habits as usual, but should not drink additional mineral water or soft drinks. Besides that, subjects were advised to maintain their usual diet and physical activity levels throughout the intervention. The consumption of the test waters was monitored using a daily protocol, which the subjects had to fill in. After the

**Table 1.** Mineral content of the test waters.

| Minerals | HBS mineral water | LBS mineral water |
|---|---|---|
| $HCO_3^-$ (mg/L) | 4368 | 228 |
| $Na^+$ (mg/L) | 1708 | 8.4 |
| $Cl^-$ (mg/L) | 322 | 11 |
| $SO_4^{2-}$ (mg/L) | 174 | 15 |
| $K^+$ (mg/L) | 110 | 2.3 |
| $Ca^{2+}$ (mg/L) | 90 | 67.5 |
| $Mg^{2+}$ (mg/L) | 11 | 6.9 |

HBS = High Bicarbonate and Sodium, LBS = Low Bicarbonate and Sodium.

intervention, this protocol was used to check compliance with the study protocol and to calculate the amount of daily test water consumption.

To evaluate the effect of water consumption on urinary parameters (calcium and sodium excretion), participants were asked to collect 24-h urine samples the day before the respective examination days ($t_0$ and $t_{28}$). To ensure complete collection of 24-h urine, all participants received written instructions for correct urine sampling and preservative-free plastic containers (Sarstedt AG & Co. KG, Nümbrecht, Germany). Subjects were asked to record both the start and end times of the collection on the plastic containers. They started the collection the day before the examination, after emptying the bladder and discarding the morning urine. The urine collection included the morning urine of the next day. Immediately after delivery at the Research Institute, the urine was mixed thoroughly, aliquoted, and stored at 5 °C until they were transferred to the laboratory for analysis. Urine volume was also measured at the research institute. To check the completeness of the 24-hour urine collection, urinary creatinine excretion was measured.

To minimize potential variations caused by circadian rhythms, $t_0$- and $t_{28}$-appointments for each participant were scheduled at approximately the same time of the morning between 6:00 and 10:00 a.m. The examination days ($t_0$ and $t_{28}$) were proceeded as follows: At first, a questionnaire on the current health status had to be filled out, and then anthropometric measurements were taken. This was followed by blood pressure measurements. At the end, a fasting (12-hour overnight) blood sample was drawn to analyze serum aldosterone levels using serum tubes (Sarstedt AG & Co. KG, Nümbrecht, Germany). Blood and urine samples were analyzed by an accredited laboratory (LADR, Laborverbund Dr. Kramer & Kollegen GbR).

### Anthropometrics

Anthropometric measurements were carried out at the beginning and at the end of the intervention period. Height was measured with a stadiometer (Seca GmbH & Co.KG, Hamburg, Germany), while body weight was measured by the use of a digital scale (Kern & Sohn GmbH, Balingen-Frommern, Germany). BMI was calculated as weight in kilograms divided by height in meters squared. Waist and hip circumference were examined at the end of a normal expiration, using a non-stretch tape.

### Assessment of blood pressure

Blood pressure was measured about 30 minutes upon arrival at the research institute under fasting conditions. It was measured by a trained physician on the left upper arm using a fully automated sphygmomanometer (Hartmann Veroval® Duo control, Heidenheim, Germany) after a resting period of at least 5 minutes in the sitting position (legs uncrossed). The measurement was repeated three times at intervals of at least one minute. Blood pressure was recorded as the mean of the last two measurements. Mean arterial pressure (MAP) was calculated as diastolic blood pressure (DBP) plus one-third of the difference between SBP and DBP [MAP = DBP + 1/3 (SBP-DBP)]. Participants were classified as normotensive or hypertensive on the basis of their baseline MAP. According to the American guidelines, a MAP <93 mmHg was considered "*normotensive*", while a MAP ≥93 mmHg was considered "*hypertensive*" [18]. In addition, participants were classified based on the change in MAP from baseline ($t_0$) to the end of the intervention ($t_{28}$). A reduction in blood pressure was defined as a decrease in MAP of more than 5%. Participants with a change in MAP within ±5% were categorized as stable MAP. Conversely, an increase in blood pressure was defined as an increase in MAP of more than 5%.

### Dietary assessment

To evaluate any potential dietary changes that may have occurred during the intervention, the participants' dietary intake was assessed before ($t_0$) and at the end of the intervention period ($t_{28}$) using 3-day food records. Participants recorded the type and amount of all foods and beverages consumed over three consecutive days (Friday, Saturday, and Sunday) before the respective examination day (Monday). Nutrient and energy intakes were estimated using PRODI 6.12 Expert® software (Nutri-Science GmbH, Freiburg, Germany). Total sodium intake was calculated as sodium intake of foods and beverages. A few subjects mentioned the use of table salt in the protocols, but most of the subjects did not.

