## 13.1. Monitoring of Calcium, Phosphate, Vitamin D and Parathyroid Hormone Levels in People with CKD

When should serum calcium, vitamin D, phosphate and intact parathyroid hormone levels be routinely measured in adults with CKD?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention/ exposure</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chonchol M, Scragg R. 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey.[see comment]. <em>Kidney International</em>. 2007; 71(2):134-139. Ref ID: 44</td>
<td>Cross-sectional population study</td>
<td>N total =14679</td>
<td>Inclusion criteria: a general health survey was conducted in USA in 1988-1994 of non-institutionalised adults 20 years or older. Random selection using a stratified cluster method.</td>
<td>Procedure: Non-Hispanic blacks, elderly, and American Mexicans were deliberately over-sampled. Participants completed a health questionnaire and had a clinical exam. Serum creatinine was measured in all participants and GFR was calculated with the MDRD equation recalibrated to the MDRD laboratory. Serum 25 (OH) D₃ was measured by a radioimmunoassay after extraction with acetonitrile. CKD was defined according to GFR and staged according to KDOQI.</td>
<td>N/A</td>
<td>N/A</td>
<td>Serum 25-hydroxyvitamin D [25 (OH) D₃]</td>
<td>Not stated</td>
</tr>
</tbody>
</table>
### Effect size
adjusted for age, sex, ethnicity, BMI, physical activity, vitamin D supplementation, milk consumption

In this American sample (N=14679), the prevalence of mild CKD (GFR 60-89 ml/min/1.73m²) was 28%. The prevalence of moderate CKD (GFR 30-59 ml/min/1.73m²) was 6% and the prevalence of severe CKD (GFR 15-29 ml/min/1.73m²) was 0.2%.

### GFR and Serum Vitamin D:

Compared with people with GFR ≥ 90 ml/min/1.73m² (N= 9687, mean 25 (OH) D₃ = 73.3 nmol/l), people with GFR 60-89 ml/min/1.73m² (N= 4094, mean 25 (OH) D₃ = 77.3 nmol/l, p=0.0002) had significantly higher 25 (OH) D₃.

Compared with people with GFR ≥ 90 ml/min/1.73m² (N= 9687, mean 25 (OH) D₃ = 73.3 nmol/l), there was NS difference in serum 25 (OH) D₃ for people with GFR 30-59 ml/min/1.73m² (N= 854, mean 25 (OH) D₃ = 75.8 nmol/l, p=0.10).

Compared with people with GFR ≥ 90 ml/min/1.73m² (N= 9687, mean 25 (OH) D₃ = 73.3 nmol/l), people with GFR 15-29 ml/min/1.73m² (N= 44, mean 25 (OH) D₃ = 61.6 nmol/l, p=0.0002, mean difference -11.7 nmol/l) had significantly lower 25 (OH) D₃.

Note: Limitations – Cross-sectional analysis.

<table>
<thead>
<tr>
<th>Ref ID: 1225</th>
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</thead>
<tbody>
<tr>
<td>Study type: Cross-sectional study</td>
</tr>
<tr>
<td>Evidence level: Evidence Level: 3</td>
</tr>
<tr>
<td>Number of patients: N total =1836 N CKD Stage 1 = 174 N CKD Stage 2 = 341 N CKD Stage 3 = 856 N CKD</td>
</tr>
<tr>
<td>Patient characteristics: Inclusion criteria: all CKD patients attending 2 nephrology clinics in Spain (similar treatment policies in each clinic) Exclusion criteria: history of primary parathyroid disease, previous parathyroidectomy, neoplasias, osteoporosis under treatment with bisphosphonates or calcitonin. Baseline Characteristics:</td>
</tr>
<tr>
<td>Intervention/ exposure: N/A Procedure: Medication use, age, gender, CKD aetiology, presence of diabetes, serum creatinine, phosphate, calcium, Ca X P product, and iPTH were determined. Serum 1, 25 OH₂ D₃ (N=522) determined with radioreceptor assay (Hybritec, normal range 18-78 pg/ml). Serum 25 (OH) D₃ (N=205) determined in October-February with radioimmunoassay (Biosource, normal range 12-80 ng/ml). Serum iPTH determined by a two-site</td>
</tr>
<tr>
<td>Comparison: N/A</td>
</tr>
<tr>
<td>Length of follow-up: N/A</td>
</tr>
<tr>
<td>Outcome measures: Serum P Serum Ca Serum intact parathyroid hormone (iPTH) Serum 1, 25-dihydroxyvitamin D (1, 25 OH₂ D₃) Serum 25-hydroxyvitamin D [ 25 (OH) D₃]</td>
</tr>
<tr>
<td>Source of funding: Not stated</td>
</tr>
<tr>
<td>Stage 4 N CKD</td>
</tr>
</tbody>
</table>

**Effect size**

Changes in serum iPTH and 1,25 Vit D precede changes in calcium or phosphate.

**Serum Ca:**
Mean levels of Ca increased from CKD Stages 1 to 3 and decreased thereafter. People with Stage 4 CKD (N=354, mean Ca 9.35 mg/dl) had significantly lower serum calcium than people with Stage 3 CKD (N=856, mean Ca 9.57 mg/dl, p<0.05).

**Serum P:**
Mean levels of P remained stable from Stages 1 to 3 CKD and then increased thereafter. People with Stage 4 CKD (N=354, mean P 3.92 mg/dl) had significantly higher serum phosphate than people with Stage 3 CKD (N=856, mean P 3.59 mg/dl, p<0.05). People with Stage 5 CKD (N=111, mean P 4.89 mg/dl) had significantly higher serum phosphate than people with Stage 4 CKD (N=354, mean P 3.92 mg/dl, p<0.05).

**Serum iPTH:**
Serum iPTH increased steadily across all stages of CKD. People with Stage 2 CKD (N=341, mean iPTH 5.97 pmol/l) had significantly higher serum iPTH than people with Stage 1 CKD (N=174, mean iPTH 4.86 pmol/l, p<0.05). People with Stage 3 CKD (N=856, mean iPTH 8.96 pmol/l) had significantly higher serum iPTH than people with Stage 2 CKD (N=341, mean iPTH 5.97 pmol/l, p<0.05). People with Stage 4 CKD (N=354, mean iPTH 16.47 pmol/l) had significantly higher serum iPTH than people with Stage 3 CKD (N=856, mean iPTH 8.96 pmol/l, p<0.05). People with Stage 5 CKD (N=111, mean iPTH 24.29 pmol/l) had significantly higher serum iPTH than people with Stage 4 CKD (N=354, mean iPTH 16.47 pmol/l, p<0.05).

**Serum Vitamin D:**
There were NS changes across all stages of CKD for serum 25 (OH) D3 (N=205). Serum 1, 25 OH2 D3 (N=522) remained stable from Stages 1 to 2 and then decreased thereafter. People with Stage 3 CKD (N=221, mean 1, 25 OH2 D3 25.7 pg/ml) had significantly lower levels of mean serum 1, 25 OH2 D3 than people with Stage 2 CKD (N=87, mean 1, 25 OH2 D3 33.9 pg/ml, p<0.05). People with Stage 4 CKD (N=156, mean 1, 25 OH2 D3 16.8 pg/ml) had significantly lower levels of mean serum 1, 25 OH2 D3 than people with Stage 3 CKD (N=221, mean 1, 25 OH2 D3 25.7 pg/ml, p<0.05). People with Stage 5 CKD (N=43, mean 1, 25 OH2 D3 13.2 pg/ml) had significantly lower levels of mean serum 1, 25 OH2 D3 than people with Stage 4 CKD (N=156, mean 1, 25 OH2 D3 16.8 pg/ml, p<0.05).
Authors also reported that percentage of patients having all 4 metabolites (Ca, P, iPTH, and Vitamin D) within K/DOQI recommended ranges were low.

Due to early elevation of iPTH and early decrease of 1.25 Vitamin D, authors suggest early treatment with calcitriol.

Limitations – X-sectional analysis shows associations, not causal relationships, CKD defined by 1 creatinine measurement, Cockcroft-Gault CrCl used to assign people to various stages of CKD (K/DOQI).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention/ exposure</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu CY, Chertow GM. Elevations of serum phosphorus and potassium in mild to moderate chronic renal insufficiency. <em>Nephrol Dial Transplant.</em> 2002; 17(8):1419-1425. Ref ID: 1401</td>
<td>Cross-sectional study</td>
<td>NHANES III, USA</td>
<td>Evidence Level: 3</td>
<td>N total =14722</td>
<td>Serum P and Ca levels in people with decreasing deciles of CrCl stratified by gender</td>
<td>Serum P and Ca levels in people with CrCl &gt; 80 ml/min stratified by gender</td>
<td>N/A</td>
<td>Serum P Serum Ca</td>
<td>NIH</td>
</tr>
</tbody>
</table>
**Effect size**

Focus of the paper is on changes in serum P and Ca.

**CrCl and serum P:**

In both men and women, serum P increased with decreasing CrCl.

Compared with women with CrCl > 80 ml/min (N=4078) significant increases in serum P were observed in women with CrCl 50-60 ml/min (N=697, change in serum P = 0.1 mg/dl (95% CI 0.1 to 0.2), p <0.0001). This trend of increasing P continued with decreasing CrCl (change in P = 0.2 mg/dl in CrCl 30-40, p<0.0001; 0.3 mg/dl in CrCl 20-30 ml/min, p=0.0003; 0.8 mg/dl in CrCl < 20 ml/min, p=0.002).

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>N total</th>
<th>% hyperphosphataemia (95% CI) - serum P &gt; 4.5 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>Not stated</td>
<td>≤ 2 (95% CI not given)</td>
</tr>
<tr>
<td>30-40</td>
<td>614</td>
<td>3 (1 to 6%)</td>
</tr>
<tr>
<td>20-30</td>
<td>224</td>
<td>7 (1 to 12%)</td>
</tr>
<tr>
<td>≤ 20</td>
<td>47</td>
<td>30 (0 to 62%)</td>
</tr>
</tbody>
</table>

**CrCl and serum ionised Ca++:**

Compared to people with CrCl > 80 ml/min, there were NS changes in ionised Ca with declining CrCl. Compared to men with CrCl > 80 ml/min (N=4347), men with CrCl < 20 ml/min (N=20) had a significant decrease in ionised serum Ca [change in ionised Ca = -0.03 mmol/l (95% CI -0.05 to -0.01), p=0.002].

Serum total Ca or serum total Ca adjusted for albumin levels were not lower at lower CrCl (data not shown).

Note: Limitations –X-sectional analysis shows associations, not causal relationships and no longitudinal follow-up, CrCl defined by 1 creatinine measurement, no PTH or vitamin D measures, serum biochemistry performed only once.

**Ref ID: 235**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention/ exposure</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>LaClair RE, Hellman RN, Karp SL et al.</td>
<td>Cross-sectional study</td>
<td>12 centres, USA</td>
<td>Evidence Level: 3</td>
<td>Inclusion criteria: people &gt; 18 years old with known CKD and GFR 15-59 ml/min</td>
<td>Serum parameters in Stage 4 N= 113</td>
<td>Serum parameters in Stage 5 N= 22</td>
<td>Procedure: GFR was measured with Cockcroft-Gault equation. Serum 1, 25 OH₂ D₃ (Nichols AdvantagexChemiluminescence, reference range 15-62 pg/ml) and 25 (OH) D₃ (Nichols Advantage chemiluminescence, reference range 10-68 ng/ml), iPTH (Nichols Advantage chemiluminescence,</td>
<td>Serum P</td>
<td>Genzyme Inc.</td>
</tr>
<tr>
<td>Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States.[see comment]. American Journal of Kidney Diseases. 2005; 45(6):1026-1033.</td>
<td>N total =201</td>
<td>N Stage 3 GFR 30-60 ml/min = 65</td>
<td>N Stage 4 GFR 15-30 ml/min = 113</td>
<td>Exclusion criteria: RRT, proteinuria &gt; 5g/24-h, poorly controlled hypertension, diabetes, or vasculitis, use of vitamin D or phosphate binders</td>
<td>N/A</td>
<td>Serum Ca</td>
<td>Serum intact parathyroid hormone (iPTH)</td>
<td>Serum 1, 25-dihydroxyvitamin D (1, 25 OH₂ D₃)</td>
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<tr>
<td>Ref ID: 235</td>
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</tbody>
</table>
N Stage 5 GFR < 15 ml/min = 22
Baseline Characteristics: Mean GFR 27 ml/min, mean age 65 years, 65% male
reference range 10-65 pg/ml, Ca (corrected for albumin), P, creatinine were analysed with autoanalyser at a central laboratory.

