Effects of Vitamin D on Blood Pressure and Cardiovascular Risk Factors

A Randomized Controlled Trial

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Abstract—Vitamin D deficiency is a risk factor for arterial hypertension, but randomized controlled trials showed mixed effects of vitamin D supplementation on blood pressure (BP). We aimed to evaluate whether vitamin D supplementation affects 24-hour systolic ambulatory BP monitoring values and cardiovascular risk factors. The Styrian Vitamin D Hypertension Trial is a single-center, double-blind, placebo-controlled study conducted from June 2011 to August 2014 at the endocrine outpatient clinic of the Medical University of Graz, Austria. We enrolled 200 study participants with arterial hypertension and 25-hydroxyvitamin D levels below 30 ng/mL. Study participants were randomized to receive either 2800 IU of vitamin D3 per day as oily drops (n=100) or placebo (n=100) for 8 weeks. Primary outcome measure was 24-hour systolic BP. Secondary outcome measures were 24-hour diastolic BP, N-terminal-pro-B-type natriuretic peptide, QTc interval, renin, aldosterone, 24-hour urinary albumin excretion, homeostasis model assessment-insulin resistance, triglycerides, high-density lipoprotein cholesterol, and pulse wave velocity. A total of 188 participants (mean [SD] age, 60.1 [11.3] years; 47% women; 25-hydroxyvitamin D, 21.2 [5.6] ng/mL) completed the trial. The mean treatment effect (95% confidence interval) for 24-hour systolic BP was −0.4 (−2.8 to 1.9) mm Hg (P=0.712). Triglycerides increased significantly (mean change [95% confidence interval], 17 [1–33] mg/dL; P=0.013), but no further significant effects were observed for secondary outcomes. Vitamin D supplementation in hypertensive patients with low 25-hydroxyvitamin D has no significant effect on BP and several cardiovascular risk factors, but it was associated with a significant increase in triglycerides.

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Apart from skeletal diseases, vitamin D deficiency is considered a risk factor for cardiovascular events and mortality.[1–6] Nevertheless, it remains unclear whether low 25-hydroxyvitamin D (25[OH]D) concentrations are a significant causal risk factor or are simply related to adverse outcomes because of reverse causation and confounding factors, such as obesity, reduced mobility with low sunlight exposure, poor nutrition, or inflammation.[1–6] Because high blood pressure (BP) has emerged as the leading risk factor for the global disease burden, it is important to evaluate whether vitamin D has a beneficial effect on lowering BP to clarify the potential role of vitamin D for public health.[7]

Large observational studies and meta-analyses have shown that low 25(OH)D concentrations are a significant risk marker for arterial hypertension.[8,9] Molecular effects of vitamin D receptor activation, such as suppression of the renin–angiotensin–aldosterone system (RAAS), nephroprotective actions, or improvements in endothelial/vascular function, suggest

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antihypertensive properties of vitamin D.[6,9] Several randomized controlled trials (RCTs) on vitamin D supplementation and BP have already been performed but have shown mixed results with most studies reporting no significant effect and only some showing that vitamin D lowers BP.[9–28] In a meta-analysis of RCTs, vitamin D supplementation resulted in a nonsignificant reduction in systolic and diastolic BP.[10] A significant decrease in diastolic BP was observed among RCTs including participants with pre-existing cardiometabolic disease.[10] Most previous RCTs were, however, not adequately designed to answer the question whether correction of vitamin D deficiency is effective for the treatment of arterial hypertension because these RCTs, except for 3 trials, did not include participants with both vitamin D deficiency and high BP.[11,13,18] Subsequently, we performed a RCT in hypertensive patients with low 25(OH)D levels to address the question whether vitamin D supplementation lowers 24-hour systolic ambulatory BP monitoring (ABPM) values and improves cardiovascular risk factors.