### Statistical analysis

Data are presented as mean ± standard deviation or median and interquartile range (IQR), depending on the distribution. Non-normally distributed data were transformed using the natural logarithm (ln) or square root (sqrt), whichever was more appropriate. Two-way repeated measures ANOVAs were conducted to detect intervention effects (interactions between time and group). Chi-squared test was used to test for group differences in the frequency of the occurrence of blood pressure responses (decreased MAP, stable MAP, and increased MAP). Differences in changes in serum aldosterone, urinary sodium and urinary calcium excretion between the three blood pressure response groups were detected by Kruskal-Wallis-Test or ANOVA in both intervention groups. Differences in blood pressure changes and changes in serum aldosterone, sodium and calcium excretion between normotensive and hypertensive subjects were tested using unpaired t-Test or Mann Whitney-U-Test. Subgroup analyses (gender, age) for changes in aldosterone were performed using unpaired t-Test or Mann-Whitney-U-Test, depending on the distribution of the data. The relationship between total sodium intake, as reflected by urinary sodium excretion and changes in aldosterone levels was tested using Spearman correlation. Moreover, multiple linear regressions were calculated separately for the HBS and the LBS group. This was done in order to identify possible factors influencing the changes in blood pressure and aldosterone levels caused by the respective mineral water. Due to violation of the normal distribution condition, all multiple linear regressions were calculated with bootstrap (n = 2000) and BCa method to obtain robust results. Model 1 was the unadjusted model. Fully adjusted multiple linear regression models for the change in blood pressure and aldosterone were adjusted for age, BMI, baseline creatinine, baseline uric acid, baseline HbA1c and for baseline blood pressure or baseline serum aldosterone, respectively.

Two-tailed p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software for Windows (version 28.0.1.0; SPSS Inc., Chicago, IL, USA).

## 3. Results

### Study population

A total of 85 participants (60 women and 25 men) aged 53 ± 9 years were included in the analysis, after excluding 9 participants due to drop outs and missing values. One subject in the HBS group withdrew from the study due to gastrointestinal discomfort. Both intervention groups, the bicarbonate- and sodium-rich mineral water (HBS) group and the low bicarbonate/low sodium mineral water (LBS) group, comprised approximately equal numbers of participants (HBS: n = 43, LBS: n = 42). In terms of urine data there was one missing data in the LBS group, resulting in 41 evaluable 24-h urine samples. No subjects were excluded from the evaluation due to insufficient 24-hour collection or insufficient mineral water consumption.

At baseline, there were no significant differences in anthropometric parameters between the two groups (Table 2), and these parameters did not change significantly during the intervention period.

The majority of the participants in both groups (HBS: 65.1%, LBS: 76.2%) had a MAP in the normotensive range (<93 mmHg) at the beginning of the study, with a slightly higher SBP observed in the HBS group compared to the LBS group (p = 0.007) (*Table* 2).

Participants maintained their physical activity levels and did not change their dietary habits (apart from beverages) during the intervention period (data not shown). In both intervention groups, mineral intake from beverages and foods did not change significantly between the beginning and end of the study, except for potassium intake in the LBS group. While it remained stable in the HBS group (p = 0.185), potassium intake decreased significantly in the LBS group (p = 0.002). The decrease in the LBS group was in the reference range (IQR).

### Test water volumes and urine volumes

In general, there was no significant interaction between time and group for mineral water

**Table 2.** Baseline ($t_0$) characteristics of the study groups.

| Parameter | | HBS group n = 43 | LBS group n = 42 | p-value* |
|---|---|---|---|---|
| Women/Men | | 31/12 | 29/13 | 0.758 |
| Age (years) | | 56 (17) | 55 (10) | 0.567 |
| Body weight (kg) | | 69.7 (17.9) | 69.8 (17.9) | 0.733 |
| Height (m) | | 1.70 (0.11) | 1.70 (0.10) | 0.374 |
| BMI (kg/m$^2$) | | 23.8 (4.25) | 24.6 (5.63) | 0.479 |
| Waist circumference (cm) | | 84 (14) | 84 (18) | 0.441 |
| Hip circumference (cm) | | 99 (11) | 101 (9) | 0.705 |
| Waist-to-Hip Ratio | | 0.83 (0.10) | 0.85 (0.11) | 0.469 |
| SBP (mmHg) | | 114 (24) | 111 (15) | **0.007** |
| DBP (mmHg) | | 77 (9) | 75 (10) | 0.191 |
| MAP (mmHg) | | 90 (14) | 85 (10) | **0.032** |
| Blood pressure status | Normotensives | n = 28, 65.1% | n = 32, 76.2% | 0.263 |
| | Hypertensives | n = 15, 34.9% | n = 10, 23.8% | |

Data are shown as median (IQR).
HBS = High Bicarbonate- and Sodium, LBS = Low Bicarbonate and Sodium. BMI = Body-Mass-Index, WC = Waist Circumference, HC = Hip Circumference, WHR = Waist-to-Hip Ratio, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, MAP = Mean Arterial Blood Pressure.
*Distribution of gender between groups was analyzed using Chi-Quadrat test. All other group differences were assessed using unpaired t-Test/ Welch-Test or Mann-Whitney-U-Test.

consumption (p = 0.609), indicating no differences between the water groups. Specifically, on the last intervention day, HBS group consumed 1,750 (500) mL of HBS water, while LBS group consumed 1,500 (500) mL of LBS water (p = 0.152).

