Original Article

Parathyroid Hormone Replacement versus Oral Calcium and Active Vitamin D Supplementation in Hypoparathyroidism: A Meta-analysis

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Abstract

Objectives: Chronic hypoparathyroidism is treated conventionally with active vitamin D and high doses of calcium. Recombinant human parathyroid hormone (PTH) replacement is an attractive option for treating patients with hypoparathyroidism since it can replace the physiological action of native PTH. The aim of our study was to perform a comprehensive evaluation of the effects of PTH replacement on calcium homeostasis, bone metabolism, and daily requirement of calcium and active vitamin D. **Materials and Methods:** Randomized controlled trials done in chronic hypoparathyroid patients were included in this meta-analysis. The PTH group included subjects receiving a subcutaneous injection of either PTH (1-84) or PTH (1-34) with oral calcium and/or active vitamin D. The control group included those receiving oral calcium and active vitamin D with/without subcutaneous placebo injection. The primary outcome of this meta-analysis was to compare serum calcium, 24-h urinary calcium, and severe adverse effects among PTH and control groups. **Results:** In this meta-analysis, we did not find any difference in serum calcium level between PTH and control groups [mean difference (MD) -0.01; 95% confidence interval (CI) -0.09, 0.06; $P = 0.71$]. Although there was a trend towards low 24-h urinary calcium in the PTH group, the difference was not statistically significant (MD -1.43; 95% CI -2.89, 0.03; $P = 0.06$). The incidence of serious adverse events was also similar in both groups (RR 1.35; 95% CI 0.58, 3.16; $P = 0.49$). **Conclusion:** Both PTH and active vitamin D therapies are associated with comparable serum and urine calcium levels with a similar incidence of serious adverse events in patients with chronic hypoparathyroidism.

Keywords: Active vitamin D, calcitriol, calcium, hypoparathyroidism, parathyroid hormone

Introduction

Chronic hypoparathyroidism is a rare disorder characterized by hypocalcemia and hyperphosphatemia. Although it can be due to various etiologies like genetic, autoimmune, or infiltrating diseases, majority of these patients are post-surgical.[1] Tetany, seizure, and laryngospasm due to hypocalcaemia are important acute complications of hypoparathyroidism which can contribute towards significant morbidity of the patients. Chronic hypoparathyroidism can also lead to long-term complications like nephrocalcinosis, nephrolithiasis, reduced renal function, and intracerebral calcification. Until recently, chronic hypoparathyroidism was treated conventionally with active vitamin D and high doses of calcium. However, this conventional treatment[2] is not physiological and leads to significant variability in serum calcium and hypercalciuria, which adversely affects the kidney. It does not have any significant beneficial effect on long-term comorbidities like altered bone metabolism.[3] Conventional treatment often requires large doses of calcium and active vitamin D to maintain serum calcium, leading to substantial pill burden and poor quality of life.[4] Moreover,

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_579_19

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Submitted: 31-Oct-2019 **Revised:** 16-Dec-2019
Accepted: 07-Jan-2020 **Published:** 30-Apr-2020

How to cite this article: Palui R, Das RR, Roy A, Kamalanathan S, Kar SS, Sahoo J, *et al.* Parathyroid hormone replacement versus oral calcium and active vitamin D supplementation in hypoparathyroidism: A meta-analysis. Indian J Endocr Metab 2020;24:206-14.

when hypoparathyroidism is associated with malabsorptive disorders (autoimmune polyendocrine syndrome type 1), oral supplementations with calcium and vitamin D are less effective.[5]

Recombinant human parathyroid hormone (PTH) replacement is an attractive option for treating patients with hypoparathyroidism since it can replace the physiological action of native PTH. Over the last few years, many studies have evaluated the effect of PTH replacement on hypoparathyroidism using both the full-length peptide PTH (1-84) and also its N-terminal fragment PTH (1-34).[6-13] US FDA has approved the use of recombinant PTH (1-84) in 2015 for chronic hypoparathyroidism patients excluding those with autosomal dominant hypocalcemia.[14] Effectiveness of PTH (1-84) is comparable to PTH (1-34) in relation to calcium homeostasis[15] and it has got conditional approval in Europe in 2017.[16]

Although a previous meta-analysis[17] reported the effect of PTH on serum calcium, phosphorus, 25-hydroxy vitamin D [25(OH)D], 1,25-dihydroxy vitamin D [1,25$(OH)_2$D], and 24-h urinary calcium excretion, it did not assess the effect of PTH replacement therapy on bone mineral density and bone turnover markers. Reduction in the requirement of calcium and active vitamin D doses were also not assessed in the previous meta-analysis. More-over both adult and pediatric populations were included together in that meta-analysis, which may not be appropriate. The grades of evidence were also not assessed in the meta-analysis. Therefore, we had planned to perform a comprehensive evaluation of the effects of PTH replacement on calcium homeostasis, bone metabolism, and daily requirements of calcium as well as active vitamin D.

Materials and Methods

This meta-analysis was conducted in accordance with the predefined protocol registered in PROSPERO (Registration number CRD42017067452).[18] Reporting of this meta-analysis was done as per PRISMA guideline.[19] As ethical approval already exists for the individual studies included in the meta-analysis, no separate approval was required.

Search strategy

To identify the eligible studies, the following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed/MEDLINE, Google Scholar, and EMBASE. We also searched for unpublished trial results in the US National Institutes of Health, Department of Health and Human Services trials registry[20] and the WHO International Clinical Trials Registry Platform (ICTRP).[21] The search terms used were "hypoparathyroidism"; "Recombinant Parathyroid Hormone"; "rhPTH"; "PTH (1-34)"; "teriparatide"; "PTH (1-84)"; "natpara". The search strategy is given in Supplemental Table 1. All the databases were searched from their date of inception till 31st July 2018. The literature available in English language was only evaluated. The references of selected studies were also manually searched to identify additional relevant studies.

