

Phosphate decreases urine calcium and increases calcium balance: A meta-analysis of the osteoporosis acid-ash diet hypothesis

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Abstract

Background: The acid-ash hypothesis posits that the excretion of “acidic” versus “alkaline” ions derived from the diet, such as phosphate (PO_4), contribute to net acid excretion, calciuria, demineralization of bone, and osteoporosis. The objectives of this meta-analysis were to quantify the contribution of PO_4 to bone loss in healthy adult subjects; specifically, to assess the effect of PO_4 on a) urine calcium and calcium balance, and to assess whether these effects are altered by the b) level of calcium intake, c) the degree of protonation of the PO_4 and d) superior methodology for calcium balance studies.

Methods: Literature was identified through computerized searches regarding PO_4 with surrogate and/or direct markers of osteoporosis. Studies were assessed for methodological quality.

Results: Twelve studies including 30 interventions manipulated subjects' PO_4 intakes. Three studies reported net acid excretion. All of the meta-analyses demonstrated significant decreases in calciuria in response to PO_4 . Increased PO_4 intakes led to increased calcium retention. For a ten mmol increase of PO_4 intake, calcium retention increased by 0.28 mmol/day ($p < 0.001$). b) When analyses were stratified by calcium intake: For a ten mmol increase of PO_4 intake, calcium retention increased by 0.31 and 0.13 mmol/day, for low and high calcium intake studies, respectively ($p < 0.001$ & $p = 0.035$). c) When analyses were stratified by acidic and non-acidic PO_4 supplements: For a ten mmol increase of PO_4 intake, calcium retention increased by 0.31 and 0.21 mmol/day, respectively ($p = 0.115$ & $p < 0.001$). For the superior methodology analysis: for every 10 mmol increase of phosphate dose calcium balance increased by 1.03 mmol/day ($p < 0.001$).

Conclusions: All of the findings from this meta-analysis were contrary to the acid ash hypothesis. Higher PO_4 intakes were associated with decreased urine calcium and increased calcium retention. This meta-analysis did not find evidence that PO_4 contributes to demineralization of bone or to bone calcium excretion in the urine. Dietary advice that dairy products, meats, and grains are “acidic” due to PO_4 content and therefore detrimental to bone health needs reassessment.

Keywords: Osteoporosis, Nutrition, Acid-Base Equilibrium, Bone or bones, Phosphate, Calcium/urine, meta-analysis, systematic review

Background

Phosphate is generously supplied in the diet through meat, grains and dairy products, and in recent decades, increasingly it is added to foods as food additives [1], however, the understanding of dietary phosphate's role on bone health is not clear. While phosphate is a fundamental mineral component of hydroxyapatite, the principal structural element of bone, the acid-ash hypothesis posits that dietary phosphate, a marker of the metabolic production of acid, is detrimental to bone [2-4].

According to this acid-ash hypothesis, "acidic" ions such as phosphate contribute to the diet acid load, referred to as the renal acid load, which then the skeleton buffers, causing demineralization of bone and bone calcium excretion in the urine, leading to osteoporosis [2-4]. The acid-ash hypothesis proposes that osteoporosis is caused by the modern diet since the quantity of "acidic" ions (phosphate (PO_4^{3-}), sulfate (SO_4^{2-}), chloride (Cl^-) in the diet are greater than the quantity of "alkaline" ions (sodium (Na^+), potassium (K^+), calcium (Ca^{++}), and magnesium (Mg^{++})) [2-4]. Under the hypothesis, these ions are summed in the following equation to predict the potential renal acid load of the diet: $(1.8\text{PO}_4^{3-} + \text{SO}_4^{2-} + \text{Cl}^-) - (\text{Na}^+ + \text{K}^+ + 2\text{Ca}^{++} + 2\text{Mg}^{++})$ [2].

Although the acid-ash hypothesis has been widely accepted and broadly stated as the primary risk factor for bone health in well cited scientific papers [4,5], as well as textbooks [6], reference works [7,8], and lay literature, this hypothesis has not been subjected to critical review. In spite of little critical review, this hypothesis is heavily promoted to the public to consume the "alkaline diet" or commercial products via the internet and through salespeople.

Many of the foods in the modern diet are considered detrimental to bone health, under the acid-ash hypothesis, due partially to their phosphate contents. The foods purported to be detrimental to bone health under the hypothesis include meats, fish, dairy products [2,9-14], and grains [3,4,14], as well as many processed foods [3,4,14]. In contrast, this hypothesis posits that sodium is protective of bone health, which is not in agreement with concerns that sodium may compete with calcium for resorption in the kidney, and thus may compromise calcium metabolism

and bone health [15,16]. The foods that are considered to protect skeletal mineral under this hypothesis are fruit and vegetables since these foods supply organic molecules that are metabolized to bicarbonate and therefore are considered “alkaline” [2-4,14,17,18].

Although the quantity of excess urinary calcium excretion associated with the acid-load of the modern diet is of sufficient quantity that could, if it is not accompanied by decreased fecal losses, lead to the bone mineral loss of osteoporosis [19], however, acid-generating diets are not detrimental to whole body calcium balance [20]. This recent work raises doubt that the acid load of the modern diet contributes to the excretion of bone calcium and the development of osteoporosis.

Additional variables may influence the relationship between dietary phosphate intakes and bone health. Calcium intakes, that is whether calcium intakes are limited or insufficient, might influence the relationship between the diet acid load and bone health [21,22]. As well, the general concept of the acid-ash hypothesis is based on the “acidity” of the diet, therefore the degree of protonation of the ions in the foods (i.e. H_3PO_4 versus Na_2HPO_4) may be of importance and a meta-analysis provides an opportunity to assess this issue.

The purpose of this study is to use the techniques of meta-analysis to quantify the potential contribution of dietary phosphate toward the progression of osteoporosis, as measured by surrogate and, if possible, direct measures of this disease. Specifically, this study will assess the effect of supplemental dietary phosphate on a) urine calcium, b) calcium balance, and c) whether these affects are altered by the level of calcium intake of the subjects, d) the degree of protonation of the phosphate supplements, and on e) markers of bone metabolism.

Methods

Literature search for the systematic review

Literature relating to intervention studies of dietary phosphate supplementation on calcium metabolism was identified through computerized searches. We used four comprehensive search themes based on keywords/textwords, which were combined using the Boolean operators “OR”

within the themes and then “OR” and “AND” to combine the themes. The themes were related to phosphate (phosphorus, phosphate, phosphates), acid excretion (net acid excretion, acid-base equilibrium, acid excretion), bone health (bone, bones, bone density, bone mineral density, fractures, biopsy, bone resorption markers), calcium metabolism and excretion (calcium, calcium, calciuria, excretion, urine, urinary, balance, retention). The search was limited to adults 19+ years. Databases searched included Medline back to 1966 (OVID and PubMed), Cochrane Database of Systematic Reviews, CINAHL back to 1982, EMBASE back to 1980, the Cochrane Controlled Trials Register, and www.ClinicalTrials.gov, all up to January 2009. We developed our search strategy in PubMed and modified it for use in other databases. The literature search was not limited to English language articles or by study design. Reference lists were reviewed for additional relevant studies.

