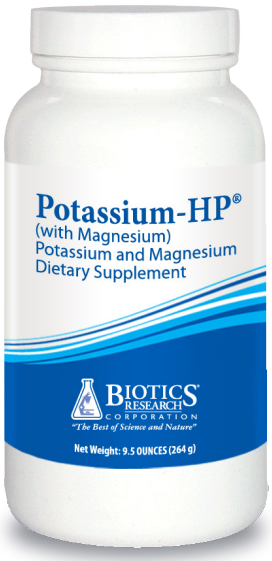
Potassium-HP®

(with Magnesium)



Potassium-HP® (with Magnesium) is an easy to use, high potency mineral supplement powder which dissolves readily in water. Each scoop supplies 1,200 mg of elemental Potassium (as potassium citrate) and 120 mg of elemental Magnesium (as magnesium citrate malate).

According to the Food and Nutrition Board of the Institute of Medicine of the National Academies (Dietary Reference intakes: Water, Potassium, Sodium Chloride and Sulfate. February 11, 2004), "Adults should consume at least 4.7 grams of potassium per day to lower blood pressure, blunt the effects of salt, and reduce the risk of kidney stones and bone loss. However, most American women 31 to 50 years old consume no more than half of the recommended amount of potassium, and men's intake is only moderately higher. There was no evidence of chronic excess intakes of potassium in apparently healthy individuals and thus no UL [upper limit of intake] was established."

Each bottle of **Potassium-HP® (with Magnesium)** supplies 60 servings.

To place your order for **Potassium-HP®** or for additional information please contact us below.

WARNING: Ask a doctor before use if you have kidney disease or a potassium-restricted diet. High-potency potassium products should only be used under the advice and supervision of a healthcare professional. Minor gastrointestinal (GI) complaints have been reported by those taking significant amounts of potassium citrate. These may be reduced by taking this product with food or reducing the dose. If GI complaints persist, discontinue the use of this product. Long-term use can result in metabolic alkalosis. Renal insufficiency and certain potassium-sparing drugs will increase the risk for elevated blood potassium, which can be dangerous. Patients should not use potassium-rich salt substitutes without the advice of their healthcare professional while taking this or any high-potency potassium product.

Potassium-HP® is available in 9.5 ounce bottles (#1718).

Supplement Facts

Serving Size: 1 scoop (approx. 4.8 g)
Servings Per Container: 60

	Amount Per Serving	% Daily Value
Magnesium (as magnesium citrate malate)	120 mg	30%
Potassium (as potassium citrate)	1200 mg	34%

This product is gluten and dairy free.

Product may settle, shake well before use.

Scoop included.

RECOMMENDATION: Mix one (1) scoop of Potassium-HP® with six (6) ounces of water each day as a dietary supplement or as otherwise directed by a healthcare professional.

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For Adult Use Only
KEEP OUT OF REACH OF CHILDREN
Store in a cool, dry area.
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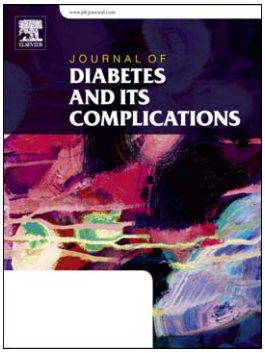

Effects of potassium citrate or potassium chloride in patients with combined glucose intolerance: A placebo-controlled pilot study

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Effects of potassium citrate or potassium chloride in patients with combined glucose intolerance:

A placebo-controlled pilot study

by

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Running title : Effect of KCl or Kcitrate on insulin secretion and sensitivity

Key words: combined glucose intolerance, prediabetes, potassium, metabolic acidosis, citrate

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Abstract

Background: Experimental K^+ depletion reversibly inhibits insulin secretion, while chronic metabolic acidosis decreases insulin sensitivity. We aimed to investigate the effects of potassium supplementation and alkali supplementation in non-acidotic, normokalemic humans with combined glucose intolerance.

Study design and results: In this double-blind, placebo-controlled study in 11 subjects (7 male, 4 female, ages 47 to 63 y), 90 meqs of oral KCl or Kcitrate per day for 2 weeks each increased insulin production as measured by homeostasis model assessment Beta [KCl = 86 (CI 81-91), Kcitrate = 88 (82-94), Placebo = 78 (73-83) %, $p < 0.04$), but only Kcitrate attenuated insulin resistance as assessed by HOMA-IR (insulin resistance, Kcitrate = 2.8 (2.5-3.1), placebo = 3.2 (2.9-3.5), $p<0.03$) and only Kcitrate increased quantitative insulin sensitivity check index (Quicki, Kcitrate = 0.355 (0.305-0.405), placebo = 0.320 (0.265-0.375 $p<0.04$). These results were confirmed by independent measurements, i.e. HOMA c-peptide and wholy body insulin sensitivity index measured during oral glucose tolerance testing. Kcitrate significantly decreased systolic and diastolic 24 hour ambulatory blood pressures (-4.0 (-3 to- 5) and -2.7 (-1.9 to -3.5), respectively as compared to placebo, $p<0.02$). while KCl was without a significant effect.

Conclusions: K^+ supplementation in the absence of overt K^+ depletion improves beta-cell function in subjects with combined glucose intolerance. The insulin-sensitizing and hypotensive effect, however, depend on citrate as the accompanying anion.

Introduction

In both humans and experimental animals, experimental potassium depletion was shown to reversibly inhibit insulin secretion, irrespective of the etiology (1-3), while chronic metabolic acidosis was shown to decrease systemic insulin sensitivity (4, 5). For both potassium depletion and metabolic acidosis, the mechanisms of these alterations in glucose or insulin metabolism are poorly characterized. In the case of acidosis, acidosis-induced hyperglucocorticoidism (6, 7) and acidosis-associated decreases in cytokines known to enhance insulin sensitivity such as (undercarboxylated) osteocalcin, adiponectin or leptin (8-11), might play a role. It is also largely unexplored whether potassium and/or alkali supplementation have any effect on glucose/insulin metabolism in the absence of overt potassium depletion or metabolic acidosis.

In non-diabetic, non-acidotic elderly, chronic HCO_3^- treatment with complete neutralization of endogenous H^+ production failed to alter insulin sensitivity (12). However, in a nested case control study (n = 1360), the prospective risk for type 2 diabetes (T2DM*) increased inversely with $[HCO_3^-]p$ (13) and serum $[K^+]$ and dietary K^+ intake inversely correlated with the risk of incident T2DM (with and without thiazide treatment, 14-16). Western diets are characterized by a low potassium content and high acid load (17) and the incidence of T2DM continues to increase dramatically in populations ingesting Western diets. Combined glucose intolerance (CGI, so-called prediabetes) is a reversible, but high risk state for the development of overt T2DM (18). In addition, CGI has been identified recently as an independent risk factor for the development of stroke (19). We, therefore, wished to evaluate the effect of potassium with and without alkali supplementation on metabolic control in subjects with CGI.

*abbreviations: Diabetes mellitus type 2 = T2DM, HOMA = homeostasis assessment model, Quicki = quantitative insulin sensitivity check index, ISI = whole-body insulin sensitivity index, CI = confidence interval, CGI = combined glucose intolerance, […] = concentration

Methods

To assess the effects of potassium and alkali supplementation on beta-cell function and insulin sensitivity in CGI (i.e. the combination of impaired fasting glucose and impaired glucose tolerance), we screened 43 overweight subjects taking no current medications at enrollment and within the preceding three months and who had a positive family history for T2DM in first or second degree relatives. Of these 43 subjects, 11 fulfilled the strict criteria of CGI, i.e. fasting plasma [glucose] >5.6 to <7.0 mmol/L AND plasma [glucose] 2 h after 75g of oral glucose > 7.7 to < 11.1 mmol/L (20). All subjects were ingesting an identical standardized meal the evening prior to the glucose tolerance test.

