World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v6.i5.260

World J Cardiol 2014 May 26; 6(5): 260-276
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (1): Hypertension

Potential pathophysiological role for the vitamin D deficiency in essential hypertension

Federico Carbone, François Mach, Nicolas Vuilleumier, Fabrizio Montecucco

Federico Carbone, Fabrizio Montecucco, Department of Internal Medicine, University of Genoa School of Medicine, IRCCS Azienda Ospedaliera Universitaria San Martino-IST Istituto Nazionale per la Ricerca sul Cancro, 16132 Genoa, Italy
Federico Carbone, François Mach, Cardiology Division, Foundation for Medical Researches, Department of Internal Medicine, University of Geneva, 1211 Geneva, Switzerland
Nicolas Vuilleumier, Fabrizio Montecucco, Division of Laboratory Medicine, Department of Genetics and Laboratory Medicine, Geneva University Hospitals, 1205 Geneva, Switzerland
Author contributions: Carbone F and Montecucco F wrote the paper; Vuilleumier N and Mach F approved the final version of the manuscript; Mach F corrected the English form as native English speaker.
Supported by European Commission (FP7-INNOVATION I HEALTH-F2-2013-602114; Athero-B-Cell: Targeting and exploiting B cell function for treatment in cardiovascular disease) to Dr. F Mach; Swiss National Science Foundation Grants to Dr. F Mach, No. #310030_118245; Swiss National Science Foundation Grants to Dr. N Vuilleumier, No. #310030_140736; and Swiss National Science Foundation Grants to Dr. F Montecucco, No. #32003B_134963/1; the Novartis Foundation and the Foundation "Gustave and Simone Prévot" to Dr. F Montecucco
Correspondence to: Dr. Fabrizio Montecucco, MD, PhD, Division of Laboratory Medicine, Department of Genetics and Laboratory Medicine, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, 1205 Geneva, Switzerland. fabrizio.montecucco@unige.ch
Telephone: +41-22-3827238 Fax: +41-22-3827245
Received: November 8, 2013 Revised: March 24, 2014
Accepted: April 11, 2014
Published online: May 26, 2014

Abstract

Vitamin D deficiency has been indicated as a pandemic emerging public health problem. In addition to the well-known role on calcium-phosphorus homeostasis in the bone, vitamin D-mediated processes have been recently investigated on other diseases, such as infections, cancer and cardiovascular diseases. Recently, both the discovery of paracrine actions of vitamin D (recognized as "local vitamin D system") and the link of vitamin D with renin-angiotensin-aldosterone system and the fibroblast growth factor 23/klotho pathways highlighted its active cardiovascular activity. Focusing on hypertension, this review summarizes the more recent experimental evidence involving the vitamin D system and deficiency in the cardiovascular pathophysiology. In particular, we updated the vascular synthesis/catabolism of vitamin D and its complex interactions between the various endocrine networks involved in the regulation of blood pressure in humans. On the other hand, the conflicting results emerged from the comparison between observational and interventional studies emphasize the fragmentary nature of our knowledge in the field of vitamin D and hypertension, strongly suggesting the need of further researches in this field.

Key words: Vitamin D; Hypertension; Cardiovascular disease; Renin; Angiotensin

Core tip: This review provides a comprehensive and critical analysis of the most recent studies investigating the relationship between vitamin D and essential hypertension. From the both observational and interventional studies, conflicting results have been shown. This review article provides some hypothesis to explain these discrepancies. In addition to the potential bias related to the study design, some pathophysiological explanation was suggested, especially involving the potential role of local vitamin D system as well as the fibroblast growth factor 23/klotho axis. This review aims at suggesting a careful reflection so that future studies might be designed for minimize bias and encompass the complex biology of vitamin D system.

Carbone F, Mach F, Vuilleumier N, Montecucco F. Potential pathophysiological role for the vitamin D deficiency in essential hypertension. *World J Cardiol* 2014; 6(5): 260-276 Available

from: URL: http://www.wjgnet.com/1949-8462/full/v6/i5/260.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i5.260

INTRODUCTION

Vitamin D deficiency has recently emerged as a public health problem, affecting almost 50% of the population worldwide[1]. In addition to the reduced exposition to sunlight[2], also genetic and environmental factors have been suggested as a cause of this pandemic, such as pollution, diet, sedentary life style and stress[3]. Moreover, vitamin D is no longer considered as only a pivotal mediator of calcium metabolism and skeletal health, but it also regulates several cell functions, including differentiation and metabolism. This aspect may explain the reason why hypovitaminosis D has been proved to be an independent risk factor for overall mortality in various cohort analyses[4], whereas vitamin D supplementation significantly reduced mortality[5]. Moreover, similar data were collected from different clusters of inflammatory and chronic diseases, such as infections[6], autoimmunity[7], neurodegenerative pathologies[8], as well for cancer[9]. However, a special interest was conferred to the potential relationship between vitamin D and cardiovascular (CV) disorders. Although in human cohorts low vitamin D levels were associated with impaired CV outcomes[10], a causal relationship remains unknown, and the general enthusiasm about the benefits of vitamin D supplementation have been recently replaced by words of caution.

On the other hand, novel topics that might address many question in the field of vitamin D, such as fibroblast growth factor (FGF) 23-klotho axis, non-genomic effects of vitamin D and the paracrine effects of vitamin D (also called "local vitamin D system") have been identified. In the following paragraphs, we will focus on the mechanisms triggered by vitamin D in arterial hypertension, starting from the complex interplay with the renin-angiotensin-aldosterone system (RAAS) in both basic research and clinical trials.

VITAMIN D SYSTEM AND BLOOD PRESSURE

Vitamin D

In humans, more than 80% of vitamin D requirements is produced through the ultraviolet-B (UVB)-induced conversion of 7-dehydrocholesterol to vitamin D in the skin, whereas only 10%-20% is absorbed with the diet[1]. The photosynthesis of vitamin D evolved over 750 million years ago, first in the phytoplankton and then in early plants and animals[11]. From an evolutionary stand point it is interesting to note that the first living beings synthetizing vitamin D were missing calcific skeleton. This suggests that a new recognized non-metabolic role (called "non-classical effects") of vitamin D might actually be the oldest. Regardless of the source, vitamin D requires liver hydroxylation [through 25-hydroxylase (CYP2R1 or CYP27A1)] to form 25-hydroxyvitamin D [25(OH) vitamin D or calcidiol], inactive form but used as reference for vitamin D status, because abundant, stable and easier to quantify[1]. In the kidney 25(OH) vitamin D is then hydroxylated to 1,25-dihydroxyvitamin D [1,25(OH)2 vitamin D or calcitriol] the active form of vitamin D [through 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1)]. This latter step is a pivotal effector of calcium homeostasis and thus highly controlled by the up-regulation of parathyroid hormone (PTH) and the suppression of FGF23/klotho axis[12]. Although the exact contribution of extra-renal hydroxylation in determining the circulating levels of 1,25(OH)2 vitamin D is still unknown, it has been recognized also an extra-renal activity of CYP27B1. Finally, the recent identification of a role of vitamin D binding proteins on vitamin D catabolism has further increased complexity of the system[13].

Vitamin D receptor

Vitamin D receptor (VDR) is member of nuclear hormone receptors superfamily. Following binding with 1,25(OH)2 vitamin D, VDR recruits one of the retinoid X receptors (RXR α, β or γ) forming homo- or heterodimers to promote a specific, high-affinity DNA-binding interaction. This transcriptional complex binds to repeated sequences of 6 hexamers [vitamin D response elements (VDRE)] in the promoter region of target gene[1]. VDR is believed to directly or indirectly regulate 3% to 5% of human genome and the different genomic activation of vitamin D in the different cell types involves allosteric influences, VDRE location and epigenetic modification (of both DNA and histones)[14]. In addition, VDR recognizes extra-nuclear ligands including endogenous steroids and other lipophilic compounds[15,16]. Finally, VDR may be expressed also on the cell surface membrane and within mitochondria thus might modulate non-genomic signalling pathways, such as 1,25(OH)2 vitamin D-mediated rapid-response[17]. Vitamin D are deeply involved in several patterns of CV pathophysiology, including vascular inflammation[18] and endothelial dysfunction[19] as observed in patients with chronic kidney disease (CKD)[20] and type 2 diabetes[21] as well as in asymptomatic subjects[22]. For instance, in vitro VDR activation induces nitric oxide production in endothelial cells[23] and improves the angiogenic properties of endothelial progenitor cells[24], while regulates proliferation[25], migration[26], mineralization[27] and thrombogenic protein expression[28] in vascular smooth muscle cells (VSMCs). The recent recognition of specific VDR polymorphisms and genetic susceptibility in pathophysiology of hypertension has further supported these insights[29].

Vitamin D hydroxylases

The gene encoding for CYP27B1 is widespread expressed in various tissue of endodermal, ectodermal and mesenchymal origin. Since even VDR is highly represented in tissues, an autocrine/paracrine vitamin D system has been strongly suggested. In contrast to endocrine vitamin D system, local regulation of 1,25(OH)2 vitamin D levels

is independent of PTH expression, but rather relies on environmental factors[30]. CYP27B1 expression in endothelial cell is regulated by pro-inflammatory cytokines[31], in VSMCs is under estrogenic control[32] whereas many signals regulate the expression in monocyte/macrophage, including toll-like receptor[33], interferon-γ[34], FGF23[35] and uremia[36]. Accordingly, CYP27B1$^{-/-}$ mice develop an hypertensive phenotype, also characterized by increased circulating level of renin, angiotensin (Ang) II and aldosterone, then suppressed by administration of 1,25(OH)2 vitamin D independently of serum levels of calcium or phosphorus[37].

Vitamin D and FGF23/Klotho pathways

Recently, the discovery of FGF23 has extended the complexity of the endocrine network involving the vitamin D system. As vitamin D counter-regulatory hormone, FGF23 suppresses renal synthesis of 1,25(OH)2 vitamin D by inhibiting CYP27B1 and up-regulating CYP24A1. These effects are independent of VDR but require co-factor klotho, essential for FGF23 signal transduction[38]. Overall, 1,25(OH)2 vitamin D and FGF23 are involved in a classical hormonal loop also including PTH. High levels of 1,25(OH)2 vitamin D raise the serum concentrations of both calcium and phosphate. Concomitantly, the feedback by PTH reduces only calcium levels by enhancing its urinary excretion. Increased levels of FGF suppress the expression of sodium-phosphate cotransporter NaPi-2a on renal proximal tubules, thus resulting in increased phosphaturia[39]. Therefore, phosphorus homeostasis might be maintained by 1,25(OH)2 vitamin D *via* a direct regulation on FGF23 levels.

Thus, the discovery of FGF23 might explain some paradoxical concerns on vitamin D, especially among the ambiguous results of interventional studies. A strong correlation between an increased risk of mortality and high circulating levels of both FGF23 and phosphate has been also reported[40,41], suggesting that there is a threshold in vitamin D supplementation beyond which 1,25(OH)2 vitamin D may have detrimental effects.