<table>
<thead>
<tr>
<th>Effect size</th>
<th>GFR and serum Ca:</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with Stage 4 CKD (N=113, mean Ca 2.30 mmol/l) or Stage 5 CKD (N=22, mean Ca 2.25 mmol/l) had significantly lower serum Ca than people with Stage 3 CKD (N=65, mean Ca 2.37 mmol/l, p not stated). 43% of people with Stage 3 CKD (N=65) and 71% of people with Stage 4 CKD (N=113) had serum Ca &lt; 2.37 mmol/l.</td>
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</table>

<table>
<thead>
<tr>
<th>GFR and serum P:</th>
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</thead>
<tbody>
<tr>
<td>People with Stage 4 CKD (N=113, mean P 1.32 mmol/l) or Stage 5 CKD (N=22, mean P 1.42 mmol/l) had significantly higher serum P than people with Stage 3 CKD (N=65, mean P 1.13 mmol/l, p not stated). 3% of people with Stage 3 CKD (N=65) and 22% of people with Stage 4 CKD (N=113) had serum P &gt; 1.52 mmol/l.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR and serum iPTH:</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with Stage 4 CKD (N=113, mean iPTH 235 pg/ml) or Stage 5 CKD (N=22, mean iPTH 310 pg/ml) had significantly higher serum iPTH than people with Stage 3 CKD (N=65, mean iPTH 114 pg/ml, p not stated). Only 35% of people with Stage 3 (N=65) and 31% of people with Stage 4 CKD (N=113) had iPTH within K/DOQI target range (&lt; 70 Stage 3, &lt; 110 Stage 4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR and serum 25 (OH) D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with Stage 4 CKD (N=113, mean 25 (OH) D3 46.4 nmol/l) or Stage 5 CKD (N=22, mean 25 (OH) D3 29.9 nmol/l) had lower serum 25 (OH) D3 than people with Stage 3 CKD (N=65, mean 25 (OH) D3 58.2 nmol/l, p not stated). No discussion of the significance of this result. 57% of people with Stage 3 CKD (N=65) and 58% of people with Stage 4 CKD (N=113) had 25 (OH) D3 insufficiency (25 (OH) D3 10-30 ng/ml). 14% of people with Stage 3 CKD (N=65) and 26% of people with Stage 4 CKD (N=113) had 25 (OH) D3 deficiency (25 (OH) D3 &lt; 10 ng/ml).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR and serum 1, 25 OH2 D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with Stage 4 CKD (N=108, mean 1, 25 OH2 D3 62.3 pmol/l) or Stage 5 CKD (N=20, mean 1, 25 OH2 D3 54.3 pmol/l) had significantly lower serum 1, 25 OH2 D3 than people with Stage 3 CKD (N=63, mean 1, 25 OH2 D3 79.6 pmol/l, p not stated).</td>
</tr>
</tbody>
</table>

Limitations – population is older people, X-sectional analysis shows associations, not causal relationships

Reference: Study Number Patient characteristics Intervention/ exposure Comparison Length of Outcome Source

Chronic kidney disease: evidence tables DRAFT

<table>
<thead>
<tr>
<th>type Evidence level</th>
<th>of patients</th>
<th>follow-up measures of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional study</td>
<td>Baseline analysis of SEEK 153 centres, USA</td>
<td>Evidence Level: 3</td>
</tr>
</tbody>
</table>

N total = 1814
N GFR > 60 ml/min = 408
N GFR 59-30 ml/min = 1109
N GFR < 30 ml/min = 297

- Inclusion criteria: Study for the Evaluation of Early Kidney disease (SEEK) participants: > 40 years old, MDRD eGFR < 60 ml/min
- Exclusion criteria: RRT, history of primary parathyroid disease, use of any prescription-based vitamin D therapy 12 months prior to screening
- Baseline Characteristics: Mean GFR 47 ml/min, 85% hypertensive, 71% > 65 years old, mean age 70 years, 35% CAD, 47% diabetic, 12% African American, 48% male, 25% receiving Ca supplementation, 8.7% hormone replacement therapy, 8% receiving bisphosphonates, 38% ACEI use, 34% ARB use, 64% diuretic use

N/A Procedure: Participant charts screened for serum creatinine in 2003-04 to determine eligibility for inclusion in the study. Medical history, medications, blood and urine samples collected at baseline (June 2004 to October 2004). Serum 1, 25 OH₂D₃ and 25 (OH) D₃ determined with Diasorin radioimmunoassay. Serum Ca, P, creatinine analysed with autoanalyser. Total Ca was corrected for serum albumin. Serum iPTH determined by chemiluminescence assay. Lab references 10-65 pg/ml for iPTH, 8-60 ng/ml for 25 (OH) D₃ and 25-65 pg/ml for 1, 25 OH₂ D₃. Dietary supplementation of vitamin D and multivitamin intake up to 400 IU/day permitted.

N/A N/A (Baseline analysis) Serum P Serum Ca Serum intact parathyroid hormone (iPTH) Serum 1, 25-dihydroxyvitamin D (1, 25 OH₂ D₃) Serum 25-hydroxyvitamin D [25 (OH) D₃]

**Effect size**
Discrepancy between screening serum creatinine and baseline creatinine measurement resulted in some people with eGFR > 60 ml/min being included in the study (N=408)

**GFR and serum P and Ca:**
Median Ca and P levels remained stable and within normal levels across GFR (patients stratified by decile GFR). P levels increased at GFR < 20 ml/min. Of people with eGFR 20-29 ml/min (N=204), 15% had abnormal phosphorus levels (P > 4.6 mg/dl). Of people with GFR < 20 ml/min (N=93) 40% had abnormal phosphorus levels (P > 4.6 mg/dl). (Note that original Levin et al. paper stated abnormal P levels as P < 4.6 mg/dl. EC and PS think this was a misprint and should be P > 4.6 mg/dl).
Of people with eGFR 20-29 ml/min (N=204), < 10% had abnormal Ca levels (Ca < 8.4 mg/dl). Of people with GFR < 20 ml/min (N=93) 15% had abnormal Ca levels (Ca < 8.4 mg/dl).

**GFR and serum iPTH:** iPTH levels were relatively stable until GFR decreased to 45 ml/min.

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73 m²)</th>
<th>N</th>
<th>Prevalence (%)</th>
<th>Hyperparathyroidism (iPTH &gt; 65 ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>61</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>117</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>230</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>59-50</td>
<td>396</td>
<td>* 30</td>
<td></td>
</tr>
<tr>
<td>49-40</td>
<td>355</td>
<td>* 40</td>
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</tr>
<tr>
<td>39-30</td>
<td>358</td>
<td>* 55</td>
<td></td>
</tr>
<tr>
<td>29-20</td>
<td>204</td>
<td>* 70</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>93</td>
<td>* 85</td>
<td></td>
</tr>
</tbody>
</table>

*EC estimated from Figure 4

**GFR and serum Vitamin D:** 1, 25 OH₂ D₃ and 25 (OH) D₃
Both levels of 1, 25 OH₂ D₃ and 25 (OH) D₃ decreased with decreasing eGFR. The decrease in 1, 25 OH₂ D₃ was more rapid than the decrease in 25 (OH) D₃.

Multiple regression analysis showed a relationship between eGFR and 1, 25 OH₂ D₃ ($R^2 = 0.3827$, $p < 0.0001$) but not between eGFR and 25 OH D₃ ($p=0.8932$).

Deficiency of 1, 25 OH₂ D₃ was seen as GFR decreased to approx. 45 ml/min/1.73 m² (about the GFR as iPTH levels approached hyperparathyroidism levels). The prevalence of deficiency in 25 OH D₃ (25 OH D₃ < 15 ng/ml) remained stable until GFR < 30 ml/min, when the prevalence of 25 OH D₃ deficiency increased.

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73 m²)</th>
<th>N</th>
<th>** Prevalence (%) 1, 25 OH₂ D₃ deficiency (1, 25 OH₂ D₃ &lt; 22 pg/ml)</th>
<th>** Prevalence (%) 25 OH D₃ deficiency (25 OH D₃ &lt; 15 ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>61</td>
<td>12</td>
<td>10</td>
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<tr>
<td>70-79</td>
<td>117</td>
<td>15</td>
<td>10</td>
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<tr>
<td>60-69</td>
<td>230</td>
<td>15</td>
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<td>29-20</td>
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<td>20</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>93</td>
<td>65</td>
<td>25</td>
</tr>
</tbody>
</table>

** EC estimated from Figure 6.

49% of people with low 1, 25 OH₂ D₃ levels had high iPTH (irrespective of 25 OH D₃ levels), whereas 35% of those with low 25 OH D₃ levels had high iPTH levels ($p<0.05$).

Multivariate analysis (adjusted for age, gender, race, GFR, diabetes, urinary ACR, Ca, P):
Diabetes, decreased GFR, and increased urinary ACR independently predicted low 1, 25 OH₂ D₃.

Note: Limitations – population is older people, X-sectional analysis shows associations, not causal relationships, CKD defined by 1 creatinine measurement.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention/ exposure</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>St John A., Thomas MB, Davies CP et al. Determinants of intact parathyroid hormone and free 1,25-dihydroxyvitamin D levels in mild and moderate renal failure. <em>Nephron.</em> 1992; 61(4):422-427. Ref ID: 1811</td>
<td>Observational study 2 nephrology clinics, Australia</td>
<td>N total =51  N mild CRF (GFR 40-90 ml/min/1.73 m²) = 27 N moderate CRF (GFR 20-39 ml/min/1.73 m²) = 12 N healthy subjects = 12</td>
<td>Inclusion criteria: patients with mild (GFR 40-90) or moderate (GFR 20-39) age 22-68 years were recruited from 2 nephrology units in July 1988-June 1989. Healthy subjects with no prior renal disease were controls. Exclusion criteria: patients taking prednisolone, vitamin D derivatives, high dose oral calcium, or phosphate binders Baseline Characteristics: Primary diagnosis of renal disease: 28% glomerulonephritis, 28% hypertensive, 15% polycystic kidney disease, 13% chronic interstitial nephritis, 8% diabetic nephropathy, 8% renal transplant donors. Mean age: 34 (healthy), 48 (mild CRF), 45 (moderate CRF). Mean GFR: 115 ml/min/1.73m² (healthy), 56 ml/min/1.73m² (mild CRF), 32 ml/min/1.73m² (moderate CRF)</td>
<td>Serum markers of bone metabolism in people with mild renal failure (GFR 40-90 ml/min/1.73 m²) N = 27 Serum markers of bone metabolism in people with moderate renal failure (GFR 20-39 ml/min/1.73 m²) N = 12 Procedure: Following an overnight fast, GFR was determined by clearance of [⁹⁹mTc]DTPA from the plasma. Blood samples assayed for total Ca, P, albumin, creatinine, bicarbonate, alkaline phosphatase. Serum 1, 25 OH₂ D₃ was determined with a bovine thymus cytoreceptor assay. Serum 25-hydroxyvitamin D [25 (OH) D₃] was determined using rat kidney cytosol. Serum iPTH determined by an immunochemiluminometric assay.</td>
<td>Serum markers of bone metabolism in healthy people N=12</td>
<td>N/A</td>
<td>Serum P Serum Ca Serum intact parathyroid hormone (iPTH) Serum 1, 25-dihydroxyvitamin D (1, 25 OH₂ D₃) Serum 25-hydroxyvitamin D [25 (OH) D₃]</td>
<td>Telethon Foundation and Sir Charles Gairdner Hospital Research Foundation grants</td>
</tr>
</tbody>
</table>

**Effect size**

Changes in plasma iPTH and 1,25 Vit D precede changes in calcium or phosphate.
Plasma Ca:
There were NS differences in mean Ca levels for people with mild CRF (GFR 40-90 ml/min/1.73m², N=27, mean Ca 2.31 mmol/l) compared with healthy controls (N=12, mean Ca 2.27 mmol/l).