Selection criteria for the literature

Intervention studies were included if they manipulated human subjects' dietary phosphate intake through supplemental phosphate salts and reported outcomes related to urinary calcium excretion, calcium balance, and/or the development of osteoporosis (bone biopsy, change of bone mineral density (BMD) or fractures, bone resorption markers) in healthy adult subjects. Calcium balance was defined as calcium intake minus excretion (urinary plus fecal) [23]. Studies with an observational design were not included since they were likely to have confounded effects due to changes in protein, energy or calcium intakes, since these nutrients are correlated with phosphate in foods. Since the aim of this meta-analysis was to study the potential for the acid-ash diet hypothesis to have a role in the development of osteoporosis in apparently healthy adults, studies were restricted to adult subjects; we excluded studies of subjects with chronic conditions such as renal diseases or conditions which could alter calcium absorption or excretion such as inflammatory bowel disease or cancer.

Description of studies

The literature search identified 32 dietary phosphate intervention studies (Table 1). Twelve of the studies met all the inclusion criteria [21,24-34]. No non-English language papers met the criteria for acceptance. Since this study was designed to study conditions similar to the modern diet, we did not include two interventions, one in each of two included studies [27,31], since the subjects were provided very high calcium intakes (2700 & 2600 mg/day, 68 & 65 mmol/day), greater than the Tolerable Upper Limit of the Institute of Medicine Dietary Reference Intake for calcium [35], and therefore we considered them experimental.

Within the 12 included studies were 30 intervention trials (Table 2) with outcomes related to bone, calcium excretion and/or calcium balance. One of the studies included in this review [28] had other outcomes reported in a second paper [10]. The interventions assessed the effect of supplemental dietary phosphate salts on urine calcium over 24-hours in healthy adults administered orally [10,22,25-27,31-34,36-39] while one administered the phosphate intravenously [32] and calcium balance over one to 66 days. Some studies were not included since they: used study periods of less than 24 hours [38,40-43]; had more than one intervention performed [36,44-51]; reported no numerical results in the paper or in response to a written request [37,52,53]; had an observational design [54-56]; or the subjects had chronic conditions [22,39,57]. None of the studies assessed bone related outcomes such as changes in BMD, as measured using absorptiometry, or incidence of fractures. One study [25] included changes in BMD as measured using bone biopsies of the subjects while on supplemental phosphate, but did not report biopsy results during the control phase.

Phosphate was supplemented in all of the studies by providing a daily dietary phosphate salt, and some provided some additional sodium with the phosphate (Table 2). Two studies [29,32] controlled for changes in sodium intake from the phosphate supplement reducing NaCl when the sodium and phosphate were provided.

Methodological quality

The studies were assessed for the following indicators of methodological quality [58,59]: randomization to order of treatments, the recommendations of the Institute of Medicine's Panel on Calcium and Related Nutrients for calcium studies [35]. The Institute of Medicine recommends calcium balance studies control the subjects' calcium intakes for the seven or more days prior to measurement of the outcomes, provision of all the food to subjects, accurate measurement of the amounts consumed, and laboratory analysis to determine the nutrient composition of the food [35].

Regression analysis methods

Five meta-analyses were conducted to examine the effect of increasing daily dietary phosphate on urinary calcium excretion, calcium balance, and markers of bone metabolism. The effect of varying daily dietary phosphate doses on urinary calcium and calcium balance were assessed for, 1) all of the interventions, and then 2) stratified by calcium intakes and 3) stratified by the degree of protonation of the phosphate supplement. The fourth meta-analysis was 4) limited to studies with superior methodological quality. The fifth meta-analysis 5) the effect of phosphate supplementation on markers of bone metabolism (percent changes of hydroxyproline and N-terminal telopeptide of collagen). The stratification cut-point for the second meta-analysis was the calcium intake of greater or less than that intake considered adequate by the Institute of Medicine of 1000 mg/day (25 mmol/day) for adults aged 19 through 50 years; 1200 mg/day (30 mmol/day) for those aged 51 or older [35]. Phosphate supplements were stratified into acidic (e.g. H_3PO_4) and non-acidic (e.g. Na_2HPO_4) categories.

Since a total of twelve comparisons were made in this study, a Bonferroni correction was made to adjust the alpha level to compensate for the multiple comparisons [60].

Stata, Version 10.1 (StataCorp, College Station, Texas, USA), was used for the data analyses.

Results

All 30 of the interventions to increase dietary phosphate intake revealed a decrease in urine calcium, 16 of these changes were statistically significant [25-34], six were not significant [24,31],

six interventions in one study did not report statistical significance nor information that permitted statistical testing [21]. Of the 22 interventions of calcium retention, only one study [29] demonstrated a significant change in calcium balance from the phosphate supplement. The direction of this effect was a statistically significant increase in calcium retention in response to the dietary phosphate supplement [29].

Only three of the studies reported the phosphate induced change of net acid excretion [10,28,30,32]. All three studies noted increases in net acid excretion (45, 21, and 41 mEq/day) in response to the phosphate supplements of 49, 25, and 10 mmol/day, respectively.

Methodological quality

All of the interventions except one [24] noted that calcium intakes were controlled (Table 2). Three of the studies used a randomized study design (randomized cross-over) [21,33,34], while the remainder used non-randomized cross-over designs (Table 1).

The subjects consumed their usual calcium intakes in two studies [24,25] while the other subjects consumed a specified calcium intake for zero to 14 days prior to collecting outcome data. Eight of the 12 studies weighted the food intake of the subjects and analyzed identical portions for calcium content (Table1). Only one of the studies had superior methodology since it used both random methods and followed the recommendations of the Institute of Medicine's Panel on Calcium and Related Nutrients for calcium studies [21].

Regression analysis

For the inclusive meta-analysis, in which all studies were included, as phosphate dose increased, urinary calcium decreased. For every 10 mmol increase of dietary phosphate dose, urinary calcium decreased by 0.31 mmol/day in the inclusive analysis ($p < 0.001$, **Table 3 and Figure 1a**). In terms of calcium balance for the inclusive analysis, there was a statistically significant relationship between the phosphate dose and the change in calcium balance. For every 10 mmol increase of phosphate dose in the inclusive analysis, calcium retention increased by 0.28 mmol/day ($p < 0.001$, **Table 3 and Figure 1b**).

The same pattern of results was seen in the second meta-analysis, stratified by calcium intakes. For increasing phosphate doses there was a significant decrease in change of urine calcium and a significant increase in the change of calcium balance for both low and high calcium intakes (**Table 3 and Figures 2a**). For low and high calcium intakes, for every 10 mmol increase of phosphate dose, urinary calcium decreased by 0.30 and 0.41 mmol/day, respectively ($p < 0.001$ for both, **Table 3, Figure 2b**). In terms of calcium balance for the calcium intake stratified analysis, for every 10 mmol increase of phosphate dose, the change of calcium retention increased by 0.31 and 0.13 mmol/day, for the low and high calcium intake studies, respectively ($p < 0.001$ and $p = 0.035$, **Table 3 and Figure 2b**).

Similar results were seen among the third meta-analysis, stratified by whether the phosphate supplements were “acidic” versus neutral or alkaline. For both “acidic” and non-acidic phosphate supplements, for every 10 mmol increase of phosphate dose, urinary calcium decreased by 0.63 and 0.27 mmol/day, respectively ($p < 0.001$ for both, **Table 3, Figure 3a**). For the acidic phosphate supplements, phosphate supplementation caused a non-significant increase in the change of calcium balance ($p = 0.151$, **Table 3 and Figure 3b**). For increasing non-acidic phosphate supplements, there was a significant increase in the change of calcium balance ($p < 0.001$) (**Table 3 and Figures 3b**). The quantity of calcium balance change for the acidic and non-acidic phosphate supplements stratified analysis, for every 10 mmol increase of phosphate dose, the change of calcium retention increased by 0.31 and 0.21 mmol/day, respectively ($p = 0.115$ and $p < 0.001$, **Table 3 and Figure 3b**).