Moreover, there was no significant interaction between time and group for urine volume (p = 0.595). Both groups showed a significant increase in urine volume over time (p < 0.001 and p = 0.004 for HBS and LBS group, respectively). In the HBS group urine volume increased from 2,341 (1,251) mL at the beginning of the study to 2,689 (1,024) mL at the end of the intervention. In the LBS group, urine volume raised from 2,193 (1,098) ml to 2,704 (1,021) mL.

### Blood pressure and related parameters

There was no significant interaction between time and group for SBP (p = 0.227), DBP (p = 0.310) and MAP (p = 0.224) (Table 3). This shows that blood pressure change did not differ between the two water groups. Moreover, subgroup analysis of SBP, DBP and MAP changes showed no differences between men and women or between younger (<50 years) and older participants (≥50 years) in both intervention groups (data not shown).

Changes in blood pressure are shown in figure 2. Chi-squared test showed that the number of subjects experiencing a decrease, stable or increase in MAP was not significantly different between the two water groups (p = 0.551). Based on changes in MAP, the majority of participants in both intervention groups showed reductions in blood pressure (HBS: 32.6%, LBS: 42.9%) or stable blood pressure (HBS: 46.5%, LBS: 42.9%). Only a minor proportion of participants in both groups exhibited an increase in blood pressure (LBS: 14.3%, HBS: 20.9%).

Both normotensive and hypertensive subjects showed similar changes in SBP, DBP and MAP in response to the different test waters (Table 4). However, subjects with higher blood pressure at baseline (according to MAP $t_0$) were more likely to show a reduction in SBP than subjects with lower blood pressure. In both intervention groups, normotensive subjects did not experience a significant change in blood pressure from $t_0$ to $t_{28}$ ($p_{HBS}$=0.512, $p_{LBS}$=0.429). Hypertensive subjects showed a decrease in SBP that was statistically significant in the LBS group (p = 0.002) but not in the HBS group (p = 0.117).

Regarding serum aldosterone levels, there was a significant interaction between time and group (p < 0.001), indicating a different response to water consumption (Table 3). Both intervention groups showed a reduction in aldosterone, which was higher in the HBS group. Subgroup analysis of aldosterone changes showed no differences between men and women or between younger (<50 years) and older participants (≥50 years) in both intervention groups (data not shown). Urinary calcium excretion showed a marginal non-significant interaction between time and group (p = 0.060). Nevertheless, the observed decrease in calcium excretion was significant in HBS (p = 0.002), but not in the LBS group (p = 0.341).

Moreover, the interaction between time and group for urinary sodium excretion and total sodium intake was significant (p < 0.001). There was an increase in total sodium intake and urinary sodium excretion in the HBS group, but no change in the LBS group (Table 3). The study water accounted for approximately half of the total sodium intake in the HBS group.

Subgroup analysis of blood pressure changes (decreased MAP, stable MAP, increased MAP) showed no significant differences in serum aldosterone, urinary sodium excretion, and urinary calcium excretion (Table S1). In addition, there were no significant differences between normotensive and hypertensive subjects in each study group regarding changes in these parameters (all p > 0.05), except for urinary sodium excretion in the HBS group: The change in urinary sodium excretion was significantly higher in normotensive subjects compared to hypertensive subjects (p < 0.001) (Table 4).

**Table 3.** Blood pressure, serum aldosterone, urinary calcium and sodium excretion, and total sodium and total potassium intake (food and water).

| | | Group | | p-value* (time x group) |
|---|---|---|---|---|
| Parameter | Time | HBS | LBS | |
| SBP (mmHg) | $t_0$ | 114 (24) | 111 (15) | 0.227 |
| | $t_{28}$ | 116 (24) | 105 (19) | |
| DBP (mmHg) | $t_0$ | 77 (9) | 75 (10) | 0.310 |
| | $t_{28}$ | 76 (11) | 73 (9) | |
| MAP (mmHg) | $t_0$ | 90 (14) | 85 (10) | 0.224 |
| | $t_{28}$ | 90 (16) | 83 (12) | |
| Serum aldosterone (ng/L) | $t_0$ | 103 (61) | 104 (94) | **<0.001** |
| | $t_{28}$ | 65 (63) | 98 (78) | |
| Calcium excretion (mmol/24 h) | $t_0$ | 3.90 (3.50) | 3.70 (1.90) | 0.060 |
| | $t_{28}$ | 3.40 (2.90) | 3.30 (2.50) | |
| Sodium excretion (mg/24 h) | $t_0$ | 3357 (1425) | 2920 (1747) | **<0.001** |
| | $t_{28}$ | 5977 (2000) | 2851 (1471) | |
| Total sodium intake (mg/d) | $t_0$ | 2699 (930) | 2601 (1155) | **<0.001** |
| | $t_{28}$ | 5792 (1225) | 2249 (958) | |
| Total potassium intake (mg/d) | $t_0$ | 3267 (771) | 3411 (1650) | **<0.001** |
| | $t_{28}$ | 3460 (875) | 2713 (1183) | |