People with moderate CRF (GFR 20-39 ml/min/1.73m², N=12, mean Ca 2.24 mmol/l) had significantly lower Ca levels than people with mild CRF (GFR 40-90 ml/min/1.73m², N=27, mean Ca 2.31 mmol/l, p<0.05)

Plasma P:
There were NS differences in mean phosphate levels for people with mild CRF (GFR 40-90 ml/min/1.73m², N=27, mean P 1.0 mmol/l) compared with healthy controls (N=12, mean P 1.1 mmol/l).

People with moderate CRF (GFR 20-39 ml/min/1.73m², N=12, mean P 1.2 mmol/l) had significantly higher P levels than people with mild CRF (GFR 40-90 ml/min/1.73m², N=27, mean P 1.0 mmol/l, p<0.05)

Plasma iPTH
People with mild CRF (GFR 40-90 ml/min/1.73m², N=27, mean iPTH 57.5 pg/ml) had significantly higher levels of iPTH than healthy people (N=12, mean iPTH 25.4 pg/ml, p<0.05).

People with moderate CRF (GFR 20-39 ml/min/1.73m², N=12, mean iPTH 139 pg/ml) had significantly higher iPTH levels than people with mild CRF (GFR 40-90 ml/min/1.73m², N=27, mean iPTH 57.5 pg/ml, p<0.05).

People with moderate CRF (GFR 20-39 ml/min/1.73m², N=12, mean iPTH 139 pg/ml) had significantly higher iPTH levels than healthy people (N=12, mean iPTH 25.4 pg/ml, p<0.05).

Note that 17/39 (44%) people with CRF were still within the reference range of iPTH (even at low GFR). The increase in iPTH above reference values began at GFR < 60 ml/min/1.73m².

Plasma Vitamin D:
People with mild CRF (GFR 40-90 ml/min/1.73m², N=27, mean 1, 25 OH2 D3 = 42.1 pg/ml) had significantly lower levels of 1, 25 OH2 D3 compared with healthy people (N=12, mean 1, 25 OH2 D3 = 54.6 pg/ml, p<0.05).

People with moderate CRF (GFR 20-39 ml/min/1.73m², N=12, mean 1, 25 OH2 D3 = 39.2 pg/ml) had significantly lower levels of 1, 25 OH2 D3 compared with healthy people (N=12, mean 1, 25 OH2 D3 = 54.6 pg/ml, p<0.05).

Note that 9/39 (23%) people with CRF were BELOW the reference range of 1, 25 OH2 D3. This occurred at GFR < 60 ml/min/1.73m².

There were NS differences in 25 (OH) D3.

Note: – accurate measure of GFR used, but in small number of patients. Observational study.

13.2 BISPHOSPHONATE TREATMENT IN PEOPLE WITH CKD

What are the risks and benefits of bisphosphonates for preventing osteoporosis in adults with CKD?

Ref ID: 3990
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, Cummings SR. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. Journal of Bone and Mineral Research 2007; 22 (4): 503-508</td>
<td>RCT 1+ Secondary analysis of an RCT [Fracture Intervention Trial (FIT)]</td>
<td>N=6458 N=2027 in the vertebral fracture arm N=4432 in the clinical fracture arm</td>
<td>Inclusion criteria: women were enrolled in FIT if they were 55-80 years old, at least 2 years postmenopausal, femoral neck BMD ≤0.68 g/cm². Exclusion criteria: serum creatinine &gt;1.27 mg/dl, serum PTH &gt;85 pg/ml in isolation or serum PTH &gt; 65 pg/ml in combination with abnormal serum calcium, alkaline phosphatase or phosphate.</td>
<td>Alendronate (dose not mentioned in this paper)</td>
<td>Placebo</td>
<td>48 months in the clinical fracture arm</td>
<td>BMD Fractures: Clinical fractures as reported by patients (assessment by blinded radiologist)</td>
<td>Canadian Institute of Health Research</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Protocol: Bone mineral density (BMD) measured on whole body, femoral neck, total hip and lumbar spine using DXA. eGFR calculated by Cockroft-Gault formula. eGFR&lt;45 ml/min was considered severely reduced renal function; eGFR 45-59 ml/min moderately reduced renal function; eGFR ≥ 60 ml/min normal renal function. Incident vertebral fractures assessed by blinded radiologists. Blood chemistry (Ca, P, creatinine, ALP, PTH) measured at baseline and annually. Adverse events assessed over the phone or at clinic visits every 3 months.</td>
<td></td>
<td>36 months in the vertebral fracture arm</td>
<td>Radiographic vertebral fractures: identified by morphometric and semi-quantitative techniques</td>
<td>Adverse events</td>
</tr>
</tbody>
</table>
Effect size
Standard WHO definition of osteoporosis used: BMD at femoral neck, total hip or lumbar spine of ≤ 2.5 SD below mean BMD for young adult women (T score of ≤ -2.5); T score between -1 and -2.5 classified as osteopenia; T score >-1 classified as 'normal BMD'.

Change in BMD [%change (95%CI)], alendronate vs. placebo, by eGFR

<table>
<thead>
<tr>
<th></th>
<th>All women</th>
<th>Severely reduced eGFR (eGFR&lt;45)</th>
<th>Moderately reduced or normal eGFR (eGFR ≥45)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women (N=6458)</td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Total hip</td>
<td>4.9 ± 8.7%</td>
<td>5.6 (4.8-6.5)</td>
<td>4.8 (4.6-5.0)</td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>5.0 (4.0-5.9)</td>
<td>4.5 (4.2-4.8)</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Spine</td>
<td>6.6 ± 5.8%</td>
<td>6.7 (5.7-7.8)</td>
<td>6.6 (6.3-6.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>Women with osteoporosis (N=3214)</td>
<td></td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>Total hip</td>
<td>4.9 (3.7-6.3)</td>
<td>4.7 (4.4-5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>4.5 (3.2-5.8)</td>
<td>4.2 (3.8-4.7)</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Spine</td>
<td>5.9 (4.3-7.5)</td>
<td>6.4 (6.2-7.1)</td>
<td></td>
<td>0.33</td>
</tr>
</tbody>
</table>

Fracture risk [Odds ratio (95%CI)], alendronate vs. placebo, by eGFR

<table>
<thead>
<tr>
<th></th>
<th>All women</th>
<th>Severely reduced eGFR (eGFR&lt;45)</th>
<th>Moderately reduced or normal eGFR (eGFR ≥45)</th>
<th>p for interaction</th>
<th>Risk of fracture in women with eGFR&lt;45 vs. eGFR≥45</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women (N=6458)</td>
<td></td>
<td></td>
<td></td>
<td>0.90</td>
<td>1.3 (1.0-1.6)</td>
</tr>
<tr>
<td>Clinical fractures</td>
<td>0.8 (0.7-0.9)</td>
<td>0.78 (0.51-1.2)</td>
<td>0.81 (0.70-0.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine fractures</td>
<td>0.54 (0.37-0.78)</td>
<td>0.72 (0.31-1.7)</td>
<td>0.50 (0.32-0.76)</td>
<td>0.44</td>
<td>2.5 (1.6-3.9)</td>
</tr>
<tr>
<td>Women with osteoporosis (N=3214)</td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Clinical fractures</td>
<td>0.84 (0.45-1.54)</td>
<td>0.74 (0.61-0.91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine fractures</td>
<td>1.01 (0.29-3.6)</td>
<td>0.62 (0.36-1.10)</td>
<td></td>
<td>0.49</td>
<td></td>
</tr>
</tbody>
</table>

Serum creatinine: there was an increase in serum creatinine that was the same in those with and without reduced renal function (mean increase in both groups: 0.01 ± 0.10; p=0.88); and was the same in the placebo and alendronate treated groups (mean increase: 0.01 ± 0.10; p=0.99)

Adverse events
NS differences in adverse events experienced by people with severe renal dysfunction or reduced/normal renal function.

<table>
<thead>
<tr>
<th>Frequency of reported adverse events</th>
<th>SeVERELY REDUCED eGFR (eGFR&lt;45)</th>
<th>MODERATELY REDUCED or NORMAL eGFR (eGFR ≥45)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (%)</td>
<td>99.1</td>
<td>99.5</td>
<td>0.189</td>
</tr>
<tr>
<td>Gastrointestinal events (%)</td>
<td>4.5</td>
<td>5.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Conclusions: oral bisphosphonates are effective at increasing BMD and decreasing fracture risk and are not associated with an increase in serum creatinine, reduction in creatinine clearance, or an increase in adverse events.

Assessment of bias: RCT details of which are not mentioned in this paper, no mention of ITT, method of randomisation, concealment. Assessors of radiographic evidence were blinded. This was a post-hoc analysis.

Reference Study type/Evidence level Number of patients Patient characteristics Intervention Comparison Length of follow-up Outcome measures Source of funding
Kikuchi Y, Imakiire T, Yamada M, Saigusa T, Hyodo T, Kushiyama T, Higashi K, Hyodo N, Yamamoto K, Suzuki S, Miura S. Effect of risedronate on high-dose corticosteroid-induced bone loss in patients with glomerular disease. Nephrol Dial Transplant 2007; 22: 1593-1600 RCT 1+ Randomised, open-label, prospective study Randomisation using envelope randomisation method. ITT N=38 Drop out rate 0% Japanese population Inclusion criteria: patients with glomerulonephritis initiating high-dose corticosteroid therapy (>30 mg/day prednisolone, including steroid pulse therapy Exclusion criteria: severe renal dysfunction due to rapidly progressive glomerulonephritis, very high (>130%) or very low (<80%) BMD Baseline characteristics: There were NS differences in sex, age, BMI, BMD or the biochemical markers of bone metabolism among the groups. N=12 Group R: risedronate 2.5mg/day N=15 Group A: alfacalcidol 0.5 µg/day (an active vitamin D3 analogue) Procedure: Patients randomised to risedronate alone, alfacalcidol alone, or risedronate + alfacalcidol. Drugs were simultaneously started with the initiation of steroid therapy. No patients received Ca supplementation. BMD (assessed by DEXA) measured at baseline and 12 months following randomisation. CrCl N=11 Group R+A: risedronate 2.5mg/day and alfacalcidol 0.5 µg/day 1 year BMD GFR Urinary protein Serum blood urea nitrogen and creatinine (BUN) ALP iPTH osteocalcin urinary cross-linked N-telopeptide of type I collagen (NTx) Not stated
Mean GFR was 78 ml/min (Group R), 74 ml/min (Group R + A), 81 ml/min (Group A)

Urinary protein was higher in the R+A group than in group R or A, but this was not significant.

