Active vitamin D therapy increases the risk of hypercalcemia in non-dialysis chronic kidney disease patients with secondary hyperparathyroidism: a systematic review and meta-analysis

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INTRODUCTION

Secondary hyperparathyroidism (SHPT), characterised by an excessive secretion of parathyroid hormone (PTH), is a common complication in patients with chronic kidney disease (CKD).[1] The prevalence and severity of SHPT increases with declining kidney function.[1] If left untreated, SHPT leads to bone disease, and vascular and valvular calcification, which are linked to increased risks of morbidity and mortality.[1,2] SHPT affects 40–82% of patients with Stage 3 or 4 CKD.[1] One approach for the management of elevated PTH levels is treatment with active vitamin D (1-α-hydroxylated) analogues. Randomised controlled trials (RCTs) have demonstrated the efficacy of these agents in suppressing PTH levels in patients with non-dialysis (ND)-CKD, but they are associated with an increased risk of hypercalcemia.[3–5] As a result, the Kidney Diseases: Improving Global Outcomes (KDIGO) 2017 guidelines recommended that active vitamin D analogues are not routinely used in ND-CKD.[2] The key evidence for these KDIGO 2017 recommendations was primarily based on two RCTs, the PRIMO and the OPERA studies, which showed a higher rate of hypercalcemia with paricalcitol versus placebo in patients with ND-CKD and SHPT.[4,5]

STUDY OBJECTIVE

The objective of this systematic review and meta-analysis was to evaluate the effect of active vitamin D analogues on hypercalcemia in patients with ND-CKD and SHPT.

METHODS

LITERATURE SEARCH. A systematic literature search of PubMed was performed, from inception until 19 June 2018, using a pre-defined search strategy.

INCLUSION & EXCLUSION CRITERIA. Studies were included if they were randomised, double-blind, placebo-controlled trials in adults with ND-CKD and SHPT, evaluating single-agent active vitamin D analogues, with ≥30 participants per arm, ≥6 weeks in duration, and specified the number of patients exhibiting hypercalcemia per arm, deemed as related or possibly related to the study drug by the investigator. Single-dose studies and studies with unknown numbers of randomised patients, or patients who needed dialysis or renal transplant at baseline, were excluded.

DATA REVIEW, SELECTION AND COLLECTION. Two scientific experts screened each abstract independently to check that the inclusion and exclusion criteria were met. For all articles where the inclusion and exclusion criteria were met, relevant information relating to the primary outcome was extracted from the full article and collated for data analysis.

PRIMARY OUTCOME. The primary outcome of interest was the number and percentage of patients with hypercalcemia deemed as related, or potentially related, to the study drug by the investigator.

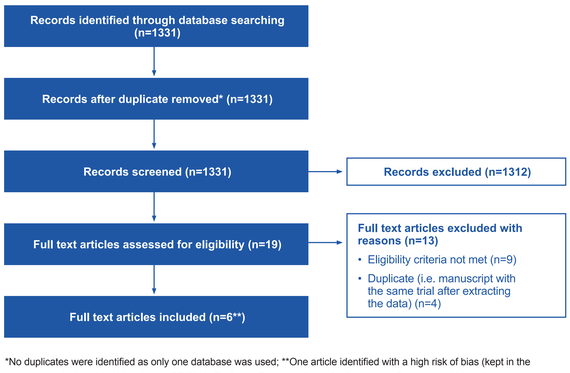
DATA ANALYSIS. The statistical analysis was performed using Comprehensive Meta-Analysis software version 3.0 (Biostat, Inc.). The odds ratio (OR) and its 95% confidence intervals (CI), in addition to the combined OR and corresponding 95% CI, were calculated using only eligible studies.

RISK OF BIAS ASSESSMENT. The risk of bias of each included study was evaluated using methodology defined by the Cochrane Collaboration.[6] Heterogeneity in effect sizes across the studies was assessed using: Cochran's Q-statistic; I^2 index and Tau-squared (T^2).

RESULTS

LITERATURE SEARCH OUTPUTS. The literature search identified 1331 records, of which six full-text articles were eligible for the meta-analysis (**Figure 1**). These comprised six placebo-controlled RCTs, including one study that evaluated alfacalcidol and five studies that evaluated paricalcitol, which involved a total of 799 patients (**Table 1**). The duration of the studies ranged from 16 weeks to 2 years. The weekly doses of paricalcitol administered were 7 µg (three studies) and 14 µg (two studies), whereas the weekly dose in the alfacalcidol study was 1.75−7.0 µg (**Table 1**). Across the six studies, the hypercalcemia events ranged from 1.1−43.3% versus 0−3.4% in the active vitamin D analogue and placebo groups, respectively.