Fourth, for the analysis of superior methodology, only one study qualified by our *a priori* criteria, which was randomized subject allocation to the interventions and to have the subjects consume the calcium intake for seven days prior to the measurement of the outcome [21]. For the analysis of superior methodology, there was a statistically significant inverse relationship between the dietary phosphate dose and urinary calcium ($p < 0.001$). For every 10 mmol increase of phosphate dose, urinary calcium decreased by 0.41 (**Table 3 and Figure 4a**). In terms of calcium

balance for the superior methodology analysis, there was a statistically significant relationship between the phosphate dose and the change in calcium balance ($p < 0.001$). For every 10 mmol increase of phosphate dose in the superior study, the change of calcium increased by 1.03 mmol/day ($p < 0.001$, **Table 3 and Figure 4b**).

Markers of Bone Metabolism

The change of phosphate intake on the change of bone markers, hydroxyproline and N-terminal telopeptides, did not appear to have straight line relationships (**Figure 5a & 5b**), so no attempt was made to combine this data in regression analyses. Bell reported an increase in hydroxyproline of 20% [26] in response to phosphate supplementation, while three studies reported decreases between 5 and 20% [28-30] (**Figure 5a**). For the N-telopeptide results, in response to the phosphate supplements in the first interventions by both Whybro et al and Kemi et al saw slight but non-important decreases (-5.3% and -1.5%), while Kemi et al's high dose phosphate dose increased N-telopeptide by 29% ($p = 0.05$) (**Figure 5b**) [33,34].

The Bonferroni correction did not change the statistical significance of any test except for the calcium balance regression for high calcium intakes, which became non-significant upon correction ($p = 0.035 \times 12 = 0.42$).

Discussion

All of these meta-analyses demonstrated that when dietary phosphate was increased, calcium balance increased, and all of the increases in calcium balance were statistically significant except one. Whether calcium intakes were high or low, and whether the phosphate supplement was acidic or not, phosphate supplementation decreased urine calcium excretion and increased calcium balance. The phosphate supplements induced net acid excretion, but calcium excretion was lower with the higher net acid excretion. All of the findings of this study contradict the acid ash hypothesis.

To improve accuracy of calcium balance studies, the Institute of Medicine recommends that subjects should consume the study calcium intake for at least a week prior to the outcome measurement when calcium balance studies do not keep the subjects on their habitual calcium intake [35]. This recommendation is designed to allow the subjects to adapt to experimental calcium intake which is important to lessen the chance that the adaption confuses or biases the effect of the intervention [35]. Randomization of the interventions is very important in cross-over studies of calcium balance since the adaptations would be uneven in the two arms of before-after non-randomized cross-over studies.

Overall, the methodological quality of the studies of phosphate supplementation was poor since only one of the studies used superior methodology [21]: both randomization and the Institute of Medicine's recommendations for calcium balance studies. Therefore, there is a chance that the results of the other studies are biased due to poor methodology. The magnitude of this bias would vary depending on whether the study calcium intakes were greater or less than the subjects' usual intakes. In spite of the questionable methodological quality, all of the other meta-analyses were in congruence with the one study [21] that used superior methodology, which suggests that the bias may not have been severe.

Most of the evidence in favor of the acid-ash hypothesis is based on the outcomes of changes of urinary calcium and changes of bone mineral markers [2,5,10,12,13,28,61-65]. Both of these outcomes, urinary calcium and bone mineral markers, are not direct measures of osteoporosis. Changes in calcium balance are much better measures of changes of calcium status than changes of urinary calcium, particularly when the studies are well designed [35]. Changes in urine calcium excretion are poor surrogate measures of osteoporosis, as intestinal calcium absorption [66] and/or secretion [67] may precede renal losses. The National Institutes of Health Consensus Panel defined Osteoporosis as "... a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture" [68]. The only currently available and clinically valid osteoporosis outcome measures that address bone strength are low trauma

fractures and or biomechanical testing of bone biopsy material [69,70]. Bone density provides a significant component of bone strength, but is not considered an adequate outcome measure in the assessment of osteoporosis treatments.

Two randomized controlled studies of the acid ash hypothesis have used changes of BMD as the outcome measure [71,72]. BMD is a more direct measure of osteoporosis than urine calcium, but only a partial measure of bone strength [68]. Both of these studies tested the BMD response to potassium citrate [71,72] and one of these studies also increased fruit and vegetable intakes in an additional study arm [72]. The results of these studies were opposite, one observed a decreased loss of spine BMD among the potassium citrate arm [71], while the other study BMD change did not differ significantly between study arms [72]. In terms of study rigor, the latter study reported adequate allocation concealment [72] while the former did not [71]. Inadequate allocation concealment is associated with a 41% overestimation of effect [73], therefore it is possible that the results from the former trial [71] overestimated the effect of potassium citrate on bone.

Two recent prospective cohort studies have used fractures as the outcome measure. Fractures are considered a direct and clinically valid measure of osteoporosis [69,70]. A study among 1865 vegetarian and omnivorous peri- and postmenopausal women found that the risk of wrist fracture decreased significantly as protein intakes increased, whether the protein was from plants or meat [74]. This study provides further support for the concept that dietary protein is supportive of bone health [75,76]. A French study among 36,217 women examined the association between protein or the diet acid load on fractures (excluded high trauma or metastases fractures) found no overall support for the acid ash hypothesis as neither protein nor the diet acid load were associated with fracture risk [77]. However, in a subgroup analysis, both higher protein intake and diet acid load were associated with higher fracture risk [77]. In comparison, in this meta-analysis we found no real difference between phosphate intakes and calcium metabolism between those with low or high calcium intakes.

Both the findings of this meta-analysis and the other recent studies with better outcomes for the assessment of osteoporosis (change of BMD and fractures) do not support the acid-ash hypothesis [72,74,77] [78].

The acid-ash hypothesis posits that meats, grains and dairy products are detrimental to bone health due to their phosphate contents [2,6] [3,4,14], however, this meta-analysis revealed that higher dietary intakes of phosphate do not increase urinary calcium excretion or whole body calcium loss. Further to question the acid ash hypothesis, the evidence regarding higher net acid excretion from changes in dietary protein type or amount does not support the hypothesis [78]. No studies have evaluated the effect of grain foods on bone health. Dairy products are an important dietary calcium source [79] and an inexpensive source of high quality protein. Considering that this study has not upheld the concept that higher intakes of phosphate are detrimental to bone mineral maintenance, the consideration of meats, grains and dairy products as detrimental to bone health on the basis of their phosphate content must be questioned. Additionally, these foods are important sources of nutrients that are important for bone health, including calcium [80] (dairy products), protein [81,82] (dairy products and meats), and vitamin D [83] (some dairy products).

Concern has been raised about the phosphate, as well as caffeine, contents of cola soft drinks and their potential deleterious effects on bone health. Observational studies that measured BMD [84] or asked subjects about previous fractures [85] in relation to carbonated beverage intake documented associations between these beverages and poorer bone health. As well, a non-randomized cross-over intervention study identified higher bone resorption markers from colas compared to milk [86]. The results from this meta-analysis does not support the concept that the phosphate in soda is deleterious, therefore, these potentially deleterious effects could be due to lower milk consumption, and therefore protein, calcium or other nutrient intakes [86] since those that consume more carbonated beverage drink less milk [87,88], however generalizations from the studies on soft drinks are limited by the study designs used.

