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Title:

The effect of supplementation with alkaline potassium salts on bone metabolism: a meta-analysis

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Abstract

Purpose: the role of acid-base homeostasis as a determinant of bone health, and the contribution of supplemental alkali in promoting skeletal integrity, remain a subject of debate.

The objective of this study was, therefore, to conduct a meta-analysis to assess the effects of supplemental potassium bicarbonate ($KHCO_3$) and potassium citrate (KCitr) on urinary calcium and acid excretion, markers of bone turnover and bone mineral density (BMD) and to compare their effects with that of potassium chloride (KCl).

Methods: a total of 14 studies of the effect of alkaline potassium salts on calcium metabolism and bone health, identified by a systematic literature search, were analysed with Review Manager (Version 5; The Cochrane Collaboration) using a random effects model. Authors were contacted to provide missing data as required. Results are presented as the standardised (SMD) or unstandardized mean difference (MD) (95% confidence intervals).

Results: urinary calcium excretion was lowered by intervention with both $KHCO_3$ (P=0.04) and KCitr (P=0.01), as was net acid excretion (NAE) (P=0.002 for $KHCO_3$ and P=0.0008 for KCitr). Both salts significantly lowered the bone resorption marker NTX (P<0.00001). There was no effect on bone formation markers or BMD. KHCO3 and KCitr lowered calcium excretion to a greater extent than did KCl.

Conclusions: this meta-analysis confirms that supplementation with alkaline potassium salts leads to significant reduction in renal calcium excretion and acid excretion, compatible with the concept of increased buffering of hydrogen ions by raised circulating bicarbonate. The observed reduction in bone resorption indicates a potential benefit to bone health

Key words: Potassium, alkali, markers of bone turnover; bone mineral density

Mini Abstract

The role of acid-base metabolism in bone health is controversial. In this metaanalysis, potassium bicarbonate and potassium citrate lowered urinary calcium and acid excretion, and reduced the excretion of the bone resoption marker NTX. These salts may thus be beneficial to bone health by conserving bone mineral.

Introduction

The role of acid-base balance as a determinant of bone health, and the potential contribution of potassium, abundant in fruit and vegetables, in promoting skeletal integrity is contentious.

Acid-base homeostasis in the body is tightly controlled (pH 7.35 -7.45) by buffering or neutralization by plasma proteins and other tissues, including bone, the excretion of protons (H^+) and reabsorption of bicarbonate by the kidneys, and the excretion of carbon dioxide in the lungs. Acid loading in healthy subjects which exceeds the capacity of these systems leads to higher levels of H^+ and lower levels of plasma bicarbonate, within the range considered to be normal, increasing the requirement for buffering/neutralization. This is known as low-grade metabolic acidosis. Diet contributes to acid-base balance according to the type of acid or alkaline precursors which it provides, with fruit and vegetables amongst the contributors of alkaline precursors [1]. Long-term consumption of a high acid-generating diet, typical of "Western" diets, promotes a chronic state of low grade metabolic acidosis. This is compounded by the decline in renal function with aging that leads to the decreased ability of the kidney to excrete H^+ ions [2], [3].

Severe acute and chronic metabolic acidosis have well-established physiological effects on bone [4], which provides a large reserve of alkaline calcium salts. These are released in

response to the increased acid load. While bicarbonate and other anions buffer the increased circulating H^+, the excess calcium and other cations released are excreted in the urine. In vitro, and in disease states with severe metabolic acidosis, the rise in extracellular acid-concentrations promotes an increase in osteoclastic activity [5], [6] and decrease in osteoblast activity [7] [8], [9]. What is less clear is whether a milder diet-induced chronic state of metabolic acidosis has similar detrimental effects on bone and calcium homeostasis in the long term.

A meta-analysis was therefore undertaken to assess the effect of alkaline potassium salts on calcium metabolism and bone health. The specific objective was to investigate the effects of potassium bicarbonate ($KHCO_3$) and potassium citrate (KCitr), compared with placebo, on urinary calcium and acid excretion, markers of bone turnover and bone mineral density. A secondary objective was to examine the role of $KHCO_3$ and KCitr compared with potassium chloride (KCl) on the same outcome measures, in order to attempt to clarify the respective roles of the potassium cation and the basic anions.

We hypothesised that supplementary $KHCO_3$ and KCitr would decrease urinary excretion of calcium and net acid excretion (NAE), as well as reducing bone turnover as observed by a decrease in urine and serum markers of bone formation and resorption. The supplements would also lead to an increase in bone mineral density (BMD).

