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Aldosterone changes after consumption of a sodium-bicarbonated mineral water in humans. A four-way randomized controlled trial

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A**bstract**

Abnormally high aldosterone levels are associated to hypertension and cardiovascular disease. A sodium-rich mineral water was previously shown to reduce several markers of cardiovascular risk and did not increase blood pressure in healthy adults. We aimed to study the effects of consuming the same mineral water compared to a control water on aldosterone levels, and if the effects vary due to the presence of meal in healthy adults. The design was a 4-way randomized controlled crossover 120 min-postprandial trial. Twenty-one healthy men and women participated in the study. Exclusion criteria: diabetes, hypertension and being a usual consumer of carbonic mineral water. Two different mineral waters, high sodium and bicarbonate mineral water (BW, sodium, 1 g/L; bicarbonate, 2 g/L) and low mineral content control water (CW), were consumed with or without a standard meal (500 mL per meal). Statistical analysis was performed by repeated measures ANOVA. Results: Serum sodium did not vary and serum potassium decreased throughout the assay ($p=0.01$) without water influence. Consumption of BW significantly decreased aldosterone levels at 30 ($p=0.046$), 60 ($p=0.009$) and 120 ($p=0.025$) min when consumed alone, and at 120 min ($p=0.019$) when consumed with meal, compared to CW. Moreover, the effect of BW on aldosterone levels was significant in women but not in men. In conclusion, consumption of a sodium-bicarbonated mineral water, in presence or absence of meal, induces aldosterone inhibition in healthy women, which is suggested to be a physiological response that protects them against hypertension. This trial is registered at c*linicaltrial.gov* as NCT01334840.

Keywords: Aldosterone; sodium; mineral water; human; randomized controlled trial; cardiovascular risk.

Introduction

Under normal conditions, the renin-angiotensin-aldosterone system controls electrolyte and water balance. Aldosterone is a major regulator of sodium and potassium balance and plays an important role in regulating extracellular volume. It enhances the reabsorption of sodium and water and promotes potassium excretion. Therefore, high aldosterone levels are associated to hypertension, endothelial dysfunction, cardiovascular disease and heart failure [1,22]. Factors like excessive weight [2] and androgens [13] are involved in increasing aldosterone production, even in non-hypertensive subjects.

Sodium is the principal cation in the extracellular fluid of the body, and it is essential for maintenance of plasma volume, acid–base balance, transmission of nerve impulses and normal cell function. Current public health recommendations, for adults, with or without hypertension, are focused on reducing sodium intake to <2 g/day (5 g/day salt) [24]. However, under normal renal and vascular conditions, healthy individuals are capable to maintain their hydro-saline equilibrium. The response to a high-salt intake involves the inhibition of the renin-angiotensin-aldosterone system, whereas a low-sodium intake stimulates it [8].

Our research group has shown that a mineral water rich in sodium, bicarbonate, chloride and other electrolytes reduces several markers of cardiovascular risk in adults. Consumption of this water, as part of the usual diet, reduces total cholesterol, LDL-cholesterol, postprandial lipemia and did not increase blood pressure in postmenopausal women or in moderately hypercholesterolemic young adults [16,17,19,21].

Consistently, we observed in postmenopausal women that postprandial aldosterone levels decreased at 120 min after the consumption of 0.5L of the bicarbonated mineral water with a meal, compared to a control water [18]. However, there are not reports in men and it is not known if the aldosterone response is modulated by the presence of meal. We hypothesized that aldosterone levels decrease after consumption of sodium bicarbonated mineral water independently of the presence of meal in healthy men and women.

The present study is a 4-way randomized controlled crossover trial designed to confirm the effects of consuming the same sodium-bicarbonated mineral water observed in postmenopausal women, on aldosterone levels, and specifically to know if the effects vary when the water is consumed in presence or absence of a standard meal, and if there are differences between men and women.

Methods

Subjects

Volunteers selected for the study were adults, men and women, with body mass index (BMI) >18 and <30 kg/m^2. Exclusion criteria were as follows: age <18 and > 40 years, triglycerides > 2.82 mmol/L (250 mg/dL); being a usual consumer of carbonic mineral water; obesity; diabetes; hypertension; digestive, liver or renal diseases; biliary obstruction; eating disorders; being under medication or consumption of functional foods that could affect lipid metabolism(foods containing n-3 fatty acids or phytosterols).