This meta-analysis has three strengths: First, this is the first study to systematically assess the calcium balance literature in response to changes of phosphate supplementation. Second, this meta-analysis includes an evaluation of methodological quality, and therefore an assessment of potential confounding or bias. Third, the stratified analyses allowed assessment of the effect of calcium intakes and the degree of protonation of the phosphate supplement on the findings.

This meta-analysis also has limitations. First, calcium balance is neither a direct measure of bone health nor of the progression of osteoporosis, but rather it is a surrogate measure of this disease; therefore our meta-analysis is not definitive regarding the association between phosphate intake and osteoporosis. Second, this study is limited by the poor methodological quality of the majority of the studies of phosphate intake on surrogate measures, and the lack of direct measures on bone health.

In conclusion, this meta-analysis revealed that raising phosphate intakes decreases urine calcium and slightly increases calcium retention over a broad range of calcium intakes. This work does not support the acid-ash hypothesis concepts that “acidic” ions such as phosphate contribute to demineralization of bone and bone calcium excretion in the urine, or that an “alkaline diet” is health promoting. A definitive study is needed that follows all of the recommendations for methodological quality for both calcium balance studies [35] as well as recommendations for intervention studies [58,89], with measurement of outcomes that are direct measures of bone strength, to determine whether or not there is an association between phosphate intake and osteoporosis.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

The author's responsibilities were as follows: TRF & AWL designed the study, TRF searched the literature, extracted the data, performed the statistical analysis and graphic representation and wrote the manuscript, ME directed the study's statistical analysis and graphic representation, AWL contributed to data analysis and writing of manuscript, SCT & DAH helped design the study and interpret the findings. All authors read and approved the final manuscript.

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Figures

Figure 1: The relationships between change in phosphate dose and calcium metabolism. Change in phosphate dose with change in urine calcium (Figure 1a) and change in calcium balance (Figure 1b).

Figure 2: The relationships between change in phosphate dose with change in urine calcium and change in calcium balance. Stratified by calcium intakes: Figure 2a: Change of phosphate dose with change in urine calcium Figure 2b: Change of phosphate dose with change in calcium balance; Low calcium intakes: -----; High calcium intakes: ———.

Figure 3: The relationships between change in phosphate dose with change in urine calcium and change in calcium balance. Stratified by “acidic” versus “non-acidic” phosphate supplements: Figure 3a: Change of phosphate dose with change in urine calcium Figure 3b: Change of phosphate dose with change in calcium balance; “Acidic” phosphate supplement: ———; “Non-acidic” phosphate supplement:-----.

Figure 4: The relationships between change in phosphate dose with change in urine calcium and change in calcium balance. Superior methodology: Figure 4a: Change of phosphate dose with change in urine calcium Figure 4b: Change of phosphate dose with change in calcium balance.

Figure 5: The relationships between change in phosphate dose and change bone metabolism markers: Figure 5a: hydroxyproline, Figure5b: N-telopeptides.

Tables

Study	Year	Subjects	Study design	Food weighted	Food lab analysis	Usual Calcium intake
Patton [21]	1953	young women	RCO	yes	yes	no
Malm [24]	1953	male prisoners	CO	yes	yes	yes
Goldsmith [25]	1976	postmenopausal women with osteoporosis	CO	no	no	yes
Bell [26]	1977	young adults	CO	yes	yes	no
Spencer [27]	1978	adult men	CO	yes	yes	no
Hegsted [28]	1981	adult males	CO	yes	yes	no
Zemel [29]	1981	young men	CO	yes	yes	no
Schuetz [30]	1982	young men	CO	yes	yes	no
Spencer [31]	1986	adult males	CO	yes	yes	no
Whybro [33]	1998	healthy men	RCO	no	no	no
Kemi [34]	2006	young women	RCO	no	no	no
Krapf [32]	1995	young men	CO	no	no	no

Table 1: Included studies in the meta-analysis of calcium balance from a change of phosphate intake

Study	n	Phosphate dose (mmol/day)	Phosphate source	Calcium Intake (mmol/day)	Days on Calcium intake*	Days on each balance study after adaption**	Change uCalcium (mmol/day)	Change Calcium balance (mmol/day)
Patton [21]	18	10	Na ₂ HPO ₄ & Na glycerophosphate	9	7	7	-0.4	-0.2
Patton [21]	18	19	"	9	7	7	-1.0	0.6
Patton [21]	18	10	"	24	7	7	-0.4	-0.6
Patton [21]	18	19	"	24	7	7	-1.5	0.3
Patton [21]	18	10	"	39	7	7	-1.0	0.03
Patton [21]	18	19	"	39	7	7	-0.4	1.1
Malm [24]	4	24	H ₃ PO ₄	-	98	7	-0.9	n/a
Malm [24]	2	32	H ₃ PO ₄	11	98	28	-0.7	0.7
Malm [24]	4	26	H ₃ PO ₄	20	98	28	-0.9	0.1
Malm [24]	2	19	H ₃ PO ₄	13	56	56	-1	0.03
Goldsmith [25]	7(4)	32	K ₂ H & KH ₂	21	7+	4	-0.9	0.45
Bell [26]	5	37	Na PolyP	18	6	22	-1.7	n/a
Spencer [27]	10	37	Na glycerophosphate	5	0	22	-0.8	0.03
Spencer [27]	8	37	Na glycerophosphate	21	0	40	-1.7	0.70
Spencer [27]	3	39	Na glycerophosphate	36	0	34	-2.3	-0.35
Spencer [27]	6	36	Na glycerophosphate	50	0	31	-2.1	0.10
Heagsted [28]	8	49	KH ₂ PO ₄	13	0	12	-2.5	0.94
Zemel [29]	8	32	KH ₂ PO ₄	10	2	11	-2.0	2.7
Zemel [29]	8	32	(NaPO ₃) ₆	10	2	11	-2.0	1.3
Schuetz [30]	8	25	KH ₂ PO ₄	15	2	6	-0.9	0.03
Spencer [31]	1	35	Na glycerophosphate	6	0	66	-3.2	0.5
Spencer [31]	4	34	Na glycerophosphate	20	0	42	-3.0	1.3
Spencer [31]	2	41	Na glycerophosphate	34	0	33	-3.6	0.00
Spencer [31]	3	40	Na glycerophosphate	51	0	40	-3.5	0.2
Whybro [33]	9	32	NaH ₂ PO ₄	25	5	2	-1.1	n/a
Whybro [33]	11	48	Not stated	25	5	9	-2.4	n/a
Kemi [34]	14	8	Na ₂ Na ₃ HPO ₄	6	0	1	-0.2	n/a
Kemi [34]	14	24	Na ₂ Na ₃ HPO ₄	6	0	1	-0.5	n/a
Kemi [34]	14	48	Na ₂ Na ₃ HPO ₄	6	0	1	-0.5	n/a
Krapf [32]	6	9.6	IV PO ₄ vs Cl	35.02	4	3	-3.5	n/a

Table 2: Study control of calcium intakes, phosphate dose, urine calcium and calcium balance outcomes