Data are shown as median (IQR).
HBS = High Bicarbonate and Sodium, LBS = Low Bicarbonate and Sodium.
SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, MAP = Mean Arterial Pressure.
n = 85 (HBS n = 43, LBS n = 42), except sodium and calcium excretion: n = 84 (HBS n = 43, LBS n = 41)
*Time x group interactions were analyzed using two-way repeated measurement ANOVA.

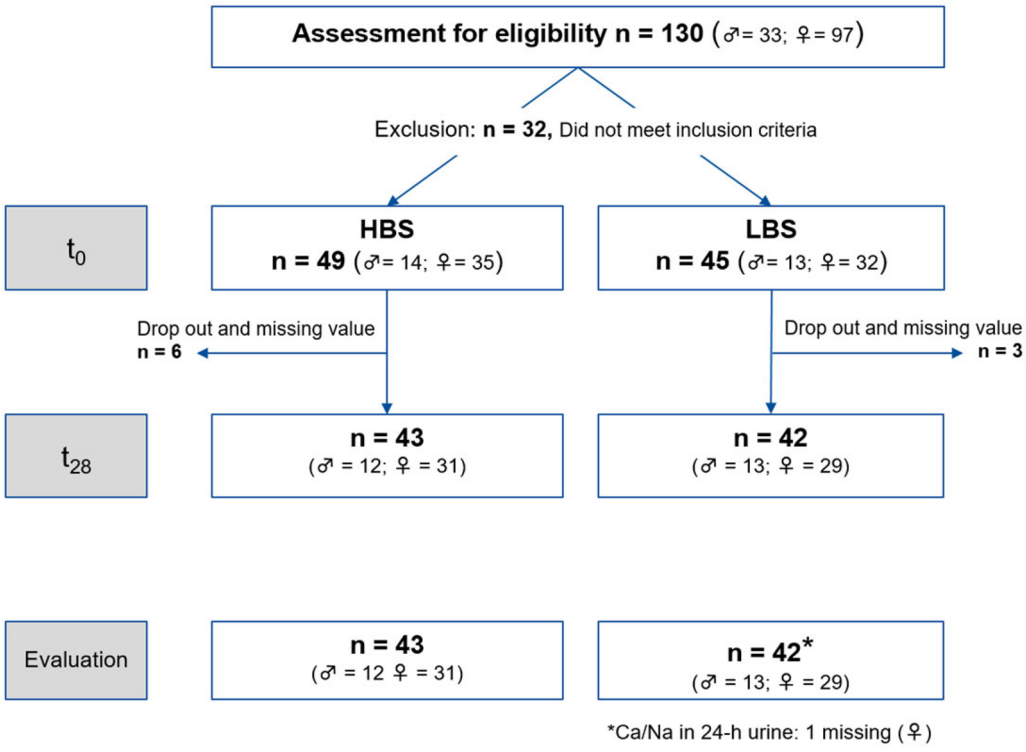


**Figure 1.** Flow chart of the study

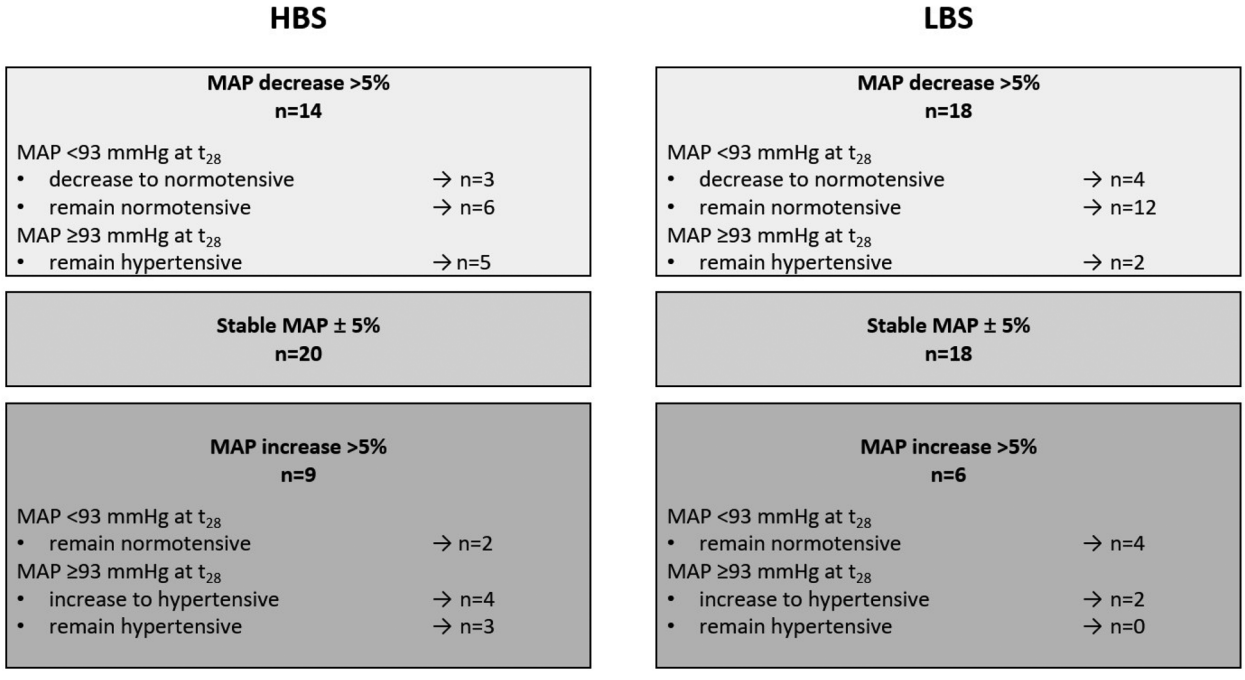


**Figure 2.** Changes in blood pressure by subgroups

### *Linear regression analyses*

The relationship between urinary sodium excretion, and/or calcium excretion and serum aldosterone and changes in SBP is shown in Tables S2 and S3. In the HBS group, regression analysis revealed a slight association between changes in urinary sodium excretion and changes in SBP (B = 0.072, p = 0.005), indicating a small increase in SBP with increasing sodium excretion as an indicator of sodium intake. However, this effect lost significance after adjusting for baseline

**Table 4.** Changes in SBP, DBP and MAP by blood pressure status.

| Parameter | Subgroup | Water groups | | p-value* | p-value** (treatment x group) |
|---|---|---|---|---|---|
| | | HBS | LBS | | |
| Δ SBP (mmHg) | normotensive | 0.00 (17.3) | −0.25 (14.0) | 0.306 | 0.736 |
| | hypertensive | −6.50 (18.0) | −8.00 (10.5) | 0.241 | |
| Δ DBP (mmHg) | normotensive | 0.75 (7.75) | −1.50 (8.50) | 0.358 | 0.548 |
| | hypertensive | −5.00 (17.0) | −6.75 (8.00) | 0.413 | |
| Δ MAP (mmHg) | normotensive | −0.58 (7.17) | −1.75 (8.42) | 0.317 | 0.586 |
| | hypertensive | −8.00 (14.5) | −8.50 (5.67) | 0.238 | |
| Δ serum aldosterone (ng/L) | normotensive | −29.5 (42.5) | −3.00 (64.0) | **0.007** | 0.862 |
| | hypertensive | −17.0 (51.0) | 8.50 (43.0) | 0.166 | |