For instance, the age-associated suppression of Klotho expression[42] may promote a vitamin D toxicosis during therapeutic supplementation characterized by over-hyperphosphatemia and thus increased cardiovascular risk[43]. Although it is likely a failure of the normal feedback mechanism regulating vitamin D and FGF23, the molecular bases of these clinical features have not been identified yet. Furthermore, Camalier *et al*[44] recently provided evidence of both rapid and late effects induced by FGF23 on mesenchymal stromal cells, involving cell proliferation and extracellular matrix (ECM) regulation. In addition, Jimbo *et al*[45] showed that FGF23 promoted osteoblastic differentiation of aortic VSMCs from uremic rats by inducing ERK1/2 phosphorylation pathway. However, it should be noted that these features were shown only in primary rat VSMCs and other studies failed to recognize the relevance of FGF23-Klotho signalling in mouse arteries[46,47].

Ultimately, although further studies in humans are warranted, we agree with Glade M.J., who suggested that there may be an age at which vitamin D deficiency may become life-sustaining, not life-threatening[48].

PATHOPHYSIOLOGICAL PATHWAYS OF VITAMIN D IN HYPERTENSION

Although the effects of vitamin D on blood pressure have been known for several decades, some physiological aspects on the modulation of vascular cells and the vascular tone still remain to be clarified.

RAAS

RAAS plays a pivotal role in maintaining sodium and blood volume homeostasis even by modulating the renal function and blood pressure. RAAS up-regulation was shown to promote the development of hypertension and increased CV risk[49,50].

Salt- and volume-independent RAAS up-regulation (documented by an increase in renin and Ang II levels) was associated with hypertension and cardiac hypertrophy in VDR$^{-/-}$ mice[51]. Similarly, in wild-type mice, 1,25(OH)2 vitamin D inhibition (through dietary intake of strontium) increased renin expression, while 1,25(OH)2 vitamin D supplementation down-regulated RAAS in a VDR-dependent manner[51].

Also the evidence of a preserved CV function in VDR$^{-/-}$ mice undergoing RAAS inhibition (using Angiotensin converting enzyme inhibitors or Angiotensin receptor I blockers) confirmed a direct connection between RAAS and vitamin D system[52]. Interestingly, similar results were also reported in CYP27B1$^{-/-}$ mice[37]. Among the several cross-sectional and prospective studies investigating the association of vitamin D deficiency and hypertension only Forman *et al*[53] provided a mechanistic role of vitamin D system in the RAAS regulation. Lower 25(OH) vitamin D levels correlated with both higher Ang II at baseline (P = 0.03), and blunted renal plasma flow response to Ang II infusion in a cohort of 184 normotensive subjects treated with high-salt diet. These findings were confirmed in subsequent studies[54,55].

From a molecular point of view, the research group directed by Li *et al*[52] discovered a direct effect of 1,25(OH)2 vitamin D on renin gene transcription. They identified that vitamin D is capable of suppressing renin gene transcription by a cAMP response element, identified on the promoter region of *Ren-1c* gene[56]. In addition, the same authors confirmed a central role of active vitamin D by excluding the control of PTH or serum calcium levels on renin expression[57]. On the other hand, Ferder and co-workers have recently proposed a new hypothesis about the dependency instead of complementarity vitamin D system and RAAS. Overturning the classical view, the authors suggested the RAAS-induced inflammatory response as regulator of vitamin D status thus representing the "primum movens" of current vitamin D deficiency pandemic[58]. Anyway, although suggestive, this hypothesis of a reciprocal counter-regulatory

effect between vitamin D and RAAS is currently highly speculative. Research models identifying effectors shared by RAAS and vitamin D are still missing[59]. Angiotensin Ⅱ is a main mediator responsible for adverse vascular remodelling in hypertension[60]. By promoting endothelial dysfunction and vascular permeability, RAAS induces recruitment and activation of inflammatory cells within the vessel wall. This inflammatory behaviour stimulates hyperplasia and hypertrophy of VSMCs, but also their release of pro-inflammatory molecules (VCAM-1, monocyte chemoattractant protein-1, interleukin 6 and 8)[61]. Furthermore, angiotensin Ⅱ was shown to mediate the shift of VSMCs toward a fibroblast phenotype that alters the ECM composition by suppressing the activity of matrix metalloproteinases and enhancing the production of their inhibitors[62]. Among the intracellular signalling pathways involved in angiotensin Ⅱ signalling a key role is played by oxidants and their downstream signalling cascades including mitogen-activated protein kinase, protein kinase C, phospholipase A2 and the transcription factors NFκB and activator protein-1[63].

PTH

PTH is a crucial regulator of calcium and phosphate homeostasis, achieved in different ways, such as osteoclast/osteoblast activation, enhancement of intestinal and renal calcium absorption and up-regulation of CYP27B1 expression in the kidney. Although not generally accepted[64], higher PTH concentrations were associated with an increase in several CV risk factors[65], including hypertension[66-76]. Moreover, several cohorts of sporadic primitive hyperparathyroidism were found associated with arterial stiffness[77-84]. The mechanism linking PTH and blood pressure is still unclear and several pathways might be triggered. PTH up-regulates RAAS activity promoting renin release[85,86], but it also directly promotes aldosterone release from adrenal glands[87]. Also the increase of serum calcium PTH may indirectly modulate renin release[88] and aldosterone synthesis[87] in addition to activate VSMC[89]. PTH increases sympathetic activity with additional RAAS activation (increase in renin release and aldosterone secretion)[90] and vascular contractility[90]. Finally, a cellular interaction through the PTH/PTH-related protein receptor expressed on endothelial cells[91], VSMC[92] and inflammatory cells[93] may directly affect the vascular function.

CLINICAL STUDIES

The association between vitamin D levels and blood pressure was previously reported, observing higher blood pressure trends in the winter months and location further from the equator[94]. Many clinical studies have subsequently provided consistent results but this topic is still widely debated, especially after the results observed in the interventional clinical trials.

Cross-sectional studies

A large number of cross-sectional studies investigated the relationship between vitamin D deficiency and blood pressure, as well as the prevalence of hypertension. Table 1 summarizes the studies having 25(OH) vitamin D as reference for the vitamin D status[1].

The most relevant results were acquired from the national health and nutrition examination survey (NHANES), widely representative of non-hospitalized United States civilian population. First Martins *et al*[95] showed an increased prevalence of hypertension associated with low serum 25(OH) vitamin D levels in 15088 subjects from this cohort. In addition, the very large sample size of this cohort allowed to recognize the inverse relationship between 25(OH) vitamin D and raised blood pressure also in several subgroups (such as African Americans and older people[96,97], children/adolescents[101,112], Hispanic people[113], in addition to observed an increased prevalence of pre-hypertension in 25(OH) vitamin D deficient subjects[121]). Other cross-sectional cohort studies with large sample size supporting these findings were the German National Health Interview and Examination Survey (4030 subjects)[98], the 1958 British birth cohort (6810 subjects)[100], and the Tromsø Study (4125 subjects)[104] as well as the cohorts collected from Israel people (34874 subjects)[108] and Copenhagen population[123]. Other smaller cohorts supporting these insights were collected in Europe[73,103,109,111,122,126], North America[110,118,120,124], Oceania[102] and Asia[72,105,115]. Despite the large numbers of subjects and their worldwide distribution, a clear relationship between vitamin D and blood pressure has not yet been established so far. In fact, among the studies listed in Table 1, seven did not confirm this association[64,67,70,72,73,119,123]. These conflicting results are in accordance with some unanswered questions in the field of vitamin D biology. In fact, despite the standardization of the season of subject recruitment, the latitudes, where studies were carried out, determine a confounding effect related to the pivotal role of sunlight exposure and consequent vitamin D synthesis within the skin[2]. Another potential bias is that differences in serum 25(OH) vitamin D levels might depend on the age. Elderly subjects have a reduced skin synthesis and intestinal absorption of vitamin D in addition to spend less time outdoors, limiting sunlight exposure[127]. Regardless of the latitude and season, only few studies have estimated sun exposure and dietary intake (as well as a possible supplementation) of vitamin D, especially in the elderly population. Moreover, racial differences should be recognized, since the black population correlated with a higher incidence of vitamin D deficiency (and also hypertension), because of their high skin content of melanin[128]. In this regard, it should be emphasized that most of the negative studies were made up from Caucasian[67,73,123] Hispanic[119] and Chinese[64,72] cohorts. Finally, there is still much debate about which cut-off value defines 25(OH) vitamin D deficiency. However, among the results reported in Table 1 most of the studies showed the first quartile or proposed a cut-off closed to 30 nmol/L. In addition, for higher mean 25(OH) vitamin D levels, blood pressure poorly correlated with vitamin D but rather with PTH