<table>
<thead>
<tr>
<th>Effect size</th>
<th>Group R</th>
<th>Group R+A</th>
<th>Group A</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD Changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD baseline (g/cm²)</td>
<td>1.04 ± 0.10</td>
<td>1.06 ± 0.11</td>
<td>1.02 ± 0.10</td>
</tr>
<tr>
<td>BMD at 12 months (g/cm²)</td>
<td>1.03 (NS change from baseline)</td>
<td>1.08 (p&lt;0.05 from baseline)</td>
<td>0.96 (p&lt;0.05 from baseline) [p=0.001 compared to R+A]</td>
</tr>
</tbody>
</table>

**Adverse Events:**
No patients were excluded due to adverse events and no list of adverse events given.

**Fractures:**
There were no fractures that occurred in the study.

Several factors (osteocalcin, ALP, urinary NTx, iPTH) showed significant changes from baseline; but NS significant differences between the groups.

**Predictive factors for loss of BMD:** patients were classified into 3 groups on the basis of BMD change and predictive factors for BMD loss were assessed (Group I BMD increase >1.1% (N=12); Group II mild change in BMD -3.2 to +1.1% (N=13); Group III BMD decreased > 3.2% (N=13)). There were no significant differences in sex, age, BMI, BMD or renal function at baseline among the groups. Urinary NTx was significantly higher in groups II and III than in group I. Serum osteocalcin, ALP also higher in Groups II and III than I, but NS.

Assessment of bias: ITT analysis, no drop outs, open-label study, small numbers.

**Reference:**
Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE

<table>
<thead>
<tr>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis 1+ Data</td>
<td>N=9883 dropout rate: 36% in</td>
<td>Inclusion criteria: inclusion criteria of different studies not mentioned. Population is osteoporotic women with renal disease.</td>
<td>Risedronate (5 mg daily)</td>
<td>Placebo</td>
<td>N= 4496 overall</td>
<td>Average duration of treatment 2 years.</td>
<td>Procter &amp; Gamble pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=4500 overall</td>
<td></td>
<td></td>
<td>Primary outcome: safety. Adverse</td>
<td></td>
</tr>
</tbody>
</table>

Chronic kidney disease: evidence tables DRAFT
from 9 randomised, double blind, placebo controlled, parallel group phase III trials were included, all used risedronate for the treatment of osteoporosis.

**Exclusion criteria:** patients were excluded from the individual studies if they had evidence of clinically significant systemic disease such as history of hyperparathyroidism, hyperthyroidism or osteomalacia within 1 year before enrolment; or markedly abnormal lab values including serum creatinine levels >1.1 times the ULN.

**Baseline characteristics:** within each renal impairment subgroup, the 2 treatment groups (placebo and risedronate) were very similar with respect to baseline demographic and disease characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Risedronate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4500</td>
<td>4496</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>75 (80)</td>
<td>75 (8.2)</td>
</tr>
<tr>
<td>Serum creatinine mg/dl</td>
<td>0.98 (0.208)</td>
<td>0.99 (0.22)</td>
</tr>
<tr>
<td>CrCl ml/min</td>
<td>49.5</td>
<td>49.2</td>
</tr>
</tbody>
</table>

N Severe CKD=301
N moderate CKD = 2034
N mild CKD = 2161

Protocol: Analysis of trials stratified by renal function: mild (CrCl >50 to 80 ml/min), moderate (CrCl >30 to <50 ml/min) or severe (CrCl <30 ml/min) renal impairment. BMD (assessed with DXA) measured at baseline, at 6, 12, 24 months and at endpoint. Vertebral fractures (decrease of 15% or more in vertebral height or a change from grade 0 to grade 1 or more) assessed by blinded radiologists.

N Severe CKD=271
N moderate CKD = 2037
N mild CKD = 2192

Secondary outcomes: efficacy BMD (measured by DXA) Creatinine clearance (CrCl)
Effect size
Of the 9883 women on the database 91% (8996/9883) had some degree of renal impairment. Severe 572/9883 (5.8%), moderate 4071/9883 (41.2%) and mild 4353/9883 (44.0%).

Adverse events:
The incidence of overall, urinary and renal function related adverse events were similar within and between treatment groups in the subgroups of patients with severe, moderate and mild renal impairment. Statistically and clinically there were NS differences.

Changes in serum creatinine:
There were NS differences between the placebo and risedronate groups in changes from baseline in serum creatinine in any of the renal impairment groups.

<table>
<thead>
<tr>
<th>BMD:</th>
<th>Placebo vs risedronate in mild renal impairment</th>
<th>Placebo vs risedronate in moderate renal impairment</th>
<th>Placebo vs risedronate in severe renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % change (SE) in lumbar spine BMD</td>
<td>-0.14% (0.19%) vs 3.96% (0.18%); p&lt;0.001</td>
<td>-0.47% (0.50%) vs 4.33 (0.51%); p&lt;0.001</td>
<td>-1.37% (1.72%) vs 4.23% (1.82%); p&lt;0.001</td>
</tr>
</tbody>
</table>

The mean percent increase from baseline to endpoint in BMD at the femoral neck and trochanter was significantly greater in the risedronate 5 mg group than in the placebo group in all 3 renal impairment subgroups, except at the femoral neck in the severe renal impairment subgroup.

Incidence of new vertebral fractures: Incidence of new vertebral fractures was significantly lower in the risedronate group than the placebo groups within each renal impairment subgroup. Within the risedronate treatment group, the incidence of new vertebral fractures was similar across renal impairment subgroups (p=0.124). The incidence in the placebo treated group increased significantly with the severity of renal impairments (p<0.001). [Note that Figure 2 was very difficult to interpret. Looks as if 56% of placebo and 12% of risedronate group had new fractures in the severe CKD group. Is this reasonable?]

Assessment of bias: posthoc analysis of pooled data from 9 trials, ITT analysis, all trials reported to be randomised and double blind but no details of each given.

Ref ID: 3979

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujii N, Hamano T, Mikami S, Nagasawa Y, Isaka Y, Moriyama T, Horio M, Imai E, Hori M, Ito T. Risedronate, an effective treatment for glucocorticoid–induced bone loss in CKD patients</td>
<td>RCT 1- Poorly randomised, prospective, open-label, study Per-protocol analysis</td>
<td>N=114 19.2% (1578) of patients taking risedronate withdrew</td>
<td>Inclusion criteria: CKD outpatients receiving glucocorticoid therapy (prednisone equivalent of ≥2.5 mg/day) for &gt;6 months Exclusion criteria: current treatment with bisphosphonate, native Vit D, oestrogen, selective</td>
<td>Group A: Active Vit D alone N=38 Group B: Active Vit D + risedronate 2.5 mg/day (randomisation conducted so that this group had 40% more patients than group A) N=50</td>
<td>Group C: Risedronate 2.5 mg/day N=26</td>
<td>1 year Bone mineral density (BMD) Creatinine clearance (Ccr) Serum N-terminal telopeptides</td>
<td>In part by Sanofi-Aventis (Tokyo, Japan)</td>
<td></td>
</tr>
</tbody>
</table>
DRAFT FOR CONSULTATION

with or without concomitant active vitamin D (PRIUS-CKD) Nephrol Dial Transplant 2007; 22: 1601-1607

Randomisation using computer software

<table>
<thead>
<tr>
<th></th>
<th>Group A (Vitamin D alone)</th>
<th>Group B (Vitamin D + Risedronate)</th>
<th>Group C (Risedronate alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in BMD Lumbar spine at 12 months</td>
<td>-1.2 ± 0.6% NS, no p-value given</td>
<td>+2.8 ± 1.3% Significant, no p-value given</td>
<td>+2.1 ± 1.0% Significant, no p-value given</td>
</tr>
<tr>
<td>Change in S-NTX at 6 months</td>
<td>+4.7% (p&lt;0.05 compared to B)</td>
<td>-19.6% (p&lt;0.01 for change from baseline)</td>
<td>-14.6% (p&lt;0.05 for change from baseline)</td>
</tr>
<tr>
<td>Change in bone ALP at 6 months</td>
<td>+26.9% (p&lt;0.05 compared to B or C)</td>
<td>-11.6%</td>
<td>-10%</td>
</tr>
</tbody>
</table>

Baseline characteristics: Mean age (SD) 42.5 ± 16.6 years Sex Male 47% (54/114) CrCl (SD) 99.6 ± 35.8 ml/min/1.73m²

Protocol: Subjects randomised to Vitamin D alone (Group A), Vitamin D + risedronate (Group B). Remainder allocated to risedronate alone (Group C). Diuretic, Ca supplement, beta blocker, vitamin D use not changed during study. BMD of the second to fourth lumbar vertebrae measured every 6 months and blood chemistry at baseline, 1, 3, and 6 months, after randomisation measured using a dual-energy X-ray absorptiometer. CrCl estimated using the Cockcroft-Gault formula.

Effect size

<table>
<thead>
<tr>
<th></th>
<th>Group A (Vitamin D alone)</th>
<th>Group B (Vitamin D + Risedronate)</th>
<th>Group C (Risedronate alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in BMD Lumbar spine at 12 months</td>
<td>-1.2 ± 0.6% NS, no p-value given</td>
<td>+2.8 ± 1.3% Significant, no p-value given</td>
<td>+2.1 ± 1.0% Significant, no p-value given</td>
</tr>
<tr>
<td>Change in S-NTX at 6 months</td>
<td>+4.7% (p&lt;0.05 compared to B)</td>
<td>-19.6% (p&lt;0.01 for change from baseline)</td>
<td>-14.6% (p&lt;0.05 for change from baseline)</td>
</tr>
<tr>
<td>Change in bone ALP at 6 months</td>
<td>+26.9% (p&lt;0.05 compared to B or C)</td>
<td>-11.6%</td>
<td>-10%</td>
</tr>
</tbody>
</table>

Changes in BMD at the femoral neck were not obvious in any group.

There was a mild tendency of a stepwise increase in the lumbar BMD with the greater reduction in S-NTX at 6-months (but not statistically significant). Baseline values of bone turnover markers were not associated with percentage changes in lumbar BMD after 1 year of risedronate treatment.
Changes in CrCl were similar across all groups.

Assessment of bias: only the patients in the active Vit D group were randomised, patients in group C were allocated to risedronate without any form of randomisation. Per-protocol analysis. Open-labelled study.

Conclusions: monotherapy with active vitamin D fails to maintain the bone mass of CKD patients receiving glucocorticoids. Risedronate with or without vitamin D is an effective treatment for glucocorticoid induced bone loss in CKD patients in terms of BMD.

Caution: 2.5 mg risedronate below recommended dose for treatment of osteoporosis.

