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Calcifediol supplementation to reduce pulse pressure in a limited sample of vitamin D deficient older adults with elevated parathyroid hormone levels

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SUMMARY

Vitamin D is proposed as an antihypertensive agent, but current evidence is inconclusive. Calcifediol is more potent in raising vitamin D status. It might, therefore, be more effective in lowering pulse pressure than cholecalciferol especially in patients with low vitamin D status and high levels of parathyroid hormone (PTH). This study investigated the efficacy of calcifediol on pulse pressure in older adults with vitamin D deficiency and elevated PTH levels. Supplementation with 15 μg calcifediol resulted in lower pulse pressure (Δ 35.4 mm Hg, 95%CI: 4.8, 66.1 mm Hg, $P = 0.021$) and PTH levels (Δ 1.83 pmol/l, 95%CI: −0.1, 3.7 pmol/l, $P = 0.065$) compared to 5 μg calcifediol. These effects were observed in a limited sample size of 16 older adults and therefore need confirmation in a larger trial. In conclusion, supplementation with 15 μg calcifediol might be an effective way to reduce pulse pressure in elderly with vitamin D deficiency and elevated PTH levels.

Abbreviations: 25(OH)D, vitamin D; DBP, diastolic blood pressure; PP, pulse pressure; PTH, parathyroid hormone; SBP, systolic blood pressure.

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1. Introduction

Pulse pressure, defined as the difference between systolic and diastolic blood pressure, increases after the age of 60 [1]. Elevated pulse pressure is a predictor for coronary heart disease [2]. Improving vitamin D status might lower pulse pressure via direct actions on arterial wall cells and suppression of parathyroid hormone (PTH) levels [3]. However, current evidence is inconclusive [4].

An alternative to the commonly prescribed supplementation regimen with cholecalciferol is supplementation with calcifediol. Calcifediol is 2–5 times more potent than cholecalciferol in improving vitamin D status [5] and showed beneficial effects on blood pressure [6].

This study aims to investigate the effect of calcifediol and cholecalciferol on pulse pressure, in older adults with vitamin D deficiency and elevated PTH levels.

2. Methods

2.1. Participants and study site

Data of a randomised, double-blind trial (clinicaltrials.gov: NCT01868945) were used [7]. Participants (n = 59) were aged ≥65 years, with a vitamin D status between 25 and 50 nmol/l, and classified as pre-frail or frail according to criteria of Fried et al. [8]. Main exclusion criteria were a BMI <20 or >35 kg/m^2, and conditions interfering with vitamin D status. Further details of the study protocol are described elsewhere [7]. This communication focusses on results of a subgroup of participants (n = 16, Table 1) with baseline PTH levels exceeding 6.0 pmol/l.

2.2. Intervention

Participants were randomly allocated to one of four groups: 20 μg cholecalciferol, 5 μg calcifediol, 10 μg calcifediol or 15 μg calcifediol daily for 24 weeks. Supplements (hard gel capsules, provided by DSM Nutritional Products, Kaiseraugst, Switzerland) were identical in taste and appearance. Participants and investigators were blinded towards treatment allocation.

Table 1
Baseline characteristics.

Characteristics (mean (SD))	Treatment			
	5 μg calcifediol (n = 4)	10 μg calcifediol (n = 4)	15 μg calcifediol (n = 3)	20 μg vitamin D (n = 5)
Demographics				
Males (% (n))	25 (1)	50 (2)	33 (1)	60 (3)
Age (y)	82.3 (7.3)	75.3 (2.9)	82.7 (2.5)	80.4 (6.9)
Height (cm)	172.9 (2.0)	167.1 (6.7)	168.1 (10.1)	170.0 (10.4)
Weight (kg)	75.3 (14.1)	81.0 (5.5)	69.0 (7.2)	72.2 (10.7)
BMI (kg/m^2)	25.1 (4.3)	29.1 (2.6)	24.5 (3.4)	25.1 (4.2)
Blood pressure				
PP (mm Hg)	71.5 (30.2)	64.0 (14.7)	64.0 (11.3)	61.0 (16.2)
SBP (mm Hg)	158.3 (26.1)	129.0 (18.0)	146.7 (9.5)	146.8 (24.8)
DBP (mm Hg)	86.8 (8.5)	65.0 (19.2)	82.7 (6.4)	85.8 (11.9)
Heart rate (bpm)	69.3 (12.1)	66.3 (3.9)	63.0 (12.5)	78.0 (13.9)
Use of BP medication (% (n))	50 (2)	50 (2)	100 (3)	60 (3)
Blood parameters				
25(OH)D (nmol/L)	34.8 (15.5)	40.7 (13.7)	37.7 (13.6)	39.8 (6.9)
Plasma PTH (pmol/L)	7.8 (1.0)	6.5 (0.3)	7.9 (1.6)	7.4 (0.6)
Serum calcium (mmol/L)	2.1 (0.1)	2.2 (0.2)	2.2 (0.1)	2.2 (0.0)

