ORIGINAL ARTICLE

No effect of bicarbonate treatment on insulin sensitivity and glucose control in non-diabetic older adults

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Abstract Chronic mild metabolic acidosis is common among older adults, and limited evidence suggests that it may contribute to insulin resistance and type-2 diabetes. This analysis was conducted to determine whether bicarbonate supplementation, an alkalinizing treatment, improves insulin sensitivity or glucose control in non-diabetic older adults. Fasting blood glucose and insulin were measured in stored samples from subjects who had completed a 3-month clinical trial of bicarbonate supplementation to improve indicators of bone and muscle health. One hundred and fifty three ambulatory, non-diabetic adults aged 50 years and older were studied. Subjects were randomized to one of two bicarbonate groups (67.5 mmol/day of potassium bicarbonate or sodium bicarbonate) or to one of two no-bicarbonate groups (67.5 mmol/day of placebo or potassium chloride). Subjects remained on treatment throughout the 3-month study. The primary outcome measures were changes in fasting plasma glucose, serum insulin and HOMA-IR, an index of insulin resistance. Bicarbonate supplementation reduced net acid excretion (adjusted mean ± SEM for the change in NAE/creatinine, mmol/mmol, was 0.23 ± 0.22 in the no-bicarbonate group compared with -3.53 ± 0.22 in the bicarbonate group, $P < 0.001$) but had no effect on fasting plasma glucose, serum insulin, or HOMA-IR. In conclusion, bicarbonate supplementation does not appear to improve insulin sensitivity or glucose control in non-diabetic older adults.

Introduction

Features of the typical Western diet, including its high protein content, contribute to a positive net acid load for both young and old adults. However, gradual declines in renal function with aging make it more difficult for older adults to adequately excrete excess acid, resulting in a worsening mild metabolic acidosis with age [1]. Compensatory mechanisms such as the release of buffering mineral from bone may help to maintain blood pH at a normal or only mildly decreased level, but probably not without additional and harmful effects [2]. There is mounting evidence that mild metabolic acidosis adversely affects bone and muscle health [3, 4], and there is also some evidence that it may contribute to the development of insulin resistance and type-2 diabetes, perhaps through upregulation of cortisol production [5]. Hyperglycemic and euglycemic clamp studies conducted over 30 years ago demonstrated that experimentally induced metabolic acidosis can impair glucose metabolism in humans by reducing tissue sensitivity to insulin [6]. Recently, in the National Health and Nutrition Examination Survey (NHANES), lower serum bicarbonate and higher anion gap were associated with increased insulin resistance among non-diabetic adults [7]. These outcome measures accompany many though not all cases of metabolic acidosis. These studies raise the possibility that counteracting the effects of mild metabolic acidosis could have beneficial effects on glucose control and insulin sensitivity. We recently reported beneficial effects of bicarbonate supplementation, an alkalinizing agent, on bone turnover and

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muscle performance [8, 9]. We conducted the present secondary analysis to determine whether bicarbonate supplementation in the same study also had beneficial effects on insulin resistance. To our knowledge, this is the first intervention study to examine the effect of reducing the acid load on insulin resistance or other risk factors for type-2 diabetes. Specifically, we test the hypothesis that supplementation with 67.5 mmol/day of bicarbonate for 3 months reduces fasting plasma glucose, fasting serum insulin, and HOMA-IR, an index of insulin resistance, in non-diabetic adults aged 50 years and older.