### 13.3 VITAMIN D SUPPLEMENTATION IN PEOPLE WITH CKD

| What type of vitamin D supplementation, if any, should be used in adults with CKD? |
|---|---|---|---|---|---|---|
| Ref ID: 66 | Reference | Study type/ Evidence level | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Source of funding |
| | Coyne D, Acharya M, Qiu P et al. Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD.[see comment], American Journal of Kidney Diseases. 2006; 47(2):263-276. Ref ID: | RCT 1+ Pooled analysis of 3 RCTs with identical inclusion/exclusion criteria and different dosing regimens (3X weekly or once daily) multicenter USA, Poland | N = 220 Drop out rate 11% in Paricalcitol, 17% in placebo | Inclusion criteria: identical for all 3 RCTs: people > 18 years diagnosed with CKD for at least 2 months and not expected to require dialysis for at least 6 months, 2 consecutive iPTH that average ≥ 150 pg/ml (all values must be ≥ 120 pg/ml) and 2 consecutive Ca 1.99-2.40 mmol/l and 2 consecutive P ≤ 1.68 mmol/l. Exclusion criteria: identical for all 3 RCTs: people taking vitamin D therapy 4 weeks prior to trial, acute renal failure in previous 12 months | N=107 Paricalcitol (19-nor-1,25-dihydroxyvitamin D2) Procedure: Patients attended a screening visit (to assess eligibility), pre-treatment phase (1-4 weeks to confirm eligibility), treatment phase (24 weeks of active treatment), and follow-up phase (discontinuation of drugs and monitoring of adverse events for 1 month). Participants were randomised to paricalcitol (either thrice weekly or once/daily) or placebo. The initial dose of paricalcitol was 2 microg thrice weekly in people with baseline iPTH ≤ 500 pg/ml or 4 microgram thrice weekly if baseline iPTH > 500 pg/ml. In the daily dose trial, | N=113 placebo | 6 months | N = 113 placebo | Serum Ca | P | iPTH | GFR | Osteocalcin | Bone ALP | urinary deoxy pyridinoline | urinary pyridinoline | Abbott |
### Baseline characteristics

There were NS differences between people receiving placebo or paricalcitol for sex, race, age (62 years), eGFR (23 ml/min/1.73 m²), P, iPTH, bone ALP, osteocalcin, urinary deoxypryidinoline, urinary pyridinoline. Serum Ca was significantly higher in the paricalcitol group than the placebo group, p=0.039. NS differences between baseline characteristics for thrice weekly or once daily studies.

### Effect size

In the thrice/weekly studies (2 RCTs), N=73 placebo and N=72 paricalcitol. In the once daily RCT, N=40 placebo and N=35 paricalcitol. The mean daily dose of paricalcitol was 1.3 to 1.4 microg/day. Overall paricalcitol exposure was 43.2 patient years. Average weekly dose of paricalcitol was titrated upwards, peaking at week 13 (12.2 microg) and then titrated downward thereafter. The majority of participants did NOT take Ca supplements or Ca-based phosphate binders (83/107 paricalcitol and 84/113 placebo).
Primary outcome: 2 consecutive decreases ≥ 30% of iPTH from baseline
After 6 months of treatment, 91% of people on paricalcitol (N=101) and only 13% of people on placebo (N=108) achieved 2 consecutive ≥ 30% decreases in serum iPTH from baseline (p<0.001 between groups). Similar results when thrice weekly and once/daily RCTs were analysed separately. Also similar results when stratified by baseline iPTH (150-300 ng/l, 301-500 ng/l, and > 500 ng/l)

28% of paricalcitol treated people reached the primary endpoint by week 5, 68% reached the primary endpoint by week 9, 77% achieved it by week 11.

After 6 months of treatment, 74% of people on paricalcitol (N=101) and 0% of people on placebo (N=108) achieved 4 consecutive ≥ 30% decreases in serum iPTH from baseline (p<0.001 between groups).

75% of the paricalcitol group (N=101) and only 12% of the placebo group (N=108) achieved iPTH < 110 ng/l (significant between groups but p not given).

Serum iPTH:
Serum iPTH decreased significantly from baseline to 6 months treatment with paricalcitol. A significant decrease in iPTH was seen at 3 weeks treatment with paricalcitol and a sustained decrease thereafter. The maximum mean decrease was 45.2% in the paricalcitol group compared with an increase of 13.9% in the placebo group (p<0.001 between groups).

Adverse Events:
Adverse events were similar between placebo and paricalcitol groups.

Death: N=2 paricalcitol, N=1 placebo (but not causally attributed to paricalcitol)

Serious adverse events: N=20 paricalcitol, N=18 placebo (only 1 adverse event thought to be attributed to treatment N=1 bradycardia in the paricalcitol group)

Discontinued due to adverse events: N=6 paricalcitol, N=5 placebo.

Hypercalcaemia (2 consecutive Ca > 2.62 mmol/l) occurred N=2 on paricalcitol and N=0 in placebo, p=0.237, NS.

Hyperphosphataemia (2 consecutive P > 1.78 mmol/l) occurred in N=11 paricalcitol and N=13 placebo, p=0.830 NS

Serum Ca:
Mean serum calcium increased slightly in people taking paricalcitol (change Ca 0.02 mmol/l from baseline to 6 months or 1% increase) while there were small decreases in serum Ca in the placebo group, NS between groups.

Serum P:
There were NS changes in serum P in the paricalcitol or placebo groups.

Serum osteocalcin:
Serum osteocalcin decreased from baseline to 6 months in the paricalcitol group (N=100, change osteocalcin: -21.6 ng/ml), compared with an increase in osteocalcin in the placebo group (N=104, change osteocalcin +10.7 ng/ml, p<0.001 between groups).
Bone-specific alkaline phosphatase
Bone ALP significantly decreased from baseline to 6 months in the paricalcitol group (N=101, change bone ALP: -7.89 microg/l), compared with a smaller decrease in bone ALP in the placebo group (N=107, change bone ALP: -1.44 microg/l, p<0.001 between groups).

Urinary deoxypyridinoline
There were NS differences between paricalcitol (n=96) or placebo (N=100) groups for changes in urinary deoxypyridinoline.

Urinary pyridinoline
Urinary pyridinoline decreased in the paricalcitol group (N=99, change urinary pyridinoline: -3.61 nmol/mmol creatinine), compared with an increase in the placebo group (N=104, change urinary pyridinoline +3.77 nmol/mmol creatinine, p=0.006 between groups)

Change in GFR:
After 6 months, eGFR decreased in both placebo (N=93, change in eGFR: -1.57 ml/min/1.73 m² or -6.95% change) and paricalcitol (N=82, change in eGFR: -2.52 ml/min/1.73 m² or -10.40 % change) groups, but there were NS differences between treatments (p=0.269).

Ref ID: 347

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamdy NA, KanisJA, Beneton MN et al. Effect of alfalcacidol on natural course of renal bone disease, in mild to moderate renal failure,[see comment]. British Medical Journal. 1995; 310(6976):358-363. Ref</td>
<td>RCT 1+ Randomised, double-blind prospective study 17 centres in UK, Belgium, France, Netherlands ITT</td>
<td>N =176 Drop out rate 18% in Alfacalcidol, 25% in placebo</td>
<td><strong>Inclusion criteria:</strong> people with CrCl 15-50 ml/min and no clinical, biochemical, radiographic evidence of renal bone disease <strong>Exclusion criteria:</strong> symptomatic bone disease, increased serum Ca or alkaline phosphatase (ALP) or disturbance in liver function (≥ 1.5 fold increase liver aminotransferase activity)</td>
<td>N=89 Alfacalcidol (1α-hydroxycholecalciferol or 1α-hydroxyvitamin D₃) Procedure: People randomised to alfacalcidol (0.25 microg/day and adjusted between 0.25 microg every other day up to 1 microgram/day to maintain Ca at upper normal lab limit) or placebo. Ca supplementation (max dose 500 mg/day) permitted. Phosphate binding drugs other than Ca permitted when dietary P restriction was inadequate to maintain serum P &lt; 2.2 mmol/l. Other drugs for disease management permitted. Serum creatinine, P, Ca (corrected for albumin)</td>
<td>N=87 placebo 2 years</td>
<td>Serum Ca P iPTH CrCl Osteitis fibrosa Osteomalacia (defined as ≥ 5 osteoid lamellae) Bone indices Adverse Events: hypercalcaemia GI pseudogout</td>
<td>Not stated</td>
<td></td>
</tr>
</tbody>
</table>
### Effect size

Retrospective analysis of bone biopsy showed that, at baseline, 132 people had evidence of bone disease.

### Adverse Events:

18% (N=16/89) of people on alfacalcidol and 25% of people on placebo (N=22/87) withdrew from the trial (p=0.24, NS). The main reason for withdrawal was initiation of dialysis (8 on alfa, 10 on placebo), death (4 alfa, 1 placebo), other reason (4 on alfa, 10 on placebo), hypocalcaemia (0 alfa, 1 placebo). Mild GI disturbances were reported in 6 people on alfacalcidol and 1 on placebo. Pseudogout was reported by 2 people on alfacalcidol. No withdrawal due to unexpected progression of renal disease, or hypercalcemia.

### Serum Ca:

Mean serum calcium increased significantly in people taking alfacalcidol (+0.07 mmol/l by 24 months, N=89), while there were NS changes in calcium in people taking placebo, p<0.001 between groups. Mild hypercalcaemia (Ca > 2.63 mmol/l on 2 occasions) was seen in 10 patients receiving alfacalcidol and 3 patients receiving placebo (p=0.09, NS). Severe hypercalcaemia (Ca > 3.00 mmol/l on 1 occasion) was observed in 4 people taking alfacalcidol and 0 people on placebo.

### Serum P:

Serum P increased in both placebo and alfacalcidol groups with NS differences between the groups.

### Serum iPTH:

iPTH decreased NS from baseline to 18 months treatment with alfacalcidol (-1.6 pmol/l), whereas iPTH increased significantly from baseline to 18 months in those taking placebo (+7.3 pmol/l, p<0.001). At 24 months, iPTH returned to baseline levels in those with alfacalcidol treatment.
Change in CrCl:
After 24 months, CrCl decreased in both placebo (-4.0 ml/min) and alfacalcidol groups (-5.7), NS between treatments, p=0.94.

Bone abnormalities:
The proportion of people with bone abnormalities at the beginning of the study were similar between the placebo (N=45, 73%) and alfacalcidol (N=55, 76%). After 24 months treatment, 54% of people taking alfacalcidol (N=39) and 82% on placebo (N=51) had bone abnormalities (no p given).

Fibrosis:
In people with histological bone abnormalities at baseline (N=100), fibrosis significantly decreased in people taking alfacalcidol (N=55, -0.58), while fibrosis increased in the placebo group (N=45, +0.07), p=0.0002.

Bone volume:
In people with histological bone abnormalities at baseline (N=100), There were NS differences in bone volume in the placebo (N=45, 1.09) or alfacalcidol (N=55, 1.22), p=0.75

Osteoid volume: decreased significantly in alfacalcidol (N=55, -0.30, p<0.001 from baseline) NS change in placebo (N=45, 0.09), p=0.005 between groups
Osteoid surface: decreased significantly in alfacalcidol (N=55, -6.85, p<0.01 from baseline) NS change in placebo (N=45, 1.35), p=0.008 between groups
Osteoblast surface: decreased significantly in alfacalcidol (N=55, -0.54, p<0.01 from baseline) NS change in placebo (N=45, 0.37), p=0.009 between groups
Osteoclase surface: NS change in alfacalcidol (N=55, -0.30) NS change in placebo (N=45, 0.17), p=0.002 between groups

Mineral apposition rate: NS changes in alfacalcidol or placebo and NS between groups (p=0.34)

Bone formation rate: decreased significantly in alfacalcidol (N=55, -4.66, p<0.05 from baseline) NS change in placebo (N=45, 0.51), p=0.15 NS between groups

Osteomalacia
In people with histological bone abnormalities at baseline (N=100), Osteomalacia improved in people taking alfacalcidol as the number of osteoid lamellae decreased (N=55, -0.73) whereas the number of osteoid lamellae increased in the placebo group (N=45, 0.32), p=0.002.

Bone resorption:
In people with histological bone abnormalities at baseline (N=100), Bone resorption decreased in people taking alfacalcidol compared with placebo. The eroded bone surface significantly decreased in the alfacalcidol group (N=55, -3.76 eroded surface), while it increased in the placebo group (N=45, eroded surface +0.45), p=0.04. Also, alfacalcidol (-0.86 active eroded surface) was associated with a significant decrease of active eroded surface compared with placebo (+0.49 active erode surface), p=0.0006.