Methods

Search strategy and study selection

A systematic search of the literature was conducted to identify randomised controlled trials in which the effects of either potassium bicarbonate or potassium citrate on a number of indicators of bone health were investigated. ISI Web of Knowledge (which includes Web of Science, BIOSIS, Scientific Web Plus and Medline) and PubMed were used for electronic searches of studies published between 1959 and February 2013. In addition, the Cochrane Central Register of Controlled Trials (CENTRAL) and the International Randomised Controlled Trials Number Register were searched for unpublished trials. Reference lists from relevant papers were also searched.

Studies eligible for inclusion were randomised, controlled studies and metabolic studies in human adult men or women. Parallel or cross-over design, metabolic or community-based intervention studies were eligible for inclusion. Administration of $KHCO_3$ or KCitr at all dosages and for any duration was considered. Outcome measures were: urinary calcium excretion, markers of bone resorption and formation, BMD, and NAE. Studies were also included if supplementation was combined with other forms of dietary or pharmaceutical manipulation, such as high protein or salt intake, or diuretic administration.

Studies were not eligible if they did not fulfil the above criteria, if they were conducted in patients with kidney disease, metabolic bone disease or following renal, bariatric or other surgery, or in pregnant or lactating women. Studies were also excluded from the main analysis if the control group received a treatment other than placebo or "no-treatment". However, a secondary analysis was conducted comparing the effects of alkaline potassium salts with that of potassium chloride.

Search terms used for the electronic searches were "potassium" or "potassium citrate" or "potassium bicarbonate" or "alkali", and "bone", "bone mineral density", "bone turnover markers", "fracture" or "bone health", then filtered by "clinical trials" or "randomised trials" and "human".

Publications meeting the relevant criteria were assessed for inclusion by SLN and HL.

Data extraction

Information extracted from eligible studies included: first author, year of publication, study design, characteristics of study participants, type and dose of supplementation, frequency of supplementation, duration of study, method of randomisation, type of control, extent of blinding, outcome measures, results.

In studies using multiple parallel interventions, (for example comparing $KHCO_3$ with $NaHCO_3$) only data relating to the $KHCO_3$ or KCitr and placebo (or KCl, for the secondary analysis) arms of the study were used.

Mean, standard deviation and number of participants were obtained for all outcome measures. Where means were presented with the SE, this was converted to the SD ($SE=SD/\sqrt{n}$). Where possible, both final measurements and change scores were extracted. For studies using different doses of supplement, outcomes for the highest dose was used. For studies measuring outcomes at multiple time-points, data for the final time-point was used.

For studies where the required data was not reported, authors were contacted for further information or clarification.

Quality analysis

Studies that met the inclusion criteria were assessed for risk of bias by HL using the Cochrane Collaboration criteria [10], on the basis of five domains: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data and selective reporting.

Meta-analysis

Analysis was conducted using Review Manager (Version 5; The Cochrane Collaboration). The comparisons investigated were: $KHCO_3$ versus placebo, KCitr versus placebo and either KCitr or $KHCO_3$ versus placebo or KCl, for all relevant outcome measures.

A random effects model was chosen to account for heterogeneity of the included studies, and the inverse variance method used, in which the intervention effects of individual studies are multiplied by $1/SE^2$, so that larger studies are given more weight than smaller studies. Results are presented as standardised mean differences (SMD), for outcomes other than BMD and NTx, as measurement of these outcomes differed across studies. The observed differences between means are standardised by dividing by the standard deviation (SD), and thus presented as units of SD. For BMD and NTx, units of measurement did not differ across studies and therefore the unstandardized mean differences are reported. Mean differences are reported with 95% confidence intervals.

Sensitivity Analysis

Sub-group analyses were carried out to ensure that results of the meta-analysis were not affected by decisions relating to study inclusion, such as study design, or data extraction, such as choice of dose or time-points used.

Reporting

The meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11].

Results

Study selection

The process of selection of studies for meta-analysis is shown in the PRISMA flow diagram (Figure1).