Table 1 Cross-sectional studies evaluating vitamin D blood pressure

Ref.	Year	Study design (sample size)	Country (ethnicity) Age	Correlation (lower reference range of 25(OH) vitamin D)	Findings
Snijder *et al*[67]	2007	Cross-sectional from the LASA (1205 subjects more than 65 yr old)	Netherlands (caucasian) men and women ≥ 65 yr	No (I quartile: < 25 nmol/L)	25(OH) vitamin D was not associated with systolic or diastolic BP or prevalence of hypertension. Instead, PTH correlated with both BP and hypertension incidence
Martins *et al*[95]	2007	Cross-sectional from the 1988-1994 NHANES (15088 subjects)	United States (Caucasian and African Americans and other) men and women age stratified	Yes (I quartile: < 52.5 nmol/L)	Adjusted inter-quartile analysis showed an increased prevalence of hypertension in in the lower quartile of 25(OH) vitamin D (OR = 1.30, 95%CI; 1.13-1.49; $P < 0.05$)
Scragg *et al*[96]	2007	Cross-sectional from the 1988-1994 NHANES (12644 subjects not treated with anti-hypertensive drugs)	United States (Caucasian and African Americans and other) men and women age stratified	Yes (I quintile: < 40 nmol/L)	Adjusted inter-quintile analysis of 25(OH) vitamin D showed significant inverse correlation with both systolic ($P < 0.01$) and diastolic ($P < 0.05$) BP. This association was stronger in more than 50 years old and black people
Judd *et al*[97]	2008	Cross-sectional from the 1988-1992 NHANES (7699 non-hypertensive subjects)	United States (White and black people) men and women age stratified	Yes (Vitamin D deficiency defined as < 50 nmol/L)	Lower 25(OH) vitamin D concentrations were associated with a higher blood pressure category in white people ($P < 0.01$) but after adjustment for age the association was no longer significant
Hintzpeter *et al*[98]	2008	Cross-sectional from GNHIES (4030 adults)	Germany (Caucasian) men and women 18-79 yr	Yes (Vitamin D deficiency defined as < 12 nmol/L[99])	According to 25(OH) vitamin D levels, in multivariate analysis there was a relationship between 25(OH) vitamin D and hypertension bot in men (OR = 0.97, 95%CI: 0.94-0.99; $P < 0.05$) and in women (OR 0.96, 95%CI: 0.93-0.99; $P < 0.05$)
Hypponen *et al*[100]	2008	Cross-sectional from 1958 British birth cohort (6810 subjects)	United Kingdom (Caucasian) men and women 45-47 yr	Yes (I tertile: < 45 nmol/L)	The lower 25(OH) vitamin D tertile was associated with hypertension (OR 0.72, 95%CI: 0.61-0.86; $P < 0.01$)
Reis *et al*[101]	2009	Cross-sectional from the 2001-2004 NHANES (3577 non-pregnant adolescents without diagnosed diabetes)	United States (Caucasian and African Americans and other) male and female adolescent 12-19 yr	Yes (I quartile: < 37.5 nmol/L)	25(OH) vitamin D was inversely associated with systolic BP ($P < 0.05$) also in the adjusted odds ratio for the interquartile comparison (OR = 2.36, 95%CI: 1.33-4.19; $P < 0.05$)
Pasco *et al*[102]	2009	Cross-sectional (861 subjects)	Australia (Caucasian) women: 20-92 yr	Yes (I tertile 25(OH)D: < 30 nmol/L)	In this cohort there was a significant inter-tertile difference in mean BP ($P < 0.001$) as well as in anti-hypertensive medication use ($P < 0.01$)
Almirall *et al*[103]	2010	Cross-sectional (237 subjects more than 64 years old)	Spain (Caucasian) men and women 64-93 yr	Yes (cut-off for vitamin D deficiency: < 62.5 nmol/L)	A significant negative association was observed between serum 25(OH) vitamin D levels and both systolic ($P < 0.05$) and diastolic BP ($P < 0.05$) also in multivariate analysis
Jorde *et al*[104]	2010	Cross-sectional from the Tromsø Study (4125 subjects not treated with anti-hypertensive drugs)	Norway (Caucasian) Men and women age stratified	Yes (I quartile: < 41.4 nmol/L)	At adjusted inter-quartile analysis serum 25(OH) vitamin D was inversely correlated with systolic BP ($P < 0.01$)
Kim *et al*[105]	2010	Cross-sectional (1330 subjects)	South Korea (Asian)	Yes (I quintile: < 29.7 nmol/L)	At adjusted inter-quintile analysis, both systolic and diastolic BP decreased linearly with increasing of 25(OH) vitamin D (quintile 1-5; P for trend < 0.01). Moreover, inter-quintile comparison of BP had OR of 0.42 (95%CI: 0.24-0.73; $P < 0.05$)
Zhao *et al*[106]	2010	Cross-sectional from the 2003-2006 NHANES (5414 subjects not assuming anti-hypertensive drugs)	Men and women < 40 yr United States (Hispanic, Caucasian and African Americans) men and women ≥ 20 yr	Yes (I quintile: < 37.5 nmol/L	Across 25(OH) vitamin D quintiles systolic and diastolic BP decreased linearly and inversely (P < 0.01). Moreover, the prevalence ratio for hypertension was lower in the highest quintile (OR = 0.82, 95%CI: 0.73-0.91; $P < 0.05$)
Fraser *et al*[107]	2010	Cross-sectional from the 2001-2006 NHANES (3958 subjects)	United States (Caucasian and African Americans and other) men and women ≥ 20 yr	Yes (linear correlation)	25(OH) vitamin D has an inverse linear correlation with systolic blood pressure in various adjusted models ($P < 0.05$)

Steinvil *et al*[108]	2011	Cross-sectional case-control study (34874 subjects of which 8387 hypertensive)	Israel men and women 38-72 yr	Yes (vitamin D deficiency defined as < 37.5 nmol/L)	The age-adjusted OR for hypertension among normal and deficient serum 25(OH) vitamin D was 1.19 (95%CI: 1.09-1.31; $P < 0.01$) in women, whereas in men there was not statistical difference
Burgaz *et al*[109]	2011	Cross-sectional from the ULSAM (833 adult men)	Sweden (Caucasian) Men 71 yr	Yes (vitamin D deficiency defined as < 37.5 nmol/L)	Adjusted logistic regression confirmed the association between 25(OH) vitamin D concentration < 37.5 nmol/L and hypertension (OR = 3.3, 95%CI: 1.0-11.0; $P < 0.05$)
Bhandari *et al*[110]	2011	Cross-sectional (2722 subjects of which 1415 hypertensive)	United States (Caucasian and African Americans and other) men and women mean age 58.5 yr	Yes (I quartile: < 37.5 nmol/L)	The prevalence rate of hypertension was inversely correlated with serum 25(OH) vitamin D. Inter-quartile comparison showed an adjusted OR of 2.70 (95%CI: 1.41-5.19; $P < 0.05$)
Pacifico *et al*[111]	2011	Cross-sectional case-control study (452 children and adolescent of which 304 over-weight/ obese and 148 normal weight)	Italy (Caucasian) Male and female children	Yes (I tertile of 1,25(OH)2 vitamin D: < 42.5 nmol/L)	1,25(OH)2 vitamin D was inversely correlated with systolic BP both in the whole population ($P < 0.01$) and over-weight ($P < 0.01$) population as well as in control group ($P < 0.01$). Regardless of model for adjusted analysis, the OR for hypertension among tertile categories had a P value < 0.05.
Williams *et al*[112]	2011	Cross-sectional from 2003-2006 NHANES (5617 adolescent)	United States (Caucasian and African Americans and other) male and female children 12-19 yr	Yes (linear correlation)	In this cohort, 25(OH) vitamin D showed a linear inverse association with systolic BP in multivariate analysis ($P < 0.01$).
Forrest *et al*[113]	2011	Cross-sectional from 2005-2006 NHANES (4495 adults subjects of which 1482 hypertensive)	United States (Caucasian and African Americans and other) Men and women age stratified	Yes (vitamin D deficiency defined < 50 nmol/L[114])	Vitamin D deficiency independently correlated with prevalence of hypertension ($P < 0.01$).
He *et al*[70]	2011	Cross-sectional from 2003-2006 NHANES (7561 of which 1849 treated with anti-hypertensive drugs)	United States (Caucasian and African Americans and other) Men and women age stratified	No (I quintile: < 33 nmol/L)	25(OH) vitamin D was inversely associated with systolic BP. However, 25(OH) vitamin D lost its statistical significance in a multivariate analysis including PTH. Instead, PTH maintained a strong correlation with BP in multivariate analysis regardless of covariates.
Dorjgochoo *et al*[115]	2012	Cross-sectional study from two, population-based, prospective cohort studies (1460 subjects of which 547 hypertensive)	China (Asian) men and women 40-74 yr	Yes (lowers range defined by I quintile 23.5 nmol/L and cut-offs of 37.5 nmol/L[116] and 27.5 nmol/L[117])	Among men cohort, BP was inversely and significantly correlated with 25(OH) vitamin D ($P < 0.05$). Moreover, prevalence of hypertension was inversely associated with non-deficient status of vitamin D (adjusted OR = 0.29, 95%CI: 0.10-0.82; $P < 0.05$)
Sakamoto *et al*[118]	2013	Cross-sectional from the AHS-2 (568 subjects)	United States (equally matched Caucasian and African Americans) men and women 30-95 yr	Yes (vitamin D deficiency defined as < 50 nmol/L)	Regardless of adjusted analysis models, Caucasian people showed a linear inverse correlation between 25(OH) vitamin D and BP ($P < 0.05$). Also the comparison between vitamin D deficient and non-deficient showed statistical difference ($P < 0.05$).
Li *et al*[64]	2012	Cross-sectional (1420 subjects of which 487 hypertensive)	China (Asian) Men and women ≥ 65 yr	No (I quartile: < 42 nmol/L)	Serum 25(OH) vitamin D levels were not associated with risk of hypertension in single and multiple regression models. Similarly, PTH is not independently associated with BP or risk of hypertension
Caro *et al*[119]	2012	Cross-sectional (219 subjects of which 115 hypertensive)	Puerto Rico (Hispanic) Men and women 21-50 yr	No (cut-off used to define non optimal: 75 nmol/L)	Vitamin D status was not found to be associated with BP
Chan *et al*[72]	2012	Cross-sectional (939 men aged 65 yr and older)	China (Asian) men ≥ 65 yr (age strafied)	No (I quartile: < 63 nmol/L)	Vitamin D status was not found to be associated with BP. Instead, PTH was directly and independently associated with BP also in multivariate analysis.
Parikh *et al*[120]	2012	Cross-sectional (701 adolescents)	United States (Caucasian and African Americans) Male and female 14-18 yr	Yes (I tertile: < 54.8 nmol/L)	Serum 25(OH) vitamin D has a linear inverse correlation with both systolic ($P < 0.05$) and diastolic ($P < 0.01$) BP. However, in the adjusted analysis only the relationship with systolic BP remained significant.
Sabanayagam *et al*[121]	2012	Cross-sectional from NHANES III (9215 subjects of which 3712 with pre-hypertension)	United States (Caucasian and African Americans and other) men and women age stratified	Yes (I quartile: < 44.25 nmol/L)	In this cohort the systolic BP are inversely correlated with the vitamin D status ($P < 0.05$) and lower values of 25(OH) vitamin D were associated with increase prevalence of pre-hypertension (adjusted OR = 1.48, 95%CI: 1.16-1.90; P value for trend < 0.01).

van Ballegooijen *et al*[122]	2012	Cross-sectional from the Hoorn study (256 subjects)	The Netherlands (Caucasian) men and women 50-75 yr	Yes (I quartile: < 60.8 nmol/L)	In this cohort there was an inverse correlation between 25(OH) vitamin D and both systolic and diastolic BP (*P* value for trend < 0.01 for both)
Skaaby *et al*[123]	2012	Cross-sectional 4330 subjects)	Denmark (Caucasian) men and women 30-60 yr	No (I quartile: < 33 nmol/L)	Mean 25(OH) vitamin D levels did not differed between hypertensive and normotensive subjects. There was not increased prevalence of hypertension in vitamin D deficient subjects
Kruger *et al*[124]	2013	Cross-sectional form the PURE study (291 African women)	All over the world countries (African) women > 47 yr	Yes (vitamin D deficiency defined as < 30 nmol/L[125])	Both systolic and diastolic BP correlated linearly and inversely with serum 25(OH) vitamin D level ($P < 0.05$ for both). However, only systolic BP maintain statistical significance in multivariate analysis ($P < 0.05$).
Mateus-Hamdan *et al*[73]	2013	Cross-sectional (284 geriatric patients of which 106 hypertensive)	France men and women mean age 85 ± 6 yr	No (linear correlation)	Means PTH but not 25(OH) vitamin D levels are significant different in hypertensive compared to normotensive patients.
Ke *et al*[126]	2013	Cross-sectional from the ATBC (2271 subjects of which 1430 hypertensive)	Finland (Caucasian) men and women 50-69 yr	Yes (I quartile: < 25 nmol/L)	Serum 25(OH) vitamin D level has a significant and inverse association with systolic BP ($P < 0.05$), also if stratified in groups. Moreover, the lower group was associated with increased prevalence of hypertension in multivariate analysis (*P* value for trend < 0.05).

LASA: Longitudinal aging study amsterdam; 25(OH)D: Cholecalciferol; BP: Blood pressure; PTH: Parathyroid hormone; NHANES Ⅲ: Third United States national health and nutrition examination survey; OR: Odds ratio; GNHIES: German national health Interview and examination survey; ULSAM: Uppsala Longitudinal study of adult men; AHS-2: Adventist health study-2; PURE study: Prospective urban and rural epidemiology study; ATBC: Alpha-tocopherol and beta-carotene study.

levels[67,70].