The subjects continued their usual life-style and diet behavior during the study. They were assigned in a double-blinded, randomized cross-over design to KCl (90 meq per day, 9 tablets, 3 divided doses), trivalent Kcitrate (90 meq per day, 9 tablets, three divided doses) or placebo (9 tablets, three divided doses) of identical taste and appearance (purchased from Mission Pharmacal, San Antonio, TX) for 14 days each. At the end of each period, two consecutive 24 hour urine collections with a fasting blood draw at the end of the collection periods and 24 hour ambulatory blood pressure recordings (Spacelabs, Redmond WA) were performed. The results given are the means of values obtained on these two days. After the second collection

period, an oral glucose tolerance test (see below) was performed at 0800 am in all three study periods. There was a washout period of at least 14 days between the three periods.

Data from screening visits (oGTT and blood pressure) were used as baseline data (see “calculation of beta-cell function and insulin sensitivity” below)

Calculation of beta-cell function and insulin sensitivity

Using morning fasting plasma [glucose] and fasting serum [insulin], homeostasis model assessment beta (for beta cell function) and insulin resistance (HOMA-beta and HOMA-IR) as well as HOMA beta-C-peptide were calculated using the HOMA 2.2 calculator (21-23).

Insulin sensitivity was also analysed by use of the quantitative insulin sensitivity check index (Quicki, 24) and by measuring an index of whole-body insulin sensitivity (ISI) during the oral glucose tolerance test. ISI was shown to have excellent correlation with euglycemic insulin clamping (25). Quicki equals 1/[log(Io) + log(Go)], where Io is the fasting insulin concentration and Go is the fasting glucose concentration. ISI is calculated as 10 000 / [(fasting glucose x fasting insulin) x (mean glucose x mean insulin during OGTT)]1/2.

All acid-base, electrolyte and creatinine determinations were performed using the established routine procedures of the division of laboratory medicine. Renal net acid excretion (NAE) was calculated in 24 hour urines as the sum of ammonium (NH_4^+) plus calculated titratable acidity minus HCO_3^- excretion values.

Analytical methods

Serum insulin and C-peptide were measured by electrochemiluminescence (ECL) method on an Elecsys 2010 system (Roche, Switzerland). Plasma leptin concentrations were determined using a sandwich immunoassay based fluorometric xMAP technology on Luminex 200 machines (luminex muti-analyte profiling system, Luminex, Corp., Austin, TX, USA). The immunoassay kit is commercially available from Millipore Corporation. Serum adiponectin concentrations were determined by ELISA “EZHADP-61K (Millipore, USA). The total osteocalcin concentrations were measured by the enzyme amplified sensitivity immunoassay Kit from DRG Instruments GmbH. Serum total and undercarboxylated osteocalcin concentrations were measured by electrochemiluminescence immunoassay (Roche). Urinary tetrahydrocortisol was measured by HPLC. This metabolite was chosen as it is freely filtered at the glomerulus and has additional tubular reabsorption/secretion.

Statistical methods

Values given are means ± standard deviation. Statistical analysis was made by ANOVA for repeated measurements using SSPS for Windows NT software, version 20.0 (SSPS Inc., Chicago, IL). Data for which baseline measurements were available (i.e. HOMA-Beta, HOMA-IR, HOMA Beta-C-peptide, Quicki, ISI and blood pressure) were tested using analysis of covariance (ANCOVA) with baseline values as covariates. These data are reported as adjusted means with confidence intervals. Since there was no significant interaction between baseline data and treatment group results a p value of <0.05 was considered significant.

Ethical approval

The study protocol was approved by the Ethics committee of both Cantons of Basel (Switzerland).

Results

11 subjects (7 male, 4 female, ages 47 to 63 y, mean BMI = 30.5 ± 2.1 kg/$m^{2,}$ mean HbA1C = 6.2 ± 0.2 %) with combined glucose intolerance were enrolled in and completed the entire study protocol. Tables 1 a-c show the plasma and 24 hour urinary electrolyte and acid-base composition as well as fractional renal electrolyte excretion rates at the end of the KCl (90 meq per day), Kcitrate (90 meq per day) and placebo periods (2 weeks each). Neither K salt had a significant effect on plasma [K^+]. Kcitrate resulted in reversal to negative renal net acid excretion (NAE), while KCl had no significant effect on NAE. As described previously, Kcitrate significantly decreased renal fractional excretion of calcium (7, 20). The remainder of the results are shown in table 2: Homeostasis model assessment Beta (HOMA-Beta), a measure of beta-cell function/insulin production significantly increased in response to both KCl and Kcitrate [Kcitrate = 88 (CI 82-94), Kchloride = 86 (81-91), placebo = 78 (73-83)%*p < 0.04 or both comparisons,]. However, only Kcitrate improved insulin sensitivity significantly as estimated by a reduced HOMA-IR (insulin resistance) and increased quantitative insulin-sensitivity check index (Quicki, Table 2). As HOMA-Beta, HOMA-IR and Quicki calculations rely on the use of the same parameters, we wished to test beta-cell function and insulin sensitivity with an additional set of independent parameters, i.e. HOMA-Beta c-peptide and whole body insulin sensitivity index as calculated from multiple insulin/glucose values during an oral glucose tolerance test. As shown in the Table 2, HOMA-Beta c-peptide increased significantly both in response to KCl as well as Kcitrate confirming the HOMA-Beta insulin results. Whole body insulin sensitivity index was significantly increased in Kcitrate period as compared to placebo [Kcitrate =5.5 (5.1-5.9) , placebo =4.6 (4.2-5.0), p<0.0]), but KCl administration had no significant effect (Table 2).

Potassium supplementation increases pancreatic insulin output but only alkalinization improves insulin sensitivity

In these normotensive prediabetics, mean 24 hour systolic and diastolic ambulatory arterial blood pressures significantly decreased in response to Kcitrate by -4.0 (-3 to-5) and by -2.7 (-1.9 to -3.5) mmHg , respectively, as compared to placebo. KCl did not affect blood pressure significantly (Table 2). Kcitrate induced a significant weight loss of 1.5 ± 0.5 kg (p= 0.018), while no significant changes in body weights were observed during KCl and placebo periods.

Neither K salt induced significant changes in circulating serum concentrations of adiponectin (Kcitrate = 15.1 ± 7.1, KCl = 16.0 ± 7.4, placebo = 15.5 ± 7.5 ng/ml, respectively) or in carboxylated osteocalcin (Kcitrate = 6.1 ± 1.9, KCl = 6.3 ± 1.8 , placebo = 6.6 ± 1.9 ng/ml, respectively) and in undercarboxylated osteocalcin (Kcitrate = 44 ± 16, KCl = 43 ± 15 , placebo = 41 ± 17 %, respectively). Similarly, in the male subjects, serum leptin levels were 15.0 ± 7.9 ng/mL during placebo and not affected significantly by both Kcitrate and KCl administration (16.1 ± 8.1 and 16.7 ± 8.4 ng/ml, respectively). In the female subjects leptin levels were also similar during all periods: 19.4 ± 7.1, 20.1 ± 8.3, 17.8 ± 7.5, for placebo, KCl and Kcitrate periods, respectively.

Urinary excretion of tetrahydrocortisol (THF) decreased slightly, but significantly from 2 810 ± 310 to 2 678 ± 290 mcgr/24 h (p = 0.044) during the Kcitrate period confirming our results in non-diabetic subjects (7), while KCl had no significant effect.

