Cholecalciferol Supplementation and Inflammation: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Background

Cholecalciferol supplementation is common clinical practice in chronic kidney diseases. Its effects on mineral metabolism are well documented. However, pleiotropic effects on inflammation independent of active vitamin D are discussed controversially. In a recent randomized controlled trial in hemodialysis patients we could not confirm beneficial effects of cholecalciferol on markers of cellular inflammation [1]. In parts this may have been due to co-medication with active vitamin D and pre-existing chronic inflammation. In this trial we investigated biomarkers of cellular inflammation in healthy subjects without pre-existing inflammation or co-medication.

Methods

105 healthy subjects received either 800 I.E./d Cholecalciferol (n=54) or Placebo (n=51) for 12 weeks during winter months. All investigated variables were analysed at baseline and after 12 weeks.
Frequency of monocyte subsets was determined flow cytometrically (MACS Quant, Miltenyi). Monocytes were subdivided according to their expression of the lipopolysaccharide (LPS) receptor CD14 and the immunoglobulin Fcγ receptor CD16 into CD14++CD16-(Mo1), CD14++CD16+(Mo2) and CD14+CD16++(Mo3) cells [2,3]. Relative quantities (RQ) of total leukocyte mRNA expression of inflammatory markers were determined by qRT-PCR normalized on ribosomal protein LP0.

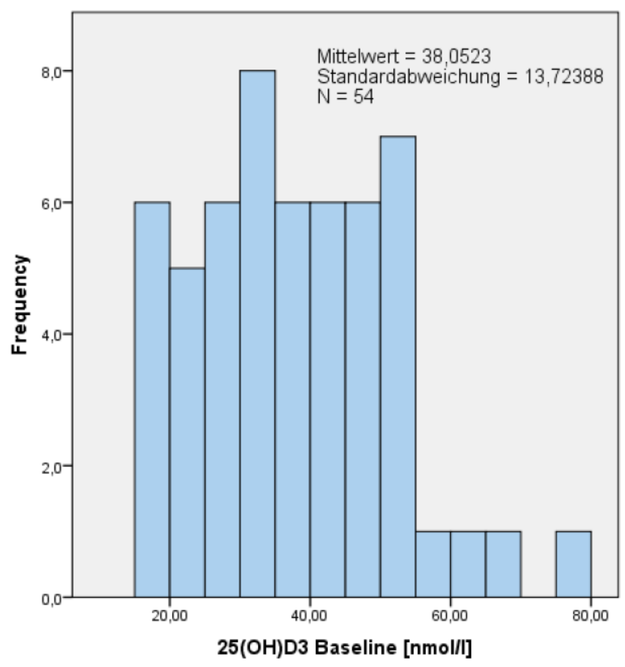

Figure 1: Distribution of 25(OH)D3 levels at baseline (Cholecalciferol group)

Results

At baseline, vitamin D Status was impaired and mean 25(OH)D3 level in the cholecalciferol group was 38.1 nmol/l (fig. 1). 25(OH)D3-levels rose significantly within 12 weeks (38.1±13.7 vs. 72.5±15.4 nmol/l,p<0.001) whereas in the placebo group 25(OH)D3-levels declined (37.7±14.7 vs. 31.9±13.1 nmol/l, p<0.001; fig. 2).
Anti-inflammatory Interleukin-10 (IL-10) and Toll-like-receptor 2 (TLR2) increased significantly in the verum group over 12 weeks (IL10: 0.88±0.45 vs. 1.08±0.67 RQ, p=0.017; TLR2: 1.52±0.57 vs. 1.97±1.06 RQ, p=0.002; fig. 3). However, when compared to placebo, there was no statistical significant difference (IL-10: 1.08±0.67 vs. 1.04±0.64, p=0.29; TLR 2: 1.97±1.06 vs. 1.89±1.0, p=0.47).
Mo1 monocytes with less inflammatory properties were significantly higher in the verum group after 12 weeks (420.0±159.4 vs. 358.6±122.8/µl, p=0.03, fig. 4). Proinflammatory Mo2 and Mo3 monocytes showed no difference (Mo2: 19.9±12.5 vs. 17.0±8.4/µl, p=0.17; Mo3: 35.2±16.1 vs. 33.5±18.5, p=0.61, fig. 4).