Assessment of bias: ITT analysis only for biochemical analysis, not bone histology, European multicentre trial, applicable to people with mild/moderate CKD with subclinical/early bone disease, no discussion of concealment.

Ref ID: 428

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
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</table>

Chronic kidney disease: evidence tables DRAFT

<table>
<thead>
<tr>
<th>RCT 1+</th>
<th>N =30</th>
<th>Inclusion criteria: consecutive non-dialysed people with serum creatinine &gt; 180 micromol/l and stable renal function for previous 4 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised, double-blind prospective study</td>
<td>Drop out rate 9.9% in 1,25-dihydroxyvitamin D3, 9.9% in placebo</td>
<td></td>
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<tr>
<td>1 centre Norway</td>
<td></td>
<td></td>
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<tr>
<td>No ITT</td>
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<td></td>
</tr>
</tbody>
</table>

**Exclusion criteria:** not stated

**Baseline characteristics:** Creatinine range 186-840 micromol/l. NS differences between 2 groups for age (48 years), creatinine, Ca, ionised Ca, P, ALP, PTH, bone histomorphometric measures

**Procedure:** People randomised to 1,25-dihydroxyvitamin D3 (0.25 microg/day for the first 14 days, and then 0.5 microg/day for duration of study) or placebo. Treatment was stopped if hypercalcemia occurred (Ca > 2.7 mmol/l), and then once levels were normal, treatment resumed at half the previous dose. Other drugs for disease management permitted. Serum creatinine, P, Ca, ALP, PTH (mid-region radioimmunoassay) and CrCl (24-h urine collection) measured at baseline and at 1, 2, 4, 6, weeks and then once monthly thereafter. A transiliac crest bone biopsy was performed at baseline and at end of the study.

**Effect size**

NS difference in cumulative or daily dose of phosphate binders between placebo or calcitriol. Median values of most bone indices were within normal range in both trial arms.

Normal range: Ca 2.2-2.6 mmol/l; P 0.8 to 1.6 mmol/l; ALP 60-180 U/l; PTH <0.6 microg/l

**Adverse Events:**

8 patients on 1,25-dihydroxyvitamin D3 had hypercalcemia. There was no discussion of hypercalcemia in placebo group.
Serum Ca:
Median serum calcium significantly increased in people taking 1,25- dihydroxyvitamin D3 (N=14, 2.30 mmol/l at baseline to 2.50 mmol/l at 8 months, p<0.01), whereas Ca decreased significantly in the placebo group (N=14, 2.40 mmol/l at baseline and 2.30 mmol/l at 8 months). P<0.01 for end of study values in placebo versus 1,25- dihydroxyvitamin D3.

Serum P:
Median serum P did NS change in either the placebo or 1,25- dihydroxyvitamin D3 groups. 8 patients in each group took aluminium-containing phosphate binders.

Serum iPTH:
Median serum iPTH decreased significantly from baseline to 8 months treatment with 1,25- dihydroxyvitamin D3 (N=14, 1.33 at baseline to 0.98 microg/l at 8 months, p<0.01). In the placebo group iPTH significantly increased (N=14, 0.94 at baseline to 1.37 microg/l at 8 months, p<0.01).

Serum alkaline phosphatase (ALP):
Median serum ALP decreased significantly in people taking 1,25- dihydroxyvitamin D3 (N=14, 201 U/l at baseline to 155 U/l at 8 months, p<0.05). By contrast, ALP did NS change in the placebo group (209 U/l at baseline to 200 U/l at 8 months, NS). P<0.05 for end of study values in placebo versus 1,25- dihydroxyvitamin D3.

Change in CrCl:
After 8 months, median CrCl decreased in both placebo (approx. – 5 ml/min estimated from Figure 1) and 1,25- dihydroxyvitamin D3 (approx. – 5 ml/min estimated from Figure 1) groups, but there were NS differences between treatments.

Bone Indices:
Bone volume: NS change in bone volume in placebo or 1,25- dihydroxyvitamin D3 groups. Both groups within normal reference range (13-32%).

Osteoid volume: significantly decreased in the 1,25- dihydroxyvitamin D3 group (5% at baseline to 3% after 8 months, p<0.01) but not in the placebo group (8% at baseline to 6% at 8 months, NS). P<0.01 for end of study values in placebo versus 1,25- dihydroxyvitamin D3.

Osteoid thickness significantly decreased in the 1,25- dihydroxyvitamin D3 group (9.6 micrometer at baseline to 6.1 micrometer after 8 months, p<0.01) but not in the placebo group (9.0 micrometer at baseline to 10 micrometer at 8 months, NS).

Osteoid surface significantly decreased in calcitriol group (p<0.05 change from baseline and p<0.01 compared with placebo), whereas there was NS change in the placebo group.

Eroded surface significantly decreased in calcitriol group (p<0.05 change from baseline and p<0.05 compared with placebo), whereas there was NS change in the placebo group.

Osteoclast surface significantly decreased in calcitriol group (p<0.01 change from baseline and p<0.01 compared with placebo), whereas there was NS change in the placebo group.

Bone formation rate significantly decreased in calcitriol group (p<0.01 change from baseline and p<0.05 compared with placebo), whereas there was NS change in the placebo group.
**Bone mineralization:**

Mineralization surface: significantly decreased in the calcitriol group (12% at baseline to 6.5% at 8 months, p<0.01) and significantly increased in placebo group (10% at baseline to 19% at 8 months, p<0.01 compared with end value of calcitriol treatment).

Mineral apposition rate: significantly decreased in calcitriol group (0.53 micrometer/day at baseline to 0.44 micrometer/day at 8 months, p<0.05). There was NS change in the placebo group ((0.55 micrometer/day at baseline to 0.50 micrometer/day at 8 months).

Doubly labelled trabecular surfaces: NS decrease in 1,25-dihydroxyvitamin D3 and a NS increase in placebo group. Neither group was significantly different from normal controls.

Singly labelled trabecular surfaces: significant decrease in calcitriol group (p<0.01 from baseline). NS increase in placebo group.

Note: authors caution about dosing with calcitriol due to hypercalcemia. Must monitor Ca and CrCl closely.

Assessment of bias: no ITT analysis.

<table>
<thead>
<tr>
<th>Ref ID: 4010</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Przedlacki J, Manelius J, Huttunen K. Bone mineral density evaluated by dual-energy X-ray absorptiometry after one-year treatment with calcitriol started in the predialysis phase of chronic renal failure, Nephron. 1995; 69(4):433-437. Ref ID: 4010</td>
<td>RCT 1+ Randomised, double-blind prospective study 1 centre Finland No ITT</td>
<td>N =26 N=25 completed the study Drop out rate 0% in 1,25-dihydroxyvitamin D3, 7% in placebo</td>
<td>Inclusion criteria: consecutive non-dialysed people with GFR &lt; 51.2 ml/min, age &lt; 70 years. Exclusion criteria: pregnancy, renal stones, hypercalcemia (Ca &gt; 2.6 mmol/l), diabetes, GI diseases, treatment with anticonvulsants, anticoagulants, vitamin D metabolites, steroids</td>
<td>N=13 Calcitriol (1,25-dihydroxyvitamin D3) Procedure: Patients randomised to 1,25-dihydroxyvitamin D3 (0.25 microg/day steady dose) or placebo. Patients were on a low-protein (0.6g/kg) and low-phosphate (800 mg/day) diets. Calcium acetate (0.75-1.5 g/day phosphate binder) prescribed to all patients when Ca &lt; 2.6 mmol/l, P &gt; 0.8 mmol/l). Other drugs for disease management</td>
<td>N=12 placebo 12 months</td>
<td>Serum Ca P iPTH GFR Alkaline phosphatase (ALP) osteocalcin Bone Mineral Density (BMD) Adverse Events: hypercalcaemia hyperphosphataemia</td>
<td>Hoffmann-La Roche</td>
<td></td>
</tr>
</tbody>
</table>
Baseline characteristics: NS differences between placebo and calcitriol groups for clinical and biochemical results, baseline BMD, or for dose of calcium acetate phosphate binders. Serum 1,25-dihydroxyvitamin D3 was higher in the placebo group (p<0.01).

Effect size
NS difference in cumulative or daily dose of phosphate binders (calcium acetate) between placebo or calcitriol.

Adverse Events:
1 patient in placebo withdrew due to death from MI.

Dialysis initiated in 2 from placebo group (at 11 and 9 months of the study) and in 1 from the calcitriol group (at 10 months).

Hypercalcaemia (Ca > 2.6 mmol/l): N=2 calcitriol and N= 0 in placebo. Resolved after calcium acetate was stopped for a few days.

Hyperionised calcaemia (blood ionised Ca > 1.29 mmol/l) in N=5 calcitriol and N=3 placebo group. Resolved after calcium acetate was stopped for a few days.

Hyperphosphataemia (P>1.5 mmol/l) occurred in N=3 placebo and N=10 calcitriol (NS between groups).

Bone Mineral Density (BMD):
BMD of the lumbar spine L2-L4 significantly increased in the calcitriol group (N=13, mean BMD 1.111 g/cm² at baseline to 1.133 g/cm² at 12 months, p<0.001). BMD of the lumbar spine L2-L4 significantly decreased in the placebo group (N=12, mean BMD 1.214 g/cm² at baseline to 1.201 g/cm² at 12 months, p<0.05).

The change in BMD of the lumbar spine was significantly different between the calcitriol (+0.028 g/cm² or +3.93%/year) and the placebo (- 0.022 g/cm² or -0.62%/year, p<0.01) groups.

BMD of the femoral neck significantly increased in the calcitriol group (N=13, mean BMD 0.806 g/cm² at baseline to 0.832 g/cm² at 12 months, p<0.001). BMD of the femoral neck significantly decreased in the placebo group (N=12, mean BMD 0.860 g/cm² at baseline to 0.845 g/cm² at 12 months, p<0.05).
The change in BMD of the femoral neck was significantly different between the calcitriol (+0.035 g/cm² or + 3.37%/year) and the placebo (- 0.016 g/cm² or - 2.17%/year, p<0.001) groups.

There was NS change in the BMD of Ward’s triangle in the calcitriol group, whereas BMD of Ward’s triangle significantly decreased in the placebo group (0.720 g/cm² at baseline to 0.702 g/cm² at 12 months, p<0.05)

BMD of the trochanter significantly increased in the calcitriol group (N=13, mean BMD 0.708 g/cm² at baseline to 0.724 g/cm² at 12 months, p<0.05). BMD of the trochanter significantly decreased in the placebo group (N=12, mean BMD 0.800 g/cm² at baseline to 0.783 g/cm² at 12 months, p<0.05).

**Serum Ca:**
There were NS changes in mean serum calcium in people taking 1,25- dihydroxyvitamin D3 or placebo.

**Serum P:**
Mean serum P did NS change in either the placebo or 1,25- dihydroxyvitamin D3 groups.

**Serum iPTH:**
Mean serum iPTH decreased significantly from baseline to 12 months treatment with 1,25- dihydroxyvitamin D3 (N=13, 150 ng/l at baseline to 105.8 ng/l at 12 months, p<0.05). In the placebo group there were NS changes in iPTH (N=13, 122.6 ng/l at baseline to 151.4 ng/l at 12 months, p not stated).

**Serum alkaline phosphatase (ALP)**
Mean serum ALP decreased significantly in people taking 1,25- dihydroxyvitamin D3 (N=13, 165.0 U/l at baseline to 143 U/l at 12 months, p<0.05). ALP did NS change in the placebo group.

**Serum osteocalcin:**
Mean serum osteocalcin significantly decreased in the calcitriol group (26.3 micromol/l at baseline to 20.0 micromol/l at 12 months, p<0.05). Mean serum osteocalcin significantly increased in the placebo group (24.6 micromol/l at baseline to 28.3 micromol/l at 12 months, p<0.05).