Longitudinal studies

Few studies have investigated the incidence of hypertension in vitamin D-deficient subjects. In addition, no study among them had this aim as a primary outcome, suggesting some potential limitation in the statistical power estimation. In addition, the majority of the cohorts investigated was limited to the Caucasian race and female gender, further limiting the generalizability of the results. However, we believe that the main limitation is represented by the lack of prospective risk evaluation in the elderly. In fact, even if the follow-up is extended over 65 years, this overlap does not recognize the critical alterations in vitamin D metabolism during aging. Taking those important limitations into the account, Table 2 summarizes the most important longitudinal observational studies, starting from the results of health professionals' follow-up study (HPFS) and the nurse health study (NHS)2.

Forman *et al*[129] firstly reported an increased risk of incident hypertension in 1811 subjects selected from these two matched cohorts at 4-year follow-up (pooled RR = 3.18; 95%CI: 1.39-7.29, $P < 0.05$). In addition, the investigators extended this risk prediction, as a surrogate, to the overall study population including 38388 man from HPFS (adjusted RR = 2.31; 95%CI: 2.03-2.63, $P < 0.05$) and 77531 women from the NHS 2 (adjusted RR = 1.57; 95%CI: 1.44-1.72, $P < 0.05$). Afterwards, the same authors also designed a prospective nested case-control study including 1484 normotensive women from the NHS 2 that confirmed the previous results (interquartile OR = 1.66; 95%CI: 1.11-2.48, *P* value for trend = 0.01)[132]. Also the Intermountain Heart Collaborative Study Group provided similar results prospectively analyzing a large electronic medical database of a general healthcare population. In addition to recognize a wide prevalence of vitamin D deficiency, very low levels of 25(OH) vitamin D were directly associated with an increased risk of developing CV disease, including hypertension (HR = 1.62; 95%CI: 1.48-2.02, $P < 0.01$)[133]. Significant association between vitamin D deficiency and incidence of hypertension was also observed in a smaller subgroup analysis from both woman cohort of Michigan Bone Health and Metabolism Study (OR = 3.0; 95%CI: 1.01-8.7, $P < 0.05$)[134] and for male population of Physicians' Health Study (HR = 0.69; 95%CI: 0.50-0.96, $P < 0.05$)[136]. On the other hand, other large sample size studies such as subgroup analyses from Ely study[131], Tromsø study (burdened with a 40% dropout rate)[104], Women's Health Initiative[135] and Alpha-Tocopherol and Beta-Carotene study cohort[126], as well as cohort of general Copenhagen population[123] did not confirm any association between vitamin D levels and incidence of hypertension.

Randomized clinical trials

Table 3 summarizes randomized interventional clinical trials investigating the link between vitamin D and blood pressure.

Although most of the studies reported a significant serum 25(OH) vitamin D increase after supplementation, they are impeded by several limitations, mostly related to study design issues. The first one consists in the limited number of trials investigating blood pressure as a primary outcome. In addition, only few studies focused on vitamin D-deficient cohorts, more suitable for investigating the effectiveness of a supplementation with vitamin D. In this regard, a subgroup analysis of vitamin D-deficient

Table 2 Longitudinal studies addressing the association between vitamin D and blood pressure

Ref.	Year	Study design and follow-up (sample size)	Country (ethnicity) Age	Correlation (lower reference range of 25(OH) vitamin D)	Findings
Forman *et al*[129]	2007	Prospective observational nested case-control study from HPFS and NHS-2 4 yr (1811 subjects)	United States (Caucasian) men 47-82 yr women 43-68 yr	Yes (vitamin D deficiency defined as < 37.5 nmol/L[130])	Multivariate RR of incident hypertension among vitamin D deficient subject was 3.18 (95%CI: 1.39-7.29; $P < 0.05$)
Forouhi *et al*[131]	2008	Prospective observational from the Ely study 10 yr (534 subject)	United Kingdom (Caucasian) men and women 40-69 yr	No (vitamin D deficiency defined as < 25 nmol/L)	There were not significant changes in BP during the follow-up
Forman *et al*[132]	2008	Prospective observational nested case-control study from the NHS 2 7 yr (1484 normotensive women)	United States (Caucasian) women: 32-52 yr	Yes (I quartile: < 21 nmol/L)	Median 25(OH) vitamin D were lower in women developing hypertension (P < 0.01). Moreover, interquartile analysis showed significant and inverse correlation between 25(OH) vitamin D and hypertension (OR = 1.66, 95%CI: 1.11-2.48; P value for trend < 0.05)
Jorde *et al*[104]	2010	Prospective observational from the Tromsø Study 14 yr (4125 subjects not treated with anti-hypertensive drugs)	Norway (Caucasian) men and women 25-84 yr	No (I quartile: < 41.4 nmol/L)	At adjusted analysis, 25(OH) vitamin D did not predict future hypertension or increase in BP: Moreover there was not any association between change in serum 25(OH) vitamin D and BP
Anderson *et al*[133]	2010	Prospective observational average 1.3 yr (maximum 9.1 yr) (41497 subjects)	United States men and women 34-76 yr	Yes (vitamin D deficiency defined as < 37.5 nmol/L)	Lower 25(OH) vitamin D levels were associated with higher incidence of hypertension (HR = 1.62, 95%CI: 1.48-2.02; $P < 0.01$)
Griffin *et al*[134]	2011	Prospective observational from MBHMS 14 yr (559 women)	United States (Caucasian) women 24-44 yr	Yes (vitamin D deficiency defined as < 80 nmol/L)	25(OH) vitamin D insufficiency has an increased risk of systolic hypertension at multivariate analysis (OR = 3.0, 95%CI: 1.01-8.7; $P < 0.05$)
Margolis *et al*[135]	2012	Prospective observational from the WHI 7 yr (4863 post-menopausal women)	United States (Caucasian, African, Hispanic, Asian and others) women 50-79 yr	No (I quartile: < 34.4 nmol/L)	There was not significant linear or nonlinear trend in the risk of incident hypertension
Wang *et al*[136]	2012	Prospective observational form PHS 15.3 yr (1211 normotensive men)	United States men 40-84 yr	Yes (I quartile: < 39.9 nmol/L)	There was significant difference only between I and Ⅲ quartile (HR = 0.69, 95%CI: 0.50-0.96; $P < 0.05$)
Skaaby *et al*[123]	2012	Prospective observational 5 yr (4330 subjects)	Denmark (Caucasian) men and women 30-61 yr	No (I quartile: < 33 nmol/L)	Multivariate logistic regression analyses did not show any association between 25(OH) vitamin D incidence rate of hypertension.
Ke *et al*[126]	2013	Prospective observational from the ATBC 4 yr (2271 subjects of which 1430 hypertensive)	Finland (Caucasian) men and women 50-69 yr	No (I quartile: < 25 nmol/L)	25(OH) vitamin D did not predict future hypertension.

HPFS: Health professionals' follow-up study; NHS 2: Nurse heatlh study 2; 25(OH)D: Cholecalciferol; RR: Relative risk; BP: Blood pressure; OR: Odds ratio; HR: Hazard ratio; MBHMS: Michigan bone health and metabolism study; WHI: Women's health initiative; PHS: Physicians' health study; ATBC: Alpha-tocopherol and beta-carotene study cohort.

subjects, from a sample of 112 Danish hypertensive patients randomized to high-dose 25(OH) vitamin D supplementation (75 μg/d) versus placebo, showed a significant decrease of 24-h systolic and diastolic blood pressure values ($P < 0.05$)[155]. These findings confirmed previous results from other small sample size cohorts of vitamin D-deficient patients[141,142,150]. For this reason, the recently results by Forman *et al*[157] from the largest published cohort of hypertensive patients ($n = 283$) randomized to vitamin D supplementation versus placebo appear of particular interest. The oral administration of 25(OH) vitamin D (25 to 100 μg/d) significantly decreased the blood pressure levels. Unfortunately, these studies present additional limitations, such as taking into account the different approaches used for vitamin D supplementation. Although sunlight exposition might be the more physiological way, the ultraviolet (UV)-B rays-induced skin synthesis of vitamin D is hard to quantify and thus poorly investigated[140,151]. Oral supplementation has been preferred because easier to manage (despite some variability in intestinal absorption may exist) if provided through diet regimen[147], nutritional supplements[146] or direct vitamin D administration (daily intake[137-139,141,143,144,152-157] or loading dose[142,148-150,158]). Finally, it should be reported

Table 3 Randomized clinical trial investigating the protective effect of vitamin D supplementation on blood pressure

Ref.	Year	Study design	Country (ethnicity) Age	Intervention	Findings
Lint *et al*[137]	1988	(sample size) Prospective randomized double-blind placebo-controlled trial (65 men with glucose intolerance of which 26 hypertensive)	Sweden (Caucasian) 61-65 yr	(follow-up) α-calcidol 0.75 μg (12 wk)	In hypertensive patients supplementation has addictive effect to concomitant antihypertensive therapy in reducing BP ($P < 0.01$). In the whole population there was only non-significant trend in BP lowering
Pan *et al*[138]	1993	Prospective randomized double-blind 2 × 2 interventional trial (58 institutionalized elderly persons)	Taiwan (Asian) not provided	calcium 800 mg/d or 1,25(OH)2 vitamin D 5 μg/d or calcium 800 mg/d + 1,25(OH)2 vitamin D 5 μg/d, or placebo (11 wk)	Any type of supplementation failed to reduce BP
Scragg *et al*[139]	1995	Prospective randomized double-blind placebo-controlled trial (189 elderly subjects)	United Kingdom (not provided) 63-76 yr	25(OH) vitamin D 2.5 μg/d or placebo (5 wk)	Although treatment was effective in increasing serum 1,25(OH)2 vitamin D ($P < 0.01$) and decreasing PTH ($P < 0.01$), there was not difference in BP change
Krause *et al*[140]	1998	Prospective randomized double-blind controlled trial (18 patients with untreated mild essential hypertension)	Germany (Caucasian) 26-66 yr	Full body UVB or UVA thrice weekly (6 wk)	In accordance with a 162% rise in plasmatic 25(OH) vitamin D ($P < 0.01$) and 15% fall in serum PTH ($P < 0.01$), the UVB group showed also a reduction in 24-h ambulatory systolic and diastolic BP ($P < 0.01$)
Pfeifer *et al*[141]	2001	Prospective randomized double-blind controlled trial (148 elderly subject with 25(OH)D < 50 nmol/L)	Germany (Caucasian) 70-86 yr	Calcium 600 mg × 2/d or calcium 600 mg + 25(OH) vitamin D 10 μg twice daily (8 wk)	In accordance with a 72% rise in plasmatic 25(OH) vitamin D ($P < 0.01$) and 17% fall in serum PTH ($P < 0.05$), combined supplementation significantly reduced systolic BP ($P < 0.05$)
Sudgen *et al*[142]	2008	Prospective randomized double-blind placebo-controlled trial (34 elderly type 2 diabetic patients with 25(OH)D < 50 nmol/L)	United Kingdom (not provided)	Loading dose ergocalciferol 2500 μg or placebo (8 wk)	Supplementation significantly rise plasmatic 25(OH) vitamin D ($P < 0.01$) and reduced systolic BP, whereas there was only a trend in diastolic BP decrease
Alborzi *et al*[143]	2008	Prospective randomized double-blind placebo-controlled trial (24 elderly type 2 diabetic patients with 25(OH)D < 50 nmol/L)	mean 64 years United States (Caucasian and African Americans) 56-80 yr	Paricalcitol 1 or 2 μg/d or placebo (4 wk)	Any dose of paricalcitol failed to reduce BP
Margolis *et al*[144]	2008	Prospective randomized double-blind controlled trial (36282 n post-menopausal women from WHI study)	United States (Caucasian, Asian, Hispanic, African American) 50-79 yr	Calcium 500 mg × 2/d or calcium 500 mg + 25(OH) vitamin D 5 μg twice daily (7 yr)	There was no significant difference in over time change of BP in the whole population. In addition, supplementation failed to reduce the risk of developing hypertension in non-hypertensive patients at baseline
Nagpal *et al*[145]	2008	Prospective randomized double-blind placebo-controlled trial (71 older overweight men)	India (Indian population) 36-54 yr	25(OH) vitamin D 3000 μg every 2 wk for 3 times or placebo (7 wk)	Supplementation failed to reduce BP
Daly *et al*[146]	2009	Prospective randomized double-blind controlled trial (124 community-dwelling men)	Australia (Caucasian) 55-69 yr	Milk fortified with calcium (500 mg) and 25(OH) vitamin D (10 μg) twice a day or standard milk (2 yr)	Supplementation failed to reduce BP
Hilpert *et al*[147]	2009	Prospective randomized double-blind controlled trial (23 hypertensive adults)	United States (not provided)	Dairy-rich, high fruits and vegetables diet or a high fruits and vegetables diet or an average Western diet (5 wk)	High fruits and vegetables diet dairy-rich or not significantly reduced BP ($P < 0.05$). Moreover, in dairy-rich, high fruits and vegetables diet there was a greater lowering of intracellular calcium ($P < 0.01$), strongly associated with fall in diastolic BP ($P < 0.05$)
Witham *et al*[148]	2010	Prospective randomized double-blind placebo-controlled trial (56 patients with history of stroke and baseline 25(OH)D < 75 nmol/L)	United Kingdom (not provided) 53-79 yr	Loading dose ergocalciferol 2500 μg or placebo (8 and 16 wk)	Supplementation significantly increased serum 25(OH) vitamin D to both controls ($P < 0.01$). However, treatment failed to reduced BP