Discussion

The results of this placebo-controlled, randomized cross-over pilot study demonstrate that even in the absence of overt, pre-existing K^+ depletion, K^+ supplementation improved beta-cell function (measures of insulin secretion) in subjects with CGI (prediabetes). The insulin-sensitizing and hypotensive effect, however, critically depended on citrate as the accompanying anion. Whether these effects are

specifically dependent on citrate or by its oxidation to bicarbonate should be tested by comparing citrate`s effect with those of other equipotent alkali. The insulin-sensitizing effect of Kcitrate/alkali administration was shown herein to be independent of the best characterized circulating, insulin sensitivity modulating factors, i.e. total and undercarboxylated osteocalcin, adiponectin and leptin. All of these cytokines, with the exception of undercarboxylated osteocalcin, have previously been shown to be affected by systemic acid loading and all are associated with altered insulin sensitivity (8-10). In contrast and as previously reported (7), Kcitrate/alkali administration significantly decreased adrenal glucocorticoid production which may have contributed to improved insulin sensitivity. Future studies should investigate the relative importance of the effect of Kcitrate/alkali administration on indirect mechanisms of insulin sensitivity (glucocorticoid activity, other cytokines) and possible direct effects on cellular and intracellular insulin signalling pathways.

In contrast to studies in patients with essential hypertension employing office blood pressure measurements (21), the 24h ambulatory blood pressure lowering effect of K^+ critically depended on citrate as the accompanying anion in these normotensive subjects with CGI (prediabetes). The blood-pressure lowering effect of Kictrate/alkali administration in this patient population needs further clarification. Both metabolic factors, i.e. improved insulin sensitivity or renal factors (decrease in body weight during the Kcitrate period) may be important.

We have no clear mechanistic explanation for the unexpected weight change in the Kcitrate period of minus 1.5 kg as compared to placebo and Kchloride. However, dietary potassium has been shown to be natriuretic via rapid inhibition (i.e. by phosphorylation) of the thiazide-sensitive sodium/chloride cotransporter in the distal convoluted tubule (28). The excess supplementation of chloride in the Kchloride

period may have counteracted this by causing greater volume expansion than Kcitrate.

The placebo-controlled, randomized crossover design are among the prinicipal strengths of this study, while the small sample size currently precludes generalization of these results to all patients with CGI (prediabetes). Also, the relatively high dose of both KCl and Kcitrate may not be an optimal one..While the hyperinsulinemic euglycemic clamp technique is still the gold standard, our indices of insulin resistance have been shown to have good, linear correlation to the clamp (24, 25). In addition, we used several indices employing different, independent parameters and eliminated the problem of interindividual variation by our study design (each individual being its own control).

The present results suggest that K^+ supplementation with and without citrate/alkali may have a role in T2DM prevention and treatment. It will be important, therefore, to evaluate the dose-response relation of K and citrate/alkali supplementation and to investigate in larger populations whether progression of CGI to T2DM can be retarded or prevented and/or whether control of established T2DM can be improved by K with citrate/alkali administration. In addition, it will be of interest to evaluate the effect of long term differences in potassium and alkali intake on the epidemiology of T2DM (i.e. by analysis of large population cohorts).

Disclosures

Competing financial interests: none

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Table 1a: Plasma electrolyte and arterialized blood acid-base parameters in patients with CGI during placebo, KCl and Kcitrate adiministration

Parameter	$[Na]_p$ mmol/l	[K]p mmol/l	[CL]p mmol/l	$[PO_4]p$ mmol/l	ion[Ca]p mmol/l	[Mg]p mmol/l	[creatinine]p umol/l	Blood pH (U)	Arterialized PCO_2 mmHg	[HCO3-] mmol/l
Placebo	139 ± 3	3.9 ± 0.2	105 ± 2	1.0 ± 0.1	1,13 ± 0.04	0.87 ± 0.06	69 ± 5	7.399 ± 0.005	40.3 ± 0.4	24.4 ± 0.3
KCl (90 mmols/day)	138 ± 2	3.9 ± 0.3	104 ± 3	0.9 ± 0.1	1.15 ± 0.04	0.85 ± 0.06	65 ± 7	7.394 ± 0.007	39.6 ± 0.5	23.7 ± 0.5
Kcitrate (90 mmols/day)	139 ± 3	3.7 ± 0.3	104 ± 3	0.9 ± 0.1	1.17 ± 0.05	0.86 ± 0.08	64 ± 6	7.404 ±0.006	41.9 ± 0.7*	25.0 ± 0.4*

*denotes $p < 0.05$ for the comparison to both placebo and KCl

Table 1b: Mean 24 hour urine electrolyte and net acid excretion during administration of placebo, KCl and Kcitrate (14 days)

Parameter	Body weight kgs	Na mmol/24 h	K mmol/24 h	Cl mmol/24 h	PO_4 mmol/24 h	Ionized Ca mmol/24 h	Mg mmol/24h	creatinine mmol/24 h	pH (U)	Urinary net acid excretion mmol/24 h
Placebo	92.1 ± 6.3	181 ± 22	72 ± 14	178 ± 28	30.8 ± 3.7	5.2 ± 1.1	3.10 ± 0.37	13.7 ± 1.1	5.640 ± 0.145	53.4 ± 10.2
KCl (90 mmols/day)	92.5 ± 6.7	198 ± 25	123 ± 17“	251 ± 34	31.6 ± 4.1	4.9 ± 0.9	2.85 ± 0.32	13.5 ± 1.0	5.861 ± 0.127	48.6 ± 11.2
Kcitrate (90 mmols/day)	90.6 ± 6.4*	194 ± 21	126 ± 18“	225 ± 32	32.5 ± 4.4	4.4 ± 0.9*	3.00 ± 0.39	14.5 ± 1.2	6.101 ± 0.111“	-8.5 ± 10.2[&]
Baseline (screening)	92. 5 ± 6.5									

*denotes p< 0.05 and [&] denotes p <0.005 for the comparisons to placebo and KCl. “ denotes p < 0.01 for the comparison of KCl and of Kcitrate to placebo

Table 1c: Mean fractional electrolyte excretion rates (FE, %) during placebo, KCl and K citrate administration in
patients with combined glucose intolerance

Parameter	FE Na	FE K	FE Cl	FE Ca	FE PO4	FE Mg
Placebo	0.56 ± 0.11	7.9 ± 1.6	0.78 ± 0.16	1.99 ± 0.47	13.8 ± 4.1	2.49 ± 0.60
KCl (90 mmols/day)	0.57 ± 0.09	12.4“ ± 1.9	0.89 ± 0.18“	1.72 ± 0.51	13.4 ± 3.8	2.25 ± 0.51
Kcitrate (90 mmols/day)	0.57 ± 0.08	13.7“ ± 2.0	0.88 ± 0.11“	1.48* ± 0.32	14.5 ± 4.9	2.28 ± 0.49

“denotes $p < 0.015$ for the comparison with placebo- * denotes $p < 0.04$ for the comparison to placebo

Table 2: Parameters of insulin sensitivity, beta-cell function and 24 h mean systolic and diastolic blood pressures

Parameter	Baseline	Placebo	Kcitrate	Kchloride
HOMA-Beta (%)	77 ± 8.0	78 (73-83)	88 (82-94)*	86 (81-91)*
HOMA-IR	3.3 ± 0.4	3.2 (2.9-3.5)	2.8 (2.5-3.1)“	3.4 (3.1 – 3.7)
Quantitative Insulin sensitivity check index (Quicki)	0.319 ± 0.07	0.320 (0.265-0.375)	0.345 (0.295-0.395)*	0.320 (0.245-0.395)
HOMA-Beta C-peptide (%)	114 ±12	116 (106-126)	129 (119-139)“	133 (122-144)”
Whole body insulin sensitivity index (ISI)	4.4 ± 0.3	4.6 (4.2-5.0)	5.5 (5.1-5.9)$^{+}$	4.2 (3.7-4.7)
24 hour ambulatory mean systolic blood pressure (mm Hg)	131 ± 7	132 (126-139)	128 (122-136)$^{\&}$	135 (127-143)
24 hour ambulatory mean diastolic blood pressure (mm Hg)	93 ± 5	92 (86-98)	89 (84-94)$^{\&}$	92 (85- 99)

Values are means + SD (baseline values) and) means adjusted for baseline values for placebo, Kcitrate and Kchloride. Values in brackets are confidence intervals, p values were estimated using ANCOVA. * equals $p< 0.04$, “ equals $p < 0.03$, $^{\&}$ equals $p<0.02$ and + equals $p < 0.01$ for the comparison to placebo.