A total of 142 men and women contacted the research group to receive information and 88 sent the health questionnaires. Volunteers who did not meet the inclusion criteria or declined to participate were excluded (n=54). Finally, a total of 24 volunteers agreed to participate in the nutritional intervention and were randomly assigned to start with one of the four treatments described below. During the study, 1 person was excluded from analysis (gallstones) and 2 volunteers were lost to follow-up (problems with the cannula for blood extraction; did not give reasons). Therefore, 21 volunteers (10 men and 11 women) completed the study and were analyzed. Study participants were instructed not to deviate from their regular habits and to maintain their normal diet, body weight, alcohol consumption and exercise levels. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethics Committee of the Spanish National Research Council and the Clinical Research Ethics Committee of Hospital Clínica Puerta de Hierro, Majadahonda, Madrid. Written informed consent was obtained from all subjects. This trial was register at clinicaltrials.gov as NCT01334840.

Postprandial Study

The design was a four-way randomized controlled crossover trial. Volunteers attended the clinic on 4 occasions at 1-week intervals, between 8:00 and 8:30 h, having fasted overnight for at least 12 h. In order to control study conditions, the subjects followed written instructions regarding dinner composition (lettuce and tomato with olive oil, vinegar and salt; grilled chicken fillet; bread and fruit) the evening before the study. On the morning of the visit, blood pressure, weight and height were measured. Compliance with dinner instructions and no water intake in the previous 12 hours were verified with a questionnaire. A cannula was inserted into a vein for blood sampling and baseline samples were obtained. Four different treatments were applied in a randomized four-way crossover design. On the first day of study, volunteers were randomly assigned to an individual sequence of treatments until every subject had completed the study with all 4 treatments. As all volunteers arrived in the same conditions and each volunteer was each own control the effect of the aldosterone circadian rhythms [9] is not a bias in this assay.

Two different mineral waters were used in the study: control water (CW) and sodium-bicarbonated mineral water (CW). The waters were provided in 0.5-L bottles (Vichy Catalán, Barcelona). BW contained carbon dioxide and was rich in bicarbonate, sodium and chloride, while CW was low in mineral content (Table 1).
The treatments were as follows: 0.5 L of CW; 0.5L of BW; 0.5 L of CW + standard meal and 0.5L of BW + standard meal.

The standard meal contained whole cow's milk with decaffeinated instant coffee, avocado and crabstick salad, white flour cake, and bread toast (Table 2). The energy profile was as follows (as percentage of total energy): lipids 62%, carbohydrates 30% and protein 8%, and the lipid profile was: monounsaturated fatty acid (MUFA) 39.7%, saturated fatty acid 11.8% and polyunsaturated fatty acids (PUFA) 6.6%. This standard meal has been designed and validated by our research group. It reproduced a fat rich meal with a lipid profile similar to that of the Mediterranean Diet [19-21].

Volunteers consumed the water in presence or absence of meal. On average, the meal was eaten in 30 min, while the water alone was drunk in 15 min.

Blood samples were obtained at basal and at 30, 60 and 120 minutes postprandial times in Venoject tubes with Gel+Clot Activator to obtain serum.

Analytical determinations

Baseline total-cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides and glucose were determined by an automatic analyzer (RA 2000; Technicon) and insulin concentration was analyzed by chemiluminescence (Centre Inmunològic de Catalunya, Barcelona, Spain).

Aldosterone was determined at baseline and at 30, 60 and 120 min after the water consumption with or without the meal by a commercial kit (Aldosterone ELISA, Ref. RCAN-ALD-450R, Biovendor, Czech Republic). Intra- and inter-assay coefficients of variations were 4.1 and 9.7%, respectively. All determinations of the 4 treatments of each volunteer were carried out in the same run to avoid inter-assay variation.

Serum sodium and potassium were determined at baseline and at 30, 60 and 120 min by high-resolution atomic absorption spectroscopy (contrAA®700 de Analytik Jena's, Germany). Samples were diluted in a 1% HCL and 0.2% CsCl solution and read at 330.23 nm (relative sensitivity of 0.5%) and 769.98 nm (relative sensitivity of 56%) for sodium and potassium, respectively.

Statistical analysis

Aldosterone values followed a normal distribution as determined by the Kolmogorov–Smirnov test. Baseline data of men and women were compared by ANOVA

A three-way repeated measures ANOVA was carried out for aldosterone levels for time, time x water, time x meal, and time x water x meal interaction effects. As significant time x meal interaction was found ($p=0.03$), data were separated into two groups for meal and no meal conditions, and a two-way repeated measures ANOVA was carried out for time and time x water interactions. The paired t-student test was used to compare the waters at each time point.

A three-way repeated measures ANOVA was also carried out for time, time x water, time x gender, and time x water x gender effects, for the meal or no meal condition. As significant time x gender interactions were found ($p=0.01$ and $p=0.022$, respectively), data were separated into two groups for women and men, and a two-way repeated measures ANOVA was carried out for time and time x water interactions. A paired t-student test was used to compare effect of the waters at each time point and each gender.