Methods

Study Design

The Styrian Vitamin D Hypertension Trial was sponsored by the Medical University of Graz, Austria, and is a single-center, double-blind, placebo-controlled, parallel-group study conducted at the Medical University of Graz, Austria. The publication of this trial adheres to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement.[29] The trial was initially registered at http://www.clinicaltrialsregister.eu (EudraCT number, 2009-018125-70) and was additionally registered at clinicaltrials.gov (ClinicalTrials.gov Identifier NCT02136771).

Participants

Eligible study participants were adults aged ≥18 years with arterial hypertension and a 25(OH)D serum concentration below 30 ng/mL (multiply by 2.496 to convert ng/mL to nmol/L). Arterial hypertension was classified in patients with an office BP of systolic ≥140 mm Hg or diastolic ≥90 mm Hg, a mean 24-hour ABPM of systolic ≥125 mm Hg or diastolic ≥80 mm Hg, a home BP of systolic ≥130 mm Hg or diastolic ≥85 mm Hg, or ongoing antihypertensive treatment. Exclusion criteria were hypercalcemia (plasma calcium concentrations, >2.65 mmol/L), pregnancy or lactating women, drug intake as part of another clinical study, acute coronary syndrome or cerebrovascular event in the previous 2 weeks, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease formula <15 mL/min per 1.73 m^2,[30] 24-hour systolic BP >160 mm Hg or <120 mm Hg, 24-hour diastolic BP >100 mm Hg, change of antihypertensive treatment (drugs or lifestyle) in the previous 4 weeks or planned changes of antihypertensive treatment during the study, any disease with an estimated life expectancy of <1 year, any clinically significant acute disease requiring drug treatment, chemotherapy or radiation therapy, and regular intake (in addition to study medication) of >880 IU vitamin D per day during the last 4 weeks before the study or during the trial. All study participants gave written informed consent, and the study was approved by the ethics committee at the Medical University of Graz, Austria. The study was designed to comply with the Declaration of Helsinki.

Participants were recruited from the outpatient clinics at the Department of Cardiology and the Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Austria. Patients were informed about the Styrian Vitamin D Hypertension Trial either by a conversation in the outpatient clinic or by a telephone call. There was no additional specific advertisement for the trial. The study took place at the outpatient clinic at the Division of Endocrinology and Metabolism from June 2011 to August 2014.

Intervention

Study medication was placed into numbered bottles according to a computer generated randomization list. Randomization procedures were conducted using a web-based software (http://www.randomizer.at/) with good clinical practice compliance as confirmed by the Austrian Agency for Health and Food Safety. Eligible study participants were randomly allocated in a 1:1 ratio to receive 2800 IU vitamin D3 as 7 oily drops per day (Oleovit D3, producer: Fresenius Kabi Austria, A-8055 Graz, Austria; 1 bottle contains 180 000 IU vitamin D3 in 12.5 mL) or otherwise a matching placebo as 7 oily drops per day for 8 weeks. We performed a permuted block randomization with a block size of 10 and stratification according to sex. All investigators/authors who enrolled participants, collected data, and assigned intervention were masked to participant allocation.

Primary Outcome Measure

The primary outcome measure was the between-group difference in 24-hour systolic BP.

Secondary Outcome Measures

Secondary outcome measures were between-group differences in 24-hour diastolic BP, N-terminal-pro-B-type natriuretic peptide, corrected QT interval (Bazett formula), plasma renin concentration, plasma aldosterone concentration, 24-hour urinary albumin excretion, homeostasis model assessment-insulin resistance, triglycerides, high-density lipoprotein cholesterol, and pulse wave velocity. Initially, pulse wave velocity was not listed as an outcome during the first trial registration (EudraCT number, 2009-018125-70) but, as with all the other outcomes, it was prespecified before the beginning of the study.

Measurements

Physical examinations, blood samplings, and patient interviews about medication use and medical history were performed at study visits between 7 and 11 AM. Then, the patients left the hospital for ABPM measurements and 24-hour urine collections before returning to the outpatient clinic the next day. That day, eligible study participants were randomized, and they started intaking of the study medication.