Witham *et al*[149]	2010	Prospective randomized double-blind placebo-controlled trial (61 patients with type 2 diabetes and baseline 25(OH)D < 100 nmol/L)	United Kingdom (not provided) 55-76 yr	Loading dose ergocalciferol 2500 μg or 5000 μg or placebo (8 and 16 wk)	Supplementation significantly increased serum 25(OH) vitamin D to both controls (P < 0.01 for both). However, supplementation failed to reduced BP
Judd *et al*[150]	2010	Prospective randomized double-blind controlled trial (9 patients with baseline 25(OH)D within 25 and 75 nmol/L in addition to systolic BP between 130 and 150 mmHg)	United States (African American) mean 45 yr	loading dose ergocalciferol 2500 μg or placebo weekly for 3 wk or 25 (OH) vitamin D 0.5 μg twice a day for 1 wk (3 wk)	Only supplementation with 25(OH) vitamin D decrease by 9% mean systolic BP (P < 0.01) in accordance with rise of serum 25(OH) vitamin D (P < 0.05)
Scragg *et al*[151]	2011	Prospective randomized double-blind controlled trial (119 patients with baseline 25(OH)D < 50 nmol)	New Zealand (Pacific islander, Caucasian and Maori) 23-87 yr	24 whole body exposures of either UVB or ultraviolet A (6 and 12 wk)	In the UVB arm there was a significant increase in serum 25 (OH) vitamin D after both 6 and 12 wk (P < 0.01 for both). However, treatment failed to reduced BP
Salehpour *et al*[152]	2012	Prospective randomized double-blind placebo-controlled trial (77 pre-menopausal overweight and obese women)	Iran (Arabian) 30-46 yr	25 (OH) vitamin D 25 μg daily or placebo (12 wk)	Supplementation significantly rise plasmatic 25 (OH) vitamin D (P < 0.01) and fall PTH (P < 0.01). Moreover, although treatment improved lipid profile, there was no effect on BP
Gepner *et al*[153]	2012	Prospective randomized double-blind placebo-controlled trial (110 post-menopausal women with baseline 25(OH)D within 10 and 60 nmol/L)	United States (not provided) 60-67 yr	25 (OH) vitamin D 62.5 μg daily or placebo (16 wk)	Supplementation, although significantly raised serum 25(OH) vitamin D (P < 0.01), failed in improving BP control assessed by changes in FMD, PWV and Aix
Wood *et al*[154]	2012	Prospective randomized double-blind placebo-controlled trial (305 healthy post-menopausal women)	United Kingdom (not provided) 48-72 yr	25 (OH) vitamin D 10 μg or 25 μg/d or placebo (1 yr)	Supplementation failed in improving CV risk profile, including BP control
Larsen *et al*[155]	2012	Prospective randomized double-blind placebo-controlled trial (112 hypertensive patients)	Denmark (Caucasian) 48-72 yr	25 (OH) vitamin D 75 μg/d or placebo (20 wk)	Supplementation significantly rise plasmatic 25 (OH) vitamin D (P < 0.01) and fall PTH (P < 0.01) but failed in improving BP control. However, in a post-hoc subgroup analysis of patient with 25 (OH) vitamin D deficiency at baseline supplementation significantly decrease 24-h systolic and diastolic BP (P < 0.05)
Zhu *et al*[156]	2013	Prospective randomized double-blind placebo-controlled trial (43 healthy subjects)	China (Asian) 20-22 yr	Calcium 600 mg + 25 (OH) vitamin D 3.12 μg daily or placebo, in addition to 500 kcal/d of caloric deficit (7 yr)	Except a reduction in visceral fat mass, supplementation failed in improving CV risk profile, including BP control
Forman *et al*[157]	2013	Prospective randomized double-blind placebo-controlled trial (283 healthy black subjects)	United States (African American) mean 51 yr	25 (OH) vitamin D 25 μg or 50 or 100 μg/d or placebo (12 and 24 wk)	Supplementation significantly decrease BP consistent with increasing dose (P < 0.05). Moreover, there was linear correlation between systolic BP decrease and rise of serum 25 (OH) vitamin D (P < 0.05)
Witham *et al*[158]	2013	Prospective randomized double-blind placebo-controlled trial (159 with isolate systolic hypertension)	United States (not provided) mean 77 yr	Loading dose 25 (OH) vitamin D 2500 μg or placebo (12, 24 and 36 wk)	Supplementation significantly rise plasmatic 25 (OH) vitamin D (P < 0.01) but failed in improving BP control. Moreover, treatment failed to achieve secondary outcomes including 24-h blood pressure, arterial stiffness and endothelial function

α-calcidol: Synthetic analog of 1,25(OH)2D; BP: Blood pressure; 1,25(OH)2D: Calcitriol; UVB: 94.5% UVA and 3.5% UVB; UVA: 99.5% UVA and 0.05% UVB; 25(OH)D: Cholecalciferol; PTH: Parathyroid hormone; WHI: Women's Health Initiative Calcium/vitamin D trial; HyD: 25(OH)D metabolite with hydrophilic properties and much shorter half-life; FMD: Brachial artery flow-mediated vasodilation; PWV: Carotid-femoral pulse wave velocity; Aix: Aortic augmentation index; CV: Cardiovascular.

the failure of Women's Health Initiative study to prove changes in blood pressure in a very large sample size of post-menopausal women (n = 36282) randomized to receive calcium versus calcium plus 25(OH)D over 7-year follow-up[144].

Meta-analyses of clinical studies

Five meta-analyses were recently performed to quantify the prospective associations of vitamin D status with the risk of hypertension. Pittas *et al*[159] included the results of four observational longitudinal cohorts with 32181 subjects with a follow-up of 7 to 10 years. The pooled analysis showed an increased risk of developing hypertension in vitamin D-deficient subjects (RR = 1.76; 95%CI: 1.27-2.44, P < 0.05). Conversely, another meta-analysis of ten randomized clinical trials failed to prove the effectiveness of vitamin D supplementation in promoting blood pressure decrease[159]. Therefore, this mismatch between

observational studies and randomized interventional clinical trials is retrieved in other meta-analyses The lack of relationship in interventional studies was reported by Witham *et al*[160] and Wu *et al*[161], while pooled analysis of observational studies showed a strong association between vitamin D status and blood pressure[162]. In particular, the meta-analysis of observational longitudinal studies by Kunutsor *et al*[163] recently reported that subjects in the higher tertiles of vitamin D levels have a 30% lower risk of developing hypertension as compared to those in the bottom tertiles (pooled RR = 0.70; 95%CI: 0.58-0.86, $P < 0.05$).

OPEN ISSUES AND PERSPECTIVES

Many questions recently emerged from efficacy and safety in interventional trials using vitamin D supplementation. In experimental mouse models, excessive intake of vitamin D induces vascular and soft-tissue calcifications. Thus, in human beings, caution has to be used on the pro-calcifying effects of exogenous vitamin D. In addition to derangement in calcium homeostasis, it should take into account the detrimental effects of vitamin D-induced phosphate overload involving also FGF23/klotho axis. On the other hand, the definition of the optimal vitamin D status from a CV point of view remains matter of debate and general consensus is still missing. "Bone health-driven" recommendations agree to define insufficient a 25(OH) vitamin D levels < 20 ng/mL, suggesting a target of 30 ng/mL. Similarly, reports from large cohorts (such as NHANES[164] and The Framingham offspring study[165]) showed a linear inverse association with CV outcome for 25(OH) vitamin D levels up to 30ng/mL. Considering hypertension, the results from the Vitamin D and Omega-3 Hypertension Trial (VITAL Hypertension) that is still enrolling patients[166] might clarify this point. Finally, the "local vitamin D system" is emerging as a pivotal topic that might explain the conflicting results between observational and interventional trials[167].

CONCLUSION

Neither the European society of Cardiology nor American Heart Association have published CV-focused algorithms regarding vitamin D deficiency and this is because the first results from randomized clinical trials have provided more questions than answers. Certainly, several factors involved in vitamin D biology are under-recognized or hard to assess, including physical activity, sunlight exposure, health status or dietary habits. Moreover, several confounding factors have not been considered in several studies, such as comorbidities, concomitant medications or differences in gender, age and race. In addition, also vitamin D compounds proposed were highly variable, ranging from native (cholecalciferol or ergocalciferol) or synthetic (α-calcidol) inactive vitamin D to active vitamin D (calcitriol) up to selective VDR activators (paricalcitol). However, it is likely that other unidentified factors are also involved in vitamin D biology, such as the possible relationship with other endocrine networks, emphasizing the need of pre-clinical studies.