* days on calcium intake prior to the measurement of outcomes

** the shortest number of days on the balance study is reported if it varied within the comparison interventions

	Analysis	Change of urine calcium from phosphate	Change of calcium balance from phosphate
1	Inclusive analysis	$B_1 = -0.031$ 95% CI for $B_1 = -0.038$ to -0.024 $p < 0.001$ $R^2 = 0.216$ $n = 269$	$B_1 = 0.028$ 95% CI for $B_1 = 0.020$ to 0.036 $p < 0.001$ $R^2 = 0.196$ $n = 192$
2	Low calcium intakes	$B_1 = -0.030$ 95% CI for $B_1 = -0.038$ to -0.022 $p < 0.001$ $R^2 = 0.270$ $n = 153$	$B_1 = 0.031$ 95% CI for $B_1 = .019$ to 0.043 $p < 0.001$ $R^2 = 0.202$ $n = 106$
2	High calcium intakes	$B_1 = -0.041$ 95% CI for $B_1 = -0.053$ to -0.029 $p < 0.001$ $R^2 = 0.292$ $n = 112$	$B_1 = 0.013$ 95% CI for $B_1 = .001$ to 0.026 $p = 0.035$ $R^2 = 0.052$ $n = 86$
3	“Acidic” phosphate supplement	$B_1 = -0.063$ 95% CI for $B_1 = -0.075$ to -0.051 $p < 0.001$ $R^2 = 0.774$ $n = 36$	$B_1 = 0.031$ 95% CI for $B_1 = -0.008$ to 0.069 $p = 0.115$ $R^2 = 0.081$ $n = 32$
3	“Non-acidic” phosphate supplement	$B_1 = -0.027$ 95% CI for $B_1 = -0.035$ to -0.019 $p < 0.001$ $R^2 = 0.168$ $n = 233$	$B_1 = 0.021$ 95% CI for $B_1 = 0.014$ to 0.029 $p < 0.001$ $R^2 = 0.163$ $n = 160$
4	Analysis of superior methodology study	$B_1 = -0.041$ 95% CI for $B_1 = -0.057$ to -0.025 $p < 0.001$ $R^2 = 0.192$ $n = 108$	$B_1 = 0.103$ 95% CI for $B_1 = 0.090$ to 0.115 $p < 0.001$ $R^2 = 0.707$ $n = 108$