Characteristics of included studies/included data

The characteristics of included studies are shown in supplemental **table 1**. A total of 14 studies met the criteria for inclusion in the main meta-analysis (intervention vs placebo). Of these, 7 studies used potassium bicarbonate as a supplement [12], [13], [14], [15], [16], [17], [18], and 7 used potassium citrate [19], [20], [21], [22], [23], [24], [25]. Seven studies were randomised, placebo-controlled intervention studies (4 weeks – 3 years) with a parallel design, [19,13], [14,15], [21], [22], [25], and seven were metabolic cross-over studies of short duration (≤ 4weeks). Four of these were randomised, placebo-controlled [12,16], [20,24], and three used the "treatment-free" phase as the control, [17], [18], [23]. Two of the studies used in the main meta-analysis were included in the secondary analysis (intervention vs KCl), both of which used $KHCO_3$ [14], [16]. Two additional randomised, double-blind studies were included in this secondary analysis, one comparing $KHCO_3$ with KCl [26], and one using KCitr [27].

Authors of eight studies were contacted for clarification of their data, and all responded by providing the information requested.

Risk of Bias

Eight studies explicitly stated the method of randomisation. The majority of the studies (n=8) were deemed to be at low risk of bias with respect to randomisation, blinding, analysis and reporting (supplemental **table 2**). Separate meta-analysis of available baseline data showed

no significant differences between treatment and control groups with respect to age, calcium intake, urinary calcium excretion, BMD and N-terminal telopeptide of type 1 collagen (NTX), suggesting adequate randomisation for these studies (data not shown). There was no heterogeneity among studies in these analyses (I^2=0%).

Results of main meta-analysis

Urinary calcium excretion

Both $KHCO_3$ and KCitr supplementation significantly reduced calcium excretion compared to a placebo (figure 2a). For $KHCO_3$, the overall standardised mean difference (95% CI) in the change in calcium excretion was -1.03 SD (-2.03,-0.03), P=0.04. For KCitr the SMD was similar, -1.03 SD (-1.85, -0.21), P=0.01. When results for both $KHCO_3$ and KCitr were combined, the overall effect of a potassium supplement on calcium excretion was -1.30 SD (-2.06, -0.54), P=0.0008 (data not shown). The results did not differ if crossover studies were excluded.

NAE

There was a clear effect of both $KHCO_3$ and KCitr on NAE. The SMD was -5.73 SD (-9.30, -2.16), P=0.002 for $KHCO_3$ and -4.88 SD (-7.73, -2.04), P=0.0008 for KCitr (figure 2b**).**

Bone turnover markers

The mean difference in the effect of a potassium supplement on the bone resorption marker NTX was -7.62 nmolBCE/mmol creatinine (-14.97, -0.26), P= 0.04 for $KHCO_3$, and -4.36 nmolBCE/mmol creatinine (-5.19, -3.53), P<0.00001 for KCitr (figure 2c). The effect on markers of bone formation was not significant (figure 2d).

186 Bone mineral density

187 Two studies reported bone mineral density following supplementation, both of which
188 supplemented with KCitr for 2 years [19,21]. The mean difference in BMD at the lumbar
189 spine (LS2-4) was 0.05 g/cm^2 (-0.01, 0.11), P=0.09, and for the total hip (TH) 0.02 g/cm^2 (-
190 0.03, 0.07), P=0.43 (figure 3). Jehle et al reported a significant positive effect of KCitr
191 relative to placebo at both sites [21], whereas MacDonald et al did not observe any significant
192 differences at either site [19].

193 $KHCO_3$ or KCitr vs KCl

194 Urinary calcium excretion and NAE were both lower following supplementation with
195 $KHCO_3$ or KCitr than with KCl, and this difference was significant for NAE, with a SMD of
196 -5.27 SD (-10.30, -0.24), P=0.04 (figure 4).

197

198

199 Sensitivity analysis and heterogeneity

200 Sub-group analyses exploring the effect of study duration, study design and the inclusion of
201 pre-menopausal women on outcomes revealed no significant effects.

202 The reasons for the high heterogeneity among the included studies with respect to calcium
203 excretion and NAE is not clear, but could be due to size of study groups, as well as age and
204 bone health. Although the majority of studies (n=10) were in postmenopausal women and
205 older men, two were in young men, one in young women and one covered ages 18-75 years
206 in men and women; study group size ranged from n=5 to n=276. T-scores for baseline BMD
207 were all > -1 in the four studies where this was reported, but this may not have been so for the

other studies. Baseline calcium intakes were all in the range 650-1080 mg/d, and baseline urinary calcium excretion was in the range 100-240 mg/d. It is therefore unlikely that there were major differences in intakes of other nutrients (such as sodium and protein) that might affect calcium metabolism. Removing crossover studies from the analysis did not alter the heterogeneity. It should, however, be noted that heterogeneity with respect to bone turnover markers was low (I^2 0-47%).