| Δ sodium excretion (mmol/24 h) | normotensive | 144 (83.0) | 14.0 (99.0) | **<0.001** | **0.033** |
| | hypertensive | 48.0 (66.0) | −28.0 (45.0) | **<0.001** | |
| Δ calcium excretion (mmol/24 h) | normotensive | −1.25 (2.85) | −0.20 (1.60) | 0.067 | 0.627 |
| | hypertensive | −0.50 (1.50) | −0.60 (1.80) | 0.501 | |

Data are shown as median (IQR).
BSW = High Bicarbonate and Sodium, LBS = Low Bicarbonate and Sodium.
SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, MAP = Mean Arterial Pressure.
Normotensive subjects: HBS n = 28, LBS n = 32
Hypertensive subjects: HBS n = 15, LBS n = 10
*Group differences were analyzed using unpaired t-Test or Mann-Whitney-U-Test.
**Treatment x group interactions were analyzed using two-way repeated measurement ANOVA.

SBP, age and BMI (B = 0.046, p = 0.170) (Table S2). Further adjustments for baseline uric acid excretion, urinary creatinine excretion, and HbA1c did not change the results. In addition, the overall model including urinary sodium excretion, calcium excretion and serum aldosterone was significant only without adjustment for baseline SBP, age and BMI (p = 0.041), but lost significance after adjustment for baseline SBP, age and BMI (p = 0.134, Table S3). Further adjustments for baseline uric acid excretion, urinary creatinine excretion, and HbA1c did not change the results. This suggests that the changes in urinary sodium and calcium and serum aldosterone are not associated with changes in SBP. There were no associations between changes in DBP or MAP and changes in serum aldosterone, urinary sodium excretion, and urinary calcium excretion in the HBS group. Regression analysis in the LBS group showed no effect of changes in urinary sodium excretion, urinary calcium excretion and serum aldosterone on changes in SBP, DBP and MAP.