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Correction of metabolic acidosis improves insulin resistance in chronic kidney disease

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Abstract

Background: Correction of metabolic acidosis (MA) with nutritional therapy or bicarbonate administration is widely used in chronic kidney disease (CKD) patients. However, it is unknown whether these interventions reduce insulin resistance (IR) in diabetic patients with CKD. We sought to evaluate the effect of MA correction on endogenous insulin action in diabetic type 2 (DM2) CKD patients.

Methods: A total of 145 CKD subjects (83 men e 62 women) with DM2 treated with oral antidiabetic drugs were included in the study and followed up to 1 year. All patients were randomly assigned 1:1 to either open-label (A) oral bicarbonate to achieve serum bicarbonate levels of 24–28 mmol/L (treatment group) or (B) no treatment (control group). The Homeostatic model assessment (HOMA) index was used to evaluate IR at study inception and conclusion. Parametric and non-parametric tests as well as linear regression were used.

Results: At baseline no differences in demographic and clinical characteristics between the two groups was observed. Average dose of bicarbonate in the treatment group was 0.7 ± 0.2 mmol/kg. Treated patients showed a better metabolic control as confirmed by lower insulin levels (13.4 ± 5.2 vs 19.9 ± 6.3; for treated and control subjects respectively; $p < 0.001$), Homa-IR (5.9[5.0-7.0] vs 6.3[5.3–8.2]; $p = 0.01$) and need for oral antidiabetic drugs. The serum bicarbonate and HOMA-IR relationship was non-linear and the largest HOMA-IR reduction was noted for serum bicarbonate levels between 24 and 28 mmol/l. Adjustment for confounders, suggests that serum bicarbonate rather than treatment drives the effect on HOMA-IR.

Conclusions: Serum bicarbonate is related to IR and the largest HOMA-IR reduction is noted for serum bicarbonate between 24 and 28 mmol/l. Treatment with bicarbonate influences IR. However, changes in serum bicarbonate explains the effect of treatment on HOMA index. Future efforts are required to validate these results in diabetic and non-diabetic CKD patients.

Trial registration: The trial was registered at www.clinicaltrial.gov (Use of Bicarbonate in Chronic Renal Insufficiency (UBI) study - NCT01640119)

Keywords: CKD, Diabetes, Metabolic acidosis, Homa-test, Sodium bicarbonate

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Background

Incidence of chronic kidney disease (CKD) as well as the prevalence of diabetic subjects among CKD patients are steadily increasing [1, 2]. As renal function declines, metabolic acidosis and insulin resistance (IR) commonly arise. Among others, these metabolic complications are associated with serious consequences on bones and nutritional status [3, 4] and likely contribute to some of the abysmal risk of death associated with CKD.

Insulin resistance (IR) is characterized by suboptimal biological responses of the liver, skeletal muscle and adipose tissue to normal amounts of insulin secreted [4]. Conditions such as metabolic acidosis, anemia, inflammation, hyperactivity of the Renin-Angiotensin-Aldosterone System (RAAS), vitamin D deficiency, physical inactivity, excess of fat mass as well as nitrogen catabolites accumulation have all been implicated in IR in CKD subjects [5]. Notably, several clinical consequences have been linked to IR. Indeed, IR may promote endothelial dysfunction and portends increased cardiovascular mortality. Although evidence is not conclusive, some data also suggest that IR is a harbinger of CKD incidence and progression. Based on these lines of evidence, it is conceivable that IR represents a modifiable risk factor and a potential therapeutic target to improve CKD outcome [4–6].

The association between metabolic acidosis, IR and the cardiovascular risk has been documented in the scientific literature since 1924 [7]. However, in spite of the fact that correction of metabolic acidosis with nutritional therapy and/or oral administration of sodium bicarbonate in CKD is widely used [8–10], it is unknown whether correction of metabolic acidosis reduces IR and/or improves insulin effects on target cells in diabetic subjects.

We aim to evaluate whether metabolic acidosis correction by sodium bicarbonate administration may improve peripheral endogen insulin utilization by target organs in diabetic subjects with CKD treated with oral antidiabetic drugs.

Methods

For current analyses, we analyzed the first 145 subjects (83 men and 62 women) with Diabetes Mellitus type 2 not treated with insulin participating in the Use of Bicarbonate in Chronic Renal Insufficiency (UBI) study (NCT NCT01640119) with at least 1 year of follow-up. The UBI study protocol has been published previously [11]. Briefly, the UBI study is an on-going multi-center, open-label, randomized controlled study designed to test the impact of metabolic acidosis correction on CKD progression to End Stage Renal Disease (ESRD). CKD-3b-4 patients of 18 to 80 year of age, able to provide written informed consent and serum bicarbonate levels below 24 mEql/l are randomized (allocation ratio 1:1) to either oral sodium bicarbonate (treatment group) or conventional therapy for CKD (control group). Study investigators are free to adjust medications to achieve the targets for glycated hemoglobin, bone mineral metabolism, blood pressure, anemia, iron status, dyslipidemia as suggested by guidelines on CKD patients' management available at the time of the study design [11]. The randomization process is centralized to ensure allocation concealment. Patients with evidence of neoplastic diseases, autoimmune diseases, chronic heart failure NYHA class III-IV, uncontrolled arterial hypertension, severe peripheral arterial disease (defined as limb amputation), cerebrovascular disease, neobladder or ureterosigmoidostomy, severe metabolic acidosis (defined as serum bicarbonate <18 mEq/l) or use of calcium carbonate in the 3-month prior to study inclusion are excluded from the trial. Oral sodium bicarbonate is administered at the dose of 0.5 mmol/kg of body weight (1 g of sodium bicarbonate contains 11.9 mmol – initial dose about 3–4 g) two times a day until the achievement of the desired serum bicarbonate target of 24–28 mmol/l. If a serum value of 28 mmol/l is exceeded, the administration of bicarbonate is tapered each 3 days until the desired serum target level is achieved [11].

Demographic, clinical and laboratory characteristics

Demographic and clinical characteristics were assessed as study inception. Self-reported variables included age, sex. Medical chart reviews were conducted to determine the presence of diabetes mellitus status or the use of oral antidiabetic medications, history of atherosclerotic cardiovascular disease (ASCVD) and the use of different medications. History of ASCVD was a composite measure that included myocardial infarction, angina, and peripheral and cerebrovascular disease. Blood pressure was measured after a 15 to 20 min rest, using a manual aneroid sphygmomanometer.

Routine biochemical laboratory measurements were obtained at baseline and completion 12 months of follow-up and analyzed at the facilities usual laboratories as part of the standard patients care. All blood samples were in a fasting condition. Insulin resistance was evaluated via the Homeostatic Model Assessment (HOMA) test at baseline and at completion of 12 months of follow-up.

Finally, 25-OH vitamin D was measured every 3 months; the correction of low levels was started at values lower than 20 ng/ml and stopped at values higher than 50 ng/ml.

Patients using steroids and other drugs interfering directly with glucose levels were excluded from the study.

Insulin resistance measurement and HOMA test

Insulin resistance was assessed indirectly by the Homeostatic model assessment (HOMA) index as suggested by Wallace and coworkers [12]. Briefly, the HOMA index is

a mathematical model that allows to calculate insulin sensitivity (HOMA-IR) and evaluate ß pancreatic cell function (HOMA-%B) from fasting plasma glucose and insulin levels [12]. It is a simple test, appropriate to perform in large epidemiological studies that nicely correlates with experimental data obtained with direct measurement techniques such as the euglycemic clamp [13–16].