Inclusion of articles

Randomized controlled trials (RCTs) done in adult chronic hypoparathyroid patients were included in the analysis. Observational studies, reviews, case series, and case reports were excluded. Studies done in children, patients with severe liver disease, any disease or drugs affecting mineral metabolism, patients receiving PTH therapy by continuous subcutaneous infusion, and pregnant or lactating women were excluded. At the initial stage of study selection, abstracts of the studies were screened independently by two of the authors (RP and AR) to identify potentially eligible studies. Subsequently, full texts of the screened articles were examined thoroughly to identify the studies meeting the selection criteria. Consensus following disagreement about eligibility of the studies was reached by discussion with another author (JPS).

Data extraction

Two of the authors (RP and AR) extracted the data from the included studies in a standardized predesigned format. Following study characteristics were extracted: author names, institution(s), number of participating centers, study design, number of patients, and duration of the study. All the data were extracted from text, tables, or figures of the article. When data were not available in the text or table, it was extracted from the figures. For missing data, the corresponding authors of the included studies were contacted and the raw data if provided were included in analysis. Any discrepancy between the two authors was resolved by discussion with a senior author (SKK). Data of the following parameters were extracted: serum calcium (mmol/l), 24-h urinary calcium (mmol/day), serious adverse effects, urinary creatinine clearance (ml/min), serum phosphorus (mmol/l), 25(OH)D (nmol/l), 1,25$(OH)_2$D (pmol/l), serum osteocalcin (ng/ml), urinary deoxy-pyridinoline (nmol/mmol of creatinine), bone mineral density (BMD) at the lumbar spine (g/cm^2), BMD at femoral neck (g/cm^2), dose of oral calcium (g), dose of oral active vitamin D (μg), and proportion of subjects with successful withdrawal of active vitamin D.

Risk of bias

We have included only RCTs in this meta-analysis. The bias risk was determined according to the standards laid down by Cochrane handbook of meta-analysis.[22] The following domains of the RCTs were identified to assess the risk of bias: sequence generation, allocation concealment, blinding of participants, blinding of assessor, incomplete outcome data, selective reporting, and other bias. Risk of bias was ascertained by two authors independently (RD and SS). Any discrepancy was sorted out after discussion with another author (AS).

Specifications of outcomes

The primary outcome of this meta-analysis was to compare serum calcium, 24-h urinary calcium, and serious adverse effects among PTH and control groups. The PTH group

included subjects receiving a subcutaneous injection of either PTH (1-84) or PTH (1-34) with titrated oral calcium and/or active vitamin D. The control group included oral calcium and active vitamin D with/without subcutaneous placebo injection. The serious adverse effects and their possible relation with the therapy were defined as per the categorization done by the primary authors of the included articles. The secondary outcomes of this study were to determine differences in the following parameters between the two groups: urinary creatinine clearance, serum phosphorus, serum 25(OH)D, serum $1,25(OH)_2D$, serum osteocalcin, urinary deoxy-pyridinoline, BMD at lumbar spine and femoral neck, change in oral calcium and active vitamin D dose, and proportion of subjects with successful withdrawal of active vitamin D after therapy with recombinant PTH.

Statistical analysis

The statistical analysis for this pooled data meta-analysis was done by RevMan5.3 (Review Manager) software.[23] For continuous outcomes like serum calcium, 24-h urinary calcium, urinary creatinine clearance, serum phosphorus, 25(OH)D, $1,25(OH)_2D$, osteocalcin, deoxy-pyridinoline, BMD, change in oral calcium and active vitamin D requirement, mean difference (MD) with 95% confidence interval (CI) were calculated. For dichotomous outcomes like serious adverse effects and successful withdrawal of active vitamin D, risk ratio (RR) with 95% CI were calculated by Mantel-Haenszel methods. Random effect model was used for the calculation of effect size with the assumption that the true effect size varies from study to study as the studies were done from different background. Heterogeneity was analyzed by standard I^2 statistics. P value of <0.05 was considered statistically significant. Subgroup analysis, sensitivity analysis, and meta-regression could not be done because of less number (only four) of eligible studies. We have used GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess the quality of generated evidence.[24]

Results

Search and selection of studies

The summary for the selection of eligible studies is depicted in the PRISMA-flow chart [Figure 1]. After an initial screening of abstracts of 4081 articles, 31 studies were selected in the first stage. From these 31 studies, four studies were finally included in this meta-analysis based on the selection criteria as mentioned above. Rest of the studies were excluded because of the following reasons: study done in children;[10] prospective design or unrelated population[11-13,25-36]; duplication of data[37,38]; comparison of different PTH doses[39-41]; evaluation of cost-effectiveness of PTH therapy[42]; and use of either pump therapy or continuous subcutaneous PTH infusion.[5,43-46]

Study characteristics and quality assessment

The summary of the included studies[6-9] is described in Table 1. All the included studies were RCTs, of which one was cross-over trial and the rest were parallel-arm studies. The studies were published between 1996 and 2013. Two studies were from United States and one was from Europe. The REPLACE trial was a multicentric trial involving several countries.[6] Out of the four studies, two[6,7] used PTH (1-84) and two used PTH (1-34).[8,9] The etiologies of hypoparathyroidism were different among the studies. The assessment of the study quality based on the risk of bias is summarized in Supplemental Table 2.