No significant correlation was observed between changes in urinary sodium excretion and changes in serum aldosterone in the HBS group (r=-0.146, p = 0.350). Subgroup analyses for MAP status at baseline showed similar correlations for normotensives (r = 0.012, p = 0.950) and hypertensives (r=-0.005, p = 0.985), which were also non-significant. Multiple linear regression analysis also indicated no significant influence of urinary sodium excretion or urinary calcium excretion on changes in serum aldosterone in the HBS group (Table S4). Regression analysis in the LBS group showed no effect of changes in urinary sodium excretion and urinary calcium excretion on changes in aldosterone.

## 4. Discussion

In this study, the effect of drinking mineral water high in bicarbonate and sodium on blood pressure was investigated over a period of four weeks. The results showed that there was no significantly different effect on blood pressure between the test water (HBS) and the control water (LBS). Only a minor proportion of the participants experienced an increase in blood pressure, regardless of the sodium content of the water.

Previous studies have shown no adverse effect of mineral water high in sodium and bicarbonate on blood pressure [7–10, 19, 20]. Some studies have even demonstrated a hypotensive effect after consuming mineral water rich in sodium and bicarbonate [10–12]. Overall, there are a few studies on this topic, and half of them are more than 15 years old.

One possible explanation for the inconsistent results among studies could be the different bicarbonate and sodium contents of the tested waters. Compared to the aforementioned studies, the daily doses of bicarbonate and sodium in this study were the highest ($HCO_3^-$: 6,552 to 8,736 mg/d, $Na^+$: 2,562 to 3,416 mg/d), yet stable blood pressure was observed. Bicarbonate and sodium doses in previous studies varied largely from 992 to 5,210 mg/d and from 289 to 2,034 mg/d, respectively. In the studies that showed a reduction in blood pressure, neither particularly high amounts of bicarbonate nor particularly low amounts of sodium were consumed [10–12]. This indicates that the additional bicarbonate and sodium intake from mineral water is not the cause of the different blood pressure responses. However, the results

of previous studies suggest that sodium chloride and sodium bicarbonate behave differently with respect to blood pressure effects [10, 12]. While sodium chloride leads to an increase in blood pressure, $NaHCO_3^-$ leads to blood pressure reduction or no changes in blood pressure [21]. In the aforementioned studies, the amount of chloride consumed via mineral water varied between 15 mg/d and 2,261 mg/d [7–12, 19]. Nevertheless, different blood pressure effects for sodium bicarbonate and sodium chloride were shown in a study with approximately the same amount of chloride (450 mg/d) consumed via water [10].

Besides bicarbonate and sodium, mineral waters contain a number of other minerals. It is worth noting, that the supplementation of calcium, magnesium, and potassium has been shown to have a positive impact on blood pressure regulation [17, 22, 23]. This may explain the blood pressure decrease in some studies. For example, the high magnesium content present in the mineral water utilized in the study conducted by Luft et al. [10] might have contributed to the reduction in SBP. In contrast, in the study presented here, the content of magnesium, calcium, and potassium in the test waters was relatively low and may therefore explain the stable blood pressure in both study groups. With the exception of potassium intake in the LBS group, mineral intake did not change during the study. The change in potassium intake observed in the LBS group is within the range of the IQR and can be attributed, at least in part, to variations in dietary intake. Nevertheless, the results suggests that some participants in the LBS group did not maintain their dietary habits. This may have affected blood pressure in the control group.

In previous studies subgroup data on baseline blood pressure status and the respective effects of the intervention have not been reported [7, 8, 19, 20], with the exception of Luft et al. [10]. They observed a decrease in SBP but only among hypertensive subjects who consumed mineral water rich in bicarbonate and sodium. No changes in blood pressure were observed in normotensive subjects who consumed either bicarbonate- and sodium-rich mineral water or a placebo water containing only sodium chloride. These findings differ from the data presented here.

As anticipated, the consumption of HBS water, which had a high sodium content, led to a significant increase in sodium excretion within the HBS group. This finding is consistent with the results reported by Luft et al. [10], who demonstrated an increase in sodium excretion following the consumption of both sodium-bicarbonate-rich mineral water and a control water containing sodium chloride. However, when conducting subgroup analyses based on blood pressure status at baseline, the results between the study conducted by Luft et al. [10] and the present study revealed differences. In Luft et al.'s study, no significant differences were observed in urinary sodium excretion between hypertensive and normotensive subjects. However, in the HBS group of the present study, there was a significant difference in urinary sodium excretion between normotensive and hypertensive subjects. Normotensive subjects showed a greater increase in urinary sodium excretion than hypertensive subjects. However, there was no change in blood pressure in normotensive subjects but a tendency towards a decrease in blood pressure in hypertensive subjects. This indicates that the higher sodium retention in hypertensives did not negatively affect the blood pressure.