Results were considered significant with p value <0.05. Data analyzes were performed using SPSS version 22.0 for Windows.

Results

Baseline characteristics of the volunteers (n=21, 10 men and 11 women) are shown in Table 3. Significantly higher values of BMI ($p=0.001$) and systolic blood pressure ($p=0.01$) and lower HDL-cholesterol ($p=0.003$) were observed in men compared to women Non-significant differences were found between men and women for the rest of parameters.

Serum sodium did not vary and serum potassium decreased ($p=0.01$) within normal ranges during the assay, without time x water interaction. Fig. 1 shows aldosterone changes with the consumption of the waters in presence or absence of meal. For both conditions of consumption (water alone and water + meal), aldosterone levels presented significant time effect ($p<0.001$) and time x water interaction ($p<0.05$). Values were significantly lower at 30 ($p=0.046$), 60 ($p=0.009$) and 120 ($p=0.025$) min when BW was consumed in absence of meal, and at 120 min ($p=0.019$) when it was consumed in presence of meal, compared to CW.

Table 4 shows men and women postprandial aldosterone values. A time effect was observed in both genders and for both condition of consumption. However, only in the case of women and when BW was consumed alone a time x water interaction was found ($p=0.042$). Aldosterone levels were lower at 60 ($p<0.024$) and 120 ($p=0.011$) min when women consumed BW alone and at 120 ($p=0.042$) min when it was consumed with meal, compared to control water.

Discussion

This study shows that consumption of 0.5 L of BW induces aldosterone inhibition, either consumed with or without a meal, in healthy adults.

Participants were healthy with all parameters within normal ranges. Women presented higher levels of HDL-cholesterol and lower systolic blood pressure than men, which is in agreement with epidemiological studies [6]. The American Heart Association reports that 20 to 54 years old men present higher blood pressure than age-matched women [6]. In this line, it is known that premenopausal women are protected from cardiovascular diseases, as this protection weakens after menopause, sex hormones are believed to play an important role in the pathogenesis of cardiovascular diseases [10]. In fact, both estrogens and androgens have been implicated in the development of cardiovascular disease and hypertension, with estrogens being protective and androgens being detrimental [13].

This study demonstrates that aldosterone levels decreased with the four treatments. The meal effect can be explained, at least partially, by two factors, the digestive signals as it is known that several hormones decrease after eating, including ghrelin and aldosterone [14] and the 276 mg sodium provided by the standard meal, as aldosterone decreases after sodium intake [8].

Concerning the influence of the type of water, consumption of BW induced a higher reduction in aldosterone levels compared to CW which is in agreement with our previous results found in postmenopausal women [18]. Present results shows that differences between experimental waters were higher in the absence of meal. In addition women showed higher aldosterone postprandial response than men. It is noteworthy that after 120 min of consumption of BW by men aldosterone levels were similar to those of postmenopausal women (mean values approximately 100 pg/ml) but much higher than those of the young women (mean values between 60-70 pg/ml), which reinforces the role of sexual hormones in electrolyte and water regulation.

In the present study no changes in serum sodium and potassium levels were observed due to water intake. This adds information to the urinary electrolyte excretion reported previously. Excretion of calcium, phosphorus, magnesium, chloride, and potassium in 7-h postprandial urine did not differ between waters, however, sodium excretion was significantly higher with the consumption of BW [19]. This is associated to the decrease in aldosterone levels induced by BW as urinary sodium excretion is favored by inhibition of the renin-angiotensin-aldosterone system.

The American Heart Association [24], the European Societies of Hypertension and Cardiology [12] and the European Food Safety Authority (EFSA) [5], among other scientific authorities, promote a reduction in sodium/salt intake in order to prevent hypertension. However, controversy exists on the feasibility of reducing salt intake in the whole population and if the beneficial effects are limited to blood pressure or have an impact in cardiovascular disease [3,7,16]. In this regard, the renin-angiotensin-aldosterone system physiologically maintains electrolyte and water equilibrium under a range of conditions from shortage to excess of sodium. Consistently, in the present study drinking the sodium-rich mineral water induced a decrease in aldosterone levels. This explains why blood pressure does not increase after consumption of 1 L/day of sodium bicarbonated water during 8 weeks either by postmenopausal women or moderately hypercholesterolemic men and women [16,17, 22].