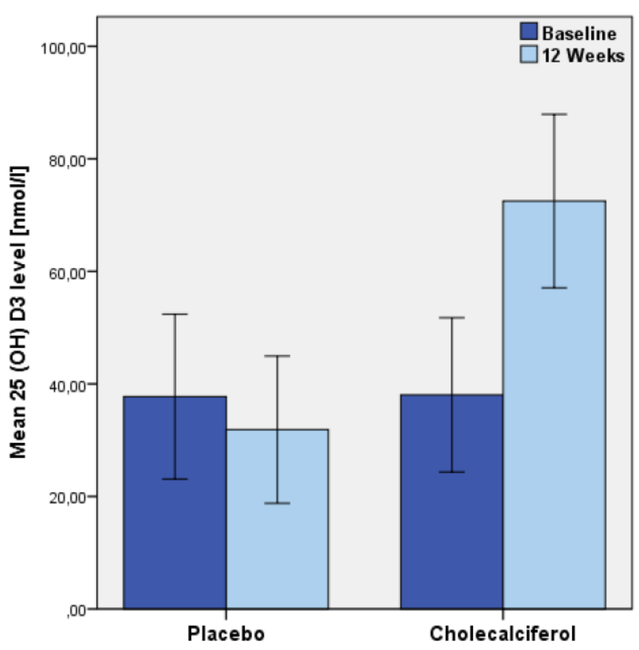

Figure 2: Plasma 25(OH)D3-levels

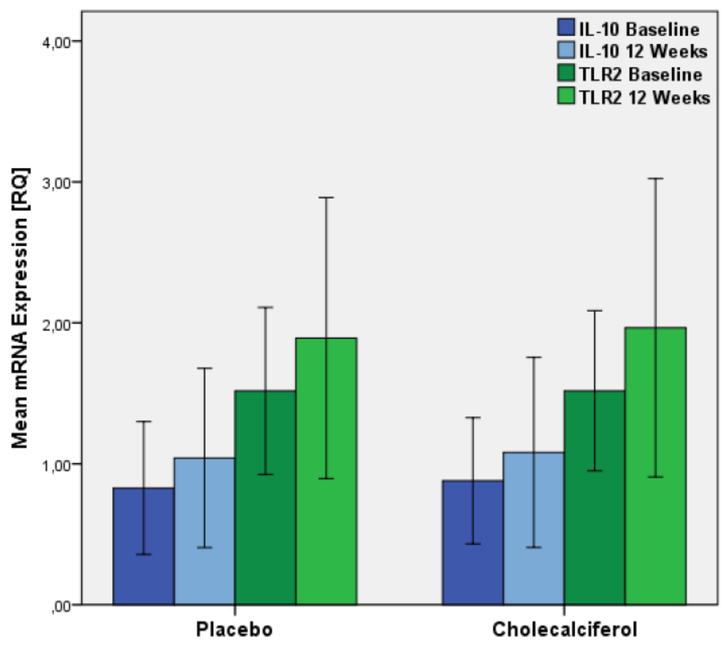

Figure 3: mRNA Expression of IL-10 and TLR2

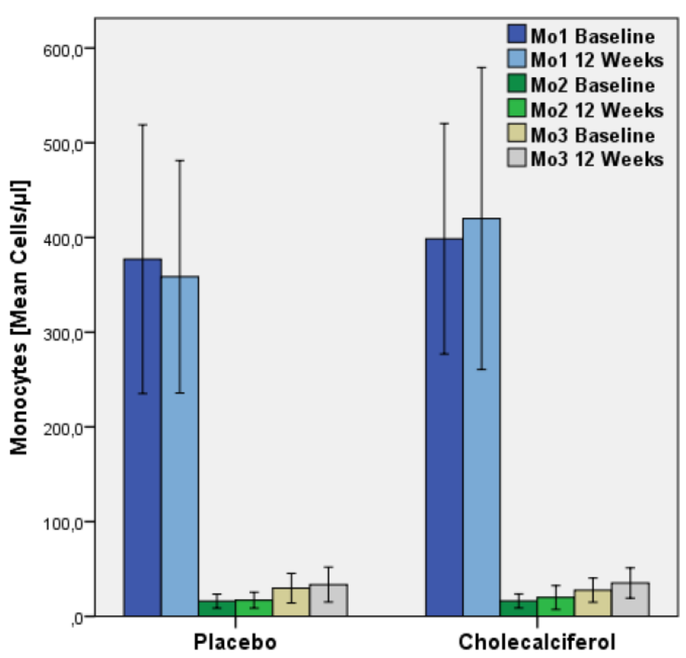

Figure 4: Monocyte subsets

Conclusions

An alteration of cellular inflammatory markers due to cholecalciferol substitution could not be confirmed in healthy subjects under the chosen experimental conditions.

References

1. Seibert E, Heine GH, Ulrich C, Seiler S, Köhler H, Girndt M: Influence of Cholecalciferol Supplementation in Hemodialysis Patients on Monocyte Subsets: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Nephron Clin Pract 2013;123:209–219
2. Heine GH, Ulrich C, Seibert E, Seiler S, Marell J, Reichart B, Krause M, Schlitt A, Köhler H, Girndt M: CD14(++)CD16+ monocytes but not total monocyte numbers predict cardiovascular events in dialysis patients. Kidney Int. 2008;73(5):622-9.
3. Ulrich C, Heine GH, Seibert E, Fliser D, Girndt M: Circulating monocyte subpopulations with high expression of angiotensin conversion enzyme predict mortality in patients with end-stage renal disease. Nephrol Dial Transplant. 2010;25(7):2265-72.

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DOI: 10.3252/pso.eu.52era.2015