B_1 = slope coefficient for regression analysis

R^2 = the proportion of variance explained by the regression analysis

Table 3: Regression analysis results



Fig 1a: All included studies: Effect of PO₄ dose on Urine calcium

Figure 1

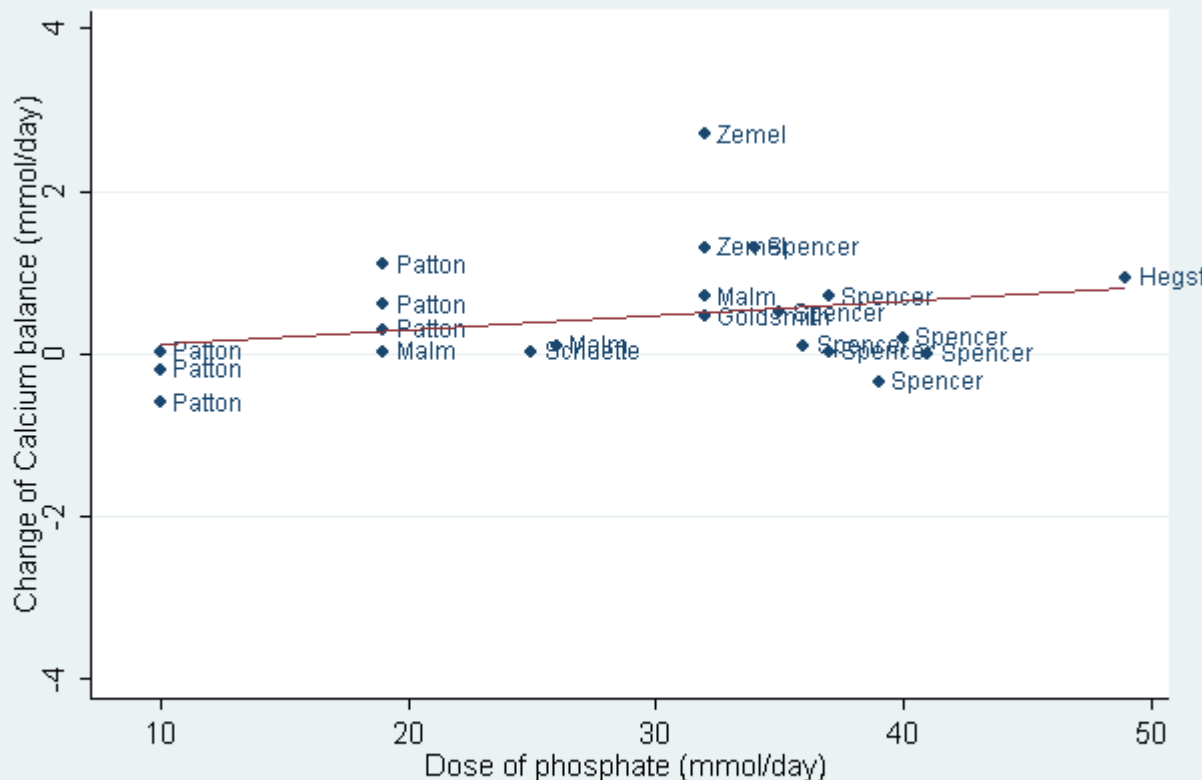


Fig 1b: All included studies: Effect of PO₄ dose on Calcium balance

Figure 2

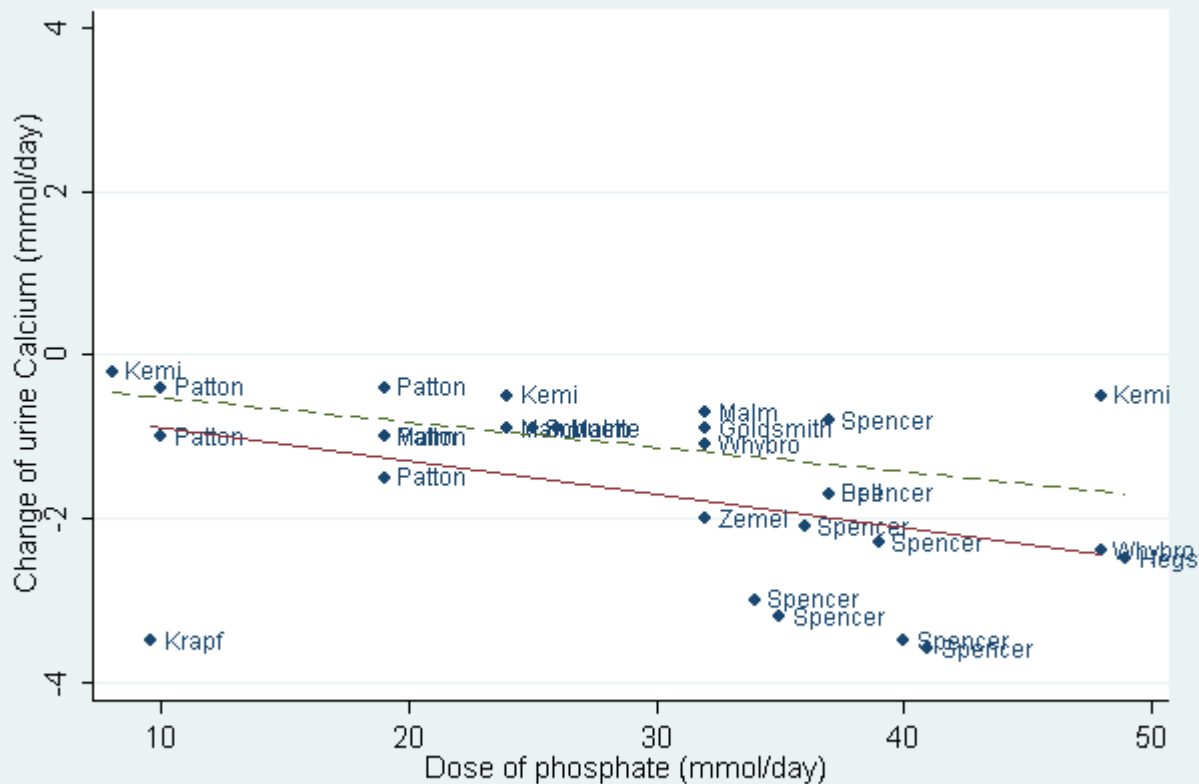