To perform the HOMA test, blood samples are drawn twice (30 min apart) in 3 consecutive days. Patients are kept at rest, in a fasting status for at least 8 h before the blood sampling. Tobacco use is forbidden for the 12 h before blood tests. The presented values for HOMA test at baseline and study completion are the mean values of the three consecutive blood samples. For HOMA-IR and HOMA-%B calculation, the following formulas are used [12]:

- HOMA-IR = (FPI * FPG)/22.5;
- HOMA-%B = (20 * FPI)/(FPG - 3.5)

where FPI stands for fasting plasma insulin concentration (mU/l) and FPG stands for fasting plasma glucose (mmol/l) (FPG conversion factor from mg/dl to mmol/l: 10.018).

HOMA-IR estimates of insulin resistance. Normal values are <0.25. Values greater or equal than 5.5 indicate insulin resistance typical of early stages of Diabetes Mellitus. HOMA-B% estimates ß pancreatic cells function. It's value ranges from 0 % (no pancreatic cell function) to 100 % (all pancreatic cell functioning). FPI and FPG measurements were performed centrally at P.O. "A Landolfi" – Solofra (AV), Italy, via COBAS 6000 or COBAS C 501 (Roche Diagnostics) and IMMULITE 2000 (Siemens Healthcare Global), respectively.

Study objective and endpoint

Current analyses aim at testing the impact of metabolic acidosis correction in CKD 3b-4 diabetic patients with serum bicarbonate <24 mEq/l on insulin resistance evaluated via the Homeostatic Model Assessment (HOMA) test. The HOMA was performed at study inception and after 12 months of treatment with either oral sodium bicarbonate (treatment group) or conventional therapy for CKD (control group).

Statistical analysis

Data are reported as mean ± SD or counts (percentage) when appropriate. Un-paired *T*-test and Chi-square test were used to assess difference between study groups at baseline and study completion (Tables 1 and 2). The bagplot (Fig. 1) was used to describe the bivariate association of serum bicarbonate and HOMA test in subjects randomized to oral sodium bicarbonate (treated) or conventional therapy (controls) at study inception and completion. Because of the random allocation to treatment groups, the selection criterion was independent of study investigators' beliefs (i.e., we analyzed data of the first 145 diabetic type 2 patients randomized in the UBI study who completed 1 year of follow-up) and the the optimal balance between groups at study inception, the Wilcoxon rank sum test was used to assess between- and within-group (treated vs control subjects) differences in HOMA-IR and HOMA-%B at study inception as well as completion of 12 months of follow-up (Table 3). Linear regression was used to assess the independent association of treatment and/or metabolic acidosis correction and HOMA test at study completion. First, we tested for the unadjusted association of (i) treatment allocation, (ii) serum bicarbonate values at follow-up and (iii) changes of serum bicarbonate (serum bicarbonate at follow-up – serum bicarbonate at study inception) with HOMA-IR (Table 4). Subsequently, we tested the independent contribution of metabolic acidosis correction (i.e., serum bicarbonate at study completion or changes in serum bicarbonate) vs oral bicarbonate supplementation, forcing both variables in the same regression model (Table 4). However, due to the non-linear relationship between serum bicarbonate (Fig. 2a) or changes in serum bicarbonate (Fig. 2b) and HOMA index at study completion, we tested for an interaction effect of treatment and values of serum bicarbonate at study completion or changes of serum bicarbonates (Table 4). Because of the significant effect modification of serum serum bicarbonate levels on treatment effect on HOMA test and because at visual inspection (Fig. 2a) the association between serum bicarbonate and HOMA test was different for values greater than 28 mmol/l, we performed some additional analyses by applying regression splines with a knot set at serum bicarbonate level of 28 mEq/l and tested for the independent association between serum bicarbonate, treatment and HOMA test at study completion (Table 5). All analyses were conducted as *intention-to-treat*. Two-tailed probability values ≤ 0.05 were considered statistically significant. Analyses were completed using R version 3.1.3 (2015-03-09) (The R Foundation for Statistical Computing).

Results

A total of 145 (57 % men) diabetic type 2, middle-age (65.5 ± 11.4 years) patients on oral antidiabetic medication were included in current analyses. At study inception, no significant differences in anthropometric, clinical and laboratory characteristics between subjects allocated to oral sodium bicarbonate or conventional therapy were observed (Table 1). In particular, treated subjects and controls exhibited similar renal function (mean creatinine clearance: 32 ± 14 ml/min and 35 ±

Table 1 Demographic, clinical, laboratory characteristics and use of oral anti-diabetic medications of patients randomized to oral sodium bicarbonate (Treated) or conventional therapy (controls) at study inception

	Overall (*N* = 145)	Treated (*N* = 71)	Control (*N* = 74)	*p*-value
Males, N (%)	83 (57 %)	47 (66 %)	36 (48 %)	NS
Age, years	65.5 ± 11.4	64.9 ± 11.8	66.0 ± 12.9	NS
Body Weight, kg	75.5 ± 14.1	76.5 ± 14.6	73.4 ± 11.2	NS
Cardiovascular disease, N(%)	36 (25)	17 (24)	19 (26)	NS
Systolic blood pressure, mmHg	122 ± 20	124 ± 19	120 ± 22	NS
Disatolic blood pressure, mmHg	73 ± 9	73 ± 8	73 ± 10	NS
Serum Bicarbonate, mEql/l	21.4 ± 1.9	21.2 ± 1.9	21.6 ± 2.0	NS
Serum Gucose, mg/dl	150 ± 44	149 ± 41	151 ± 47	NS
HbA1C %	6.76 ± 1.2	6.74 ± 1.0	6.8 ± 1.4	NS
Serum creatinine,mg/dl	2.1 ± 0.8	2.3 ± 0.8	2.0 ± 0.7	NS
BUN, mg/dl	87 ± 32	93 ± 35	81 ± 28	NS
Creatinine clearance, ml/min	33 ± 14	32 ± 14	35 ± 15	NS
Uric Acid, mg/dl	5.4 ± 1.8	5.6 ± 1.9	5.1 ± 1.8	NS
Serum sodium, mEql/l	139 ± 3	139 ± 3	139 ± 2	NS
Serum potassium, mEq/l	4.82 ± 0.7	4.85 ± 0.6	4.79 ± 0.7	NS
Total serum calcium, mg/dl	9.13 ± 0.6	9.14 ± 0.62	9.12 ± 0.58	NS
Serum phosphate, mg/dl	3.7 ± 0.7	3.8 ± 0.7	3.7 ± 0.7	NS
Serum albumin, g/dl	3.86 ± 0.42	3.85 ± 0.39	3.89 ± 0.46	NS
Hemoglobin, g/dl	12.3 ± 1.7	12.26 ± 1.82	12.39 ± 1.68	NS
C-Reactive Protein, mg/l	11.20 ± 28.1	11.08 ± 34.37	11.34 ± 18.53	NS
Serum PTH, pg/ml	122 ± 83	119 ± 34	124 ± 88	NS
Serum total cholesterol, mg/dl	154 ± 34	158 ± 34	151 ± 33	NS
Serum LDL cholesterol, mg/dl	91 ± 32	93 ± 31	87 ± 32	NS
Serum HDL cholesterol, mg/dl	45 ± 14	45 ± 12	45 ± 16	NS
Serum triglicerides, mg/dl	134 ± 58	130 ± 56	138 ± 60	NS
vitamin D (25-OH.D), ng/ml	39 ± 11	39 ± 10	38 ± 10	NS
Homa-IR	7.17 ± 2.4	7.13 ± 2.5	7.20 ± 2.36	NS
HOMA % B	49 ± 21	50 ± 22	48 ± 21	NS
Serum insulin, mcIU	18.3 ± 6.6	17.6 ± 6.1	19.0 ± 7.0	NS
Antidiabetic medications				
Biguanides, number (%)	98 (67.5)	52 (73.2)	46 (62.2)	NS
dose, mg/day	1740 ± 417	1760 ± 611	1725 ± 670	NS
Solfonylureas, number (%)	46 (31.7)	17 (23.9)	29 (39.2)	NS
dose, mg/day	5.25 ± 1.19	5.29 ± 1.38	5.23 ± 1.14	NS
Meglitinides, number (%)	41 (28.3)	21 (29.6)	20 (27)	NS
dose, mg/day	3.13 ± 1.35	3.52 ± 0.91	2.76 ± 1.59	NS
Use of > 1 medication, number (%)	37 (25.5)	20 (28.1)	17 (23)	NS
Antihypertensive DRUGS				
Furosemide, number (%)	131 (90.3)	62 (87.3)	69 (93.3)	NS
dose, mg/day	55 ± 19	55 ± 21	55 ± 17	NS
ARB inhibitors, number (%)	75 (51.7)	37 (23.9)	38 (39.2)	NS
ACE-Inhibitors, number (%)	74 (51)	38 (52.1)	36 (48.6)	NS