A validated 24-hour ABPM device (Spacelabs 90217A; Spacelabs Healthcare, Inc, Issaquah, WA) was used for the measurement of 24-hour systolic and diastolic BP. The circumference of the upper arm was measured in all patients to select the appropriate cuff for BP recordings. BP was recorded every 15 minutes during the day (6 AM to 10 PM) and every 30 minutes during the night (10 PM to 6 AM). ABPM were performed according to the recommendations of the European Society of Hypertension.[31] Further methods are described in the online-only Data Supplement.

Analysis

Sample size calculation for our primary outcome was based on a meta-analysis of RCTs on the antihypertensive effects of vitamin D.[32] Assuming an effect size of −6 mm Hg (E) and a SD of 12 mm Hg (S), we calculated a standardized effect size (E/S) of 0.5. For a 2-sided alternative hypothesis with an α of 0.05 and a power ($1-\beta$) of 90%, we calculated a sample size of 86 study participants per group. To compensate for potential dropouts during the study, we included 100 patients per group resulting in an overall sample size of 200 study participants.

Continuous data with a normal distribution are shown as means with SD, and variables with a skewed distribution are shown as medians with interquartile range. Categorical data are presented as percentages. Skewed variables were log(e) transformed before use in parametric statistical analyses. Group comparisons at baseline were done by unpaired Student t test or χ^2 test. Analyses of outcome variables were performed according to the intention-to-treat principle with no data imputation and inclusion of all participants with baseline

Table 1. Outcome Variables at Baseline and Follow-Up and Changes From Baseline in Study Participants With Available Values at Both Study Visits

Characteristics	Baseline	Follow-Up	Mean Change From Baseline	Treatment Effect	*P* Value
24-hour systolic blood pressure, mm Hg					
Vitamin D, n=91	131.4±8.1	130.3±9.3	−1.1 (−2.8 to 0.5)	−0.4 (−2.8 to 1.9)	0.712
Placebo, n=92	131.6±9.8	130.9±12.4	−0.7 (−2.5 to 1.0)		
24-hour diastolic blood pressure, mm Hg					
Vitamin D, n=91	78.1±7.5	77.8±8.2	−0.3 (−1.5 to 0.8)	0.2 (−1.3 to 1.7)	0.751
Placebo, n=92	77.4±8.0	76.9±8.9	−0.5 (−1.5 to 0.5)		
N-terminal pro-B-type natriuretic peptide, ng/L*					
Vitamin D, n=93	62 (34–133)	79 (38–128)	−13 (−42 to 17)	−20 (−58 to 18)	0.445
Placebo, n=95	98 (50–167)	91 (38–155)	10 (−22 to 41)		
Corrected QT interval, ms*					
Vitamin D, n=83	413 (387–438)	420 (401–434)	1 (−7 to 10)	0 (−11 to 12)	0.789
Placebo, n=90	417 (392–444)	417 (398–438)	0 (−9 to 9)		
Plasma renin concentration, μU/mL*					
Vitamin D, n=89	15.5 (9.6–35.8)	16.3 (10.2–35.6)	−1.5 (−8.1 to 5.0)	−19.0 (−68.7 to 30.5)	0.128
Placebo, n=92	16.7 (9.3–53.7)	20.9 (9.8–55.1)	28.8 (−23.0 to 80.6)		
Plasma aldosterone concentration, ng/dL*					
Vitamin D, n=92	15.1 (9.5–19.1)	16.3 (11.5–20.7)	0.9 (−1.0 to 2.8)	−2.3 (−4.5 to −0.3)	0.125
Placebo, n=94	14.5 (10.5–19.7)	19.1 (13.2–24.0)	3.3 (1.5 to 5.0)		
24-hour urinary albumin concentration, mg/24 h*					
Vitamin D, n=42	7.6 (5.2–9.6)	7.6 (5.0–11.3)	12.9 (−4.8 to 30.7)	10.9 (−4.5 to 26.4)	0.977
Placebo, n=37	10.5 (7.1–21.6)	9.4 (7.0–26.5)	2.5 (−6.0 to 11.0)		
Homeostasis model assessment insulin resistance*					
Vitamin D, n=93	2.02 (1.22–3.70)	2.46 (1.32–4.41)	0.68 (−0.23 to 1.59)	0.31 (−0.67 to 1.28)	0.543
Placebo, n=93	1.65 (1.07–3.73)	1.91 (1.20–3.72)	0.38 (0.02 to 0.73)		
Triglycerides, mg/dL*					
Vitamin D, n=93	122 (80–168)	138 (85–180)	14 (−1 to 29)	17 (1 to 33)	0.013
Placebo, n=95	118 (73–163)	110 (79–167)	0 (−10 to 10)		
HDL-cholesterol, mg/dL					
Vitamin D, n=93	55.7±16.5	55.3±17.1	−0.4 (−1.6 to 0.8)	0.9 (−1.5 to 3.3)	0.469
Placebo, n=95	57.2±16.4	55.7±15.3	−1.5 (−3.7 to 0.7)		
Pulse wave velocity, m/s					
Vitamin D, n=81	8.41±1.97	8.48±2.22	0.07 (−0.28 to 0.42)	−0.28 (−0.81 to 0.25)	0.302
Placebo, n=72	8.26±2.06	8.64±2.42	0.38 (0.05 to 0.80)		