Sodium bicarbonate predominates over sodium chloride in the studied mineral water (Table 1). Few studies are available on the effects of mineral waters on aldosterone and blood pressure and the possible distinct metabolic effects of sodium chloride compared to other sodium salts. It was observed that 3 L/day of a sodium bicarbonate mineral water, which provides 78 mmol/L of sodium and 99 mmol/L of bicarbonate, compared to a control solution of equimolar amounts of cations, reduced systolic blood pressure in hypertensive individuals [11]. Ziomber et al.[27], in a hypertensive rat model observed that blood pressure was increased by NaCl but not by $NaHCO_3$ and $KHCO_3$ intake. Moreover, it has been suggested that chloride is determinant in increasing extracellular volume and blood pressure while bicarbonate plays a protective role [12,27].

The present results show individuals are capable of regulating the hydro-saline balance after the intake of 500 mg of sodium in the form of the studied mineral water (500 ml of water) by acting on the renin-angiotensin-aldosterone system. Interestingly, this amount of sodium excesses the upper level proposed by the European EFSA and WHO [4,26] concerning the nutrient profiling. Calculated as daily basis, 1 L of this water (e.g. 500 mL with lunch and 500 mL with dinner) provides 1 g of sodium which is about half the daily recommended dietary intake (1.5-2 g of sodium equivalent to 5-6 g of salt) [5,24].

In this line, several authors have expressed their concerns about a severe restriction of sodium intake for the general population since sodium is essential for maintaining optimal extracellular volume [3,16]. McCarron et al (2009) [15] have calculated that a daily sodium intake of 2.3 g (100 mmol) involves a urinary sodium excretion below the limit of 117 mmol/d that, according to data form many countries and many inter-collaborative studies, are considered normal. In this regard, in a recent 8-week controlled cross-over study, we observed in healthy men and women that the intake of 1L of the same BW did not affect blood pressure but tended to decrease

fasting aldosterone levels [22]. Therefore, we suggest that the inhibition of aldosterone could be a short-term homeostatic mechanism which helps to maintain blood pressure in the long term.

Limitations of the study are that all volunteers were healthy non-obese or hypertensive adults and the results cannot be extrapolated to conditions of cardiovascular disease. In addition, genetic factors or lipoproteins composition were not analysed and urine was not collected. The main strength is the randomised 4-way crossover design, which has the advantage of comparing changes in the same volunteer and all the study conditions were well controlled.

In conclusion, the present study demonstrates that aldosterone levels decrease after drinking a sodium-bicarbonated mineral water in healthy women, which is suggested to be a physiological response that protects them against hypertension. The possible effect of this water in hypertensive patients under dietetic control should be investigated.

Conflicts of interest

Authors do not have conflict of interest to declare.

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Table 1. Composition of the mineral waters employed in the study

	CW		BW [a]	
	mg/L	mmol/L	mg/L	mmol/L
HCO_3^-	104	1.70	2120	34.75
Cl^-	11	0.31	597	16.84
SO_4^{2-}	15.6	0.16	45.3	0.47
F^-	<0.2	<0.01	0.9	0.05
Ca^{2+}	33.4	0.83	32.0	0.80
Mg^{2+}	5.0	0.20	9.4	0.39
Na^+	8.7	0.38	1102	47.91
K^+	2.0	0.05	49.5	1.27

[a] Contains 3.9 g/L of CO_2. CW: control water; BW: bicarbonated water.

Table 2. Standard meal energy and nutrient composition

Nutrient	Quantity
Energy (kcal)	1088
Protein (g)	21.5
Fat (g)	75.3
Carbohydrates (g)	86.5
Fibre (g)	2.1
Calcium (mg)	230
Phosphorous (mg)	430
Magnesium (mg)	65.8
Sodium (mg)	276
Potassium (mg)	745

Table 3. Characteristics of the study participants at the beginning of the study

Parameter	Total	Men	Women
n	21	10	11
Age (years)	27.8 ± 4.5	28.4 ± 3.6	27.3 ± 5.3
BMI (kg/m^2)	23.8 ± 2.9	25.8 ± 2.2	22.0 ± 2.3***
Systolic blood pressure (mmHg)	113.2 ± 14.0	122.7 ± 11.7	105.8 ± 11.1**
Diastolic blood pressure (mmHg)	69.1 ± 10.9	71.3 ± 15.1	67.3 ± 6.7
Total cholesterol (mmol/L)	5.4 ± 1.1	5.1 ± 1.3	5.7 ± 0.9
HDL cholesterol (mmol/L)	1.8 ± 0.3	1.6 ± 0.2	2.0 ± 0.3**
LDL cholesterol (mmol/L)	3.1 ± 0.9	3.1 ± 1.2	3.2 ± 0.6
Triglycerides (mmol/L)	1.2 ± 0.5	1.3 ± 0.5	1.2 ± 0.6
Glucose (mmol/L)	4.9 ± 0.3	5.0 ± 0.3	4.8 ± 0.4
Insulin (µU/mL)	4.5 ± 4.5	5.8 ± 6.1	3.3 ± 1.7
Aldosterone (pg/mL)	161.7 ± 72.3	157.2 ± 64.7	165.9 ± 79.5
Serum sodium (mEq/L)	125.9 ± 15.1	130.1 ± 15.9	122.1 ± 13.6
Serum potassium (mEq/L)	4.7 ± 0.25	4.6 ±0.23	4.7 ± 0.27

Values are expressed as mean ± SD.