Abbreviations: BMI, body mass index; BP medication, blood pressure medication; DBP, diastolic blood pressure; PA, physical activity; PP, pulse pressure; PTH, parathyroid hormone; SBP, systolic blood pressure.

2.3. Blood pressure

Monthly brachial blood pressure measures were performed using an Omron (Kyoto, Japan) M7 blood pressure monitor by a trained researcher. Participants were measured in fasting state, in a sitting position and after at least 10 min of rest.

2.4. Biochemical parameters

Blood was drawn every month after an overnight fast. Serum 25(OH)D3 concentration was measured by liquid chromatography-tandem mass spectrometry at Analytical Research Centre, DSM Nutritional Products, Switzerland. Intact PTH was measured in EDTA-plasma by sandwich chemiluminescence immunoassay, and serum calcium levels were assessed by colorimetric analysis, at SHO laboratory (Velp, The Netherlands).

2.5. Statistical analysis

Between treatment differences in pulse pressure change over time were estimated using linear mixed models with a random slope and an autoregressive covariance structure. Fixed factors were treatment, time, and treatment–time interaction. BMI, use of blood pressure medication and baseline values of the response variables were included as covariates. Between-group differences at specific time points were assessed with Bonferroni post hoc tests.

3. Results

As described previously for the full study population [7], supplementation with 5 μg calcifediol increased 25(OH)D levels to 55.6 nmol/l in the first four weeks, to reach a plateau in the weeks thereafter, with an endpoint status of 61.9 nmol/l. The other groups reached higher levels: 84.0 nmol/l in the 20 μg cholecalciferol group, 83.9 nmol/l in the 10 μg calcifediol group, and 92.4 nmol/l in the 15 μg calcifediol group. During follow-up, participants in the 15 μg calcifediol group had significantly higher 25(OH)D levels compared to 5 μg calcifediol (Δ 37.4 ± 6.2 nmol/l, $P = 0.001$) and 20 μg cholecalciferol (Δ 22.5 ± 6.0 nmol/l, $P = 0.023$), and borderline significantly higher 25(OH)D levels than 10 μg calcifediol (Δ 20.9 ± 6.4 nmol/l, $P = 0.054$).

A significant treatment effect on PTH levels ($P = 0.011$) was observed, but no significant time*treatment effect ($P = 0.23$, Fig. 1). Participants receiving 15 μg calcifediol had significantly lower plasma PTH levels during all follow-up measurements compared to 20 μg cholecalciferol (Δ −1.89 ± 0.6 pmol/L, $P = 0.044$), and borderline significantly lower PTH levels compared to 5 μg calcifediol (Δ −1.83 ± 0.6 pmol/L, $P = 0.065$).

Significant treatment ($P = 0.017$) and time*treatment ($P = 0.025$) effects were observed on pulse pressure. Pulse pressure was significantly lower for the 15 μg calcifediol group compared to the 5 μg calcifediol group after 4 weeks (Δ −36.4 ± 11.4 mm Hg, $P = 0.03$), 8 weeks (Δ −52.1 ± 11.4 mm Hg, $P = 0.001$), 12 weeks (Δ −41.7 ± 11.6 mm Hg, $P = 0.011$) and 20 weeks (Δ −43.0 ± 14.1 mm Hg, $P = 0.031$) of supplementation (Fig. 2). Comparison of endpoint (24 weeks) mean pulse pressure values showed no significant differences between treatment groups. In the 15 μg calcifediol group, mean pulse pressure of all follow-up measurements was 49.6 mm Hg, versus 85.1 mm Hg in the 5 μg calcifediol group (Δ 35.4 ± 9.3 mm Hg, $P = 0.021$).

