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Supplement

Supplementary Text: Changes in Vitamin D Levels by Treatment Group

Serum 25(OH)D and 1,25$(OH)_2$D levels at baseline and 6-months are presented in Figure 2. After adjustment for baseline 25(OH)D level, the treatment groups increased 25(OH)D levels by 32.6 ng/mL (95% CI: 22.3 - 42.9 ng/mL) and the placebo group decreased 25(OH)D levels by 2.6 ng/mL (95% CI: -17.0 - 11.7 ng/mL). The calcifediol group increased 25(OH)D levels by 68.3 ng/mL (95% CI: 58.0 – 78.6 ng/mL) and the calcitriol group decreased 25(OH)D levels by 2.9 ng/mL (95% CI: -13.2 - 7.4 ng/mL). The 25(OH)D changes during 6-month trial period for the treatment groups versus the placebo group, and the calcifediol group versus the calcitriol group and the placebo group, were statistically significant ($P < .001$).

The changes in 1,25$(OH)_2$D were less pronounced: the placebo group was stable, the mean 1,25$(OH)_2$D change was 0.5 pg/mL (95% CI: -3.1 - 4.1 pg/mL), while the treatment groups increased by 5.0 pg/mL (95% CI: 2.4 - 7.6 pg/mL). The calcifediol group increased 1,25$(OH)_2$D levels by 4.6 pg/mL (95% CI: 0.9 - 8.3 pg/mL) and the calcitriol group increased 1,25$(OH)_2$D levels by 5.4 pg/mL (95% CI: 1.7 - 9.1 pg/mL). The difference in 6-month 1,25$(OH)_2$D change between the treatment group and the placebo group was statistically significant ($p=0.046$), after accounting for the baseline 1,25$(OH)_2$D values, while the difference between calcifediol and calcitriol groups was not statistically significant.

The percentage of participants who achieved 25(OH)D levels of at least 30 ng/mL at 6-months was significantly higher in the calcifediol group (88%) compared with the calcitriol (22%) and the placebo (30%) groups ($p<.001$). The percentage of participants who achieved 1,25$(OH)_2$D levels of at least 24 pg/mL was slightly higher in the calcitriol group (61%) than in calcifediol (47%) and placebo (33%) groups, however this difference was not statistically significant ($p=0.08$).

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Supplement Table S1a Observational Analysis: Six-Month Changes in Primary and Secondary Outcomes by Tertiles of Achieved 25(OH)D

Variable	1st Tertile 8.4 - 22.9 ng/mL	2nd Tertile 23.0 – 40.0 ng/mL	3rd Tertile 40.0 - 210.3 ng/mL	*P* value[a]
Primary Outcome by Achieved 25(OH)D				
Pulse Wave Velocity, m/s	0.70 (-0.34 – 1.73)	1.26 (0.33 - 2.18)	-0.97 (-1.99 – 0.04)	0.006
Secondary Outcomes by Achieved 25(OH)D				
Systolic BP, mmHg	-0.81 (-5.81 – 4.18)	2.74 (-2.35 – 7.82)	4.30 (-0.79 – 9.40)	0.35
Diastolic BP, mmHg	1.59 (-1.30 - 4.49)	1.47 (-1.47 - 4.41)	1.37 (-1.57 - 4.32)	0.99
Urine ACR, ln(mg/g)	-0.06 (-0.29 - 0.16)	0.04 (-0.20 - 0.27)	0.06 (-0.17 - 0.29)	0.72
Calcium, mg/dL	-0.24 (-0.51 - 0.03)	0.03 (-0.24 - 0.30)	0.14 (-0.13 - 0.41)	0.52
Phosphate, mg/dL	0.23 (0.03 – 0.43)	0.07 (-0.13 - 0.27)	0.20 (-0.005- 0.40)	0.55
PTH, ln(pg/mL)	0.08 (-0.09- 0.26)	-0.03 (-0.20 - 0.15)	-0.60 (-0.78 - -0.43)	<0.001
FGF-23, ln(pg/mL)	0.06 (-0.11 - 0.23)	0.15 (-0.02 - 0.32)	0.31 (0.14 - 0.48)	0.11
CRP, ln(mg/L)	0.02 (-0.24 - 0.27)	-0.02 (-0.28 - 0.24)	0.03 (-0.23 - 0.29)	0.95
Serum Vitamin D by Achieved 25(OH)D				
25(OH) D, ng/mL	-11.4 (-21.6 - -1.3)	2.8 (-7.0 – 12.7)	71.4 (61.9 – 81.0)	<0.001
1,25(OH)$_2$D, pg/mL	3.28 (-0.47 - 7.02)	1.38 (-2.42 - 5.19)	5.66 (1.79 - 9.52)	0.30

Supplement Table S1b Observational Analysis: Six-Month Changes in Primary and Secondary Outcomes by Tertiles of Achieved $1,25(OH)_2D$