**Change in GFR:**
After 12 months, mean GFR significantly decreased in both placebo (31.3 ml/min at baseline to 26.3 ml/min at 1 year, p<0.05) and 1,25- dihydroxyvitamin D3 groups (21.5 ml/min at baseline to 18.7 ml/min at 1 year, p<0.05) groups, but there were NS differences between treatments.

Assessment of bias: no ITT analysis (but difficult to do this when there is no BMD-DEXA result at the end of the study). No discussion of concealment.

<table>
<thead>
<tr>
<th>Procedure: Participants randomised to calcitriol (0.125 microg/day) or placebo. Ca carbonate permitted when serum P &gt; 1.7 mmol/l and up to 1.5 g aluminium hydroxide permitted if hypercalcaemia &gt; 2.7 mmol/l. Serum creatinine, P, Ca , ALP, osteocalcin, 24-h urine collections, PTH measured at baseline and at the end of the study. Ca, P measured every 2 weeks for the first 6 months, then every 3 months for safety reasons.</th>
<th>Procedure: Participants randomised to calcitriol (0.125 microg/day) or placebo. Ca carbonate permitted when serum P &gt; 1.7 mmol/l and up to 1.5 g aluminium hydroxide permitted if hypercalcaemia &gt; 2.7 mmol/l. Serum creatinine, P, Ca , ALP, osteocalcin, 24-h urine collections, PTH measured at baseline and at the end of the study. Ca, P measured every 2 weeks for the first 6 months, then every 3 months for safety reasons.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion criteria: proteinuria &gt; 3.5 g/day, diabetes, immunosuppressive therapy, vitamin D deficiency &lt; 10 nmol/l 25 (OH) D3, anticonvulsant therapy, nephrocalcinosis</td>
<td>Exclusion criteria: proteinuria &gt; 3.5 g/day, diabetes, immunosuppressive therapy, vitamin D deficiency &lt; 10 nmol/l 25 (OH) D3, anticonvulsant therapy, nephrocalcinosis</td>
</tr>
<tr>
<td>Baseline characteristics: NS differences between people receiving placebo or calcitriol. All patients were asymptomatic with respect to renal bone disease and had serum Ca &lt; 2.7 mmol/l and P &lt; 2.2 mmol/l on three separate occasions prior to randomisation.</td>
<td>Baseline characteristics: NS differences between people receiving placebo or calcitriol. All patients were asymptomatic with respect to renal bone disease and had serum Ca &lt; 2.7 mmol/l and P &lt; 2.2 mmol/l on three separate occasions prior to randomisation.</td>
</tr>
</tbody>
</table>

**Effect size**

**Serum iPTH:**

ITT analysis: N=52

iPTH decreased from baseline in the calcitriol group (16.2 pmol/l at baseline to 18.2 pmol/l after 12 months, p not given, N=28) whereas iPTH increased from baseline in those taking placebo (14.0 pmol/l at baseline to 27.8 pmol/l at 12 months , N=24, p<0.05 between placebo and calcitriol).

Post-hoc analysis (N=45 who completed study)

NS difference between study end values of iPTH between placebo and calcitriol group. Post-hoc analysis stratifying participants by baseline serum creatinine showed NS difference end of study values of iPTH between placebo and calcitriol groups for people with creatinine < 3 mg/dl. In people with creatinine > 3 mg/dl, iPTH increased significantly in the placebo group (p<0.05 from baseline), but iPTH did not change in the calcitriol group (p=0.4, NS).
**Adverse Events:**
There was no hypercalcaemia (Ca > 2.7 mmol/l on three consecutive occasions) in either calcitriol or placebo groups. There was no hyperphosphataemia (P> 2.2 mmol/l on 3 consecutive occasions) in either calcitriol or placebo groups.

N=3 calcitriol had a doubling of serum creatinine.

N=1 calcitriol and N=1 placebo progressed to ESRD during the trial.

**Serum Ca:**
There were NS differences between the calcitriol (N=24) and the placebo (N=21) group for changes in serum calcium

**Serum P:**
There were NS differences between the calcitriol (N=24) and the placebo (N=21) group for changes in serum phosphate.

Assessment of bias: no discussion of concealment.

<table>
<thead>
<tr>
<th>Reference</th>
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<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rix M, Eskildsen P, Olgaard K. Effect of 18 months of treatment with alfalcacidol on bone in patients with mild to moderate chronic renal failure. <em>Nephrol Dial Transplant.</em> 2004; 19(4):870-876. Ref ID:</td>
<td>RCT 1+ Randomised, double-blind prospective study 1 centre, Denmark Not ITT</td>
<td>N =36 N=31 complete the study Drop out rate 11% in Alfacalcidol, 17% in placebo</td>
<td><strong>Inclusion criteria:</strong> people with CrCl 10-60 ml/min and plasma ionised Ca &lt; 1.35 mmol/l and P &lt; 2.0 mmol/l. <strong>Exclusion criteria:</strong> dialysis, renal transplantation, use of vitamin D analogues, immunosuppressive agents, anti-epileptics, hormone replacement therapy. <strong>Baseline characteristics:</strong> NS differences between people receiving N=18 Alfacalcidol (1α-hydroxycholecalciferol or 1α-hydroxyvitamin D₃) Procedure: Participants randomised to alfacalcidol (0.25 microg/day titrated up to 0.75 microg/day providing NS increase in creatinine and no Ca&gt; 1.35 mmol/l and no P&gt; 2.0 mmol/l) or placebo. Serum creatinine, iPTH, P, Ca, bone specific ALP, osteocalcin, PICP, and ICTP measured at baseline and every three months. BMD (DEXA) of the lumbar spine L2-L4, total femur, femoral neck, distal forearm, and total body were determined at baseline and N=18 placebo 18 month s</td>
<td>N=18 placebro</td>
<td>18 months</td>
<td>Serum Ca P iPTH CrCl Osteocalcin Bone ALP Carboxy-terminal propeptide of type I collagen (PICP) Carboxy-terminal telopeptide of type-I collagen (ICTP) Bone mineral density</td>
<td>Not stated</td>
<td></td>
</tr>
</tbody>
</table>
placebo or alfacalcidol for sex, age (52.5 years), Ca, P, iPTH, bone ALP, osteocalcin, BMD. Mean CrCl was 49 ml/min (alfacalcidol) and 39 ml/min (placebo), p<0.05  

**Effect size**  
The mean daily dose of alfacalcidol was 0.44 microg/day with 53% taking 0.5 microg/day, 35% taking 0.25 microg/day, and 12% taking 0.75 microg/day.  

**Adverse Events:**  
Hypercalcaemia occurred in 1 person on alfacalcidol and it resolved after decreasing the dose.  

**Bone Mineral Density**  
There was NS change in BMD of the spine from baseline to 18 months treatment with alfacalcidol (+2.9% change, NS) or in placebo (-1.1% change, NS). However, there was a significant difference for BMD of the spine in the alfacalcidol versus placebo group (4.2%, p<0.05).  

There was NS change in BMD of the femoral neck from baseline to 18 months treatment with alfacalcidol (+1.5% change, NS) or in placebo (-1.5% change, NS). However, there was a significant difference for BMD of the femoral neck in the alfacalcidol versus placebo group (4.9%, p<0.05).  

There were NS changes in total body BMD in the placebo or the alfacalcidol groups after 18 months treatment.  

There were NS changes in forearm BMD in the placebo or the alfacalcidol groups after 18 months treatment.  

**Serum Ca:**  
Mean serum calcium increased significantly in people taking alfacalcidol (N=16, mean Ca 1.20 mmol/l at baseline to 1.24 mmol/l at 18 months), while there were NS changes in calcium in people taking placebo (N=15). There was a significant difference of 4.5% between the two groups (p<0.05)  

**Serum P:**  
There were NS changes in serum P in the alfacalcidol or placebo groups.  

**Serum iPTH:**  
iPTH decreased significantly from baseline to 18 months treatment with alfacalcidol (N=16, change iPTH -29% at 3 month and -47% at 9 months, p<0.05 for 3 and 9 months from baseline), whereas there were NS changes in iPTH in the placebo group (N=15). There was a significant difference between the groups for changes in iPTH, p<0.05.  

Baseline iPTH < 60 pg/ml: N=7 alfacalcidol and N=4 placebo.  
After 18 months treatment iPTH < 60 pg/ml: N=10 alfacalcidol and N=4 placebo.
Serum osteocalcin:
Osteocalcin significantly decreased by 24% in the alfacalcidol group (N=16, p<0.05 from baseline), whereas there was NS (+25%, NS) change in osteocalcin in the placebo group. (p<0.05 between groups). At the end of the study only 1 patient in the alfacalcidol group had osteocalcin levels > reference range (4.2-31.4 ng/ml), whereas 6 people in the placebo group had osteocalcin levels exceeding reference ranges.

Bone-specific alkaline phosphatase
Bone ALP significantly decreased by 48% in the alfacalcidol group (N=16, p<0.05 from baseline), whereas there was NS change in ALP in the placebo group.

Plasma PICP:
There were NS changes in PICP in the placebo or the alfacalcidol groups.

Plasma ICTP:
There were NS changes in ICTP (bone resorption marker) in the alfacalcidol group, whereas ICTP significantly increased by 32% from baseline in the placebo group, p<0.05.

Change in CrCl:
After 18 months, CrCl decreased significantly in both placebo and alfacalcidol groups, but there were NS differences between treatments.

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<th>Outcome measures</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Al-Aly Z, Quazi RA, Gonzalez EA et al.</td>
<td>Retrospective case series</td>
<td>N total CKD =66 N Stage 3 CKD = 44 N Stage 4 CKD = 22</td>
<td>Inclusion criteria: men with Stage 3 CKD and plasma iPTH &gt; 70 ng/l or Stage 4 CKD and plasma iPTH &gt; 110 ng/l.</td>
<td>N=44 Stage 3 CKD After treatment with Ergocalciferol (vitamin D₂)</td>
<td>N=44 Stage 3 CKD Before treatment with Ergocalciferol (vitamin D₂) in N=22 Stage 4 CKD</td>
<td>Median 6 months (range 4-12 months)</td>
<td>Serum Ca, P, iPTH</td>
<td>None</td>
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</table>

Ref ID: 601
People receiving ergocalciferol with Stage 3 CKD had significantly lower iPTH, lower degree of vitamin D deficiency, and were administered phosphate binders less than people with Stage 4 CKD receiving ergocalciferol. Mean age (Stage 3 = 71.7 years, Stage 4 = 67.5 years). Mean eGFR MDRD (Stage 3 = 45.7 Stage 4 = 22.2 ml/min/1.73m²).

**Effect size**

**Serum iPTH:**
In the total group (N CKD =66), iPTH significantly decreased after 6 months of ergocalciferol treatment (231 pg/ml pre-ergocalciferol iPTH to 193 pg/ml post-ergocalciferol, p<0.005).

In the Stage 3 CKD group (N=44) iPTH significantly decreased after 6 months of ergocalciferol treatment (174 pg/ml pre-ergocalciferol iPTH to 136 pg/ml post-ergocalciferol, p<0.005).

In the Stage 4 CKD group (N=22) there was NS change in iPTH after 6 months of ergocalciferol treatment (345 pg/ml pre-ergocalciferol iPTH to 306 pg/ml post-ergocalciferol, p=0.195, NS).

**Serum Ca:**
Mean serum calcium did NS change after 6 months treatment with ergocalciferol in the whole group (N=66), Stage 3 CKD alone (N=44) or Stage 4 CKD alone (N=22).