** p≤0.01, *** p=0.001, significant differences compared to men.

Fig. 1. Changes in postprandial aldosterone levels after consuming CW and BW alone (A) or with a standard meal (B): (○) CW; (●) BW; (□) CW with meal; (■) BW with meal. Values are expressed as mean with standard error, * $p<0.05$, ** $p<0.01$.

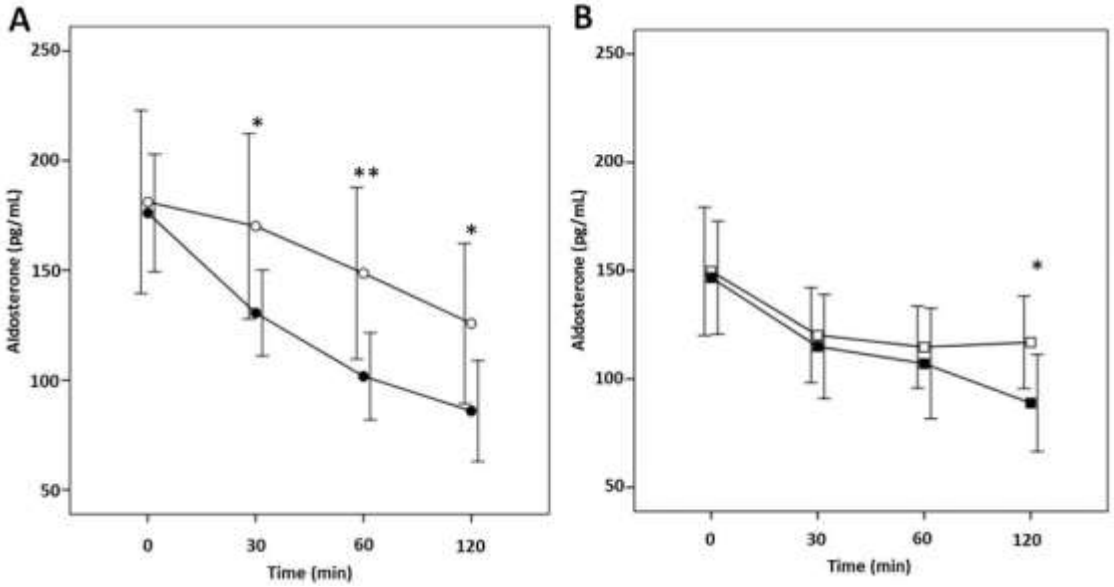

Table 4. Postprandial aldosterone values (pg/mL) when the waters were consumed without or with the meal

Condition	Gender	Water	Postprandial times				Time effect	Time x water
			Baseline	30 min	60 min	120 min		
Without meal	Men	CW	160.2 ± 50.8	145.8 ± 53.0	147.9 ± 76.8	122.6 ± 72.1	0.02	NS
		BW	171.0 ± 76.9	138.3 ± 51.7	117.0 ± 74.8	114.6 ± 52.7		
	Women	CW	216.3 ± 109.9	194.4 ± 113.5	160.7 ± 94.8	139.5 ± 87.7	<0.001	0.042
		BW	180.7 ± 38.6	114.8 ± 37.6	87.9 ± 35.6*	60.1 ± 31.5**		
With meal	Men	CW	137.4 ± 64.0	125.7 ± 51.8	129.8 ± 50.7	131.7 ± 54.0	NS	NS
		BW	164.5 ± 68.4	136.8 ± 64.2	134.4 ± 71.0	109.7 ± 64.4		
	Women	CW	162.1 ± 81.1	114.7 ± 57.2	99.7 ± 37.4	102.1 ± 48.2	<0.001	NS
		BW	129.1 ± 56.5	93.1 ± 45.2	79.8 ± 38.5	68.1 ± 34.5*		

*p<0.05; ** p=0.01, differences between bicarbonated and control waters by paired t-student. Men (n=10); women (n=11). CW: control water; BW: bicarbonated water.