Serum calcium levels increased from 2.17 ± 0.02 to 2.31 ± 0.02 mmol/l (Δ 0.13 ± 0.02 mmol/l, $P = 0.001$) during the 24 weeks, without differences between groups.

4. Discussion

In this study we observed a pulse pressure lowering effect of daily 15 μg calcifediol supplementation. The differences between treatment arms were consistent over time points, and of such a magnitude that significance was reached, despite the low sample size.

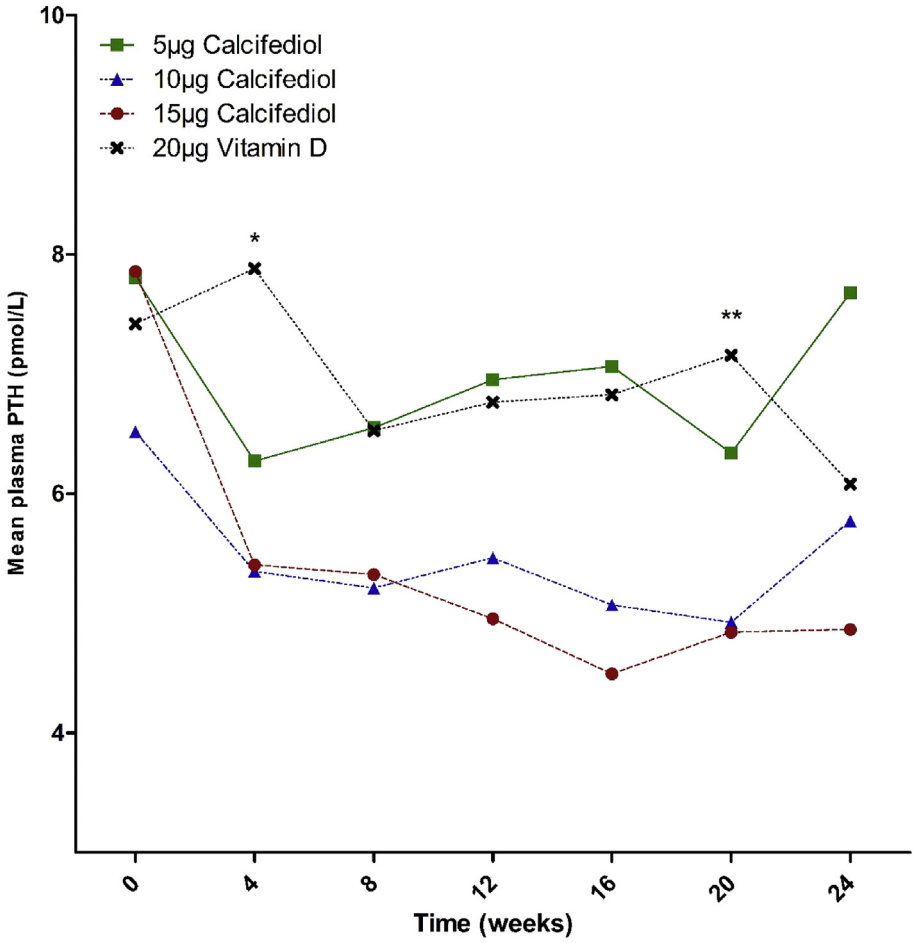

Fig. 1. Change in parathyroid hormone levels over time in the four treatment groups. All means except the baseline means are predicted means, adjusted for baseline parathyroid hormone levels and BMI. *20 µg vitamin D differs significantly from 10 to 15 µg calcifediol. **20 µg vitamin D differs significantly from 10 µg calcifediol.

During the 24 weeks of follow-up, participants receiving 15 µg calcifediol had average pulse pressure values of 49.6 mm Hg. Participants receiving 5 µg calcifediol, which barely increased vitamin D status, had a significantly higher average pulse pressure of 85.1 mm Hg.

This finding might be of clinical relevance. Pulse pressure values of ≥65 mm Hg increase the risk of acute coronary heart disease-related events with 57% compared to pulse pressure values of ≤45 mm Hg. A slightly elevated pulse pressure of 45–54.9 mm Hg does not show an increased risk [9].