**Serum P:**
Mean serum phosphorus did NS change after 6 months treatment with ergocalciferol in the whole group (N=66), Stage 3 CKD alone (N=44) or Stage 4 CKD alone (N=22).

**Adverse Events:**
There were no cases of hypercalcaemia before or after ergocalciferol.
There were no cases of hyperphosphataemia before or after ergocalciferol.
Note: Small N of people with Stage 4 CKD, therefore may not have the power to detect changes in iPTH in this subgroup. Results applicable to older men (average age 70 years). Also this was not an RCT, rather an observational study of parameters before and after ergocalciferol treatment.

<table>
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<tbody>
<tr>
<td><strong>Study type/ Evidence level</strong></td>
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</table>
| RCT 1 - Randomised, double-blind prospective study | N =13 | **Inclusion criteria:** people with CrCl 20-60 ml/min  
**Exclusion criteria:** pregnancy, hypercalcaemia, renal stones, poorly controlled hypertension, GI, or liver disease, urinary protein excretion > 3g/day, psychosis, tetracycline allergy, use of anticonvulsants, heparin, corticosteroids, vitamin D metabolites within the previous 6 months. | N=7  
1,25-dihydroxyvitamin D3  
Procedure: Ca supplements provided to ensure an intake of 800 mg/day. Patients randomised to 1,25-dihydroxyvitamin D3 (0.25 microg/day and doubled after 4-8 weeks providing Ca < 2.6 mmol/l and urinary Ca < 7 mmol/24-h.) Treatment was stopped if hypercalcaemia occurred, and then once levels were normal, treatment resumed at half the previous dose. Other drugs for disease management permitted. Serum creatinine, P, Ca (corrected for albumin), ALP, PTH (C-terminal radioimmunoassay) and CrCl measured at baseline and every month. Transiliac crest bone biopsies were | N=6 placebo | 1 year | Serum Ca  
P  
PTH  
CrCl  
Alkaline phosphatase (ALP)  
Bone structure  
Bone formation  
Bone resorption  
Mineralisation  
Adverse Events: hypercalcaemia | Dialysis Clinics Inc. |

1 centre USA  
No ITT
performed at baseline and at end of the study and samples were subjected to phase contrast and fluorescent light microscopy.

### Effect size
Retrospective analysis of bone biopsy showed that, at baseline, people had evidence of abnormal bone histology.

Normal range: Ca < 2.62 mmol/l; P < 1.65 mmol/l; ALP 110 IU/ml; PTH <0.9 microg/ml

### Adverse Events:
No participants reported adverse events.

Withdrawals: 12.5% (N=1/8 for tetracycline hypersensitivity) of people on 1,25- dihydroxyvitamin D3 and 25% of people on placebo (N=2/8, MI and no satisfactory bone biopsy).

4 patients on 1,25- dihydroxyvitamin D3 had hypercalcemia upon receiving 0.5 microg/d vit D, but resolved within 1 week of stopping treatment. 1 patient on placebo had 1 episode of hypercalcemia.

### Serum Ca:
Mean serum calcium was higher in people taking 1,25- dihydroxyvitamin D3 (2.47 mmol/l at baseline to 2.53 mmol/l at 12 months), compared with placebo (2.48 mmol/l at baseline and 2.45 mmol/l at 12 months) but there were NS differences between them.

### Serum P:
Mean serum P increased in the placebo group (1.12 mmol/l at baseline to 1.24 mmol/l at 12 months) and decreased slightly in the people taking 1,25-dihydroxyvitamin D3 (1.40 to 1.37mmol/l).

### Serum iPTH:
Mean serum iPTH decreased NS from baseline to 12 months treatment with 1,25- dihydroxyvitamin D3 (0.87 at baseline to 0.63 microg/l at 12 months, NS). There was NS change in iPTh in the placebo group (0.67 at baseline to 0.60 microg/l at 12 months, NS).

### Serum alkaline phosphatase (ALP)
Mean serum ALP decreased significantly in people taking 1,25- dihydroxyvitamin D3 (73.7 IU/ml at baseline to 56.6 IU/ml at 12 months). By contrast, ALP did NS change in the placebo group (72.3 IU/ml at baseline to 75.5 IU/ml at 12 months).

### Change in CrCl:
After 12 months, mean CrCl decreased in both placebo (~4.5 ml/min) and 1,25- dihydroxyvitamin D3 groups (~3.3 ml/min, NS between treatments).

### Bone structure:
There was NS differences between placebo and 1,25- dihydroxyvitamin D3 groups for cancellous bone mass, trabecular diameter, trabecular plate density, wall thickness.
**Bone formation**

Lamellar osteoid volume (6.27 mm³/cm³ baseline to 6.49 mm³/cm³ at 12 months) did NS change in the placebo group, whereas lamellar osteoid volume significantly decreased in the 1,25- dihydroxyvitamin D3 group (4.66 mm³/cm³ baseline to 2.21 mm³/cm³ at 12 months, p<0.05 within group and compared to placebo).

Lamellar osteoid surface did NS change in either the placebo or the 1,25- dihydroxyvitamin D3 groups.

Mean osteoid seam thickness significantly decreased in the 1,25- dihydroxyvitamin D3 group (9.47 micrometer at baseline to 6.98 micrometer at 12 months, P<0.05 within group and compared with placebo). There was NS change in osteoid seam thickness in the placebo group.

Woven osteoid volume significantly decreased in the 1,25- dihydroxyvitamin D3 group (1.95 mm³/cm³ at baseline to 0.76 mm³/cm³ at 12 months, p<0.05). By contrast, woven osteoid volume significantly increased in the placebo group (0.58 mm³/cm³ at baseline to 2.27 mm³/cm³ at 12 months, p<0.05). Both groups were significantly higher at baseline than normal age and sex matched controls.

Woven osteoid surface significantly decreased in the 1,25- dihydroxyvitamin D3 group (4.20% at baseline to 2.06% at 12 months, p<0.05, whereas it significantly increased in the placebo group (1.56% at baseline to 5.04% at 12 months, p<0.05). Both groups were significantly higher at baseline than normal age and sex matched controls.

**Bone resorption:**

Bone-osteoblast interface significantly decreased in the 1,25- dihydroxyvitamin D3 group (6.18% at baseline to 1.81% at 12 months, p<0.05). There were NS changes in bone-osteoblast interface in the placebo group (7.18% to 8.28%). Both groups had significantly higher baseline values than age and sex matched normal controls.

Osteoblastic index significantly decreased in the 1,25- dihydroxyvitamin D3 group (429 cells/100 mm boundary length at baseline to 127 cells/100 mm boundary length at 12 months, p<0.05 within group and compared to placebo). There were NS changes in osteoblastic index in the placebo group (7.18 to 8.28 cells/100 mm boundary length). Both groups had significantly higher baseline values than age and sex matched normal controls.

Bone-osteoclast interface decreased in both groups, but the changes were NS. Both groups had significantly higher baseline values than age and sex matched normal controls.

Osteoclastic index decreased in both groups, but the changes were NS. Both groups had significantly higher baseline values than age and sex matched normal controls.

**Bone mineralization:**

Mineralization rate: NS differences between the placebo and 1,25- dihydroxyvitamin D3 groups. Neither group was significantly different from normal controls.

Doubly labelled trabecular surfaces: NS decrease in 1, 25- dihydroxyvitamin D3 and a NS increase in placebo group. Neither group was significantly different from normal controls.

Note: authors caution about dosing at 0.5 microg/day with 1,25- dihydroxyvitamin D3 due to hypercalcemia. Must monitor Ca and CrCl closely.

Assessment of bias: no ITT analysis, no discussion of differences in baseline characteristics between 2 trial arms, applicable to people with mild/moderate CKD with...
subclinical/early bone disease, no discussion of concealment.

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<tr>
<td>Christiansen C, Rodbro P, Christensen MS et al.</td>
<td>Deterioration of renal function during treatment of chronic renal failure with 1,25-dihydroxycholecalciferol. Lancet. 1978; 2(8092:Pt 1):700-703. Ref ID: 480</td>
<td>RCT 1- Randomised, prospective study 1 centre Denmark No ITT No concealment mentioned No blinding mentioned No assessment of statistical power.</td>
<td>N =18 N=17 complete the study Drop out rate 11 % in 1,25-dihydroxy vitamin D3, 0 % in vitamin D3</td>
<td>Inclusion criteria: consecutive non-dialysed patients with chronic renal failure and stable renal function for 1 year and fulfilling at least 2 of the following 3 criteria: bone mineral content &lt; 90% of normal, Ca &lt; normal minus 1 S.D., and ALP &gt; normal plus 1 S.D.</td>
<td>N=8 Calcitriol (1,25-dihydroxyvitamin D3) Procedure: Patients were observed for 6 months to determine the spontaneous course of renal disease. People then randomised to 1,25-dihydroxyvitamin D3 (1 microg/day) or vitamin D3 (4000 UI/day) with dose adjustment according to serum Ca (measured 3x/week until Ca &lt; 110 mg/l achieved). All patients received 0.5g Ca supplements daily. CrCl (24-h urine collections), bone mineral content (photon absorptiometry) and serum creatinine, P, Ca, ALP, PTH (N-terminal and C-terminal radioimmunoassays), measured 6 months before baseline, at baseline and after 6 months of active treatment.</td>
<td>N=9 vitamin D3 (25-hydroxyvitamin D3)</td>
<td>6 months</td>
<td>Serum Ca, P, iPTH, CrCl, Alkaline phosphatase (ALP) Bone mineral content (BMC)</td>
</tr>
</tbody>
</table>
**Effect size**
The daily dose of 1,25- dihydroxyvitamin D3 had to be reduced in 7/8 patients due to hypercalcaemia(four to 0.5 microg/day and three to 0.25 microg/day). No reduction of dose was required in the group receiving vitamin D3.

**Adverse Events:**
1 patient on 1,25- dihydroxyvitamin D3 died (bronchopneumonia).

**Bone Mineral Content (BMC)**
After 6 months of treatment, there were NS changes in BMC in either the 1,25- dihydroxyvitamin D3 (N=8, mean change BMC =0.8%, NS) or the 25- hydroxyvitamin D3 groups (N=9, mean change BMC -2.2%, NS) (p NS between groups).

**Serum Ca:**
After six months of treatment, mean serum calcium increased significantly in people taking 1,25- dihydroxyvitamin D3 (N=8, mean change Ca +12.1 mg/l, p<0.01), whereas there were NS changes in mean Ca in people taking vitamin D3 (N=9, mean change Ca + 2.2 mg/l, NS). P<0.01 for changes between the two groups.

**Serum P:**
Mean serum P did NS change in either the vitamin D3 or 1,25- dihydroxyvitamin D3 groups.

**Serum iPTH:**
After 6 months treatment, mean iPTH decreased significantly in both the 1,25- dihydroxyvitamin D3 group (N=8, mean change iPTH -0.24 microg/l, p<0.02) and the vitamin D3 group (N=9 mean change iPTH -0.15 microg/l, p<0.02). p NS for changes in iPTH between groups.

**Serum alkaline phosphatase (ALP)**
Mean serum ALP decreased significantly in people taking 1,25- dihydroxyvitamin D3 (N=8, mean change ALP -2.1 K.A.U./dl, p<0.01). By contrast, ALP did NS change in the vitamin D3 group. There were NS differences between the groups for change in ALP.

**Change in CrCl:**
After 6 months treatment, mean CrCl significantly decreased in both the vitamin D3 (N=9, mean change CrCl -3.3 ml/min, p<0.02) and the 1,25- dihydroxyvitamin D3 groups (N=8, mean change CrCl -5.7 ml/min, p<0.01). There were NS differences between treatments.

Assessment of bias: no ITT analysis. No discussion of concealment. NO discussion of blinding. No assessment of statistical power.