Data at baseline and follow-up are shown as medians with SD or as medians with interquartile range; change from baseline data are shown as means (with 95% confidence interval); treatment effects (with 95% confidence intervals) and *P* values were calculated by ANCOVA for group differences at follow-up with adjustment for baseline values. HDL indicates high-density lipoprotein.

*Skewed variables for which logarithmic transformed values were used in ANCOVA but untransformed values are shown in the Table.

and follow-up values of the respective outcome variable. ANCOVA with adjustments for baseline values was used to test for differences in the outcome variables between the treatment and the placebo group at the follow-up visit.[33] A *P* value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 18.0 software (SPSS, Chicago, IL).

Results

Approximately 1700 persons were invited and asked to participate in the study, and 518 gave written informed consent and were assessed for eligibility. The first patient was randomized in June 2011, and the last follow-up visit was performed in August 2014. The participant flow through the study is shown in Figure S1 in the online-only Data Supplement.

Baseline characteristics of all randomized study participants are shown in Table S1. In the vitamin D group, C-reactive protein was significantly higher and angiotensin-converting enzyme–inhibitor use was significantly lower compared with the placebo group, whereas there were no significant group differences for all other study characteristics (Table S1). Of the 200 randomized study participants, 75 (37.5%) had 25(OH)D levels <20 ng/mL and 14 (7%) had 25(OH)D levels <12 ng/mL. At baseline, valid levels of 24-hour urinary albumin excretion,

Table 2. Parameters of Mineral Metabolism at Baseline and Follow-Up and Changes From Baseline in Study Participants With Available Values at Both Study Visits

Characteristics	Baseline	Follow-Up	Mean Change From Baseline	Treatment Effect	*P* Value
25-Hydroxyvitamin D, ng/mL					
Vitamin D, n=93	22.0±5.5	36.2±7.3	14.2 (12.5 to 15.8)	11.5 (9.4 to 13.7)	<0.001
Placebo, n=95	20.4±5.7	23.6±8.9	3.3 (1.8 to 4.7)		
Parathyroid hormone, pg/mL*					
Vitamin D, n=93	49.0 (40.0–61.5)	45.5 (37.8–54.4)	−4.0 (−6.5 to −1.6)	−5.7 (−9.3 to −2.1)	0.003
Placebo, n=95	51.3 (38.8–63.7)	50.4 (38.4–65.9)	1.7 (−1.2 to 4.7)		
Plasma calcium, mmol/L					
Vitamin D, n=93	2.37±0.10	2.37±0.08	0.00 (−0.02 to 0.01)	0.01 (−0.01 to 0.03)	0.259
Placebo, n=95	2.37±0.11	2.35±0.11	−0.01 (−0.03 to 0.01)		
24-hour urinary calcium excretion, mmol/24 h*					
Vitamin D, n=48	4.00 (2.18–6.30)	3.75 (2.38–6.83)	0.27 (−0.18 to 0.73)	0.16 (−0.56 to 0.87)	0.370
Placebo, n=40	4.05 (1.70–6.20)	4.15 (1.70–6.63)	0.16 (−0.32 to 0.64)		