The total study group, including both the HBS and LBS group, exhibited varied blood pressure responses, including decreases, stability, and increases. However, these different blood pressure responses could not be explained by differences in serum aldosterone, sodium and calcium excretion. Within each intervention group, there were no significant differences in the changes of serum aldosterone, sodium and calcium excretion among the subgroups with different blood pressure responses. This suggests that alterations in serum aldosterone, calcium and sodium excretion were not the underlying factors contributing to the different blood pressure responses observed.

There are several factors that could have contributed to the variations in blood pressure responses among the subgroups in both water groups. While the ingredients present in the water may contribute to these differences, it is crucial to acknowledge that external factors unrelated to water consumption, such as stress, sleep habits, and environmental noise can also significantly influence blood pressure levels [24–26]. Although both water groups showed similar blood pressure responses, the blood pressure increases in the HBS group were more pronounced than in the LBS group. For a few participants, the HBS water seems to have a slightly negative effect on blood pressure. However, a much larger proportion of subjects showed a positive effect on blood pressure, irrespective of baseline blood pressure. This suggests that the majority of individuals benefited from the consumption of HBS water in terms of blood pressure regulation.

Regression analyses were conducted to examine the factors that could potentially affect changes in blood pressure. The results revealed that neither the change in urinary sodium excretion, nor the change urinary

calcium excretion or in serum aldosterone significantly impacted DBP and MAP. However, when examining the influences on SBP, there was a potential detrimental effect observed from sodium in the HBS group, but only in the unadjusted model. Adjustments for baseline SBP, BMI, and age resulted in a loss of significance. In addition, there was no significant effect on SBP in the LBS group in either the unadjusted or adjusted model. However, when considering sodium excretion, calcium excretion, and serum aldosterone, sodium excretion lost its predictive power in the adjusted model. As sodium excretion is an indicator for total sodium intake these results suggest no influence of sodium intake on SBP in the presented study. It is important to note that both the adjusted and unadjusted model make a moderate or small contribution to explaining the variance in SBP (12.6% and 9.9% of the variance, respectively). This suggests that there are other influencing factors affecting the change in SBP in the HBS group, which were not captured by our model.

In the study conducted, a noteworthy decrease in serum aldosterone was observed after the HBS water consumption without gender or age differences. In contrast, no changes in serum aldosterone levels were observed in the LBS group. These findings suggest a physiological response to the high sodium content in the HBS water involving the renin-angiotensin-aldosterone system (RAAS) and pressure natriuresis. In normotensive subjects and salt-resistent hypertensives sodium overload leads to an increased renal perfusion pressure and an increased renal interstitial hydrostatic pressure [27]. To maintain stable blood pressure, the release of angiotensin II is lowered [27]. This results in a higher diuresis to reduce volemia and sodium levels [28]. Sodium and water excretion via urine is facilitated, modulated by a lower reabsorption of sodium via Na/H-antiporters and Na/K-ATPase [28, 29]. However, the available mineral water studies on this topic have yielded inconclusive results. While acute studies have shown a significant reduction in serum aldosterone [13, 14], this effect could not be confirmed in chronic studies until now [8, 10, 12]. Against this background, the present study is the first to show a significant decrease in serum aldosterone resulting from chronic mineral water consumption. This discrepancy between previous findings on chronic consumption and the current results may be attributed to the amount of sodium consumed. In previous studies, the additional sodium intake through mineral water may have been too low to cause long-term reductions in serum aldosterone levels.

Previous studies analyzed the effects of acute or chronic consumption of bicarbonate- and sodium-rich mineral water on urinary sodium excretion. In line with the results presented here, studies conducted by Schorr [12], Schoppen [14], and Toxqui and Vaquero [13] have demonstrated a significant increase in sodium excretion associated with the consumption of mineral water high in bicarbonate and sodium. These changes in sodium excretion can potentially be attributed to alterations in aldosterone secretion. This could explain why mineral waters high in sodium did not lead to elevated blood pressure in previous studies. However, it is important to note that all of these studies were conducted in healthy individuals who were able to effectively excrete the additional sodium consumed. Surprisingly, the decrease in aldosterone observed in the HBS group of the current study was not associated with the notable increase in urinary sodium excretion. This is different from what the authors expected.

There may also be an effect on serum aldosterone modulated by the bicarbonate content of the studied mineral water and its effect on urinary calcium excretion. In the present study, consuming 1.5 - 2 liters of HBS water led to a significant decrease in calcium excretion. These findings are consistent with the results of previous studies, where a significant reduction in urinary calcium excretion was shown after the consumption of 1.0 or 1.5 liters of bicarbonate- and sodium-rich mineral water [8, 12, 16]. The underlying mechanism seems to involve changes in urinary pH and a subsequent decrease in calcium excretion caused by the consumption of bicarbonate-rich water. It has been previously demonstrated that the consumption of mineral water high in bicarbonate increases urine pH [8, 15, 16, 30]. In addition, there is a positive correlation between urine acidity and urinary calcium excretion [31]. It could therefore be assumed that mineral water rich in bicarbonate increases urine pH, which leads to a decrease in urinary calcium excretion.