REFERENCES

1 **Holick MF**. Vitamin D deficiency. *N Engl J Med* 2007; **357**: 266-281 [PMID: 17634462 DOI: 10.1056/NEJMra070553]
2 **Lucas RM**, Ponsonby AL, Dear K, Valery PC, Taylor B, van der Mei I, McMichael AJ, Pender MP, Chapman C, Coulthard A, Kilpatrick TJ, Stankovich J, Williams D, Dwyer T. Vitamin D status: multifactorial contribution of environment, genes and other factors in healthy Australian adults across a latitude gradient. *J Steroid Biochem Mol Biol* 2013; **136**: 300-308 [PMID: 23395985 DOI: 10.1016/j.jsbmb.2013.01.011]
3 **Holick MF**. Environmental factors that influence the cutaneous production of vitamin D. *Am J Clin Nutr* 1995; **61**: 638S-645S [PMID: 7879731]
4 **Pludowski P**, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, Shoenfeld Y, Lerchbaum E, Llewellyn DJ, Kienreich K, Soni M. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. *Autoimmun Rev* 2013; **12**: 976-989 [PMID: 23542507 DOI: 10.1016/j.autrev.2013.02.004]
5 **Amer M**, Qayyum R. Relationship between 25-hydroxyvitamin D and all-cause and cardiovascular disease mortality. *Am J Med* 2013; **126**: 509-514 [PMID: 23601272 DOI: 10.1016/j.amjmed.2012.11.021]
6 **Gunville CF**, Mourani PM, Ginde AA. The role of vitamin D in prevention and treatment of infection. *Inflamm Allergy Drug Targets* 2013; **12**: 239-245 [PMID: 23782205]
7 **Pelajo CF**, Lopez-Benitez JM, Miller LC. Vitamin D and autoimmune rheumatologic disorders. *Autoimmun Rev* 2010; **9**: 507-510 [PMID: 20146942 DOI: 10.1016/j.autrev.2010.02.011]
8 **Annweiler C**, Rolland Y, Schott AM, Blain H, Vellas B, Beauchet O. Serum vitamin D deficiency as a predictor of incident non-Alzheimer dementias: a 7-year longitudinal study. *Dement Geriatr Cogn Disord* 2011; **32**: 273-278 [PMID: 22261995 DOI: 10.1159/000334944]
9 **Freedman DM**, Looker AC, Abnet CC, Linet MS, Graubard BI. Serum 25-hydroxyvitamin D and cancer mortality in the NHANES III study (1988-2006). *Cancer Res* 2010; **70**: 8587-8597 [PMID: 20847342 DOI: 10.1158/0008-5472.CAN-10-1420]
10 **Liu L**, Chen M, Hankins SR, Nùñez AE, Watson RA, Weinstock PJ, Newschaffer CJ, Eisen HJ. Serum 25-hydroxyvitamin D concentration and mortality from heart failure and cardiovascular disease, and premature mortality from all-cause in United States adults. *Am J Cardiol* 2012; **110**: 834-839 [PMID: 22658246 DOI: 10.1016/j.amjcard.2012.05.013]
11 **Reschly EJ**, Bainy AC, Mattos JJ, Hagey LR, Bahary N, Mada SR, Ou J, Venkataramanan R, Krasowski MD. Functional evolution of the vitamin D and pregnane X receptors. *BMC Evol Biol* 2007; **7**: 222 [PMID: 17997857 DOI: 10.1186/1471-2148-7-222]
12 **Bergwitz C**, Jüppner H. Regulation of phosphate homeostasis by PTH, vitamin D, and FGF23. *Annu Rev Med* 2010; **61**: 91-104 [PMID: 20059333 DOI: 10.1146/annurev.med.051308.111339]
13 **Malik S**, Fu L, Juras DJ, Karmali M, Wong BY, Gozdzik A, Cole DE. Common variants of the vitamin D binding protein gene and adverse health outcomes. *Crit Rev Clin Lab Sci* 2013; **50**: 1-22 [PMID: 23427793 DOI: 10.3109/10408363.2012.750262]
14 **Haussler MR**, Whitfield GK, Kaneko I, Haussler CA, Hsieh D, Hsieh JC, Jurutka PW. Molecular mechanisms of vitamin D action. *Calcif Tissue Int* 2013; **92**: 77-98 [PMID: 22782502 DOI: 10.1007/s00223-012-9619-0]
15 **Haussler MR**, Haussler CA, Bartik L, Whitfield GK, Hsieh

JC, Slater S, Jurutka PW. Vitamin D receptor: molecular signaling and actions of nutritional ligands in disease prevention. *Nutr Rev* 2008; **66**: S98-112 [PMID: 18844852 DOI: 10.1111/j.1753-4887.2008.00093.x]

16 **Bartik L**, Whitfield GK, Kaczmarska M, Lowmiller CL, Moffet EW, Furmick JK, Hernandez Z, Haussler CA, Haussler MR, Jurutka PW. Curcumin: a novel nutritionally derived ligand of the vitamin D receptor with implications for colon cancer chemoprevention. *J Nutr Biochem* 2010; **21**: 1153-1161 [PMID: 20153625 DOI: 10.1016/j.jnutbio.2009.09.012]

17 **Haussler MR**, Jurutka PW, Mizwicki M, Norman AW. Vitamin D receptor (VDR)-mediated actions of 1α,25(OH)$_2$ vitamin D$_3$: genomic and non-genomic mechanisms. *Best Pract Res Clin Endocrinol Metab* 2011; **25**: 543-559 [PMID: 21872797 DOI: 10.1016/j.beem.2011.05.010]

18 **Peelen E**, Knippenberg S, Muris AH, Thewissen M, Smolders J, Tervaert JW, Hupperts R, Damoiseaux J. Effects of vitamin D on the peripheral adaptive immune system: a review. *Autoimmun Rev* 2011; **10**: 733-743 [PMID: 21621002 DOI: 10.1016/j.autrev.2011.05.002]

19 **Caprio M**, Mammi C, Rosano GM. Vitamin D: a novel player in endothelial function and dysfunction. *Arch Med Sci* 2012; **8**: 4-5 [PMID: 22457665 DOI: 10.5114/aoms.2012.27271]

20 **Chitalia N**, Recio-Mayoral A, Kaski JC, Banerjee D. Vitamin D deficiency and endothelial dysfunction in non-dialysis chronic kidney disease patients. *Atherosclerosis* 2012; **220**: 265-268 [PMID: 22071357 DOI: 10.1016/j.atherosclerosis.2011.10.023]

21 **Yiu YF**, Chan YH, Yiu KH, Siu CW, Li SW, Wong LY, Lee SW, Tam S, Wong EW, Cheung BM, Tse HF. Vitamin D deficiency is associated with depletion of circulating endothelial progenitor cells and endothelial dysfunction in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2011; **96**: E830-E835 [PMID: 21325459 DOI: 10.1210/jc.2010-2212]

22 **Al Mheid I**, Patel R, Murrow J, Morris A, Rahman A, Fike L, Kavtaradze N, Uphoff I, Hooper C, Tangpricha V, Alexander RW, Brigham K, Quyyumi AA. Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans. *J Am Coll Cardiol* 2011; **58**: 186-192 [PMID: 21718915 DOI: 10.1016/j.jacc.2011.02.051]

23 **Molinari C**, Uberti F, Grossini E, Vacca G, Carda S, Invernizzi M, Cisari C. 1α,25-dihydroxycholecalciferol induces nitric oxide production in cultured endothelial cells. *Cell Physiol Biochem* 2011; **27**: 661-668 [PMID: 21691084 DOI: 10.1159/000330075]

24 **Grundmann M**, Haidar M, Placzko S, Niendorf R, Darashchonak N, Hubel CA, von Versen-Höynck F. Vitamin D improves the angiogenic properties of endothelial progenitor cells. *Am J Physiol Cell Physiol* 2012; **303**: C954-C962 [PMID: 22932684 DOI: 10.1152/ajpcell.00030.2012]

25 **Chen S**, Law CS, Grigsby CL, Olsen K, Gardner DG. A role for the cell cycle phosphatase Cdc25a in vitamin D-dependent inhibition of adult rat vascular smooth muscle cell proliferation. *J Steroid Biochem Mol Biol* 2010; **122**: 326-332 [PMID: 20813185 DOI: 10.1016/j.jsbmb.2010.08.007]

26 **Tukaj C**, Trzonkowski P, Pikuła M, Hallmann A, Tukaj S. Increased migratory properties of aortal smooth muscle cells exposed to calcitriol in culture. *J Steroid Biochem Mol Biol* 2010; **121**: 208-211 [PMID: 20304064 DOI: 10.1016/j.jsbmb.2010.03.044]

27 **Aoshima Y**, Mizobuchi M, Ogata H, Kumata C, Nakazawa A, Kondo F, Ono N, Koiwa F, Kinugasa E, Akizawa T. Vitamin D receptor activators inhibit vascular smooth muscle cell mineralization induced by phosphate and TNF-α. *Nephrol Dial Transplant* 2012; **27**: 1800-1806 [PMID: 22287655 DOI: 10.1093/ndt/gfr758]

28 **Wu-Wong JR**, Nakane M, Ma J. Vitamin D analogs modulate the expression of plasminogen activator inhibitor-1, thrombospondin-1 and thrombomodulin in human aortic smooth muscle cells. *J Vasc Res* 2007; **44**: 11-18 [PMID: 17159355 DOI: 10.1159/000097812]

29 **Swapna N**, Vamsi UM, Usha G, Padma T. Risk conferred by FokI polymorphism of vitamin D receptor (VDR) gene for essential hypertension. *Indian J Hum Genet* 2011; **17**: 201-206 [PMID: 22345993 DOI: 10.4103/0971-6866.92104]

30 **Schuster I**. Cytochromes P450 are essential players in the vitamin D signaling system. *Biochim Biophys Acta* 2011; **1814**: 186-199 [PMID: 20619365 DOI: 10.1016/j.bbapap.2010.06.022]

31 **Zehnder D**, Bland R, Chana RS, Wheeler DC, Howie AJ, Williams MC, Stewart PM, Hewison M. Synthesis of 1,25-dihydroxyvitamin D(3) by human endothelial cells is regulated by inflammatory cytokines: a novel autocrine determinant of vascular cell adhesion. *J Am Soc Nephrol* 2002; **13**: 621-629 [PMID: 11856765]

32 **Somjen D**, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, Jaccard N, Knoll E, Stern N. 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. *Circulation* 2005; **111**: 1666-1671 [PMID: 15795327 DOI: 10.1161/01.CIR.0000160353.27927.70]

33 **Liu PT**, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schauber J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zügel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW, Adams JS, Bloom BR, Modlin RL. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006; **311**: 1770-1773 [PMID: 16497887 DOI: 10.1126/science.1123933]

34 **Stoffels K**, Overbergh L, Giulietti A, Verlinden L, Bouillon R, Mathieu C. Immune regulation of 25-hydroxyvitamin-D3-1alpha-hydroxylase in human monocytes. *J Bone Miner Res* 2006; **21**: 37-47 [PMID: 16355272 DOI: 10.1359/JBMR.050908]