Data at baseline and follow-up are shown as medians with SD or as medians with interquartile range; change from baseline data are shown as means (with 95% confidence interval); treatment effects (with 95% confidence intervals) and *P* values were calculated by ANCOVA for group differences at follow-up with adjustment for baseline values.

*Skewed variables for which logarithmic transformed values were used in ANCOVA but untransformed values are shown in the Table.

24-hour urinary calcium excretion, and pulse wave velocity were available in 133, 141, and 181 study participants, respectively. All other parameters were available in at least 99% of the study participants with no data imputation for missing values. Despite regular monitoring, one study participant with a plasma calcium concentration of 2.69 mmol/L, thus violating the exclusion criterion of hypercalcemia, was by mistake included, randomized and treated with vitamin D. By adhering to the intention to treat principle, we did not exclude this study participant from our final analyses, but excluding this patient in a sensitivity analysis did not significantly alter any of our results.

A total of 188 study participants (mean [SD] age, 60.1 [11.3] years; 47% women; baseline 25[OH]D, 21.2 [5.6] ng/mL) completed the baseline and follow-up visit. The overall treatment period was 54±10 days in the vitamin D and 54±9 days in the placebo group. There was no significant effect of vitamin D supplementation on 24-hour systolic BP with a mean treatment effect (95% confidence interval [CI]) of −0.4 (−2.8 to 1.9) mm Hg (*P*=0.712). For the secondary outcomes, there was also no significant treatment effect except for triglycerides (Table 1). Triglycerides increased significantly in the vitamin D group with a mean treatment effect of 17 (1–33) mg/dL (*P*=0.013).

Regarding parameters of mineral metabolism, we observed a significant increase in 25(OH)D (mean treatment effect [95% CI], 11.5 [9.4–13.7] ng/mL; *P*<0.001) and a significant decrease in parathyroid hormone (−5.7 [−9.3 to −2.1] pg/mL; *P*=0.003) with no effect on plasma calcium and 24-hour urinary calcium excretion (Table 2). No patient died during the study, and there was no excess of adverse events (ie, hypercalcemia or hospitalizations) in the vitamin D group. In detail, there were 6 unplanned hospitalizations in the vitamin D group (main reasons for hospitalization: 1 fracture, 1 fall, 2 abdominal surgeries, 1 congestive heart failure, and 1 deep venous thrombosis) and 4 in the placebo group (2 pneumonias, 1 congestive heart failure, and 1 overdosing of oral anticoagulation). No patient supplemented with vitamin D had developed hypercalcemia at the final study visit.

Discussion

In this RCT in hypertensive patients with low 25(OH)D levels, there was no significant effect of vitamin D supplementation on BP and several cardiovascular risk factors, albeit there was a significant increase in plasma triglycerides in the vitamin D group.