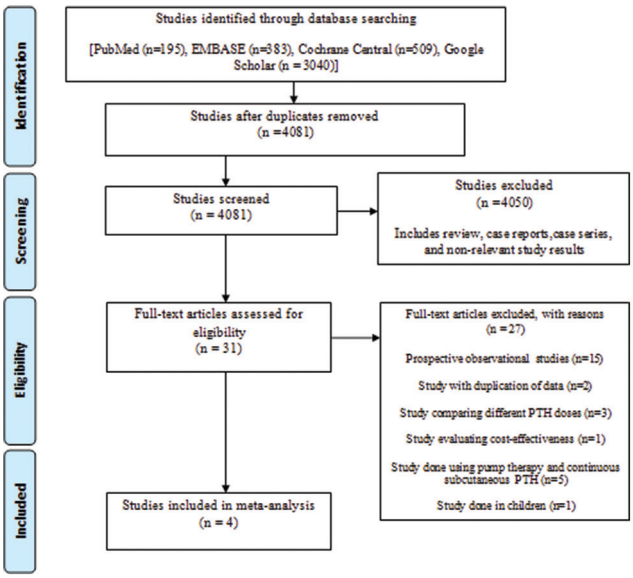

Figure 1: PRISMA flow chart of the study selection process

Heterogeneity analysis

Heterogeneity was detected for serum calcium ($I^2 = 72\%$), 24-h urinary calcium ($I^2 = 81\%$), creatinine clearance ($I^2 = 69\%$), serum phosphorus ($I^2 = 90\%$), serum 25(OH)D level ($I^2 = 31\%$), serum $1,25(OH)_2D$ level ($I^2 = 42\%$), osteocalcin ($I^2 = 90\%$), urinary deoxy-pyridinoline level ($I^2 = 40\%$), BMD spine ($I^2 = 51\%$), BMD femoral neck ($I^2 = 25\%$), and change in active vitamin D requirement ($I^2 = 91\%$). No heterogeneity ($I^2 = 0\%$) was found in the incidence of serious adverse effects, requirement of daily calcium, and incidence of complete withdrawal of oral active vitamin D requirement.

Baseline characteristics of the patients

Totally, 233 patients were included in this meta-analysis. As ten patients were in a randomized cross-over trial,[8] they are included in both PTH and control groups for effect size calculation in forest plots. The mean age of the patients was in the range of 40–52 years. The mean duration of hypoparathyroidism was in the range of 9–19.5 years and 40%–86% of patients were females in these studies. Among the etiologies of the hypoparathyroidism, post-surgical hypoparathyroidism was the most common (40%–94%). A total of 122 (83.56%) patients received PTH (1-84) and rest of the 24 (16.44%) patients received PTH (1-34).

Primary outcomes

In this meta-analysis, we did not find any difference in serum calcium level between PTH and control groups (MD -0.01;

Table 1: Characteristics of included studies

Author (year)	Mannstadt *et al.*[6] (2013)	Sikjaer *et al.*[7] (2011)	Winer *et al.*[8] (1996)	Winer *et al.*[9] (2003)
Type of study	Double-blind, placebo-controlled, randomized, phase 3 study	Double-blind, placebo-controlled, randomized study	Randomized, cross-over trial	Randomized, parallel group, open-label trial
Total Study duration	24 weeks	24 weeks	20 weeks (10 weeks in each arm)	3 years
Study place (number of centers)	33 outpatient sites in eight countries: USA (20), Canada (3), Denmark (3), Hungary (3), Belgium (1), France (1), Italy (1), and the UK (1)	Outpatient clinics in Denmark	Bethesda, Maryland	Bethesda, Maryland
Female (%)	78 (*n*=105)	86 (*n*=53)	40 (*n*=4)	62.96 (*n*=17)
Age (mean±SD) (years)	47·5±12.71	52±12	45.4±4.57	40.74±15.43
Duration of disease (mean±SD) (years)	13±10.29	9±9	19.5±4.32	14.7±11.59
Iatrogenic etiology (%)	74	94	40	40.7
PTH group	rhPTH (1-84) 50-100 µg OD + Calcium + active vitamin D	rhPTH (1-84) 100 µg OD + Calcium + active vitamin D	rhPTH (1-34) OD (0.5 to 3 µg/kg per day) + dietary elemental calcium 1-2 g/day	rhPTH (1-34) BD (37±2.6 µg/dose) + dietary elemental calcium 1 g/day
Control group	Placebo+Calcium+active vitamin D	Placebo + Calcium + active vitamin D	calcitriol (0.5 to 6 µg/d) + 1 g calcium carbonate+dietary elemental calcium 1-2 g/day	Calcitriol BD (0.91±0.2 µg/d) + calcium (1000 mg/day) +dietary elemental calcium 1 g/day
No. of patients in PTH/ control group	90/44	32/30	10/10	14/13
Duration of follow up (weeks)	24	24	10	156