Materials and methods

Subjects and study design

As previously described in more detail [8, 9], 171 men and women aged 50 years and older were enrolled in an 84-day, randomized, double-blind, placebo-controlled trial designed to determine the effects of potassium bicarbonate ($KHCO_3$) and its components, potassium and bicarbonate, on bone turnover and muscle performance. Subjects were randomized to one of four treatment groups: placebo, potassium chloride (KCl), $KHCO_3$, or sodium bicarbonate ($NaHCO_3$). The purpose of the four-group design was to allow for differentiation of potassium from bicarbonate effects on bone and muscle. As described in two prior papers [8, 9], the effects we observed on bone and muscle were due to the bicarbonate and not the potassium component of the $KHCO_3$. Thus, in those papers, subjects in the two bicarbonate and two no-bicarbonate groups were pooled for final analyses. In the present analysis, we report results by both the original four treatment groups and by the pooled bicarbonate/no-bicarbonate groups. Serum insulin and plasma glucose were measured in subjects who completed the study ($N = 164$) and had sufficient remaining archived serum and plasma samples ($N = 155$) for the assays. The hypothesis that is tested in this analysis was formulated before these measurements were made. Of the 155 subjects, one was excluded due to suspected metabolic bone disease and a second was excluded due to fasting plasma glucose values of 151 and 156 mg/dl at baseline and follow-up, respectively, consistent with diabetes that was not detected at screening. Four subjects, one in the bicarbonate group and three in the no-bicarbonate group, had fasting plasma glucose values that were just below 126 mg/dl (the cutoff for diagnosing diabetes) at baseline and just over 126 mg/dl (7.0 mmol/l) at the end of the study (range 127–132). These subjects are included in the analysis. No subjects were taking diabetes medications at baseline or during the study. All subjects were ambulatory and women were at least 6 months menopausal.

Exclusion criteria, as described previously [8], included diabetes mellitus, heart disease, uncontrolled hypertension, active malignancy, significant immune disorder, peptic ulcer, esophageal stricture, history of kidney stone, creatinine clearance <0.84 ml/s/m^2, 25-hydroxyvitamin D <40 nmol/l, and recent use of gonadal hormones, osteoporosis medications, non-steroidal anti-inflammatory drugs more than three times a week, diuretics, and sodium- or alkali-containing antacids. The study was approved by the Tufts Medical Center-Tufts University Health Sciences Campus Institutional Review Board and written informed consent was obtained from all subjects.

Measurements

Measurements were made at baseline and after 3 months of treatment. Height was measured with a stadiometer and weight with a digital scale. Physical activity from leisure, household, and occupational activity was assessed with the Physical Activity Scale for the Elderly (PASE) questionnaire [10]. Self-selected usual dietary intakes over the past 3 months were assessed by a general food frequency questionnaire that was self-administered and then reviewed by staff for completeness in the presence of the subject [11]. Blood and 24-h urine samples were frozen and stored at −70°C and batched for analysis. Blood was drawn between 0700 and 0930 h after a minimum 12 h fast. Net acid excretion (NAE) was measured by a modification of the Jorgensen titration method [12] as described by Chan [13] with intra- and inter-assay CVs of 5.0 and 6.0%, respectively, and corrected for creatinine excretion. Serum cortisol was measured by chemiluminescent immunoassay commercial kits (IMMULITE 1000, Siemens Healthcare Diagnostics, Los Angeles, CA) with intra- and inter-assay CVs of 5.8–8.8 and 6.3–10.0%, respectively. Plasma glucose was measured by an enzymatic couple method using the Olympus AU400 clinical chemistry analyzer (Olympus America Inc., Melville, NY), with intra- and inter-assay CVs are 1.0 and 2.0%, respectively. Serum insulin was measured by a competitive binding radioimmunoassay commercial kit (HI-14K Human Insulin Specific Kit, Linco Research, Inc., St Charles, MO) with intra- and inter-assay CVs of 5.0 and 6.0%, respectively. HOMA-IR (homeostasis model assessment for insulin resistance) was calculated from fasting glucose and insulin measurements as follows: HOMA-IR = (insulin (μU/ml) × glucose (mmol/l))/22.5 [14]. Serum creatinine and urine potassium and creatinine (cr) were measured on an automated clinical chemistry analyzer (Olympus AU400, Olympus America Inc., Melville, NY). Urine potassium was corrected for creatinine excretion. Creatinine clearance was calculated from urine and serum creatinine and corrected for body surface area [15].