Table 1 Demographic, clinical, laboratory characteristics and use of oral anti-diabetic medications of patients randomized to oral sodium bicarbonate (Treated) or conventional therapy (controls) at study inception *(Continued)*

Beta-blocker (%)	24 (16.5)	14 (19.7)	10 (13.5)	NS
Other antihypertensive drugs number (%)	42 (28.9)	20 (28.2)	22 (29.7)	NS
Use of > 1 medication, number (%)	70 (48.3)	38 (53.5)	32 (43.2)	NS

Continuous and dichotomous variables are expressed as mean ± standard deviation or count (%), respectively

15 ml/min), serum bicarbonate levels (21.2 ± 1.9 mmol/l and 21.6 ± 2.0 mmol/l), fasting plasma glucose levels (149 ± 41 mg/dl and 151 ± 47 mg/dl), glycated hemoglobin (6.74 ± 1.0 % and 6.80 ± 1.4 %) as well as serum insulin levels (17.6 ± 6.1 mcIU and 19.0 ± 7.0 mcIU) (Table 1). Overall, basal HOMA-IR was 7.17 ± 2.4 and no difference between study groups was noted (median [Interquartile range (IQR)]: 6.4[5.5–7.9] and 6.4[5.5–8.2]; in the bicarbonate and control group, respectively). Of interest, only 4 (5,6 %) and 6 (8.1 %) subjects in the bicarbonate and control group had a HOMA-IR <5. Finally, at baseline HOMA-%B was also comparable between study groups (median [IQR]: 50.5 % [32.0–67.2 %] and 43 % [32.7–62.2 %]; in the bicarbonate and control group, respectively) (Table 1).

Table 1 shows patients' antidiabetic and antihypertensive drugs. Moreover, Table 1 shows 25-OH vitamin D: the two groups did not show statistically significant differences of vitamin D blood levels (39 ± 10 versus 38 ± 10 ng/ml, in treated versus control, respectively)

Mean dose of oral bicarbonate administered was 0.7 ± 0.2 mmol/kg per each patient. At study inception there were no differences between the two groups in the use of oral antidiabetic drugs regarding number of pills, doses, and type of drugs (Table 1). No adverse affects were registered during oral bicarbonate administration.

At study completion, while no differences in renal function and blood pressure control were observed, a significant impact of oral sodium bicarbonate supplementation on serum bicarbonate levels (26.0 ± 2.0 vs 22.3 ± 1.9 mEq/l, in treated and control subjects, respectively) as well as diabetes control and management was apparent (Table 2). Specifically, HOMA-IR decreased in treated (p for within group comparison: 0.004) but not control subjects (p for within group comparison: 0.57) (median [IQR]: 5.9 [5.0–7.0] and 6.3 [5.3–8.2]; p for between groups comparison:0.01) (Fig. 1, Table 3). Similarly,

Table 2 Clinical, laboratory characteristics and use of anti-diabetic medications of patients randomized to oral sodium bicarbonate (Treated) or conventional therapy (controls) at study completion

	Overall	Treated	Control	*p*-value
	145	71	74	
Body Weight, kg	76.1 ± 12.8	76.3 ± 12.8	73.4 ± 15.0	NS
Systolic blood pressure, mmHg	123 ± 17	125 ± 17	121 ± 16	NS
Disatolic blood pressure, mmHg	74 ± 8	76 ± 8	72 ± 10	NS
Serum Bicarbonate, mEql/l	24.2 ± 2.7	26.0 ± 2.0	22.3 ± 1.9	0.0001
Serum Gucose, mg/dl	118 ± 29	110 ± 32	127 ± 24	0.0001
HbA1C %	7.2 ± 2.9	6.7 ± 0.9	7.7 ± 3.7	0.028
Creatinine Clearance, ml/min	30 ± 16	32 ± 15	31 ± 16	NS
Homa-IR	6.52 ± 1.8	6.1 ± 1.5	7.0 ± 2.0	0.003
HOMA % B	52 ± 20	55 ± 18	49 ± 21	0.015
Serum insulin, mcIU	16.4 ± 6.6	13.4 ± 5.2	19.9 ± 6.3	0.0001
Antidiabetic medications				
Biguanides, number (%)	89 (61.4)	45 (63.3)	44 (59.4)	NS
dose, mg/day	1570 ± 517	1377 ± 457	1615 ± 550	0.005
Solfonylureas, number (%)	40 (27.6)	12 (16.9)	28 (37.8)	0.009
dose, mg/day	5.05 ± 1.29	4.89 ± 1.7	5.20 ± 1.07	0.033
Meglitinides, number (%)	36 (24.8)	16 (22.5)	20 (27)	NS
dose, mg/day	3.13 ± 1.35	3.52 ± 0.91	2.76 ± 1.59	0.0001
Use of > 1 medication, number (%)	28 (19.3)	12 (16.9)	16 (21.6)	NS

Continuous and dichotomous variables are expressed as mean ± standard deviation or count (%), respectively