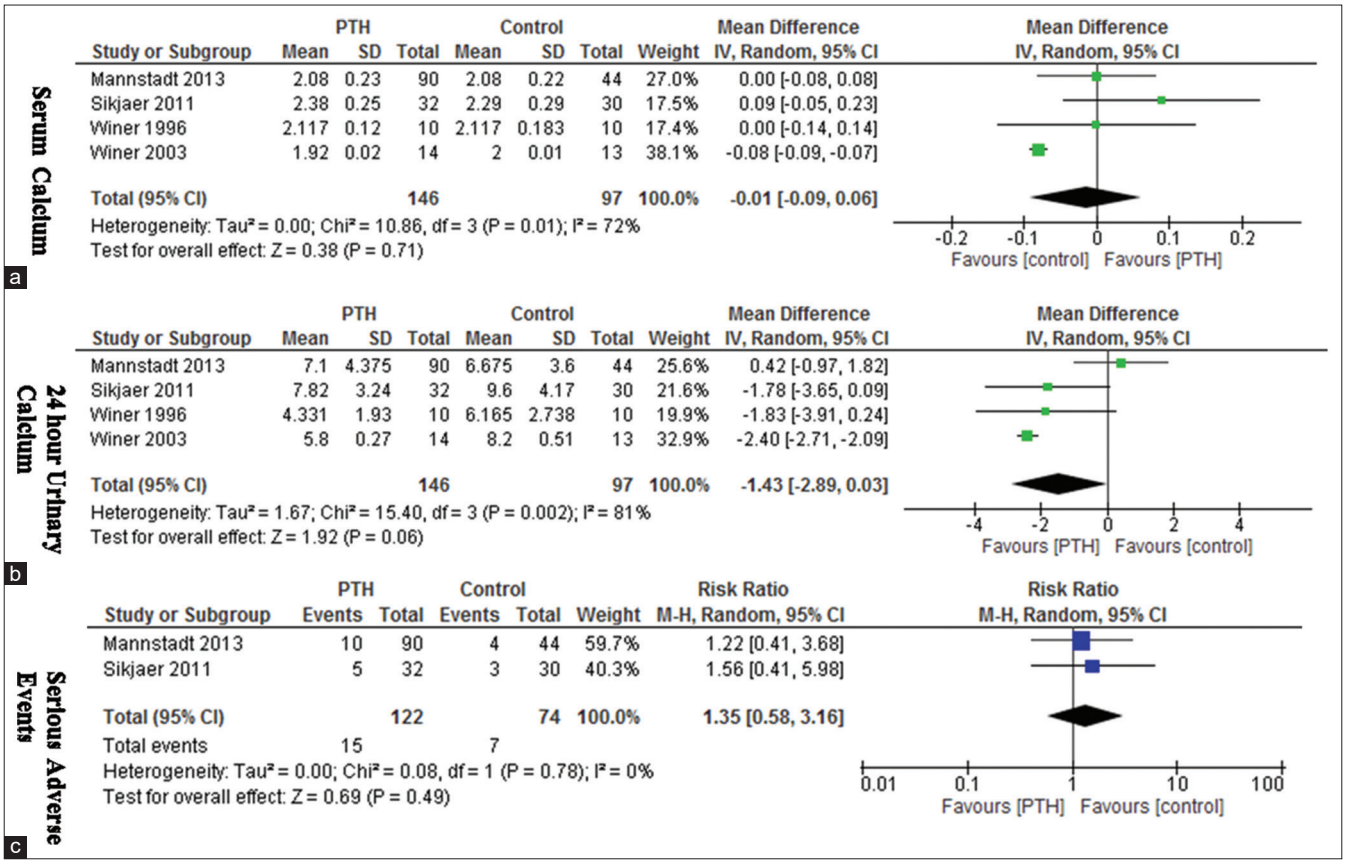

Figure 2: Forest plots showing primary outcomes (serum calcium, 24-h urinary calcium, and serious adverse effects). (a) Forest plot comparing serum calcium between PTH and control arms. (b) Forest plot comparing serum 24-h urinary calcium between PTH and control arms. (c) Forest plot comparing serious adverse events between PTH and control arms

95% CI -0.09, 0.06; P = 0.71) [Figure 2a]. Although there was a trend towards low 24-h urinary calcium in PTH group, the difference was not statistically significant (MD -1.43; 95% CI -2.89, 0.03; P = 0.06) [Figure 2b]. The incidence of serious adverse effects was also similar in both groups (RR 1.35; 95% CI 0.58, 3.16; P = 0.49) [Figure 2c].

Secondary outcomes

Urinary creatinine clearance was available for analysis only from two studies. There was no difference in urinary creatinine clearance between the two groups (MD -3.49; 95% CI -21.05, 14.07; P = 0.70) [Figure 3a]. There was no difference in serum phosphate levels in between two groups (MD -0.04; 95% CI -0.11, 0.03; P = 0.26) [Figure 3b]. The serum 25(OH)D level was lower in the PTH group (MD -13.54; 95% CI –21.94, -5.14; P = 0.002) [Figure 3c]. However, no difference in serum $1,25(OH)_2D$ level was found between the two groups (MD 6.21; 95% CI –4.75, 17.16; P = 0.27) [Figure 3d].

Serum osteocalcin level was increased in PTH treated patients (MD 52.42; 95% CI 6.42, 98.43; P = 0.03) in comparison to controls [Figure 4a]. Similarly, urinary deoxy-pyridinoline level was higher in PTH group (MD 42.58; 95% CI 8.31, 76.86; P = 0.01) [Figure 4b]. However, there was no difference in BMD of spine (MD -0.05; 95% CI -0.17, 0.07; P = 0.46) [Figure 4c] and femoral neck (MD 0.00; 95% CI –0.07, 0.07; P = 0.92) between the two groups [Figure 4d].

The required dose of oral active vitamin D and calcium was reported in only two studies. Although not statistically significant, there was a trend towards the decreased requirement of active vitamin D in PTH group (MD -0.73; 95% CI –1.55, 0.08; P = 0.08) [Figure 5a]. Active vitamin D was completely withdrawn from more patients in PTH group (RR 8.85; 95% CI 2.58, 30.35; P = 0.0005) [Figure 5b] and the requirement of daily calcium was significantly lower in PTH group (MD -0.95; 95% CI –1.21, -0.70; P < 0.00001) [Figure 5c]. The overall grades of evidence are of low or very low quality in this meta-analysis (Supplemental Table 3). Funnel plot (Supplemental Figure 1) showed visual asymmetry and was suggestive of possible publication bias.