Statistical analyses

Univariate and bivariate distributions of variables were examined graphically for evidence of outliers, non-normality and nonlinearity. HOMA-IR was modestly skewed but analyses with the log-transformed variable were so similar to the non-log-transformed ones that only the non-log-transformed results are presented. Simple Pearson correlations and partial correlations adjusted for sex and weight were used to describe linear associations between selected variables. χ^2 tests were used to compare frequencies of dichotomous variables. Unadjusted means were compared across treatment groups with analysis of variance, and adjusted means were computed and compared with analysis of covariance using the SPSS general linear modeling procedure (SPSS Inc., Chicago, IL). 95% confidence intervals around selected differences in adjusted means were also calculated with the general linear modeling procedure. All analyses were done with SPSS version 14.0. P values less than 0.05 were considered to indicate statistical significance.

Results

Baseline characteristics of the 153 subjects by treatment groups are shown in Table 1. Percentage of calories from carbohydrate, protein, and fat were similar across treatment groups. Mean baseline NAE/cr was positive in all groups and over 90% of individuals in each group had positive values, consistent with acidogenic diets. Baseline NAE/cr and urinary potassium/cr differed modestly but significantly across treatment groups and were therefore adjusted for in subsequent analyses. All subjects had urine pH within the normal range of 4.6 to 8.0. Urine pH differed across bicarbonate groups but was not adjusted for in subsequent analyses because, as expected, it was highly collinear with NAE/cr ($r = -0.75$, $P < 0.001$). Other baseline characteristics did not differ significantly by treatment group.

NAE/cr and urine pH were not correlated with glucose, insulin, or HOMA-IR at baseline ($-0.11 < r < 0.06$, $P > 0.201$). Changes in NAE/cr, urine pH, urine potassium/cr, serum cortisol, and in the outcome variables are shown in Table 2 before and after adjustment for covariates. Treatment with bicarbonate, whether as potassium bicarbonate or sodium bicarbonate, reduced NAE/cr by about 3.5 mmol/mmol. However, despite this demonstrated acid neutralization, bicarbonate treatment had no statistically significant effect on concurrent changes in cortisol, glucose, insulin, or HOMA-IR, before or after adjustment for covariates.
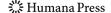
In order to describe the degree of uncertainty around our main findings, we calculated 95% confidence intervals around the differences between adjusted mean changes of our outcome variables in the no-bicarbonate and bicarbonate groups. These differences and confidence intervals were, for glucose, −0.06 mmol/l (−0.10, 0.22); for insulin, −0.07 pmol/l (−7.95, 7.80); and for HOMA-IR, −0.004 (−0.329, 0.336).

Discussion

Self-selected diets of subjects in this study were, on average, similar in macronutrient proportions to national averages for white adults in their 60s (50, 17, and 33% for carbohydrate, protein, and fat, respectively [16]). As expected for older people consuming a typical Western diet, the subjects had positive net acid excretion at baseline. Bicarbonate supplementation at a dose of 67.5 mmol/day for 3 months effectively neutralized the dietary acid load but had no effect on insulin resistance (HOMA-IR) or on fasting plasma glucose or serum insulin. Thus, this study provides no evidence that neutralizing the acid load can reduce the risk of insulin resistance and type-2 diabetes in non-diabetic older adults. We also observed no effect of bicarbonate treatment on serum cortisol, a suggested mediator of the effect of mild acidosis on skeletal muscle [17] and, potentially, insulin sensitivity [5]. In contrast, Muarer et al. observed decreases in both plasma and urine cortisol in nine subjects given bicarbonate and studied on a metabolic ward [17]. Blood measurements of cortisol drop precipitously throughout the day and, although our measurements were from fasting morning samples, our baseline and follow-up sample collection times may not have been as well matched as those in Maurer's metabolic study; this could explain our inability to detect a bicarbonate effect on cortisol.
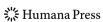
This study has limitations. First, it is a secondary analysis and, as such, was not designed or powered to look at outcomes related to glucose control. However, it is notable that in addition to the lack of statistically significant differences between groups in the outcome measures, the point estimates (means) of these measures were almost identical in those treated and not treated with bicarbonate. However, as indicated by the confidence intervals around our observed differences, it is possible that, due to chance, we failed to detect true and clinically meaningful effects of bicarbonate treatment on our outcomes. Second, HOMA-IR is a relatively crude index of insulin resistance compared with more elaborate methods. Nevertheless, it has been found to correlate moderately well with an insulin sensitivity test (S_I) derived from the insulin-assisted IV glucose tolerance test [18]. Specifically, the correlation of HOMA-IR with S_I was −0.72 in normoglycemic older adults [19].