Although most published RCTs failed to demonstrate significant BP effects of vitamin D, the existing literature on this topic is inconsistent with some studies and even meta-analyses reporting BP-lowering effects of vitamin D in either the entire study cohort or in subgroups with low 25(OH)D or cardiometabolic diseases.[6,9–28] As we enrolled a study population that is, therefore, likely to be sensitive to potential BP-lowering effects of vitamin D, our findings argue against antihypertensive effects of vitamin D that are of clinical relevance for the treatment of the individual patient. This is in line with findings from the DAYLIGHT (The Vitamin D Therapy in Individuals at High Risk of Hypertension Trial) trial that also failed to observe any significant effect of vitamin D on BP.[13] In that RCT, 532 participants with prehypertension or stage I hypertension and 25(OH)D <25 ng/mL were randomized to either 400 IU or 4000 IU vitamin D per day.[13] Despite these null findings, it still remains to be elucidated whether vitamin D supplementation reduces BP in hypertensive patients with severe vitamin D deficiency because observational studies indicate that the risk increase in cardiovascular morbidity and mortality is particularly significant in severely vitamin D–deficient individuals.[34] Another point of discussion is the hypothesis that the effect of vitamin D on BP may exist, but it is small and thus only potentially relevant at a population level. A Mendelian randomization study comprising >140 000 individuals documented that each 10% increment in genetically determined/instrumented 25(OH)D

levels was associated with a reduction in systolic BP of −0.37 mm Hg (95% CI, −0.73 to 0.003; *P*=0.052) and a reduction in diastolic BP of −0.29 mm Hg (95% CI, −0.52 to −0.07; *P*=0.01).[35] These findings highlight that the magnitude of a possible BP-lowering effect of vitamin D is far below the presumed effect (ie, −6 mm Hg), which was used for our statistical power calculation.

Regarding our secondary outcomes, we failed to observe a statistically significant effect of vitamin D supplementation on plasma renin concentration or plasma aldosterone concentration, but our results could also be interpreted as showing a hypothesis generating nonsignificant trend toward RAAS suppression by vitamin D supplementation (Table 1). It has been postulated that increased activity of the RAAS system could mediate the link between vitamin D deficiency and arterial hypertension.[6,9] This notion is well supported by molecular effects of vitamin D receptor activation, such as suppression of renin expression.[6,9] The lacking effect of vitamin D on the RAAS in our RCT could be because of the high prevalence of study participants treated with RAAS blocking agents. Although most interventional studies did not show a vitamin D effect on the RAAS, one open-level, randomized trial in patients with congestive heart failure, and thus high RAAS activity, reported on a significant reduction in plasma renin activity after vitamin D supplementation.[36] According to these data, we recommend further RCTs on vitamin D supplementation and the RAAS, which should at best be performed in populations with high RAAS activity and low 25(OH)D concentrations.

With regard to heart diseases, the missing effect of vitamin D supplementation on QTc interval and N-terminal-pro-B-type natriuretic peptide is of relevance when considering that vitamin D deficiency has been previously associated with increased risk of sudden cardiac death and heart failure.[6] In 5292 study participants of the RECORD (Randomized Evaluation of Calcium or Vitamin D) trial, the hazard ratio (95% CIs) for vitamin D supplementation compared with no vitamin D supplementation for cardiac failure was 0.75 (0.58–0.97), whereas the hazard ratio was 0.82 (0.58–1.15) in a meta-analysis, including 13 033 study participants.[37] Few but not all RCTs in patients with heart failure have shown that vitamin D treatment reduces natriuretic peptide levels.[6] Our results do not confirm this, which could be explained by the fact that most of our study participants presented with baseline N-terminal-pro-B-type natriuretic peptide concentrations within the normal range.