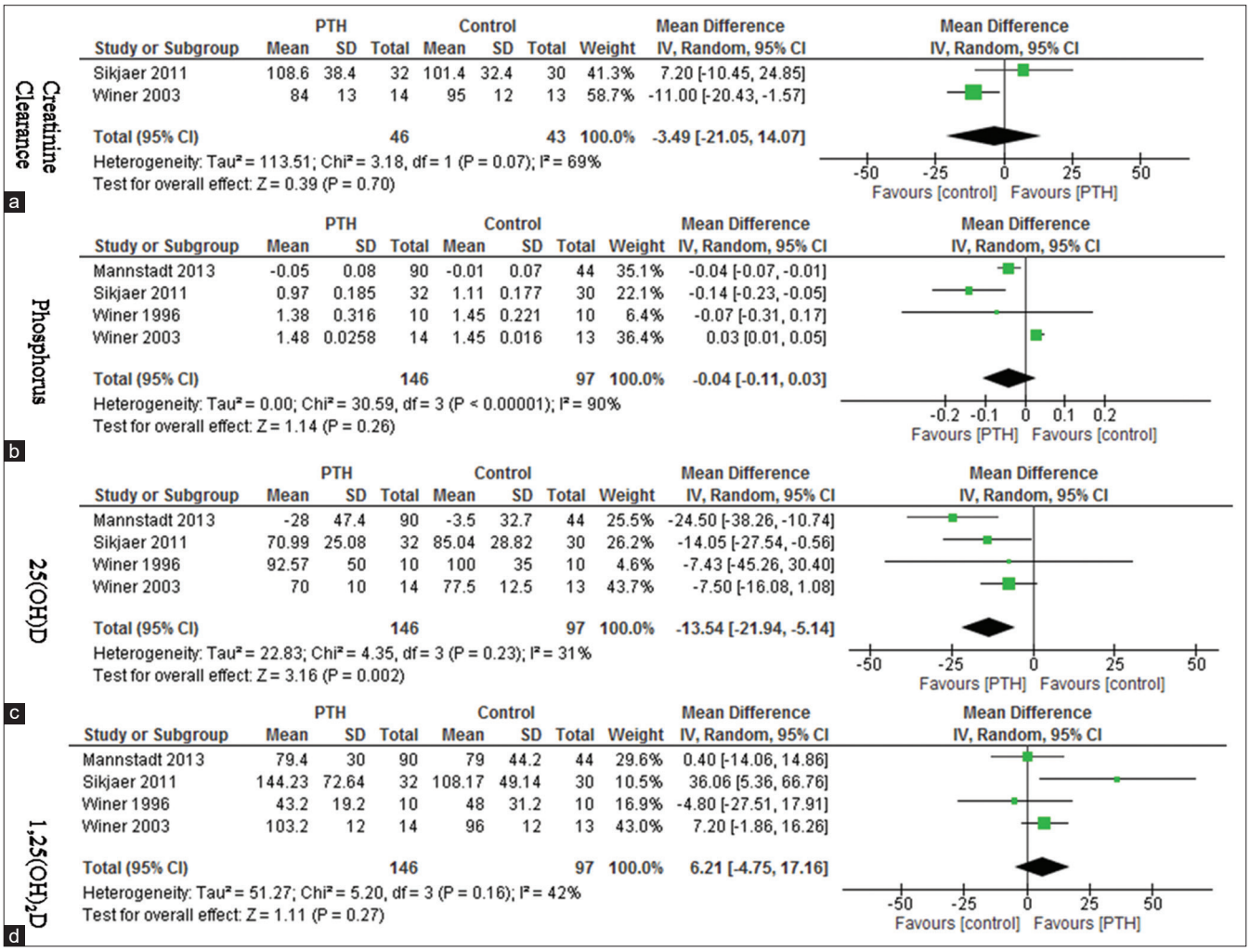

Figure 3: Forest plots showing secondary outcomes (urinary creatinine clearance, serum phosphorus, 25(OH)D, and 1, $25(OH)_2D$). (a) Forest plot comparing urinary creatinine clearance between PTH and control arms. (b) Forest plot comparing serum phosphorus between PTH and control arms. (c) Forest plot comparing serum 25(OH)D between PTH and control arms. (d) Forest plot comparing serum 1, $25(OH)_2D$ between PTH and control arms

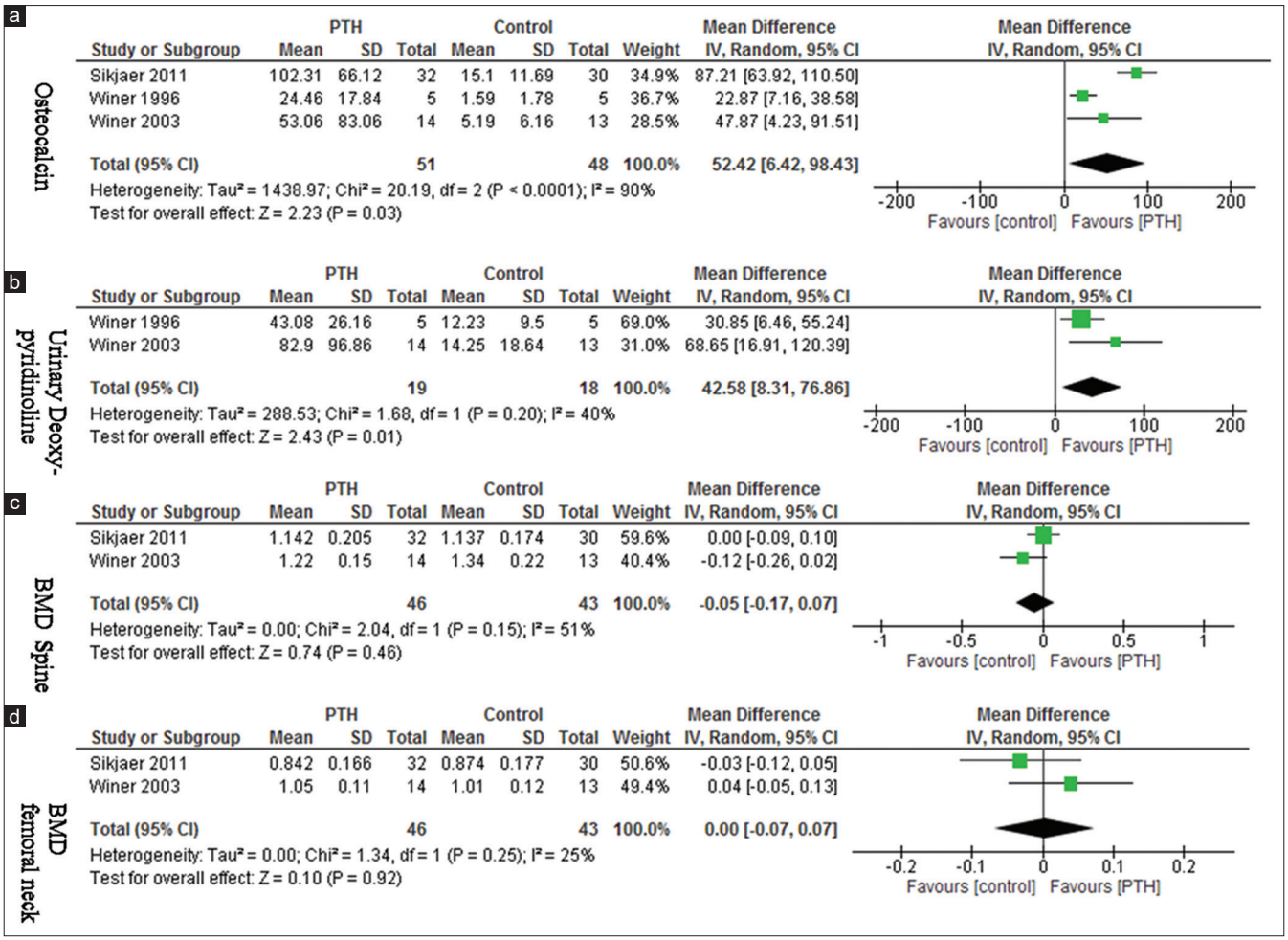

Figure 4: Forest plots showing secondary outcomes (serum osteocalcin, urinary deoxy-pyridinoline, bone mineral density (BMD) at the lumbar spine and BMD at femoral neck). (a) Forest plot comparing serum osteocalcin between PTH and control arms. (b) Forest plot comparing urinary deoxy-pyridinoline between PTH and control arms. (c) Forest plot comparing BMD spine between PTH and control arms. (d) Forest plot comparing BMD femoral neck between PTH and control arms