Fig 2a: Effect of PO₄ dose on Urine calcium: Stratified by Calcium intake

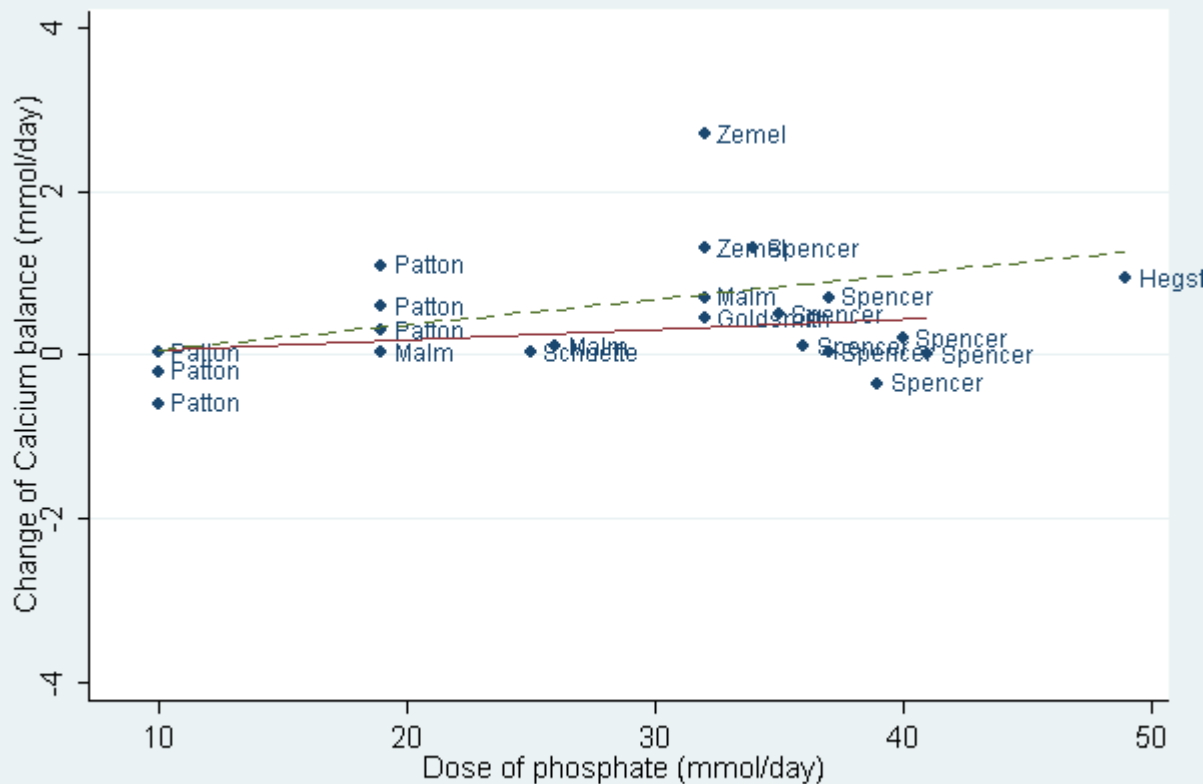


Fig 2b: Effect of PO₄ dose on Calcium balance: Stratified by Calcium intake

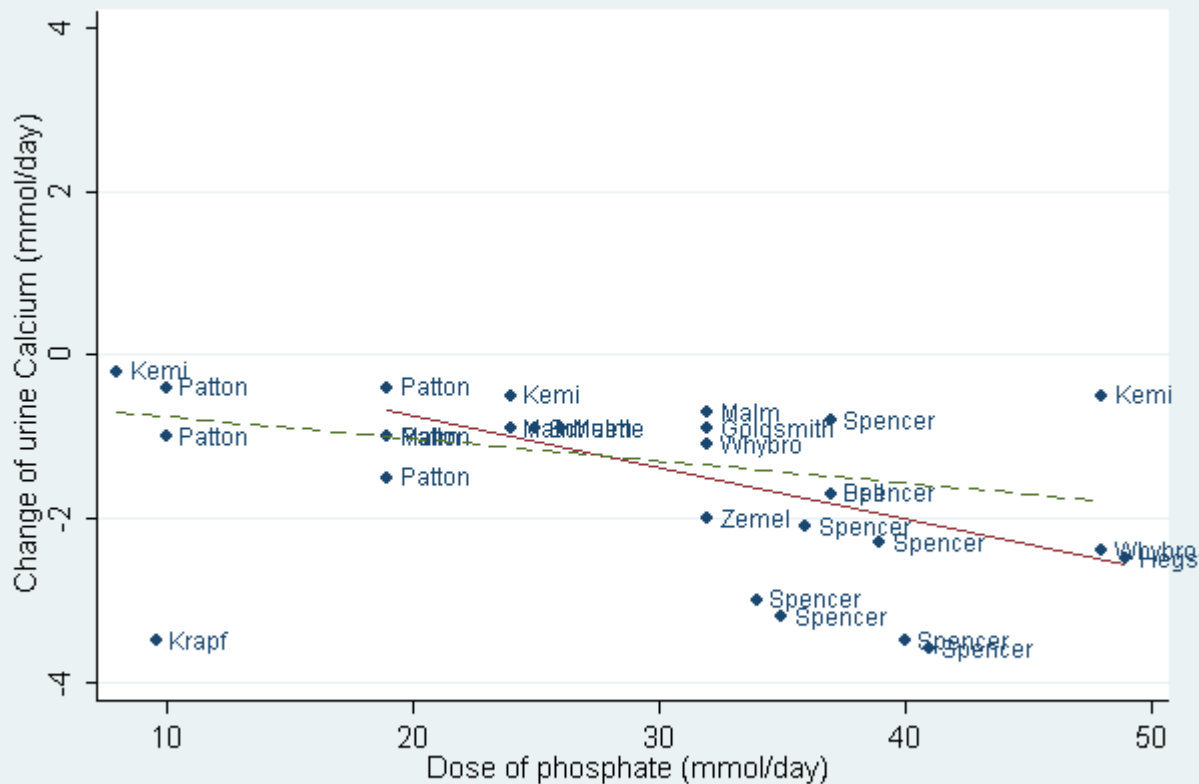


Fig 3a: Urine calcium: Stratified by "acidity" of PO₄ supplement

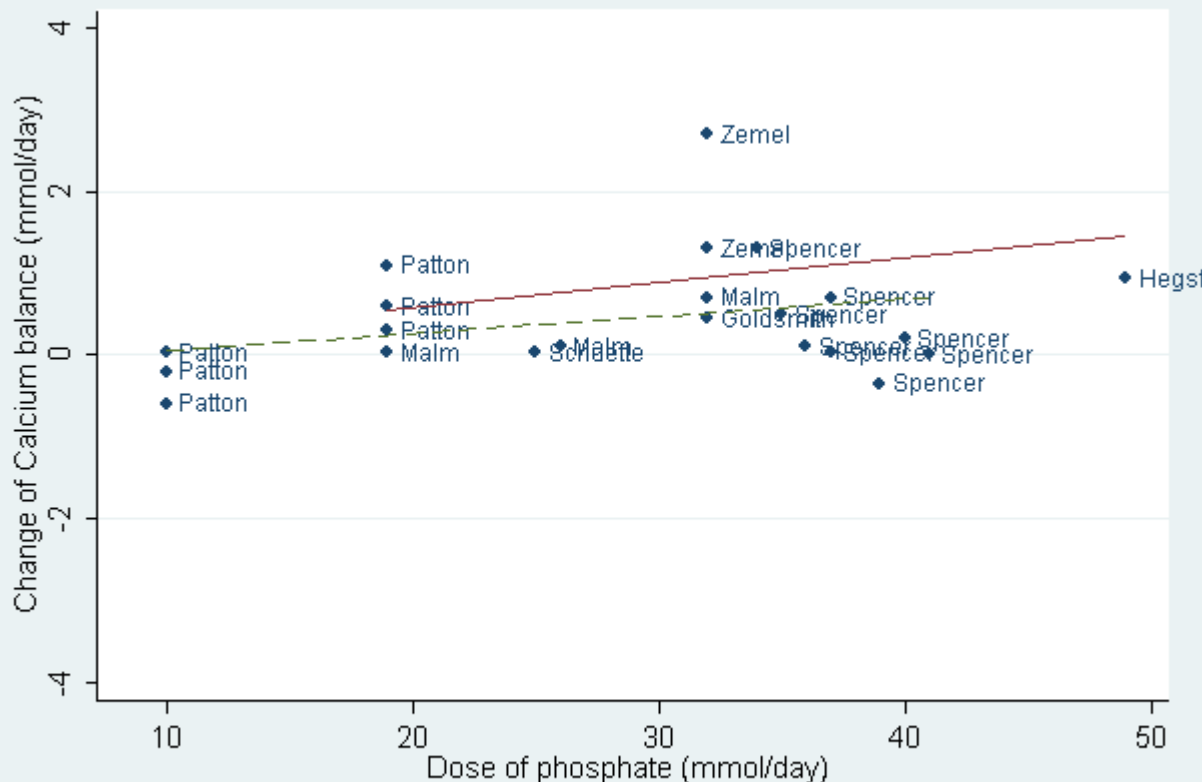


Fig 3b: Calcium balance: Stratified by "acidity" of PO₄ supplement

