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Original Article

Effects of Vitamin D3 on asymmetric- and symmetric dimethylarginine in arterial hypertension

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ABSTRACT

Background and aims: Accumulating evidence has proposed a correlation between vitamin D (25(OH)D) insufficiency and cardiovascular (CV) disease. Vitamin D associated effects on endothelial function have been suggested to be a possible culprit. The present study investigated the association of vitamin D3 treatment on markers of endothelial dysfunction in patients with arterial hypertension.
Methods and results: The Styrian Vitamin D Hypertension Trial is a double-blind, placebo-controlled, single-centre study conducted at the Medical University of Graz, Austria. A total of 200 study participants with arterial hypertension and 25(OH)D levels below 30 ng/mL were enrolled. The study participants were randomized to receive 2800 IU of vitamin D3 per day as oily drops (n = 100) or placebo (n = 100) for a duration of eight weeks. The present study uses an analysis of covariance (ANCOVA) to investigate the effect of vitamin D3 treatment on symmetric (SDMA) and asymmetric dimethylarginine (ADMA). A total of 187 participants (mean [SD] age 60.0 [11.3] years; 47% women; 25(OH)D 21.2 [5.6] ng/mL; mean systolic blood pressure of 131.4 [8.9] mmHg on a median of 2 antihypertensive drugs) completed the trial. Mean treatment effect was −0.004 (95%CI [−0.03 to 0.04]; P = 0.819) on ADMA and 0.001 (95%CI [−0.05 to 0.05]; P = 0.850) on SDMA. In the subgroup analysis patients with a 25(OH)D concentration <20 ng/mL had a significant increase in their log L-arginine/ADMA ratio (mean treatment effect 18.4 95%CI [1.84–34.9]μmol/L/μmol/L; P = 0.030). ClinicalTrials.gov Identifier: NCT02136771 EudraCT number: 2009-018125-70
Conclusions: Vitamin D3 supplementation in hypertensive patients with low 25-hydroxyvitamin D has no significant effect on ADMA and SDMA.

Contents

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1. Introduction

Vitamin D is a steroid hormone classically known to be responsible for bone mineralization [1,2]. It's deficiency is known to cause a childhood diseases called rickets, which is characterized by skeletal deformities [2]. Definition of normal vitamin D levels is based on the concentration of 25-hydroxyvitamin D (25[OH]D) – in this article referred to as vitamin D – which is the pro-hormone of the active metabolite, 1,25-dihydroxyvitamin D that subsequently activates the vitamin D receptor (VDR) [1,3]. Intriguingly, the VDR has also been found in extra-skeletal tissues, like myocardium and vasculature [4,5]. So the question raised whether there are non-bone related health effects of vitamin D insufficiency. Beside reports of children with heart failure and rickets which both improved with vitamin D supplementation [6], vitamin D insufficiency was broadly described to be a risk factor for cardiovascular (CV) diseases [2,4,7–10]. Low 25(OH)D concentrations have been even proposed to actually cause or mediate CV disease, but might also be only an epiphenomenon of poor health and low physical activity [2,9–12]. Nevertheless, in animal models the vitamin D receptor (VDR) activation led to improved endothelial function [2,7–10]. As endothelial dysfunction is a major component of CV disease[13] an interaction with vitamin D could explain – at least partially – the increased CV mortality seen in 25(OH)D insufficient patients [7,8,13–17]. Asymmetrical dimethylarginine (ADMA) is a marker of endothelial derangement and has been validated previously in cell based and clinical models. ADMA is a competitive inhibitor of NO-synthase which catalyses the production of nitric oxide, one of the most potent endogenous vasodilators. [18–22] Previous studies on vitamin D and ADMA reported cross sectional associations between them [23–25]. *Ngo* et al. observed an inverse association between 25(OH)D concentration and ADMA [23]. This was further supported by similar findings in patients with hypogonadism [24], phenylketonuria [25], Polycystic ovary syndrome (PCOS) [26], and in individuals on long-term haemodialysis (HD)[27]. The effect also seems to be associated with aging [28]. In line with this, *Syal* and colleagues observed that patients with lower 25(OH)D levels had significantly reduced flow-mediated brachial artery dilation, what strengthens hypothesis of a vitamin D associated effect on endothelial function [29]. Some authors further proposed the L-arginine to ADMA ratio as a more sensitive marker for endothelial function [18–20,30–32]. Similar results are reported in regard to symmetrical dimethylarginine (SDMA), a sensitive marker for renal function [33], which may also have indirect effects on NO synthesis [34]. Interventional data in humans on the effects of vitamin D supplementation on ADMA and SDMA are however, missing. We report results from our randomized double blind clinical trial supplementing vitamin D or

Table 1
Baseline Characteristics of the Placebo and the Vitamin D group before randomization.

	Placebo n = 99 Mean ± SD Median (IQR)	Vitamin D n = 99 Mean ± SD Median (IQR)
Age (years)	59.5 ± 11.4	60.7 ± 10.8
Females (yes)	48%	46%
Mean 24 h systolic blood pressure	131.8 ± 9.7	132.0 ± 8.4
Asymmetric dimethylaginine (μmol/L)	0.73 ± 0.09	0.70 ± 0.15
Symmetric dimethylarginine (μmol/L)	0.71 ± 0.10	0.69 ± 0.16
L-arginine/ADMA ratio μmol/L/μmol/L	183.3 ± 58.7	183.1 ± 49.7
L-arginine (μmol/L)	131.0 ± 35.5	128.6 ± 31.6
Parathyroid hormone (pg/mL)	51.5 (39.5–65.8)	48.9 (40.0–61.7)
25-hydroxyvitamin D (ng/mL)	20.4 ± 5.7	21.8 ± 5.5
25-hydroxyvitamin D (nmol/L)	50.9 ± 14.2	54.4 ± 13.7
Serum total calcium (mmol/L)	2.37 ± 0.11	2.37 ± 0.10
Estimated glomerular filtration rate MDRD6 (mL/min/1.73m^2)	77.0 ± 17.9	79.9 ± 17.9
Number of different blood pressure lowering drugs	2 (1–3)	2 (1–3)
ACE inhibitor (yes)	38%	25%
AT1 receptor blocker (yes)	31%	33%
Calcium channel blocker (yes)	25%	27%
Thiazide diuretics (yes)	45%	39%
Loop diuretics (yes)	5%	5%
Beta blockers (yes)	49%	44%
Minteralocorticoid receptor blockers (yes)	4%	2%
Smoking (yes)	16.1%	7.4%

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