Discussion

This meta-analysis evaluated the effect of recombinant PTH replacement therapy in adult patients with chronic hypoparathyroidism. We did not find any significant difference in serum calcium level between PTH and control groups. Hence, PTH can be used as an alternative to conventional treatment without causing hypercalcaemia and its related adverse effects in chronic hypoparathyroid patients. The absence of hypercalcemic and hypophosphatemic effect of PTH may be due to the study protocol of simultaneous reduction of active vitamin D and calcium dose in two of the included studies[6,7] and titrated dose of PTH in other two studies.[8,9]

Our analysis also revealed that there is no difference in 24-h urinary calcium excretion in between the two groups. Although the expected result in PTH treated patients is to have a decrement in the 24-h urinary calcium, there are several possible hypotheses to explain our finding. First, most of the studies have used daily single dose of rhPTH, which does not allow sufficient and sustained exposure of renal tubule to PTH leading to less effective renal tubular calcium reabsorption. In the study by Winer *et al.*,[43] the use of continuous infusion pump in hypoparathyroid patients resulted in marked decrease in 24-h urinary calcium, which supports the notion of the need for sustained PTH exposure to decrease 24-h urinary calcium. Second, transient hypercalcemia resulting from a peak concentration of circulating PTH after daily PTH injection can lead to increased urinary excretion of calcium. In the study done by Sikjaer *et al.*,[47] there was a correlation between serum calcium and urinary calcium excretion following a single 100 μg PTH (1-84) injection. Studies by Winer *et al.* evaluating continuous subcutaneous PTH therapy using insulin pump also showed reduced fluctuation of calcium in blood in comparison to daily large dose of subcutaneous injection, leading to less urinary calcium excretion.[43,46] Lastly, the protocol of concurrent decrease in the calcium and active vitamin D intake in two of the included studies may be the reason behind the absence of any significant difference of urinary calcium excretion between the two arms. Lack of any

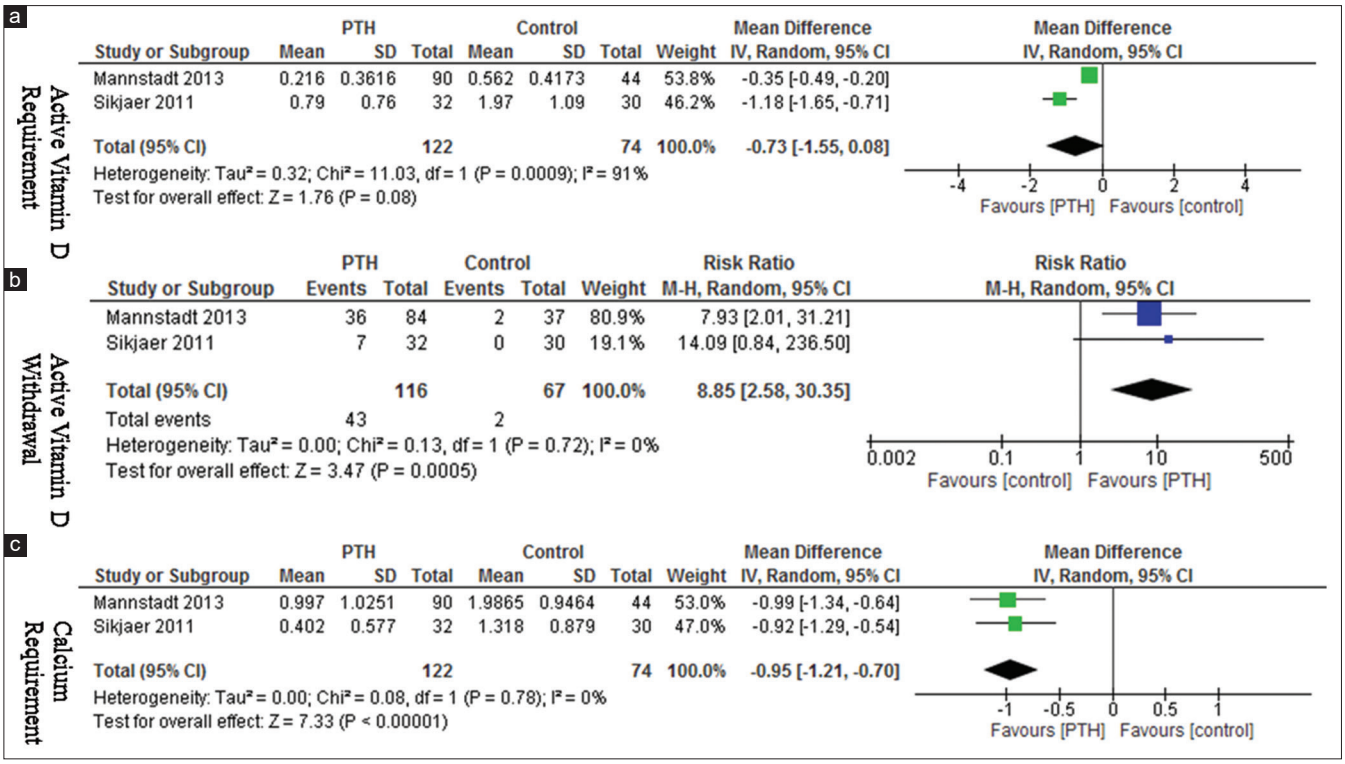

Figure 5: Forest plots showing secondary outcomes (dose of oral active vitamin D, proportion of subjects with successful withdrawal of active vitamin D, and dose of oral calcium). (a) Forest plot comparing oral active vitamin D requirement between PTH and control arms. (b) Forest plot comparing successful withdrawal of oral active vitamin D requirement between PTH and control arms. (c) Forest plot comparing oral calcium requirement between PTH and control arms

difference in urinary calcium excretion can also explain our finding of comparable urinary creatinine clearance in both groups.