Discussion

This meta-analysis of the effect of alkaline potassium salts on calcium and bone metabolism provides compelling evidence for a calcium- and bone-sparing effect of these salts.

The results strongly favour evidence for a reduction in bone resorption following supplementation with $KHCO_3$ or KCitr, as well as a reduction in calcium and net acid excretion, in support of our hypothesis. Meanwhile, the proposed effects on bone formation and BMD are not supported by the present data.

While the effect of $KHCO_3$ and KCitr on calcium and acid excretion is not widely disputed, the implications of these effects for bone health have been debated. It has been argued that the effects of alkaline potassium salts on calcium do not impact on bone as losses/gains are compensated for by changes in absorption [28]. However, none of the included balance studies [17], [18], [22] found changes in calcium absorption. Moreover, our analysis also provides evidence for an inhibition of skeletal degradation with supplementation, with the majority of studies that measured bone turnover markers showing a decrease in bone resorption [18], [12], [14], [16]. In particular, we showed a significant overall reduction in NTX excretion with both $KHCO_3$ and KCitr, with very low heterogeneity among these studies. Thus there is clearly an effect of potassium or bicarbonate/citrate on osteoclastic activity. On the other hand, few of the studies included in this analysis showed an effect on markers of bone formation, and there was no overall effect. In one long term intervention [21] there was a sustained increase in N-terminal propeptide of type 1 collagen, (but not bone alkaline phosphatase,) after 2 years of KCitr. In another short-term metabolic study [18], there was an increase in osteocalcin after 18 days of $KHCO_3$. In that study, $NaHCO_3$ had no such effect, suggesting that potassium might work independently of the alkaline anion. Similarly, Sakhaee [23] found that KCitr but not NaCitr was effective in lowing urinary

238 calcium excretion. A plausible explanation is that the beneficial effect of the base could be
239 mitigated by the negative effect of increased Na intake [17,23,29], with the resulting
240 increased Na excretion being accompanied by an increase in calcium excretion. This is
241 supported by the study by Lemann et al. in which 24-hour urinary Na excretion increased
242 following $NaHCO_3$ supplementation [17]. In that study, there was no effect on urinary
243 hydroxyproline excretion, possibly due to the change in calcium balance being too small.
244 Those authors also suggest that K, independent of HCO_3, might have had a direct positive
245 effect on tubular reabsorption of Ca. However, the relative role of the cation and anion in
246 these $KHCO_3$ or KCitr supplementation studies still remains unclear. Our analysis of studies
247 comparing $KHCO_3$ or KCitr with KCl indicates that the alkaline salts are significantly more
248 effective than KCl in reducing urinary acid excretion and bone resorption markers [16],[26],
249 [30], [27]. One of these studies [27] also shows KCitr to have a significant beneficial effect
250 on BMD compared with KCl.

251

252 Of course, the key question is whether these results have implications for fracture risk. There
253 is evidence that calcium excretion and NAE are negatively associated with BMD [31] [32],
254 and Shi et al have shown that high calcium excretion is particularly associated with lower
255 BMD in children with higher dietary acid load [33]. Two of the studies included in our meta-
256 analysis investigated BMD as an end-point [19], [21], a small number of studies with which
257 to detect an overall effect – indeed we failed to show an effect of supplementation on BMD.
258 However, in one of these studies [21], there was a marked increase in BMD at the lumbar
259 spine relative to the placebo after 2 years of KCitr supplementation, which was shown by
260 pQCT to be predominantly due to increases in trabecular thickness, volume and number. As
261 a result, FRAX (fracture prediction score) was significantly reduced in both men and women.
262 A previous study by the same group, comparing KCitr with KCl also demonstrated a positive

effect of KCitr (but not KCl) on BMD [27]. Conversely, a similar 2 year study of KCitr supplementation in healthy postmenopausal women failed to show any effect on BMD [19], and thus no overall effect was seen in the meta-analysis. Why the two similar studies produced such divergent results is not clear. The subjects in the former study [21] included men and women, and were approximately 10 years older than those in the latter study[19]. They also had slightly lower LS BMD at baseline (T-scores -0.61±1.54 vs -0.08±1.33 g/cm^2 for placebo groups). It may be that the effect on bone is inversely related to baseline BMD. The women in the study by Jehle et al cited above were osteopenic with LS T-scores of <-2 [27]. Alternatively, the diets of the women in the Scottish study were not sufficiently acidogenic for a beneficial effect of alkaline potassium salts to be demonstrated [34]. It has also been suggested that areal BMD measured by DEXA may not be the most appropriate outcome for assessing the effects of nutritional factors on bone [35].