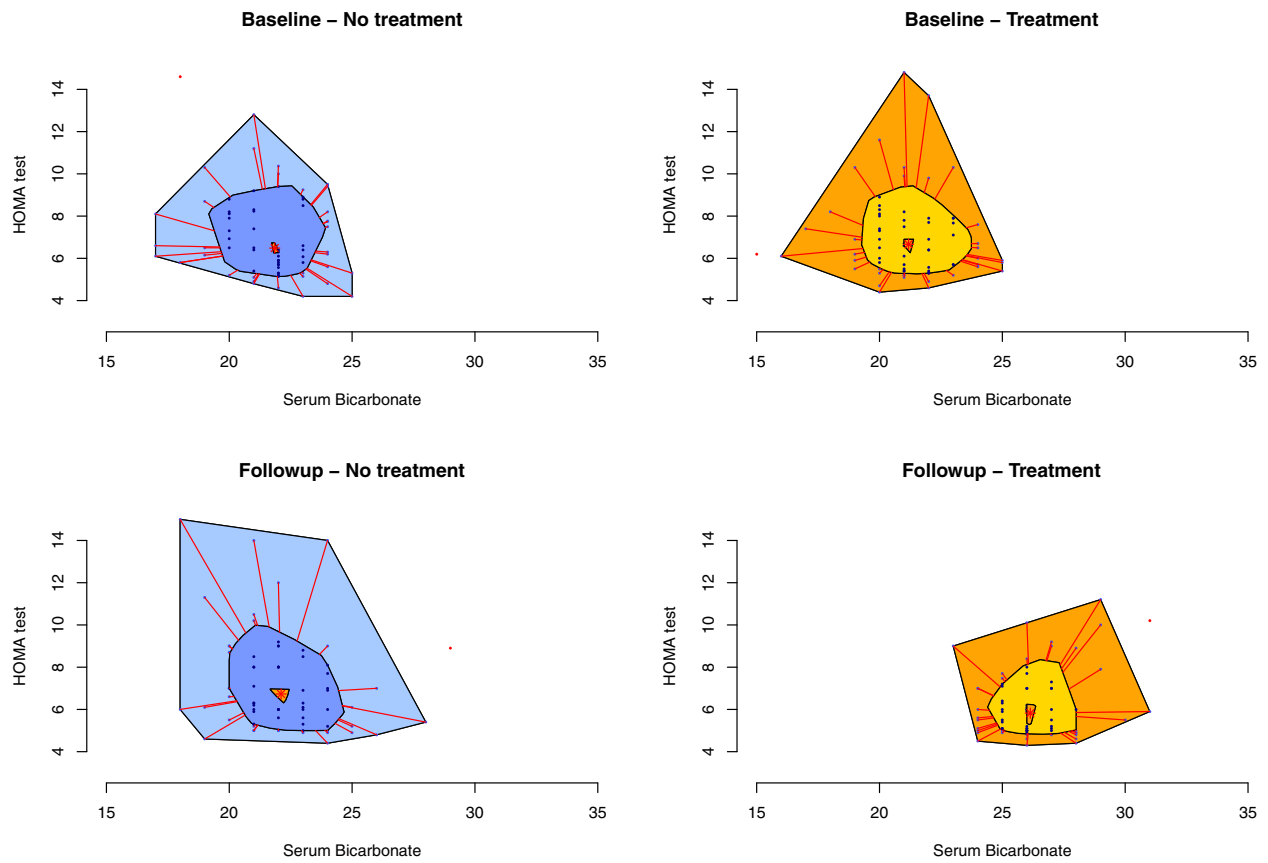

Fig. 1 The bagplots describe the association between serum bicarbonate and HOMA test in subjects randomized to oral sodium bicarbonate (Treated) or conventional therapy (controls) at study inception and conclusion. Legend: The inner polygon (called bag) contains 50 % of all points. Observations outside the outermost polygon (called fence) are outliers. The observations between the bag and fence are marked by line segments. The asterisk symbol (*) near the center of the graph represents the bivariate median

HOMA-%B increased (p for within group comparison: 0.036) in the experimental group (p for within group comparison: 0.754) from a median [IQR] value of 50.5 % [32.0 – 67.2 %] to 60.5 % [43.5 – 70.2 %] while it was unchanged in the control group (median[IQR]: 43.0 [32.7 – 62.2] vs 45 [32.7 – 64.5] for baseline and follow-up, respectively; p value for between comparison at follow-up: 0.023) (Fig. 1, Table 3).

As documented in Fig. 2a and b, serum bicarbonate levels or changes were not linearly associated with insulin resistance. Improvement of serum levels of bicarbonate was associated with HOMA improvement only if metabolic acidosis over-correction (i.e., serum levels of bicarbonate greater than 28 mEq/l) did not occur. Indeed, a significant effect reduction (interaction test for treatement*serum levels of bicarbonate: $p = 0.013$) of

Table 3 HOMA-IR and HOMA-%B at study inception and conclusion in treated and control subjects

	Treated	Control	*P* value (between group)
HOMA-IR			
Baseline	6.4 [5.5–7.9]	6.4 [5.5–8.2]	0.915
Study Completion	5.9 [5.0–7.0]	6.3 [5.3–8.2]	0.010
P-value (within group)	0.004	0.572	
HOMA-%B			
Baseline	50.5 [32.0–67.2]	43.0 [32.7–62.2]	0.543
Study Completion	60.5 [43.5–70.2]	45.0 [32.7–64.5]	0.023
P-value (within group)	0.036	0.754	

Data are expressed as median [Interquartile range]. Wilcoxon rank sum test is used for between- and within-group comparisons

Table 4 Predictor of HOMA index at study completion by unadjusted and multivariable adjusted linear regression analyses

Predictor of HOMA index at study completion			
Variable	B-coef	Standard Error	P value
Unadjusted			
- Treatment (yes vs no)	−0.8740	0.3285	0.0087
Unadjusted			
- Change in serum bicarbonate (%)	−1.5833	0.9462	0.0964
Unadjusted			
- Serum bicarbonate at study completion (mmol/l)	−0.14511	0.06026	0.0173
Adjusted for treatment, change in serum bicarbonate and interaction of change in serum bicarbonate*treatment			
- Treatment (yes vs no)	−1.4604	0.5015	0.00418
- Change in serum bicarbonate (%)	−3.0382	1.8007	0.09378
- Interaction test (change in serum bicarbonate*treatment)	4.9948	2.3578	0.03591
Adjusted for treatment, serum bicarbonate at follow-up and interaction of serum bicarbonate at followup*treatment			
- Treatment (yes vs no)	−11.6700	4.4255	0.00931
- Serum bicarbonate at follow-up (mmol/l)	−0.2328	0.1106	0.03713
- Interaction test (serum bicarbonate at follow-up*treatment)	0.4476	0.1784	0.01325

*interaction between factors

oral bicarbonate supplementation on HOMA index occurred as serum bicarbonate rose (Table 4). To explore whether the effect on insulin resistance was due to the oral bicarbonate administration *per se* or metabolic acidosis amelioration, we performed splines regression analyses to account for the change in the relationship between serum bicarbonate levels and HOMA index according to metabolic acidosis correction (i.e., below or greater/equal than 28 mEq/l). As reported in Table 5, the benefit associated with metabolic acidosis correction disappeared when serum bicarbonate exceeded 28 mEq/l. Notably, when treatment allocation and serum levels of bicarbonate achieved were both forced into the spline regression model, treatment allocation lost statistical significance ($p = 0.465$) (Table 5), suggesting that metabolic acidosis correction rather than oral bicarbonate supplementation improves insulin resistance (Table 5).

Discussion

Current findings suggest that metabolic acidosis is linked to insulin resistance in diabetic, Chronic Kidney Disease (CKD) patients and oral bicarbonate administration may correct metabolic acidosis that, in turn, improves insulin sensitivity in this population.

Insulin resistance (or reduced insulin sensitivity) is characterized by suboptimal biological responses of the

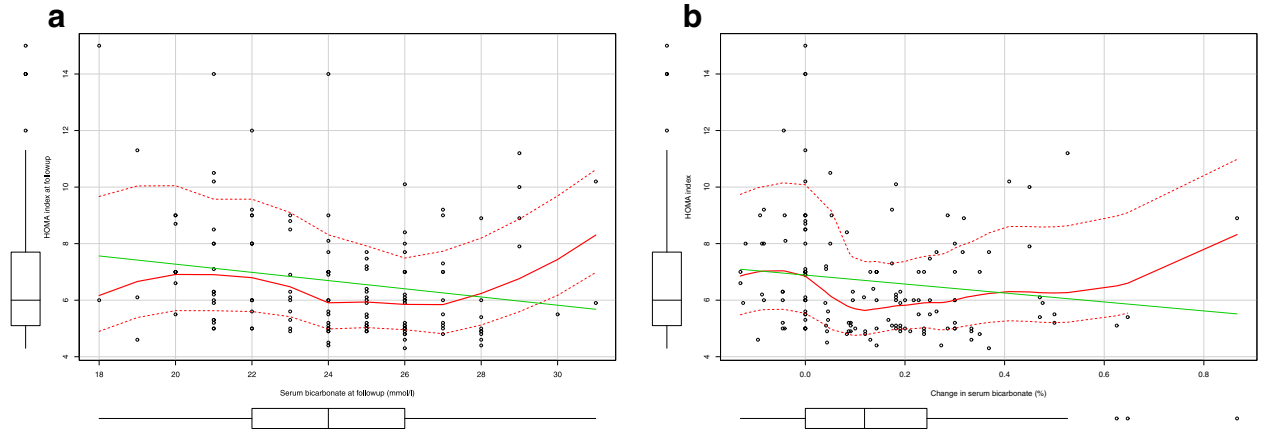

Fig. 2 The scatterplots represent the relationship between serum bicarbonate (**a**) and changes in serum bicarbonate (**b**) and HOMA index at study completion. Legend: solid green line represents the linear regression line; solid red line represents the smoothed linear regression line