35 **Bacchetta J**, Sea JL, Chun RF, Lisse TS, Wesseling-Perry K, Gales B, Adams JS, Salusky IB, Hewison M. Fibroblast growth factor 23 inhibits extrarenal synthesis of 1,25-dihydroxyvitamin D in human monocytes. *J Bone Miner Res* 2013; **28**: 46-55 [PMID: 22886720 DOI: 10.1002/jbmr.1740]

36 **Viaene L**, Evenepoel P, Meijers B, Vanderschueren D, Overbergh L, Mathieu C. Uremia suppresses immune signal-induced CYP27B1 expression in human monocytes. *Am J Nephrol* 2012; **36**: 497-508 [PMID: 23171504 DOI: 10.1159/000345146]

37 **Zhou C**, Lu F, Cao K, Xu D, Goltzman D, Miao D. Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. *Kidney Int* 2008; **74**: 170-179 [PMID: 18385669 DOI: 10.1038/ki.2008.101]

38 **Martin A**, David V, Quarles LD. Regulation and function of the FGF23/klotho endocrine pathways. *Physiol Rev* 2012; **92**: 131-155 [PMID: 22298654 DOI: 10.1152/physrev.00002.2011]

39 **Saito H**, Maeda A, Ohtomo S, Hirata M, Kusano K, Kato S, Ogata E, Segawa H, Miyamoto K, Fukushima N. Circulating FGF-23 is regulated by 1alpha,25-dihydroxyvitamin D3 and phosphorus in vivo. *J Biol Chem* 2005; **280**: 2543-2549 [PMID: 15531762 DOI: 10.1074/jbc.M408903200]

40 **Gutiérrez OM**, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; **359**: 584-592 [PMID: 18687639 DOI: 10.1056/NEJMoa0706130]

41 **Palmer SC**, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, Strippoli GF. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA* 2011; **305**: 1119-1127 [PMID: 21406649 DOI: 10.1001/jama.2011.308]

42 **Wang Y**, Sun Z. Current understanding of klotho. *Ageing Res Rev* 2009; **8**: 43-51 [PMID: 19022406 DOI: 10.1016/j.arr.2008.10.002]

43 **Prince MJ**, Schaeffer PC, Goldsmith RS, Chausmer AB. Hyperphosphatemic tumoral calcinosis: association with eleva-

tion of serum 1,25-dihydroxycholecalciferol concentrations. *Ann Intern Med* 1982; **96**: 586-591 [PMID: 6896123]
44 **Camalier CE**, Yi M, Yu LR, Hood BL, Conrads KA, Lee YJ, Lin Y, Garneys LM, Bouloux GF, Young MR, Veenstra TD, Stephens RM, Colburn NH, Conrads TP, Beck GR. An integrated understanding of the physiological response to elevated extracellular phosphate. *J Cell Physiol* 2013; **228**: 1536-1550 [PMID: 23280476 DOI: 10.1002/jcp.24312]
45 **Jimbo R**, Kawakami-Mori F, Mu S, Hirohama D, Majtan B, Shimizu Y, Yatomi Y, Fukumoto S, Fujita T, Shimosawa T. Fibroblast growth factor 23 accelerates phosphate-induced vascular calcification in the absence of Klotho deficiency. *Kidney Int* 2014; **85**: 1103-1111 [PMID: 24088960 DOI: 10.1038/ki.2013.332]
46 **Scialla JJ**, Lau WL, Reilly MP, Isakova T, Yang HY, Crouthamel MH, Chavkin NW, Rahman M, Wahl P, Amaral AP, Hamano T, Master SR, Nessel L, Chai B, Xie D, Kallem RR, Chen J, Lash JP, Kusek JW, Budoff MJ, Giachelli CM, Wolf M. Fibroblast growth factor 23 is not associated with and does not induce arterial calcification. *Kidney Int* 2013; **83**: 1159-1168 [PMID: 23389416 DOI: 10.1038/ki.2013.3]
47 **Lindberg K**, Olauson H, Amin R, Ponnusamy A, Goetz R, Taylor RF, Mohammadi M, Canfield A, Kublickiene K, Larsson TE. Arterial klotho expression and FGF23 effects on vascular calcification and function. *PLoS One* 2013; **8**: e60658 [PMID: 23577141 DOI: 10.1371/journal.pone.0060658]
48 **Glade MJ**. Vitamin D: health panacea or false prophet? *Nutrition* 2013; **29**: 37-41 [PMID: 23085014 DOI: 10.1016/j.nut.2012.05.010]
49 **Becher UM**, Endtmann C, Tiyerili V, Nickenig G, Werner N. Endothelial damage and regeneration: the role of the renin-angiotensin-aldosterone system. *Curr Hypertens Rep* 2011; **13**: 86-92 [PMID: 21108024 DOI: 10.1007/s11906-010-0171-x]
50 **Briet M**, Schiffrin EL. Vascular actions of aldosterone. *J Vasc Res* 2013; **50**: 89-99 [PMID: 23172373 DOI: 10.1159/000345243]
51 **Li YC**, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002; **110**: 229-238 [PMID: 12122115 DOI: 10.1172/JCI15219]
52 **Li YC**, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. *J Steroid Biochem Mol Biol* 2004; **89-90**: 387-392 [PMID: 15225806 DOI: 10.1016/j.jsbmb.2004.03.004]
53 **Forman JP**, Williams JS, Fisher ND. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. *Hypertension* 2010; **55**: 1283-1288 [PMID: 20351344 DOI: 10.1161/HYPERTENSIONAHA.109.148619]
54 **Kota SK**, Kota SK, Jammula S, Meher LK, Panda S, Tripathy PR, Modi KD. Renin-angiotensin system activity in vitamin D deficient, obese individuals with hypertension: An urban Indian study. *Indian J Endocrinol Metab* 2011; **15** Suppl 4: S395-S401 [PMID: 22145146 DOI: 10.4103/2230-8210.86985]
55 **Vaidya A**, Forman JP, Williams JS. Vitamin D and the vascular sensitivity to angiotensin II in obese Caucasians with hypertension. *J Hum Hypertens* 2011; **25**: 672-678 [PMID: 21124341 DOI: 10.1038/jhh.2010.110]
56 **Yuan W**, Pan W, Kong J, Zheng W, Szeto FL, Wong KE, Cohen R, Klopot A, Zhang Z, Li YC. 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. *J Biol Chem* 2007; **282**: 29821-29830 [PMID: 17690094 DOI: 10.1074/jbc.M705495200]
57 **Kong J**, Qiao G, Zhang Z, Liu SQ, Li YC. Targeted vitamin D receptor expression in juxtaglomerular cells suppresses renin expression independent of parathyroid hormone and calcium. *Kidney Int* 2008; **74**: 1577-1581 [PMID: 19034301 DOI: 10.1038/ki.2008.452]
58 **Ferder M**, Inserra F, Manucha W, Ferder L. The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system. *Am J Physiol Cell Physiol* 2013; **304**: C1027-C1039 [PMID: 23364265 DOI: 10.1152/ajpcell.00403.2011]
59 **Robey RB**, Crane-Godreau MA. "Does sunscreen promote hypertension?" and other questions. Novel interactions between vitamin D and the renin-angiotensin axis. Focus on "The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system". *Am J Physiol Cell Physiol* 2013; **304**: C1040-C1041 [PMID: 23576577 DOI: 10.1152/ajpcell.00090.2013]
60 **Marchesi C**, Paradis P, Schiffrin EL. Role of the renin-angiotensin system in vascular inflammation. *Trends Pharmacol Sci* 2008; **29**: 367-374 [PMID: 18579222 DOI: 10.1016/j.tips.2008.05.003]
61 **Funakoshi Y**, Ichiki T, Shimokawa H, Egashira K, Takeda K, Kaibuchi K, Takeya M, Yoshimura T, Takeshita A. Rho-kinase mediates angiotensin II-induced monocyte chemoattractant protein-1 expression in rat vascular smooth muscle cells. *Hypertension* 2001; **38**: 100-104 [PMID: 11463768]
62 **Castoldi G**, Di Gioia CR, Pieruzzi F, D'Orlando C, Van De Greef WM, Busca G, Sperti G, Stella A. ANG II increases TIMP-1 expression in rat aortic smooth muscle cells in vivo. *Am J Physiol Heart Circ Physiol* 2003; **284**: H635-H643 [PMID: 12388255 DOI: 10.1152/ajpheart.00986.2001]
63 **Touyz RM**, Schiffrin EL. Reactive oxygen species and hypertension: a complex association. *Antioxid Redox Signal* 2008; **10**: 1041-1044 [PMID: 18315497 DOI: 10.1089/ars.2007.2012]
64 **Li L**, Yin X, Yao C, Zhu X, Wu X. Vitamin D, parathyroid hormone and their associations with hypertension in a Chinese population. *PLoS One* 2012; **7**: e43344 [PMID: 22937036 DOI: 10.1371/journal.pone.0043344]
65 **Anderson JL**, Vanwoerkom RC, Horne BD, Bair TL, May HT, Lappé DL, Muhlestein JB. Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: dependent or independent risk factors? *Am Heart J* 2011; **162**: 331-339.e2 [PMID: 21835295 DOI: 10.1016/j.ahj.2011.05.005]
66 **Morfis L**, Smerdely P, Howes LG. Relationship between serum parathyroid hormone levels in the elderly and 24 h ambulatory blood pressures. *J Hypertens* 1997; **15**: 1271-1276 [PMID: 9383176]
67 **Snijder MB**, Lips P, Seidell JC, Visser M, Deeg DJ, Dekker JM, van Dam RM. Vitamin D status and parathyroid hormone levels in relation to blood pressure: a population-based study in older men and women. *J Intern Med* 2007; **261**: 558-565 [PMID: 17547711 DOI: 10.1111/j.1365-2796.2007.01778.x]
68 **Taylor EN**, Curhan GC, Forman JP. Parathyroid hormone and the risk of incident hypertension. *J Hypertens* 2008; **26**: 1390-1394 [PMID: 18551015 DOI: 10.1097/HJH.0b013e3282ffb43b]
69 **Zhao G**, Ford ES, Li C, Kris-Etherton PM, Etherton TD, Balluz LS. Independent associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with blood pressure among US adults. *J Hypertens* 2010; **28**: 1821-1828 [PMID: 20613627 DOI: 10.1097/HJH.0b013e32833bc5b4]
70 **He JL**, Scragg RK. Vitamin D, parathyroid hormone, and blood pressure in the National Health and Nutrition Examination Surveys. *Am J Hypertens* 2011; **24**: 911-917 [PMID: 21525968 DOI: 10.1038/ajh.2011.73]
71 **Sedighi O**, Makhlough A, Kashi Z, Zahedi M. Relationship between serum parathyroid hormone and hypertension in hemodialysis patients. *Iran J Kidney Dis* 2011; **5**: 267-270 [PMID: 21725185]
72 **Chan R**, Chan D, Woo J, Ohlsson C, Mellström D, Kwok T, Leung P. Serum 25-hydroxyvitamin D and parathyroid hormone levels in relation to blood pressure in a cross-sectional study in older Chinese men. *J Hum Hypertens* 2012; **26**: 20-27 [PMID: 21248778 DOI: 10.1038/jhh.2010.126]