Intervention studies using alkaline salts of potassium allow investigation of the effect of increasing dietary alkali without the confounding effects of other nutrients and dietary or lifestyle patterns associated with fruit and vegetable intake, nor the well-established problems with dietary assessment. In the present analysis, we show that, overall, administration of alkaline potassium salts, whether in the short- or long-term, leads to significant reduction in renal calcium excretion and acid excretion, compatible with the concept of increased buffering or neutralization of hydrogen ions by raised circulating bicarbonate. That this neutralisation of dietary acid load has beneficial effects on bone is demonstrated by the reduction in bone resorption that this analysis confirms.

The main limitation of this analysis is the heterogeneity of included studies in terms of study design, primary outcome measures and populations studied. Although all the studies included were randomised controlled trials, there were marked differences in dosage, duration and method of administration of the supplement, as well as age and gender of the

study populations. In addition, there were very few studies with BMD as the primary endpoint which fulfilled the inclusion criteria, which limits the applicability of our findings, particularly with respect to fracture risk. Nevertheless, it is important to note that the novel finding of an effect of alkaline potassium salts on bone resorption was seen among studies with little or no heterogeneity.

Thus the effect of alkaline potassium salts on calcium, acid-base and bone metabolism that has been demonstrated in this meta-analysis has the potential to translate into preventative measures for osteoporosis. In particular, dietary measures which include increasing intakes of fruit and vegetables, and thus alkaline precursors, should be considered as valuable contributors to bone health.

Conflict of Interest:

Helen Lambert, Lynda Frassetto, Bernadette Moore, David Torgerson, Richard Gannon, Peter Burckhardt and Susan Lanham-New declare that they have no conflict of interest.

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Figures

Figure 1

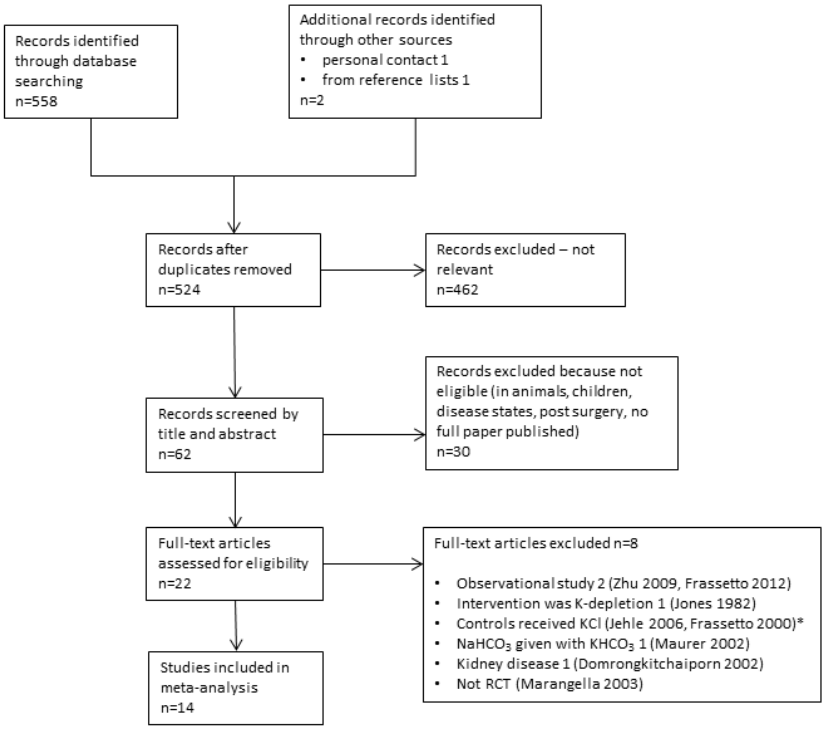


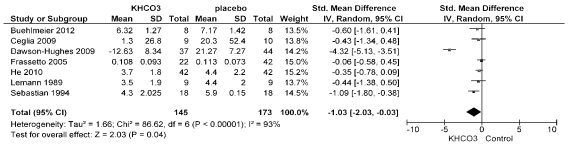
Fig.1: Summary of study selection: PRISMA statement flow diagram

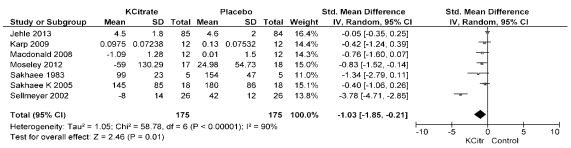
*Studies included in secondary analysis of KHCO3 or KCitr vs KCl