Table 5 Predictor of HOMA index at study completion by unadjusted and multivariable adjusted spline regression analyses

Predictor of HOMA index at study completion (further elaborations)			
Variable	B-coef	Standard Error	*P* value
Unadjusted			
- Serum bicarbonate <28 mmol/l at follow-up	−4.6008	1.1804	0.00015
- Serum bicarbonate ≥28 mmol/l at follow-up	1.9360	1.0270	0.06146
Adjusted for treatment, serum bicarbonate greater/equal or lower than 28 mmol/l			
- Treatment (yes vs no)	−0.3482	0.4757	0.4654
- Serum bicarbonate <28 mmol/l at follow-up	−3.6980	1.7085	0.0321
- Serum bicarbonate ≥28 mmol/l at follow-up	2.2055	1.0926	0.0454

Serum bicarbonate is used as a continuous variable and divided according to ≥ 28 mmol/l (knot). The HOMA-serum bicarbonate levels relationship changes for values of serum bicarbonate greater equal than 28 mmol/l

liver, skeletal muscle and adipose tissue to normal amounts of insulin secreted [4, 5, 17–19]. Several biological processes such as glucose, lipid or protein metabolism as well as single hormonal effects such as glycogen synthesis or glucose oxidation may be affected in this condition [20, 21]. Several factors may contribute to insulin resistance in CKD. Visceral adipose tissue, diet, low physical activity, cigarette smoking, drugs (glucocorticosteroids, thiazide-like diuretics, beta-blockers) may all contribute to insulin resistance [22–24]. However, few lines of evidence also suggest that metabolic acidosis, that commonly complicates CKD, is implicated in suboptimal biological responses to insulin [6, 25].

Hence, metabolic acidosis represents a modifiable risk factor for insulin resistance and an attainable therapeutic target in CKD [4]. Indeed, metabolic acidosis may exert some detrimental effects at the cellular level inducing for example an intra-extracellular shift of cations and in different tissues such as bones and muscles as well as affect nutrition and metabolism [3, 6]. As part of CKD patients' care, alkali such as sodium bicarbonate administration and/or low protein diet or diet rich in fruit and vegetables are commonly prescribed to avoid or correct metabolic acidosis. Preliminary evidence suggests that metabolic acidosis amelioration may attenuate CKD progression as well as hard outcome [17, 26–28].

Our results confirm and expand previous efforts [25, 29, 30] suggesting that metabolic acidosis correction by sodium bicarbonate administration improves insulin resistance without affecting the overall blood pressure control (Table 2). This is likely due to the better response to insulin of target organs (as suggested by the improvement of both HOMA-IR and HOMA-%B). In contrast with previous experiences [25, 29, 30], Ikizler and coworkers [31] recently failed to demonstrate an association between metabolic acidosis and insulin resistance in a cross-sectional, observational study of 42 patients with CKD stage 3–5. According to these findings, a reduced acid burden improved metabolic acidosis but not insulin sensitivity, measured via the hyperinsulinemic euglycemic clamp method [31]. Although we estimated rather than measured insulin resistance, our results suggest that, at least in diabetic CKD patients, over-correction of metabolic acidosis may also be detrimental since values of serum bicarbonate greater than 28 mEq/l are associated with decreased insulin sensitivity (Fig. 2). While Ikizler and coworkers [31] define metabolic acidosis as a dichotomous variable (i.e., serum bicarbonate level <22 mEq/l), we prospectively explored the association of serum bicarbonate as a continuous variable and insulin resistance over a broad range of values of serum bicarbonate (i.e., from 18 to 31 mEq/l). Current findings suggest that this association is non-linear (Fig. 2) and insulin sensitivity decreases for values of serum bicarbonate below 24 mEq/l and above 28 mEq/l. Of interest, accounting for the non-linear nature of the association also suggest that bicarbonate levels rather than sodium bicarbonate *per se,* is responsible for the effect on the HOMA index (Table 5).

In patients of treatment group assuming Biguanides (45 subjects), bicarbonate administration was higher (not significant) compared to other oral antidiabetic drugs (0.79 ± 0.4 mmol/kg).

Although further work is needed to validate these results in diabetic as well as non-diabetic CKD patients, the clinical relevance of these findings should be evaluated in light of the prevalence of insulin resistance and its associated complications such as hyperinsulinemia, hyperglycemia and hypertriglyceridemia [32]; the widespread use of sodium bicarbonate or alkali supplementation, low protein or vegetarian diet for CKD care [17, 33–40] as well as the safety and relative inexpensiveness of the treatment tested. Aside of confirming the link of bicarbonate and insulin resistance, current results also provide with some guidance for CKD patient care.

Our analyses suffer of a few limitations worth noting. We investigated the relationship of insulin sensitivity and metabolic acidosis in a subgroup of patients (diabetic patients on oral antidiabetic medications) randomized into the Use of Bicarbonate in Chronic Renal Insufficiency (UBI) study (NCT NCT01640119). This study aims at testing the impact of alkali administration and acidosis correction in diabetic and non-diabetic CKD patients on renal function decline. Although we analyzed a subgroup of patients, the analyses were carried out in the first 145 consecutive diabetic patients who completed at least 1 year of follow-up. This selection criterion as well as the random assignment to treatment at study inception are independent of the investigators' beliefs and influences and we

can argue that current findings are similar to a randomized clinical trial (RCT). The well balance of demographic, clinical and laboratory characteristics between groups, further corroborates this point. No power assumption or sample size calculation was performed in light of the exploratory nature of these analyses and the lack of similar data in this domain. Insulin resistance is calculated rather than measured. However, the HOMA test is widely accepted as a reliable and reproducible tool to assess insulin sensitivity in clinical and epidemiological studies [12–16, 41, 42].

Conclusions

In conclusion, current results corroborate the notion that metabolic acidosis promotes insulin resistance and shed some light on the impact of sodium bicarbonate administration in CKD diabetic patients. Although further validation is mandatory, it seems that serum bicarbonate levels rather than the treatment used is relevant to restore insulin sensitivity. Finally, acidosis overcorrection (i.e., serum bicarbonate levels >28 mEq/l) should be avoided since, as metabolic acidosis, is associated with insulin resistance.

Abbreviations

ASCVD: Atherosclerotic cardiovascular disease; CKD: Chronic kidney disease; DM2: Diabetic type 2 patients; ESRD: End stage renal disease; HOMA: Homeostatic model assessment; HOMA-%B: ß pancreatic cell function calculate by Homa test; HOMA-IR: Calculate insulin resistence by Homa test; IR: Insulin resistance; MA: Metabolic acidosis; NYHA: New York Heart Association; RAAS: Renin-Angiotensin-Aldosterone System; UBI: Use of bicarbonate in chronic renal insufficiency;

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Availability of data and materials

To comply with the current Italian regulation for sensitive personal data protection, the dataset on which the conclusions of the manuscript rely cannot be either deposited in publicly available repositories or presented in the main paper or additional supporting files. The authors remain at disposal for any additional enquire.

Authors' contributions

AB performed the statistical analysis; he has been involved in drafting and revising the manuscript. LDM has been involved in drafting the manuscript and revising it. DS has made substantial contributions to acquisition of data, and interpretation of data. SM has made substantial contributions to acquisition of data, and interpretation of data. EDS has made substantial contributions to acquisition of data, and interpretation of data. MC has made substantial contributions to interpretation of data. LDL has made substantial contributions to interpretation of data. PG has made substantial contributions to acquisition of data, and interpretation of data. BDI conceived the study, and participated in its design and coordination. He has made substantial contributions to acquisition of data, interpretation of data and he has been involved in drafting and revising the manuscript. FA has made substantial contribution to acquisition of data. All Authors have given final approval of the version to be published.

Competing interests

Authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol was approved by the Comitato Etico Campania Nord and each participating site provided institutional Ethical Review Board (information available from editor upon reasonable request). Participants provided written informed consent at study entry. Study procedures were conducted in adherence to the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

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