We could not find any difference in 1,25(OH)$_2$D level between the two groups, but PTH treated patients had significantly lower 25(OH)D levels. As PTH stimulates 1-alpha-hydroxylase (CYP27B1) enzyme in the renal tubules, 25(OH)D levels are expected to be low due to its conversion to 1, 25(OH)$_2$D.[48] Moreover, PTH can directly decrease 25(OH)D by increasing its catabolism through activation of 24-hydroxylase (CYP24A1) enzyme in certain cells, like osteoblast.[48] The low serum 25(OH)D level could be related to the reduction in calcium supplementation in PTH arm because vitamin D3 was included in the calcium tablets. Hence, precaution has to be taken to keep 25(OH)D levels within the normal range in these patients. Lack of difference in 1,25(OH)$_2$D in between two groups is likely due to concurrent intake of active vitamin D in patients with conventional therapy (control).

The dose of required calcium was significantly reduced in patients on PTH therapy. Similarly, active vitamin D was completely withdrawn in significantly more number of patients in PTH group. This reduced requirement in PTH arm while maintaining serum calcium was due to increased production of 1, 25(OH)$_2$D in renal tubules and hypercalemic action of PTH hormone on other tissues like bone and kidney. In our meta-analysis, the data regarding the reduction of active vitamin D and calcium supplementation were not available in the studies with PTH (1-34).[8-10] However, in the study by Santonati *et al.*[12] in post-surgical patients, treatment with PTH (1-34) (20 µg sc twice daily) also showed a significant reduction in calcitriol and calcium dosing after 6 months of therapy. Our analysis suggested that PTH treated patients had 8.85 times more chances of successful withdrawal of active vitamin D. Thus, PTH therapy is likely to reduce the pill burden in chronic hypoparathyroidism patients.

As bone remodeling rate is stimulated by PTH, patients with chronic hypoparathyroidism characteristically have low bone turnover markers and increased bone mass.[3,49] In our meta-analysis, there is a significant increase in both osteocalcin and urinary deoxy-pyridinoline in the PTH treated group. PTH therapy, when given as intermittent injections, significantly increases the level of bone turnover markers (BTMs). The levels remained higher than the baseline even when followed up for 6 years in the study by Rubin *et al.*[13] However, when PTH therapy was given as a continuous infusion by pump, normalization of BTMs was observed.[46]

The effect of PTH replacement on BMD has been variable and different factors like dose, duration, type of PTH and associated calcium/vitamin D intake influence BMD. On the other hand, conventional therapy with only calcium and active vitamin D does not have any effect on bone metabolism

in hypoparathyroid patients. Our meta-analysis showed no difference in either spine or femoral neck BMD in PTH-treated patients as compared to conventional treatment. This may be due to the relatively short duration of the PTH therapy in the studies included in our meta-analysis. On the contrary, PTH therapy given for a longer duration of 6 years as in the study by Rubin *et al.*[13] showed increase in BMD at lumbar spine by 3.8 ± 1%, with no change of BMD at femoral neck. This is explained by the different response of cortical and cancellous bones to PTH therapy.

The incidence of serious adverse events was similar between the two groups as mentioned in two earlier studies.[6,7] There were a total of 15 events in PTH and 7 events in placebo groups. However, only three serious adverse events were considered as treatment-related. Two subjects with hypercalcemia and one patient with hypocalcaemia in PTH (1-84) group required hospitalization. The majority of the serious adverse effects (pancreatitis, cardiovascular accident, diarrhea, erysipelas, psychosis, femoral artery occlusion, surgery, and anaphylactic reactions) were not related to PTH therapy. Analysis of other adverse events could not be done as it was not systematically reported in the included studies.

In the previous meta-analysis by Liu *et al.*[17], five RCTs involving both adult and pediatric populations were included and the effect on five parameters (serum calcium, phosphate, 25(OH)D, $1,25(OH)_2D$ and 24-h urinary calcium) were analyzed. The over-all findings in these five parameters were similar to our findings. However, on subgroup analysis, significantly low 24-h urinary calcium and serum phosphate were reported in PTH (1-34) and PTH (1-84) subgroup, respectively. The strength of our meta-analysis is a comprehensive analysis of the effect of PTH therapy on the fourteen parameters including biochemical parameters, bone metabolism, serious adverse effects, and requirement of calcium and active vitamin D supplementation. We have also assessed the grade of evidence (GRADE) and our meta-analysis was prospectively registered in PROSPERO.

However, our meta-analysis has certain limitations. First, many of the parameters assessed had significant heterogeneity. This increased heterogeneity may be due to the difference in the study protocols, type of PTH used (1-34 PTH in 2 studies and 1-84 PTH in the other 2 studies) and differences in the etiology of hypoparathyroidism. Less number of available RCTs leading to possible publication bias is another limitation of our study. Lastly, the overall quality of the generated grades of evidence is low in this meta-analysis.

Conclusion

To conclude, both PTH and calcium with/without active vitamin D and conventional therapy with calcium and active vitamin D are associated with comparable serum and urine calcium levels with a similar incidence of serious adverse effects in adults with chronic hypoparathyroidism. However, the requirement of calcium and active vitamin D pills is less in PTH group.

Acknowledgements

We sincerely thank Dr. Tanja Sikjaer for responding to our queries and sharing the required data with us.