Table 1 Baseline characteristics in 153 subjects by treatment group (mean ± SD or %)

	Treatment groups					Combined groups		
	Placebo	KCl	KHCO$_3$	NaHCO$_3$	P	No HCO$_3$	HCO$_3$	P
N	39	37	37	40	0.974	76	77	0.676
% Female	59	57	54	55	0.817	58	55	0.397
Age (years)	64.1 ± 8.9	63.2 ± 6.6	62.5 ± 8.6	62.7 ± 7.7	0.224	63.7 ± 7.8	62.6 ± 8.1	0.066
Weight (kg)	69.6 ± 12.4	72.7 ± 13.8	74.9 ± 11.5	75.2 ± 15.3	0.235	71.1 ± 13.1	75.1 ± 13.5	0.088
BMI (kg/m^2)	25.1 ± 3.7	25.6 ± 3.3	26.8 ± 4.0	25.9 ± 3.2	0.974	25.4 ± 3.5	26.3 ± 3.6	0.642
PASE[a] score	163 ± 79	164 ± 89	158 ± 77	157 ± 86		164 ± 83	157 ± 81	
Dietary intake, % of kcals								
Carbohydrate	47.9 ± 7.0	49.3 ± 6.3	46.7 ± 7.8	46.1 ± 6.6	0.193	48.6 ± 6.7	46.4 ± 7.1	0.051
Protein	18.1 ± 3.3	17.0 ± 3.2	17.5 ± 3.2	18.1 ± 4.0	0.446	17.6 ± 3.3	17.8 ± 3.6	0.647
Fat	34.0 ± 6.2	34.4 ± 6.2	35.6 ± 8.0	34.1 ± 7.1	0.732	34.2 ± 6.1	34.8 ± 7.6	0.602
NAE/cr (mmol/mmol)	2.41 ± 2.01	2.95 ± 1.54	3.55 ± 1.75	3.18 ± 1.74	0.042	2.67 ± 1.80	3.36 ± 1.75	0.018
% with NAE/cr > 0	92.3	97.3	100.0	95.0	0.354	94.7	97.4	0.334
Urine pH	6.30 ± 0.44	6.17 ± 0.47	6.04 ± 0.47	6.12 ± 0.45	0.106	6.23 ± 0.46	6.08 ± 0.46	0.045
Urine potassium/cr (mmol/mmol)	6.86 ± 2.56	6.42 ± 2.35	5.84 ± 1.83	7.45 ± 3.01	0.040	6.65 ± 2.45	6.68 ± 2.63	0.945
Creatinine clearance (ml/s/m^2)	1.54 ± 0.42	1.50 ± 0.32	1.50 ± 0.37	1.56 ± 0.41	0.858	1.52 ± 0.37	1.53 ± 0.39	0.831
Serum cortisol (nmol/l)	296 ± 83	305 ± 108	330 ± 105	288 ± 79	0.234	300 ± 90	308 ± 94	0.590
Plasma glucose (mmol/l)	5.38 ± 0.46	5.46 ± 0.56	5.48 ± 0.50	5.30 ± 0.50	0.401	5.42 ± 0.51	5.39 ± 0.50	0.720
Serum insulin, pmol/l	52.3 ± 27.4	59.8 ± 35.0	63.9 ± 36.5	56.9 ± 23.2	0.412	56.0 ± 31.3	60.3 ± 30.3	0.388
HOMA-IR[b]	1.82 ± 1.01	2.12 ± 1.30	2.27 ± 1.38	1.96 ± 0.89	0.355	1.97 ± 1.16	2.11 ± 1.15	0.443