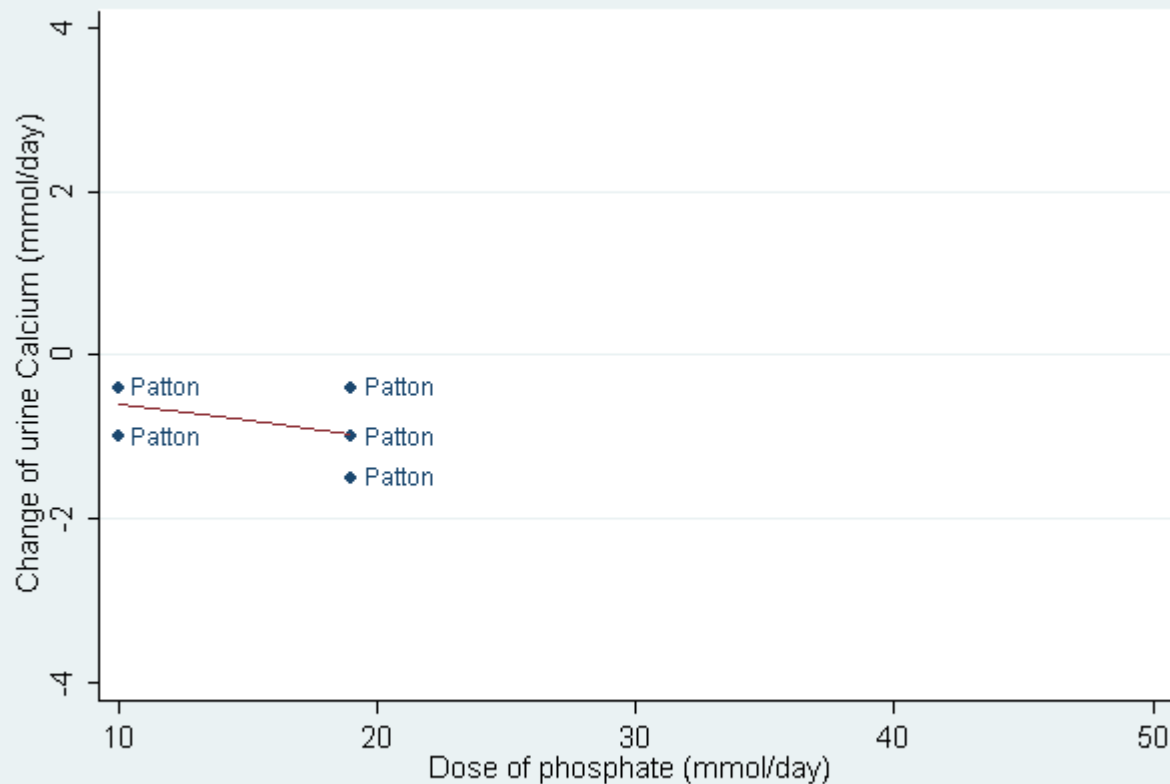


Fig 4a: Superior quality studies: Effect of PO₄ dose on Urine calcium

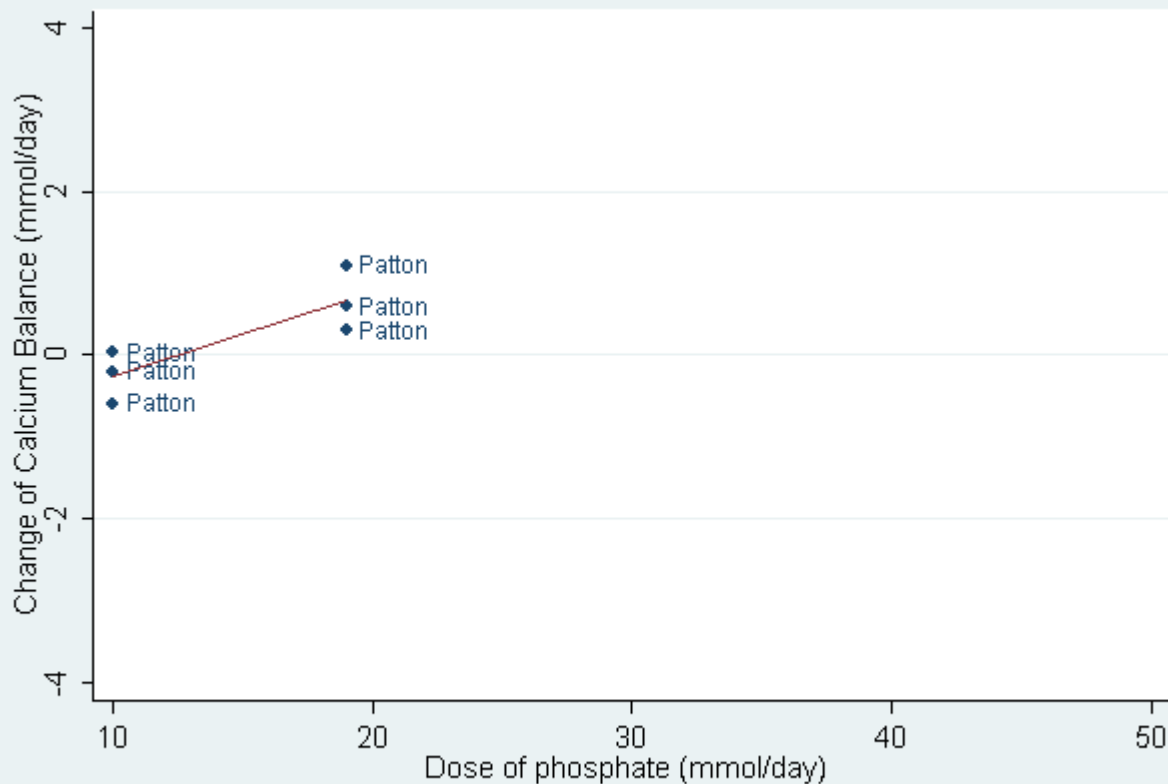


Fig 4b: Superior quality studies: Effect of PO₄ dose on Calcium balance

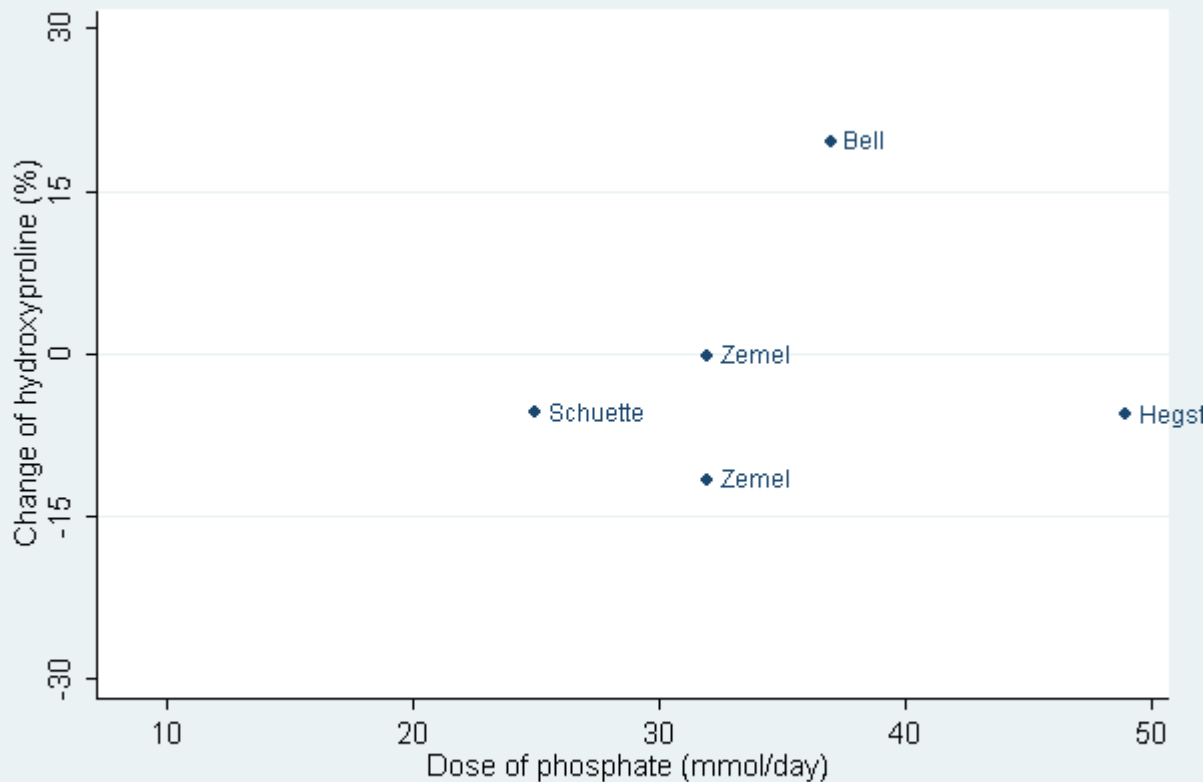


Fig 5a: Effect of PO₄ dose on hydroxyproline

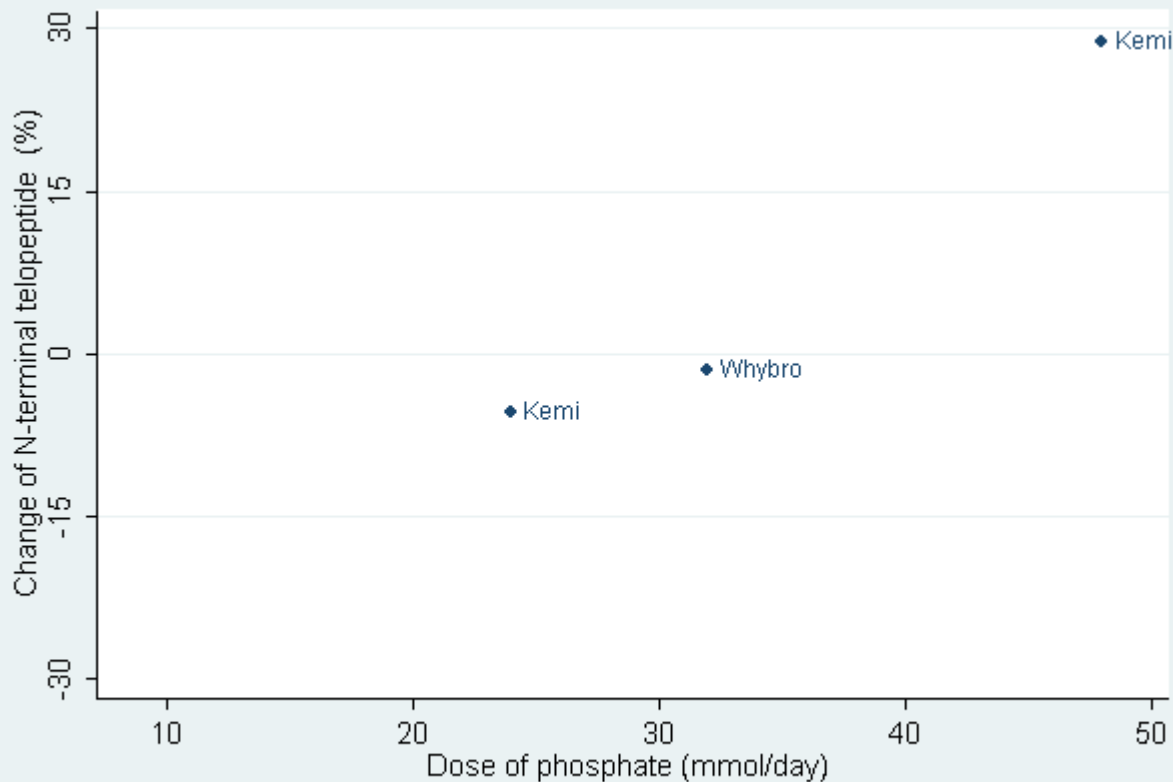


Fig 5b: Effect of PO₄ dose on N-telopeptides