A systematic review showed no consistent effects of vitamin D on blood pressure [4]. However, Bischoff-Ferrari et al. found that 20 µg calcifediol lowered systolic blood pressure on average with 5.7 mm Hg compared to 20 µg cholecalciferol [6]. The equal diastolic blood pressure values of these two groups suggest that pulse pressure was lowered more by calcifediol than by cholecalciferol. Mean baseline PTH levels of the participants were 6.3 pmol/L, which is around the upper limit of the normal range. End of study comparisons showed significantly higher 25(OH)D levels along with PTH suppression in the calcifediol group compared to the cholecalciferol group. It is, therefore, possible that the effects on pulse pressure in both studies can be explained by PTH suppression via increased 25(OH)D status.

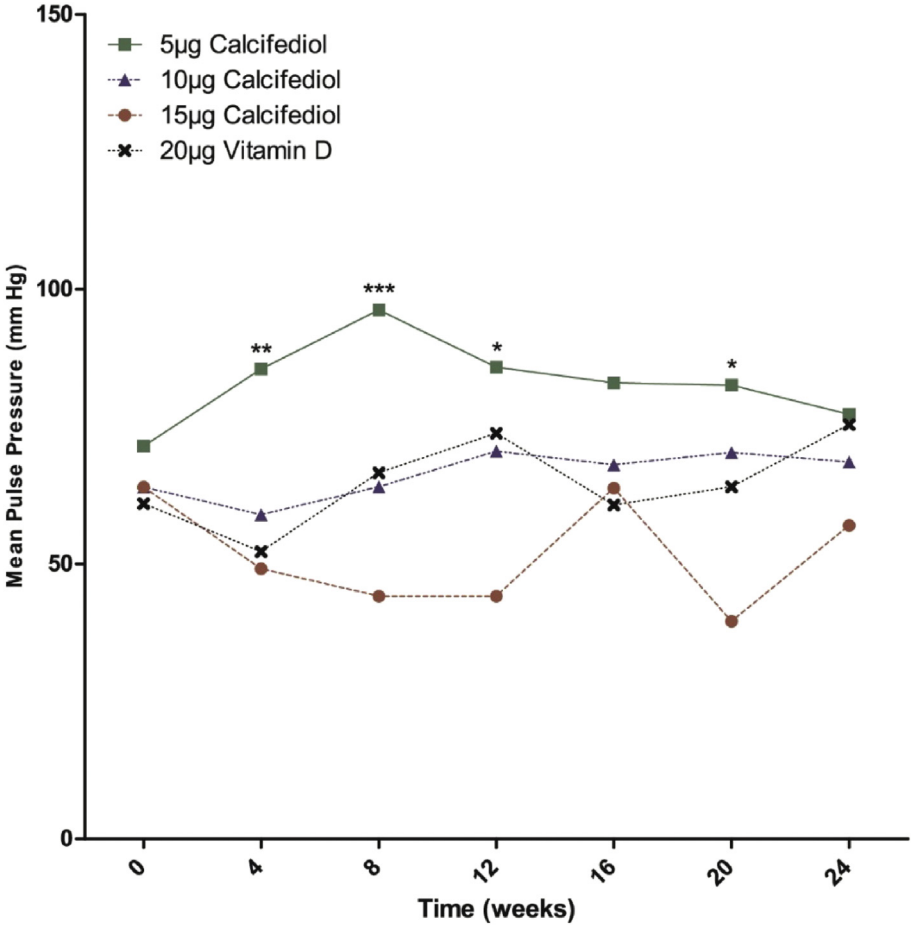

Fig. 2. Change in Pulse Pressure over time in the four treatment groups. All means except the baseline means are predicted means, adjusted for baseline pulse pressure, BMI and use of antihypertensive agents. *5 μg calcifediol differs significantly from 15 μg calcifediol. **5 μg calcifediol differs significantly from 15 μg calcifediol and 20 μg vitamin D. ***5 μg calcifediol differs significantly from 10 μg calcifediol, 15 μg calcifediol and 20 μg vitamin D.

In conclusion, supplementation with 15 μg calcifediol might be an effective way to reduce pulse pressure in elderly with vitamin D deficiency and elevated PTH levels. This finding should be studied in larger trials before considering clinical applications.

Funding and conflict of interest

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Author statements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yclnex.2019.01.003.

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