[a] Physical activity score for the elderly
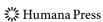
[b] Homeostatic model assessment of insulin resistance

Table 2 Changes in laboratory values by treatment group (mean ± SEM)

	Treatment groups					Combined groups		
	Placebo	KCl	KHCO$_3$	NaHCO$_3$	P	No HCO$_3$	HCO$_3$	P
N	39	37	37	40		76	77	
Unadjusted								
NAE/cr (mmol/mmol)	0.83 ± 0.37	0.12 ± 0.38	−4.06 ± 0.38	−3.55 ± 0.36	<0.001	0.49 ± 0.26	−3.80 ± 0.26	<0.001
Urine pH	−0.14 ± 0.06	−0.09 ± 0.09	0.83 ± 0.09	0.76 ± 0.09	<0.001	−0.12 ± 0.05	0.80 ± 0.06	<0.001
Urine potassium/cr (mmol/mmol)	−0.40 ± 0.40	3.58 ± 0.63	4.23 ± 0.38	−0.69 ± 0.39	<0.001	1.54 ± 0.43	1.67 ± 0.39	0.815
Serum cortisol (nmol/l)	60 ± 24	34 ± 24	45 ± 17	40 ± 17	0.834	48 ± 17	43 ± 12	0.812
Plasma glucose, mmol/l	0.20 ± 0.08	0.02 ± 0.08	0.05 ± 0.09	0.00 ± 0.08	0.325	0.11 ± 0.06	0.03 ± 0.06	0.300
Serum insulin (pmol/l)	3.12 ± 3.68	9.69 ± 4.12	8.07 ± 5.06	6.20 ± 3.61	0.707	6.31 ± 2.76	7.10 ± 3.05	0.849
HOMA-IR	0.18 ± 0.14	0.36 ± 0.16	0.36 ± 0.23	0.22 ± 0.14	0.814	0.27 ± 0.11	0.29 ± 0.13	0.904
Adjusted[a]								
NAE/cr (mmol/mmol)	0.27 ± 0.33	0.18 ± 0.33	−3.59 ± 0.34	−3.47 ± 0.33	<0.001	0.23 ± 0.22	−3.53 ± 0.22	<0.001
Urine pH	0.05 ± 0.07	−0.16 ± 0.07	0.67 ± 0.07	0.81 ± 0.07	<0.001	−0.06 ± 0.05	0.75 ± 0.05	<0.001
Urine potassium/cr (mmol/mmol)	−0.44 ± 0.43	3.47 ± 0.44	3.92 ± 0.44	−0.29 ± 0.43	<0.001	1.48 ± 0.39	1.71 ± 0.39	0.677
Serum cortisol (nmol/l)	51 ± 20	30 ± 20	39 ± 20	68 ± 22	0.572	45 ± 14	48 ± 14	0.874
Plasma glucose (mmol/l)	0.19 ± 0.08	0.03 ± 0.08	0.07 ± 0.09	0.03 ± 0.08	0.446	0.11 ± 0.06	0.05 ± 0.06	0.479
Serum insulin (pmol/l)	2.45 ± 4.20	11.67 ± 4.2	10.38 ± 4.37	4.50 ± 4.15	0.479	7.10 ± 2.79	7.18 ± 2.78	0.985
HOMA-IR[b]	0.16 ± 0.18	0.43 ± 0.18	0.44 ± 0.19	0.18 ± 0.18	0.664	0.29 ± 0.12	0.30 ± 0.12	0.982

[a] Adjusted for baseline value of dependent variable, baseline NAE/cr, baseline potassium/cr, change in potassium/cr, body weight, and sex

[b] Homeostatic model assessment of insulin resistance

Our study also had important strengths. To our knowledge, it is the only experimental study to investigate the effect of bicarbonate supplementation on indicators of diabetes risk in humans. It was a randomized, double-blind, controlled trial in which extensive covariate information was collected. Although further studies that investigate larger bicarbonate doses, different study populations or longer follow-up periods may be worthwhile, the present study suggests that bicarbonate supplementation may not be a promising strategy for preventing type-2 diabetes in older adults.

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