Figure 2

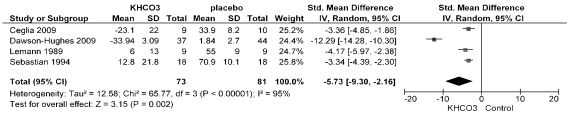
KHCO3 **KCitr**

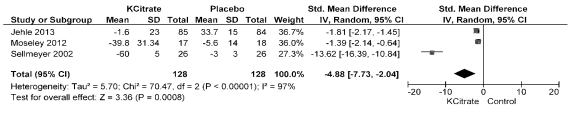
a Calcium excretion



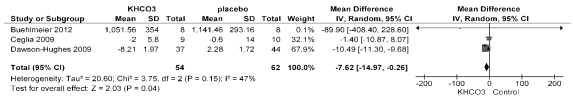


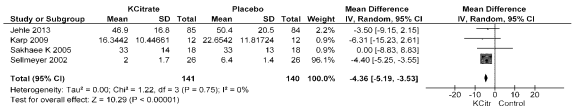
b NAE



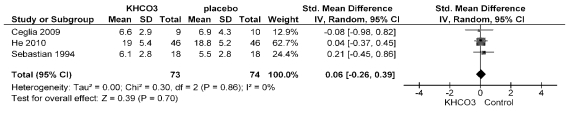


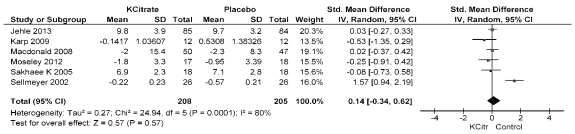
c NTX





d Combined formation markers*





***Specific bone formation markers used for comparisons**

Ceglia	Osteocalcin ng/ml
He	Δ Osteocalcin µ/L
Sebastian	Osteocalcin ng/ml

Jehle	BAP µmol/L
Karp	ΔBAP U/L
MacDonald	ΔP1NP µg/L
Moseley	ΔBAP ng/ml
Sakhaee	Osteocalcin ng/ml
Sellmeyer	ΔOsteocalcin ng/ml

Fig.2: Forest plots for effects of $KHCO_3$ and KCitr supplementation on calcium excretion, NAE and bone turnover markers

a, b, d: squares represent standardised mean difference (SMD) (95% CI), with total SMD represented by diamonds

c: squares represent mean difference (95% CI), with total mean difference represented by diamonds

