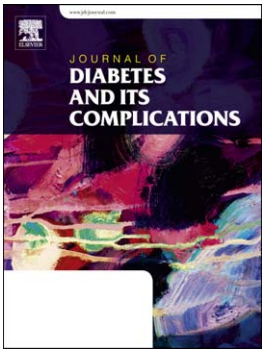

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Effects of potassium citrate or potassium chloride in patients with combined glucose intolerance:

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

References

1. Mondon CE, Burton SD, Grodsky GM et al. Glucose tolerance and insulin response of potassium-deficient rat and isolated liver. Am J Physiol 1968; **215**:779-8.
2. Rowe JW, Tobin JD, Rosa RM et al . Effect of experimental potassium deficiency on glucose and insulin metabolism. Metabolism. 1980 ; **29**: 498-502.
3. Helderman JH, Elahi D, Andersen DK, et al. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. Diabetes 1983; **32**:106-11.
4. DeFronzo RA, Beckles AD. Glucose intolerance following chronic metabolic acidosis in man. Am J Physiol 1979; **236**:E328-34.
5. Mackler B, Lichtenstein H, Guest GM. Effects of ammonium chloride acidosis on the action of insulin in dogs. Am J Physiol 1951; **166**:191-8.
6. May RC, Kelly RA, Mitch WE. Metabolic acidosis stimulates protein degradation in rat muscle by a glucocorticoid-dependent mechanism. J Clin Invest 1986; **77**:614-21.
7. Maurer M, Riesen W, Muser J, et al. Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans. Am J Physiol Renal Physiol 2003; **284**:F32-40.
8. Disthabanchong S, Niticharoenpong K, Radinahamed P et al. Metabolic acidosis lowers circulating adiponectin through inhibition of adiponectin gene transription. Nephrol Dial Transplant 2011; **26**: 592-598.

9. Gasser JA, Hulter HN, Imboden P et al. Effect of chronic metabolic acidosis on bone density and bone architecture in vivo in rats. Am J Physiol Renal Physiol 2014. **306**: F517-F524.

10. Teta D, Bevington A, Brown J et al. Acidosis downregulates leptin production from cultured adipocytes through a glucose transport-dependent post-transcriptional mechanism. J Am Soc Nephrol 2003; **14**:2248-54.

11..Bullo M, Moreno-Navarrete JM, Fernández-Real JM et al . Total and undercarboxylated osteocalcin predict changes in insulin sensitivity and β cell function in elderly men at high cardiovascular risk. Am J Clin Nut 2012; **95**: 249-255.

12. Harris SS, Dawson-Hughes B. No effect of bicarbonate treatment on insulin sensitivity and glucose control in non-diabetic older adults. Endocrine 2010;. **38**:221-6.

13. Mandel EI, Curhan GC, Hus FB et al. Plasma bicarbonate and risk of type 2 diabetes mellitus. CMAJ 2012; **184** : E719-E725.

14. Zillich AJ, Garg J, Basu S et al. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. Hypertension 2006; **48**:219-24.

15. Shafi T, Appel LJ, Miller ER 3rd et al. Changes in serum potassium mediate thiazide-induced diabetes. Hypertension 2008; **52**:1022-9.

16. Chatterjee R, Yeh HC, Shafi T et al. Serum and dietary potassium and risk of incident type 2 diabetes mellitus: The Atherosclerosis Risk in Communities (ARIC) study. Arch Intern Med 2010; **170**:1745-51.

17. Frassetto L, Morris RC Jr, Sellmeyer DE et al .Diet, evolution and aging--the pathophysiologic effects of the post-agricultural inversion of the potassium-to-

sodium and base-to-chloride ratios in the human diet. Eur J Nutr 2001; **40**:200-13.

18. Perreault L, Pan Q, Mather KJ et al. Diabetes Prevention Program Research Group: Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. Lancet 2012; **379**:2243-51.
19. Lee M, Saver JL, Hong KS et al. Effect of pre-diabetes on future risk of stroke: meta-analysis. BMJ 2012; **344**:e3564.
20. Mannucci E, Bardini G, Ognibene A et al. Screening for diabetes in obese patients using the new diagnostic criteria. Diabetes Care 1998; 21: 468-469.
21. Rudenski AS, Matthews DR, Levy JC et al. Understanding insulin resistance: Both glucose resistance and insulin resistance are required to model human diabetes. Metabolism 1991; 40: 908–917.
22. Wallace TM, Levy JC, Matthews DR. Use and abuse of the HOMA modelling. Diabetes Care 2004; 27: 1487-1495.
23. www.dtu.ox.ac.uk/homacalculator/
24. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: A simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; 85: 2402-2410.
25. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing. Diabetes Care 1999; 22: 1462-1470.
26. Jehle S, Hulter HN, Krapf R: Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab 2013; **98**:207-17.

27. HE FJ, Markandu ND, Coltart R et al. Effect of short supplementation of potassium chloride and potassium citrate on blood pressure in hypertensives. Hypertension 2005; **45** : 571-574.

28. Sorensen MV1, Grossmann S, Roesinger M et al. Rapid dephosphorylation of the renal sodium chloride cotransporter in response to oral potassium intake in mice. Kidney Int. 2013 ;83:811-24

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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.