Figure 1. PRISMA flow diagram of relevant literature identified



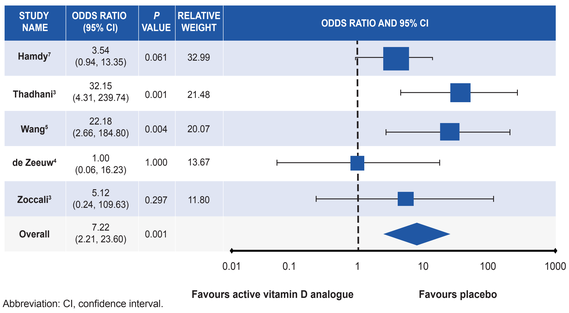
*No duplicates were identified as only one database was used; **One article identified with a high risk of bias (kept in the sensitive analysis only). Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1: Overview of the randomised controlled studies included in the meta-analysis

STUDY	ACTIVE VITAMIN D ANALOGUE (WEEKLY DOSE, µg)	STUDY DURATION	PATIENTS, N		PATIENTS EXPERIENCING HYPERCALCEMIA, %		HIGH-RISK BIAS IDENTIFIED
			ACTIVE VITAMIN D ANALOGUE ARM	PLACEBO ARM	ACTIVE VITAMIN D ANALOGUE ARM	PLACEBO ARM	
Hamdy[7]	1-alphacalcidol (1.75−7.0)	2 years	89	87	11.2	3.4	No
Zoccali[3]	Paricalcitol (14)	16 weeks	45	44	4.4	0	No
Wang[5]	Paricalcitol (7)	52 weeks	30	30	43.3	3.3	No
Thadhani[4]	Paricalcitol (14)	54 weeks	115	112	22.6	0.1	No
de Zeeuw[9]	Paricalcitol (7)	32.6 weeks	93	93	1.1	1.1	No
Fishbane[10]	Paricalcitol (7)	6 months	31	30	3.2	0	Yes

META-ANALYSIS. The risk of bias assessment indicated that the study by Fishbane et al.[10] was rated as having a 'high risk' of bias owing to the high proportion of randomized patients in this trial who were untreated or lost to follow-up (**Table 1**). After exclusion of this study, the meta-analysis showed that treatment with active vitamin D analogue was associated with a 7.2-fold greater probability of hypercalcemia versus placebo (OR: 7.22; 95% CI: 2.21, 23.60; *P*=0.001) (**Figure 2**).

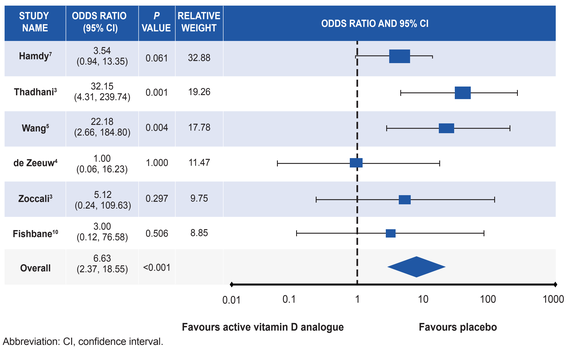
Figure 2: Forest plot showing a statistically significantly increased risk of hypercalcemia with active vitamin D analogues versus placebo (n=5 studies)



Abbreviation: CI, confidence interval.

SENSITIVITY ANALYSES. The mean effect size estimation for all six studies, including Fishbane et al. 2009, indicated that patients with ND-CKD and SHPT treated with active vitamin D analogues were at a significantly increased risk of hypercalcemia compared with those treated with placebo (*P*<0.001). There was a 6.6-fold greater probability of hypercalcemia versus placebo (OR: 6.63; 95% CI: 2.37, 18.55) in patients with ND-CKD and SHPT (**Figure 3**).

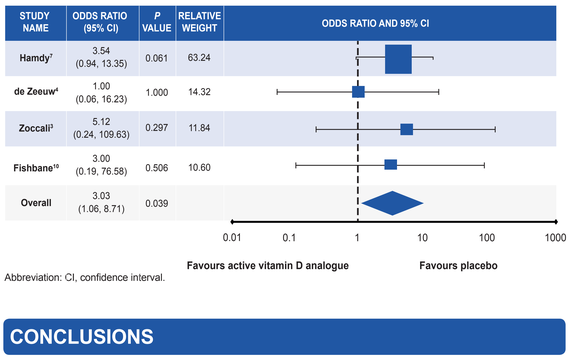
Figure 3: Forest plot showing a statistically significantly increased risk of hypercalcemia with active vitamin D analogues versus placebo (n=6 studies)



Abbreviation: CI, confidence interval.

Evaluation of heterogeneity across the six studies found that two studies (Thadhani et al. 2012[4] and Wang et al. 2014[5]) accounted for a large proportion of the observed number of hypercalcemia events. Secondary sensitivity analysis excluding these two 'outlier' studies showed that the probability of hypercalcemia was 3.0-fold greater in patients receiving active vitamin D analogue versus patients receiving placebo (OR: 3.03; 95% CI: 1.06, 8.71; *P*=0.039) (**Figure 4**).

Figure 4: Forest plot showing a statistically significantly increased risk of hypercalcemia with active vitamin D analogues versus placebo (n=4 studies)



Abbreviation: CI, confidence interval.

CONCLUSIONS

The meta-analysis indicated that, compared with placebo, treatment with active vitamin D analogues significantly increased the risk of hypercalcemia among ND-CKD patients with SHPT. These observations highlight the urgent need for new therapies for the treatment of SHPT in patients with ND-CKD that avoid undesired elevations in serum calcium.

Limitations of the present analysis comprise: the small number of studies included, the heterogeneity of the study designs, and lack of control for confounding factors.

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