Figure 3

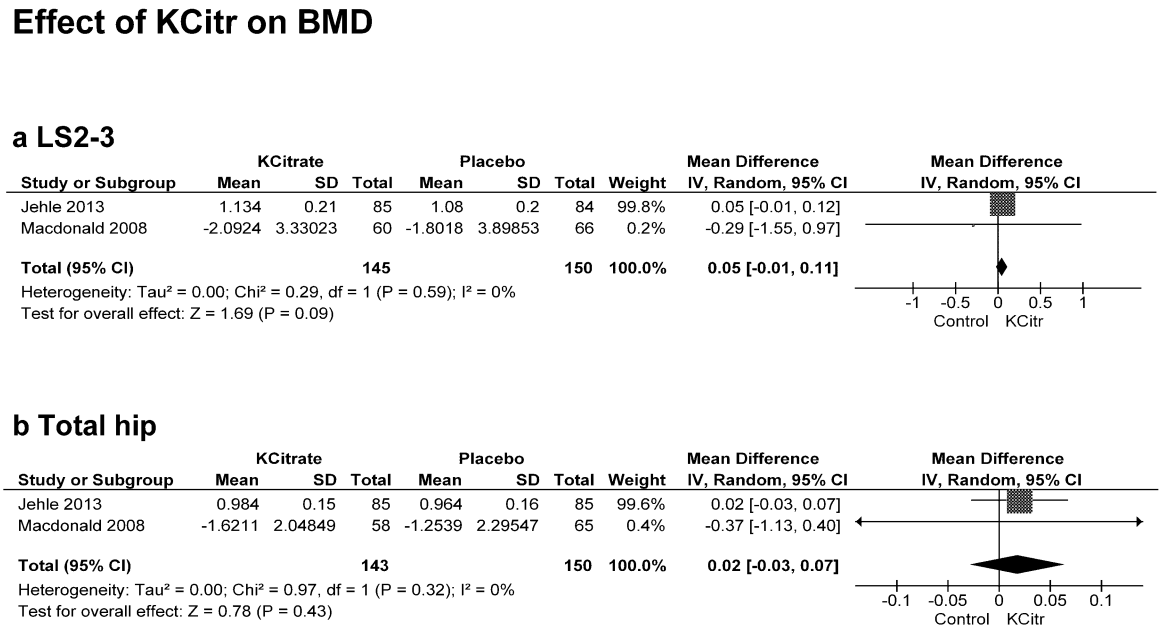


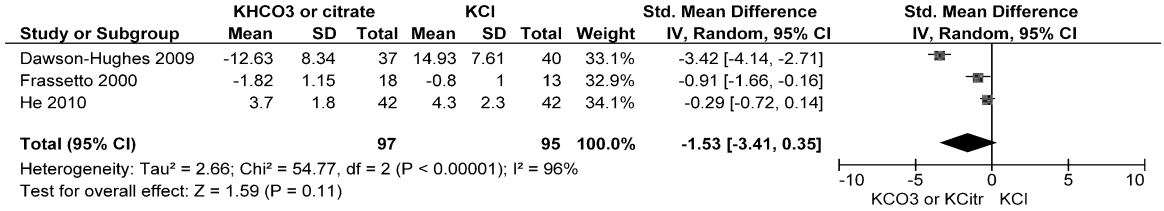
Fig.3: Forest plots for effect of KCitr supplementation on BMD

Squares represent mean difference (95% CI), with total mean difference represented by diamonds

Figure 4

Comparison of $KHCO_3$ or KCitr with KCl

a Calcium excretion



b NAE

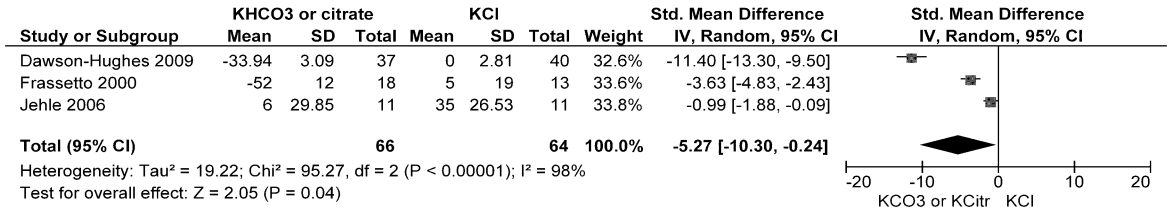


Fig.4: Forest plots for comparison of effect of $KHCO_3$ or KCitr with KCl

Squares represent standardised mean difference (SMD) (95% CI), with total SMD represented by diamonds

Supplemental data

Table 1: Characteristics of included studies

Studies using $KHCO_3$ as supplement

Study	Population: Gender; age	N	Dose/frequency	Duration	Relevant Outcome Measures	Additional information: study design; study conditions; additional supplements
Buehlmeier 2012 (12)	M mean 26 yrs (SD 4)	8	90mmol/d	10 days	NTX, CTX BAP, P1NP UCaexcr	Randomised cross-over trial. High Na-induced metabolic acidosis (2.6mmol NaCl/kg bm/d); 400IU/d vitamin D
Ceglia 2009 (13)	M & F 54-82 yrs	19	90mmol/d	41 days	UCaexcr NAE NTX Osteocalcin	RCT High/low protein diet
Dawson-Hughes 2009 (14)	M & F 50 yrs+	171	67.5mmol/d	84 days	UCaexcr NAE NTX Osteocalcin	RCT 600mg/d Ca triphospate; 525IU/d vitamin D
Frassetto 2005 (15)	PM 64-70 yrs	170	30/60/90mmol/d	3yrs	UCaexcr	RCT

						400IU/d vitamin D; $CaCO_3$
He 2010 (16)	M & F 18-75 yrs	42	64mmol/d	4 weeks	UCaexcr CTX, PYD, DPD Osteocalcin, BAP, P1NP	Crossover RCT Subjects had mild hypertension
Lemann 1989 (17)	M 23-46yrs	9	60mmol/d	12 days	UCaexcr NAE Hydroxyproline	Metabolic balance study 6 subjects on low Ca diets, of these 3 were supplemented with calcitriol 0.5µg 6-hourly
Sebastian 1994 (18)	PM 51-77 yrs	18	60-120mmol/d	18 days	UCaExcr NAE Hydroxyproline Osteocalcin	Metabolic balance study