The manuscript was presented as a poster on 19th October 2019 in 15th annual conference of Indian Society for Bone and Mineral Research (ISBMR) held at Bengaluru.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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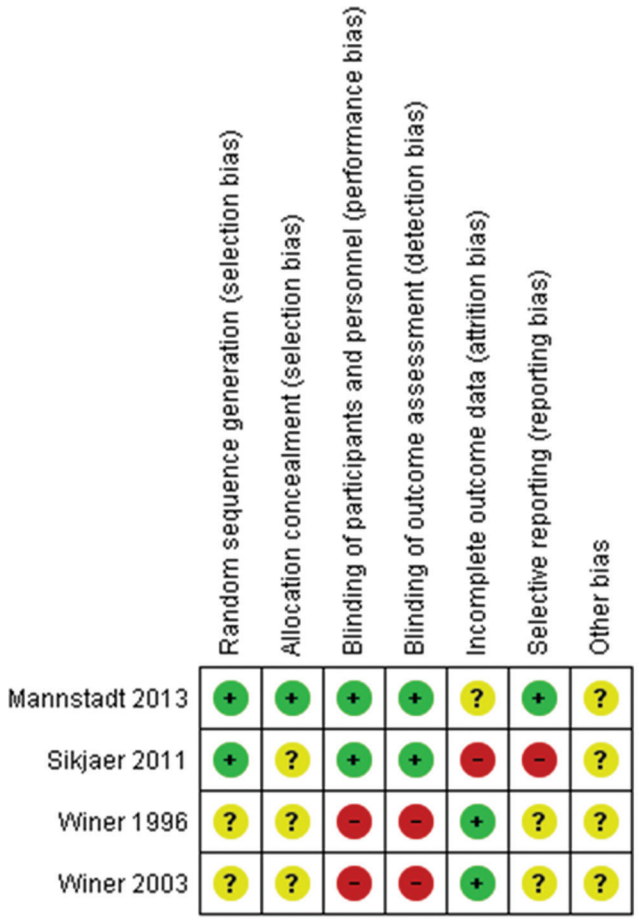
Supplemental Table 1: Search Strategy used for database

#1 hypoparathyroidism
#2 Recombinant Parathyroid Hormone
#3 rhPTH
#4 PTH (1-34)
#5 teriparatide
#6 PTH (1-84)
#7 natpara
#8 2 OR 3 OR 4 OR 5 OR 6 OR 7
#9 1 AND 8

Supplemental Table 2: Risk of bias assessment



(+) low risk ; (-) high risk ; (?) unclear risk

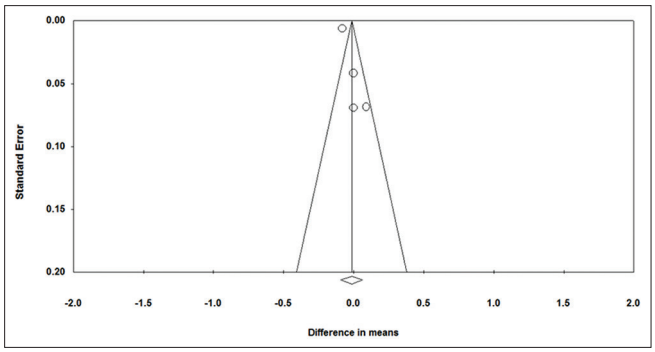
Supplemental Table 3: Summary of grades of evidence

Parathyroid hormone compared to placebo for Chronic Hypoparathyroidism

Patient or population: Chronic Hypoparathyroidism
Setting: Hospital
Intervention: Parathyroid hormone
Comparison: Placebo

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Parathyroid hormone
serum calcium	243 (4 RCTs)	⊕◯◯◯ VERY LOW[a,b,c]	-	-	MD 0.01 lower (0.09 lower to 0.06 higher)
Phosphorus	243 (4 RCTs)	⊕◯◯◯ VERY LOW[a,c,d]	-	-	MD 0.04 lower (0.11 lower to 0.03 higher)
24-h Urine calcium	243 (4 RCTs)	⊕◯◯◯ VERY LOW[a,c,d]	-	-	MD 1.43 lower (2.89 lower to 0.03 higher)
Urinary Creatinine clearance	89 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,e,f]	-	-	MD 3.49 lower (21.05 lower to 14.07 higher)
25 OH vitamin D	243 (4 RCTs)	⊕⊕◯◯ LOW[a]	-	-	MD 13.54 lower (21.94 lower to 5.14 lower)
1,25 OH Vitamin D	243 (4 RCTs)	⊕◯◯◯ VERY LOW[a,c]	-	-	MD 6.21 higher (4.75 lower to 17.16 higher)
Osteocalcin	99 (3 RCTs)	⊕◯◯◯ VERY LOW[d,e,f]	-	-	MD 52.42 higher (6.42 higher to 98.43 higher)
Urinary Deoxypyridinolone	37 (2 RCTs)	⊕◯◯◯ VERY LOW[e,f]	-	-	MD 42.58 higher (8.31 higher to 76.86 higher)
BMD Spine	89 (2 RCTs)	⊕◯◯◯ VERY LOW[b,c,e]	-	-	MD 0.05 lower (0.17 lower to 0.07 higher)
BMD Femoral neck	89 (2 RCTs)	⊕◯◯◯ VERY LOW[c,e]	-	-	MD 0 (0.07 lower to 0.07 higher)
Serious ADR	196 (2 RCTs)	⊕◯◯◯ VERY LOW[c,g]	RR 1.35 (0.58-3.16)	95 per 1,000	33 more per 1,000 (40 fewer to 204 more)
Oral Active Vitamin D Requirement	196 (2 RCTs)	⊕◯◯◯ VERY LOW[c,d,g]	-	-	MD 0.73 lower (1.55 lower to 0.08 higher)
Oral Calcium requirement	196 (2 RCTs)	⊕⊕◯◯ LOW[g]	-	-	MD 0.95 lower (1.21 lower to 0.7 lower)
Successful withdrawal of active vitamin D	183 (2 RCTs)	⊕⊕◯◯ LOW[g]	RR 8.85 (2.58-30.35)	30 per 1,000	234 more per 1,000 (47 more to 876 more)

CI: Confidence interval; MD: Mean difference; RR: Risk ratio. GRADE Working Group grades of evidence, High certainty: We are very confident that the true effect lies close to that of the estimate of the effect, Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. [a]All the trials were having unclear risk of bias in one or more domains of quality assessment and three trials having high risk of bias in one or more domains of quality assessment, [b]Moderate heterogeneity is present, [c]95% CI includes null effect, [d]Severe heterogeneity is present. [e]All the trials having high risk of bias in one or more domains of quality assessment, [f]Wide CI and small sample size, [g]All the trials were having unclear risk of bias in one or more domains of quality assessment and one trial having high risk of bias in one or more domains of quality assessment



Supplemental Figure 1: Funnel Plot for publication bias (Serum Calcium)