The only statistically significant effect of vitamin D in our RCT, ie, the increase in triglycerides, was unexpected because observational studies showed inverse associations between 25(OH)D and triglycerides, and other RCTs have either shown no vitamin D effect in most studies or a decrease of triglycerides.[6,38] In general, the topic of vitamin D and cardiovascular risk factors, such as lipids, is a story of promising results from observational studies and discouraging results from RCTs.[6,38] Our results may suggest that the association between a poor vitamin D status and adverse lipid profiles in epidemiological studies is the result of confounding by, for example, obesity, low physical activity, inflammation, or poor dietary habits in vitamin D–deficient individuals.[1,38] Considering that several previous RCTs did not observe an increase of triglycerides with vitamin D supplementation, we hypothesize that our finding of an increase in triglycerides could simply be a chance finding and is not necessarily reflecting a true effect. Nevertheless, our results require further validation from additional studies that are designed to evaluate whether vitamin D could have adverse effects on lipid profiles. In this context, it should also be noted that, although most RCTs observed no effect on low-density lipoprotein cholesterol, some studies showed an increase in low-density lipoprotein cholesterol after vitamin D supplementation, which further points toward the need for studies addressing the issue of vitamin D and lipids.[38] Apart from this, multiple tests for secondary outcomes were performed, thereby increasing the probability of statistical type 1 errors. Correction for multiple testing was, however, not performed because all end points are based on a scientifically sound rationale derived from data of molecular, observational or interventional studies.[6] Furthermore, subgroup analyses were not performed because such tests were not prespecified.[39]

Missing effects on most of our outcome variables can also be viewed as proof that vitamin D supplementation is relatively safe with regard to many cardiovascular risk factors as it was also safe with regard to parameters of mineral/calcium metabolism. Considerations relative to safety issues are important because the current indication for vitamin D treatment are beneficial effects on skeletal health.[3–5] If no (adverse) effects are observed with regard to cardiovascular health, these findings do not argue against the use of vitamin D for other outcomes, such as bone health.[3–5] Apart from this, vitamin D could hypothetically exert beneficial effects on cardiovascular health by pathophysiological mechanisms that are not reflected by the outcome parameters that we assessed in our RCT.[6]

Limitations of this study are that findings from a single-center study in a selected cohort of white hypertensive patients with low 25(OH)D levels may not be generalizable to other study populations. The low prevalence of patients with severe vitamin D deficiency and the relatively short treatment period are other drawbacks of our study as we cannot exclude significant effects of vitamin D in populations with low vitamin D levels and with longer treatment or different vitamin D doses. About our relatively short treatment period, it should be noted that when supplementing vitamin D, it usually takes ≈3 months to reach a steady state in circulating 25(OH)D concentrations.[40] Strengths of our RCT are the well-validated assessment of BP with ABPM and the relatively large study population when compared with many previous RCTs. Another strength is that our treatment increased 25(OH)D significantly along with reductions in parathyroid hormone, which has been proposed to mediate cardiovascular relevant adverse effects of vitamin D deficiency.[6]

Perspectives

In summary, we failed to show significant effects of vitamin D supplementation on BP and several cardiovascular risk factors, but we observed a significant increase in triglycerides. The latter finding warrants additional investigation into the potential adverse effects that vitamin D supplementation may have on

blood lipids. Several large vitamin D RCTs in the older general population are ongoing and will be completed in 2017 to 2020.[41] In this context, our findings along with the available literature suggest that supplementing vitamin D regardless of the prevailing vitamin D status in apparently healthy individuals is likely to show no significant cardiovascular effects.[42] Therefore, we advocate further larger RCTs or meta-analyses in participants with overt vitamin D deficiency.[42]

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Disclosures

None.

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Novelty and Significance

What Is New?

This is the largest placebo-controlled study on effects of vitamin D supplementation on ambulatory blood pressure monitoring and cardiovascular risk factors in hypertensive study participants with low vitamin D levels.

What Is Relevant?

No significant beneficial effect of vitamin D supplementation on blood pressure and cardiovascular risk factor in a hypertensive study population with low vitamin D levels argues against recommendations for treating vitamin D deficiency to improve established cardiovascular risk factors.

Summary

In this randomized controlled trial in 200 hypertensive patients with 25(OH)D concentrations <30 ng/mL, we found no significant effect on ambulatory blood pressure monitoring and several cardiovascular risk factors, but we observed a significant increase in triglycerides that deserves further investigations.