This reduced urinary calcium excretion may mediate the effect of HBS water on serum aldosterone. It has been shown that a reduced urinary calcium excretion improves calcium homeostasis [32]. In addition, high calcium intake, which also leads to a better calcium status, has been shown to reduce parathyroid hormone (PTH) secretion, which in turn has an aldosterone-lowering effect [33]. However, the regression analysis on changes in serum aldosterone did not provide support for this hypothesis. Neither changes in urinary sodium excretion ($p = 0.125$) nor changes in urinary calcium excretion ($p = 0.064$) were a significant predictor of aldosterone changes in the

HBS group. It is important to note that the calculated model including both predictors (calcium excretion and sodium excretion), yielded a moderate to high goodness of fit with an $R^2$ of 0.156 in the unadjusted model and 0.460 in the adjusted model (corrected $R^2$ of 0.114 and 0.387, respectively) according to Cohen [34]. These two predictors accounted for 11.4% or 38.7% of the variance in aldosterone, indicating a moderate to high variance clarification. However, regression analysis showed that changes in serum aldosterone occurred independently of changes in calcium. Therefore, an influence on calcium homeostasis and PTH seems unlikely. Nevertheless, the authors can only speculate on this topic, because PTH was not monitored in the study. These aspects should be clarified in further studies. Furthermore, it is likely that sodium intake (as reflected by urinary sodium excretion) influenced the changes in aldosterone, although this could not be statistically proven for this study group.

The reduction of serum aldosterone shown in the HBS group may potentially offer benefits beyond the classical targets of sodium excretion and blood pressure regulation. Results from a prospective cohort study suggest that serum aldosterone levels within the physiological range may have a considerable impact on the development of fatal cardiovascular events. In this study, higher aldosterone levels were associated with increased all-cause and cardiovascular disease (CVD) mortality [35]. Furthermore, a link has been established between pathologically elevated aldosterone levels and the increased risk for cardiovascular and cerebrovascular events in patients suffering from hyperaldosteronism [36]. The underlying changes include inflammation, end-organ fibrosis, endothelial dysfunction, and vascular damage [37–39]. Renal changes have also been observed, resulting in proteinuria and impaired renal function [40–42]. Additionally, it has been demonstrated that the prevalence of the metabolic syndrome increases with pathologically elevated serum aldosterone levels [36, 43]. However, since these negative changes were primarily observed in patients suffering from hyperaldosteronism, further studies are needed to determine whether the reduction in aldosterone demonstrated in this study can also be observed in patients with pathologically elevated aldosterone levels after the consumption of bicarbonate and sodium-rich mineral water.

### *Strengths and limitations*

In order to critically evaluate the findings of our study and provide a comprehensive analysis, it is important to consider both its strengths and limitations. One limitation arises from the study protocol. Due to the time restrictions required for the 24-hour urine collections, the study was not conducted as a cross-over study. Moreover, the absence of blinding in the study design should be recognized as a limitation. Since the taste of the water alone indicated the group assignment, blinding was not feasible. This lack of blinding should be recognized as a possible source of influence on the study outcomes. Additionally, the study relied on in-office blood pressure measurements rather than 24-hour ambulatory measurements. This choice may have overlooked the impact of diurnal fluctuations and the white coat effect on blood pressure readings. Furthermore, it would have been beneficial to include additional control groups receiving mineral water high in bicarbonate or high in sodium alone. This would have allowed for a more precise evaluation of the individual effects of bicarbonate and sodium and improved the study's ability to make specific statements regarding their respective impacts.

On the other hand, the present study has certain strengths that should be mentioned. One strength is the sample size, surpassing previous studies that examined similar effects with smaller participant groups. This increased sample size enhances the study's statistical power, making it more likely to detect true effects and enabling more precise estimates of the observed effects. Furthermore, this is the first study analyzing several subgroup effects and investigating influences on both blood pressure and aldosterone changes. This comprehensive approach provides valuable insights into the specific effects of the intervention. Another significant advantage of the study is the high daily intake of bicarbonate and sodium. The dosage chosen was intended to demonstrate the safety of prolonged and consistent consumption of these elements on blood pressure, in both normotensive and hypertensive individuals. This robust dosage strengthens the study's ability to assess the impact of bicarbonate and sodium intake on blood pressure regulation.

## 5. Conclusion

In conclusion, this study revealed no significant difference in blood pressure changes between individuals who consumed mineral water high in bicarbonate and sodium (HBS) and those who consumed a control water low in bicarbonate and sodium (LBS). Regardless of the type of water consumed, the majority of participants experienced either stable blood pressure or a

reduction in blood pressure. The study findings suggest that the additional sodium intake from the test water was effectively excreted.

Further research is needed to investigate the specific effects of consuming bicarbonate-rich water on serum aldosterone and blood pressure, independent of any potential influence of a concomitant high sodium content or intake. These studies would provide valuable insights into the isolated effects of bicarbonate-rich mineral waters on these physiological parameters.

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