Variable	1st Tertile 6.1 – 20.9 pg/mL	2nd Tertile 21.0 – 27.0 pg/mL	3rd Tertile 27.1 – 92.4 pg/mL	*P* value[a]
Primary Outcome by Achieved $1,25(OH)_2D$				
Pulse Wave Velocity, m/s	-0.06 (-1.19 – 1.08)	0.37 (-0.65 - 1.38)	0.26 (-0.86 – 1.37)	0.85
Secondary Outcomes by Achieved $1,25(OH)_2D$				
Systolic BP, mmHg	2.12 (-3.00 - 7.24)	3.57 (-1.55 - 8.68)	-0.11 (-5.24 - 5.02)	0.60
Diastolic BP, mmHg	1.75 (-1.12 - 4.63)	3.11 (0.23 - 5.99)	-0.81 (-3.69 - 2.06)	0.16
Urine ACR, ln(mg/g)	0.04 (-0.19 - 0.27)	0.00 (-0.22 - 0.23)	-0.04 (-0.26 - 0.19)	0.90
Calcium, mg/dL	-0.004 (-0.28 - 0.27)	0.09 (-0.18 – 0.37)	-0.20 (-0.48 - 0.08)	0.34
Phosphate, mg/dL	0.24 (0.05 - 0.42)	0.15 (-0.03 - 0.34)	0.04 (-0.14 - 0.23)	0.34
PTH, ln(pg/mL)	-0.01 (-0.22 - 0.19)	-0.31 (-0.51 - -0.10)	-0.23 (-0.44 - -0.02)	0.12
FGF-23, ln(pg/mL)	0.36 (0.19 - 0.53)	0.08 (-0.08 - 0.25)	0.06 (-0.12 - 0.23)	0.03
CRP, ln(mg/L)	-0.15 (-0.41 - 0.10)	0.16 (-0.10 - 0.42)	0.01 (-0.24 - 0.27)	0.23
Serum Vitamin D by Achieved $1,25(OH)_2D$				
25(OH) D, ng/mL	10.25 (-5.80 – 26.31)	29.51 (13.58 – 45.43)	22.30 (6.31 – 38.30)	0.24
$1,25(OH)_2D$, pg/mL	-4.79 (-7.73 - -1.86)	1.31 (-1.44 - 4.05)	13.80 (10.96 - 16.63)	<0.001

Abbreviations: ACR, albumin:creatinine ratio; ln, natural logarithm; PTH, parathyroid hormone; FGF-23, fibroblast growth factor-23 (FGF-23); CRP, C-reactive protein ; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D.

SI conversion factors: To convert uACR to mg/mmol multiply by 0.113; calcium to mmol/L, multiply by 0.25; phosphate to mmol/L, multiply by 0.323; PTH to pmol/L, multiply by 0.106; 25(OH)D to nmol/L, multiply by 2.496; $1,25(OH)_2D$ to pmol/L, multiply by 2.6.

[a] Adjusted mean change, 95% confidence interval and P value for treatment effects, with the respective baseline value as covariate, compared using ANCOVA.

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Supplement

Supplementary Text: Biochemical and Clinical Safety

Within the calctriol group, there was 1 episode of hypercalcemia, 1 discontinuation due to gastrointestinal intolerance adjudicated by the data safety monitoring board as probably related to treatment, and 1 death, cause unknown. Within the calcifediol group, there were 12 patients that had measured levels of vitamin D consistent with the hypervitaminosis D (levels above 250nmol/L or 100ng/mL), which were recognized at their post-treatment visit. Those that had documented hypervitaminosis D were monitored for between 3 and 5 weeks post-treatment, by which time all cases had resolved. None of these 12 patients had symptoms, nor hypercalcemia. Of patients who reported symptoms, irrespective of blood levels, 2 patients reported palpitations, possibly related to treatment and 1 patient had hypercalcemia, probably related to treatment. The cause of death for the single patient within this group was gross hematuria, unrelated to treatment. See Supplement Table S2 for complete list of adverse events.

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Supplement Table S2 Adverse Events

Adverse Event	Placebo N=30	Calcitriol N=28	Calcifediol N=29
Death	0 (0%)	1 (3%)	1 (3%)
Cancer	0 (0%)	0 (0%)	2 (5%)
Skin carcinoma	0 (0%)	0 (0%)	1 (3%)
Metastatic squamous cell carcinoma	0 (0%)	0 (0%)	1 (3%)
Cardiovascular	0 (0%)	1 (3%)	5 (13%)
Congestive heart failure	0 (0%)	0 (0%)	1 (3%)
DVT	0 (0%)	0 (0%)	1 (3%)
Palpitation	0 (0%)	0 (0%)	2 (5%)
Pulmonary Embolism	0 (0%)	0 (0%)	1 (3%)
Shortness of breath	0 (0%)	1 (3%)	0 (0%)
Gastrointestinal	0 (0%)	1 (3%)	3 (8%)
Abdominal pain	0 (0%)	0 (0%)	1 (3%)
Colorectal polyps	0 (0%)	1 (3%)	0 (0%)
Diarrhea	0 (0%)	0 (0%)	1 (3%)
Gastrointestinal intolerance	0 (0%)	0 (0%)	0 (0%)
Small Bowel Obstruction	0 (0%)	0 (0%)	1 (3%)
Infection	0 (0%)	0 (0%)	3 (8%)
Abscess	0 (0%)	0 (0%)	1 (3%)
Cellulitis	0 (0%)	0 (0%)	1 (3%)
Fungal infection	0 (0%)	0 (0%)	1 (3%)
Metabolic & hematologic	1 (3%)	2 (5%)	14 (36%)
Hypercalcemia	0 (0%)	1 (3%)	1 (3%)
Hyperphosphatemia	1 (3%)	0 (0%)	0 (0%)
Hypervitaminosis D	0 (0%)	0 (0%)	12 (31%)
Postoperative bleed	0 (0%)	1 (3%)	0 (0%)
Thyroid Storm	0 (0%)	0 (0%)	1 (3%)
Musculoskeletal	0 (0%)	0 (0%)	1 (3%)
Back pain	0 (0%)	0 (0%)	1 (3%)
Neurological	0 (0%)	0 (0%)	1 (3%)
Dizziness	0 (0%)	0 (0%)	1 (3%)
Renal	1 (3%)	0 (0%)	0 (0%)
Acute kidney injury	1 (3%)	0 (0%)	0 (0%)