Studies using KCitr as supplement

Study	Population	N	Dose/frequency	Duration	Relevant Outcome Measures	Additional information Study design; study conditions; additional supplements
Karp 2009 (20)	F 20-30 yrs	12	57.5mmol/d	24 hrs	UCaExcr NTX BAP	Crossover study. Subjects were own controls
Jehle 2013 (21)	M & F 65-80 yrs	201	60 mEq/d	24 months	aLSBMD (DXA) vBMD (pQCT) UCaExcr NAE	RCT 500mg Ca/d; 400IU vitamin D
MacDonald 2008 (19)	PM 55-65 yrs	276	55.5mEq/d	24 months	BMD (DXA) UCaExcr DPD P1NP	RCT
Moseley 2013 (22)	M & F 55 yrs +	52	60/90mmol/d	6 months	UCaExcr NAE CTX BAP	RCT 630mg/d calcium; 400IU vitamin D

Sakhaee 1983 (23)	M 42-69 yrs	5	60mEq/d	4 weeks	UCaExcr	Metabolic study. Subjects had uric acid lithiasis but adequate creatinine clearance.
Sakhaee 2005 (24)	PM 48-76 yrs	18	40mEq/d	14 days	UCaExcr NTX, CTX, Hydroxyproline Osteocalcin BAP	Randomised crossover study
Sellmeyer 2002 (25)	PM	60	90mmol/d	4 weeks	UCaExcr NAE NTX Osteocalcin	RCT Subjects on high Na diet (225mmol/d)

Studies comparing KHCO3 or KCitr with KCl

Study	Population	N	Dose/frequency	Duration	Relevant Outcome Measures	Additional information Study design; study conditions; additional supplements
Dawson-Hughes 2009 (14)	M & F 50 yrs+	77	67.5mmol/d $KHCO_3$ or KCl	84 days	UCaexcr NAE NTX Osteocalcin	RCT 600mg/d Ca triphospate; 525IU/d vitamin D
Frassetto 2000 (26)	M & F 50 yrs+	31	60mEq $KHCO_3$ or KCl	14 days	UCaexcr NAE	RCT 50mg/d HCTZ thiazide diuretic given to all subjects
He 2010 (16)	M & F 18-75 yrs	42	64mmol/d $KHCO_3$ or KCl	4 weeks	UCaexcr CTX, PYD, DPD Osteocalcin, BAP, P1NP	Crossover RCT Subjects had mild hypertension
Jehle 2006 (27)	PM <70 yrs	161	30mmol/d KCitr or KCl	12 months	LS BMD (DXA) PYR, DPD NAE	RCT 500mg/d $CaCO_3$; 400 IU/d vitamin D_3

Abbr. M male; F female; PM postmenopausal women; UCaExcr urinary calcium excretion; aLSBMD arial lumbar spine BMD; DXA dual-energy X-ray absorptiometry; vBMD volumetric BMD by pQCT; PYD pyridinoline; DPD deoxypyridinoline; HCTZ hydrochlorothiazide

Table 2: Risk of bias summary for included studies according to Cochrane Collaboration criteria (11)

("Low": study report supports judgement of low risk of bias;: *"unclear"*: insufficient information reported to indicate of low risk of bias)

Study	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Buehlmeier 2012 (12)	Unclear	Unclear	Unclear	Low	Low
Ceglia 2009 (13)	Low	Low	Low	Low	Low
Dawson-Hughes 2009 (14)	Low	Low	Low	Low	Low
Frassetto 2000 (26)	Unclear	Low	Low	Low	Low
Frassetto 2005 (15)	Unclear	Unclear	Unclear	Unclear	Low
He 2010 (16)	Low	Low	Low	Low	Low
Jehle 2006 (27)	Low	Low	Low	Unclear	Low
Jehle 2013 (21)	Low	Low	Low	Low	Low
Karp 2009 (20)	Unclear	Low	Unclear	Low	Low

Lemann 1989 (17)	Unclear	Unclear	Unclear	Low	Low
Macdonald 2008 (19)	Low	Low	Low	Low	Low
Moseley 2013 (22)	Low	Low	Low	Low	Low
Sakhaee 1983 (23)	Unclear	Unclear	Unclear	Low	Low
Sakhaee 2005 (24)	Low	Low	Low	Low	Low
Sebastian 1994 (19)	Unclear	Unclear	Unclear	Low	Low
Sellmeyer 2002 (27)	Low	Low	Low	Low	Low