73 **Mateus-Hamdan L**, Beauchet O, Bouvard B, Legrand E, Fantino B, Annweiler C. High parathyroid hormone, but not low vitamin D concentrations, expose elderly inpatients to hypertension. *Geriatr Gerontol Int* 2013; **13**: 783-791 [PMID: 22994947 DOI: 10.1111/j.1447-0594.2012.00945.x]

74 **Ulu SM**, Ulaslı A, Yaman F, Yaman G, Ozkececi G, Yuksel Ş. The relationship between vitamin D and PTH levels and cardiovascular risk in the elderly hypertensives. *Clin Exp Hypertens* 2014; **36**: 52-57 [PMID: 23701502 DOI: 10.3109/10641963.2013.783054]

75 **Garcia VC**, Schuch NJ, Catania AS, Gouvea Ferreira SR, Martini LA. Parathyroid hormone has an important role in blood pressure regulation in vitamin D-insufficient individuals. *Nutrition* 2013; **29**: 1147-1151 [PMID: 23927947 DOI: 10.1016/j.nut.2013.03.022]

76 **Bosworth C**, Sachs MC, Duprez D, Hoofnagle AN, Ix JH, Jacobs DR, Peralta CA, Siscovick DS, Kestenbaum B, de Boer IH. Parathyroid hormone and arterial dysfunction in the multi-ethnic study of atherosclerosis. *Clin Endocrinol* 2013; **79** (3): 429-436 [DOI: 10.1111/Cen.12163]

77 **Smith JC**, Page MD, John R, Wheeler MH, Cockcroft JR, Scanlon MF, Davies JS. Augmentation of central arterial pressure in mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 2000; **85**: 3515-3519 [PMID: 11061493]

78 **Rubin MR**, Maurer MS, McMahon DJ, Bilezikian JP, Silverberg SJ. Arterial stiffness in mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; **90**: 3326-3330 [PMID: 15769995 DOI: 10.1210/jc.2004-1400]

79 **Bitigen A**, Tanalp AC, Kaynak E, Karavelioglu Y, Kirma C, Adas M, Yilmaz MB. Elastic properties of aorta in patients with primary hyperparathyroidism. *Int J Clin Pract* 2006; **60**: 1572-1575 [PMID: 16919001 DOI: 10.1111/j.1742-1241.2005.00814.x]

80 **Walker MD**, Silverberg SJ. Cardiovascular aspects of primary hyperparathyroidism. *J Endocrinol Invest* 2008; **31**: 925-931 [PMID: 19092300]

81 **Rosa J**, Raska I, Wichterle D, Petrak O, Strauch B, Somloova Z, Zelinka T, Holaj R, Widimsky J. Pulse wave velocity in primary hyperparathyroidism and effect of surgical therapy. *Hypertens Res* 2011; **34**: 296-300 [PMID: 21107330 DOI: 10.1038/hr.2010.232]

82 **Schillaci G**, Pucci G, Pirro M, Monacelli M, Scarponi AM, Manfredelli MR, Rondelli F, Avenia N, Mannarino E. Large-artery stiffness: a reversible marker of cardiovascular risk in primary hyperparathyroidism. *Atherosclerosis* 2011; **218**: 96-101 [PMID: 21645899 DOI: 10.1016/j.atherosclerosis.2011.05.010]

83 **Pirro M**, Manfredelli MR, Helou RS, Scarponi AM, Schillaci G, Bagaglia F, Melis F, Mannarino E. Association of parathyroid hormone and 25-OH-vitamin D levels with arterial stiffness in postmenopausal women with vitamin D insufficiency. *J Atheroscler Thromb* 2012; **19**: 924-931 [PMID: 22785083]

84 **Luigi P**, Chiara FM, Laura Z, Cristiano M, Giuseppina C, Luciano C, Giuseppe P, Sabrina C, Susanna S, Antonio C, Giuseppe C, Giorgio de T, Claudio L. Arterial Hypertension, Metabolic Syndrome and Subclinical Cardiovascular Organ Damage in Patients with Asymptomatic Primary Hyperparathyroidism before and after Parathyroidectomy: Preliminary Results. *Int J Endocrinol* 2012; **2012**: 408295 [PMID: 22719761 DOI: 10.1155/2012/408295]

85 **Mizobuchi M**, Morrissey J, Finch JL, Martin DR, Liapis H, Akizawa T, Slatopolsky E. Combination therapy with an angiotensin-converting enzyme inhibitor and a vitamin D analog suppresses the progression of renal insufficiency in uremic rats. *J Am Soc Nephrol* 2007; **18**: 1796-1806 [PMID: 17513326 DOI: 10.1681/ASN.2006091028]

86 **Koiwa F**, Komukai D, Hirose M, Yoshimura A, Ando R, Sakaguchi T, Komatsu Y, Shinoda T, Inaguma D, Joki N, Nishida H, Ikeda M, Shigematsu T. Influence of renin-angiotensin system on serum parathyroid hormone levels in uremic patients. *Clin Exp Nephrol* 2012; **16**: 130-135 [PMID: 21912899 DOI: 10.1007/s10157-011-0534-x]

87 **Tomaschitz A**, Ritz E, Pieske B, Fahrleitner-Pammer A, Kienreich K, Horina JH, Drechsler C, März W, Ofner M, Pieber TR, Pilz S. Aldosterone and parathyroid hormone: a precarious couple for cardiovascular disease. *Cardiovasc Res* 2012; **94**: 10-19 [PMID: 22334595 DOI: 10.1093/cvr/cvs092]

88 **Atchison DK BW**. The influence of extracellular and intracellular calcium on the secretion of renin. *Pflugers Arch* 2013; **465**: 59-69 [DOI: 10.1007/s00424-012-1107-x]

89 **Kawashima H**. Parathyroid hormone causes a transient rise in intracellular ionized calcium in vascular smooth muscle cells. *Biochem Biophys Res Commun* 1990; **166**: 709-714

90 **Hong ZR**, Gil HW, Yang JO, Lee EY, Ahn JO, Hong SY. Associations between sympathetic activity, plasma concentrations of renin, aldosterone, and parathyroid hormone, and the degree of intractability of blood pressure control in modialysis patients. *J Korean Med Sci* 2007; **22**: 604-610 [PMID: 17728496]

91 **Jiang BB**, Morimoto S, Yang J, Niinoabu T, Fukuo K, Ogihara T. Expression of parathyroid hormone/parathyroid hormone-related protein receptor in vascular endothelial cells. *J Cardiovasc Pharm* 1998; **31**: S142-S144 [DOI: 10.1097/00005344-199800001-00042]

92 **Jono S**, Nishizawa Y, Shioi A, Morii H. Parathyroid hormone-related peptide as a local regulator of vascular calcification - Its inhibitory action on in vitro calcification by bovine vascular smooth muscle cells. *Arterioscl Throm Vas* 1997; **17**: 1135-1142

93 **Perry HM**, Chappel JC, Bellorinfont E, Tamao J, Martin KJ, Teitelbaum SL. Parathyroid-Hormone Receptors in Circulating Human Mononuclear Leukocytes. *J Biol Chem* 1984; **259**: 5531-5535

94 **Rostand SG**. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension* 1997; **30**: 150-156 [PMID: 9260973]

95 **Martins D**, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, Felsenfeld A, Levine B, Mehrotra R, Norris K. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2007; **167**: 1159-1165 [PMID: 17563024 DOI: 10.1001/archinte.167.11.1159]

96 **Scragg R**, Sowers MF, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the third national health and nutrition examination survey. *Am J Hypertens* 2007; **20**: 713-719 [DOI: 10.1016/j.amjhyper.2007.01.017]

97 **Judd SE**, Nanes MS, Ziegler TR, Wilson PWF, Tangpricha V. Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey. *AJCN* 2008; **87**: 136-141

98 **Hintzpeter B**, Mensink GB, Thierfelder W, Müller MJ, Scheidt-Nave C. Vitamin D status and health correlates among German adults. *Eur J Clin Nutr* 2008; **62**: 1079-1089 [PMID: 17538533 DOI: 10.1038/sj.ejcn.1602825]

99 **Lips P**, Chapuy MC, Dawson-Hughes B, Pols HAP, Holick MF. An international comparison of serum 25-hydroxyvitamin D measurements. Osteoporosis *Int* 1999; **9**: 394-397 [DOI: 10.1007/s001980050162]

100 **Hyppönen E**, Boucher BJ, Berry DJ, Power C. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. *Diabetes* 2008; **57**: 298-305 [PMID: 18003755 DOI: 10.2337/db07-1122]

101 **Reis JP**, von Muhlen D, Miller ER, Michos ED, Appel LJ. Vitamin D Status and Cardiometabolic Risk Factors in the United States Adolescent Population. *Pediatrics* 2009; **124**: E371-E379 [DOI: 10.1542/peds.2009-0213]

102 **Pasco JA**, Henry MJ, Nicholson GC, Brennan SL, Kotowicz

MA. Behavioural and physical characteristics associated with vitamin D status in women. *Bone* 2009; **44**: 1085-1091 [PMID: 19264157 DOI: 10.1016/j.bone.2009.02.020]
103 **Almirall J**, Vaqueiro M, Bare ML, Anton E. Association of low serum 25-hydroxyvitamin D levels and high arterial blood pressure in the elderly. *Nephrol Dial Transpl* 2010; **25**: 503-509 [DOI: 10.1093/Ndt/Gfp470]
104 **Jorde R**, Figenschau Y, Emaus N, Hutchinson M, Grimnes G. Serum 25-Hydroxyvitamin D Levels Are Strongly Related to Systolic Blood Pressure But Do Not Predict Future Hypertension. *Hypertension* 2010; **55**: 792-798 [DOI: 10.1161/Hypertensionaha.109.143990]
105 **Kim MK**, Kang MI, Oh KW, Kwon HS, Lee JH, Lee WC, Yoon KH, Son HY. The association of serum vitamin D level with presence of metabolic syndrome and hypertension in middle-aged Korean subjects. *Clin Endocrinol* 2010; **73**: 330-338 [DOI: 10.1111/j.1365-2265.2010.03798.x]
106 **Zhao GX**, Ford ES, Li CY, Kris-Etherton PM, Etherton TD, Balluz LS. Independent associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with blood pressure among US adults. *J Hypertens* 2010; **28**: 1821-1828 [DOI: 10.1097/Hjh.0b013e32833bc5b4]
107 **Fraser A**, Williams D, Lawlor DA. Associations of serum 25-hydroxyvitamin D, parathyroid hormone and calcium with cardiovascular risk factors: analysis of 3 NHANES cycles (2001-2006). *PLoS One* 2010; **5**: e13882 [PMID: 21085485 DOI: 10.1371/journal.pone.0013882]
108 **Steinvil A**, Leshem-Rubinow E, Berliner S, Justo D, Finn T, Ish-shalom M, Birati EY, Shalev V, Sheinberg B, Rogowski O. Vitamin D deficiency prevalence and cardiovascular risk in Israel. *Eur J Clin Invest* 2011; **41**: 263-268 [DOI: 10.1111/j.1365-2362.2010.02403.x]
109 **Burgaz A**, Byberg L, Rautiainen S, Orsini N, Hakansson N, Arnlov J, Sundstrom J, Lind L, Melhus H, Michaelsson K, Wolk A. Confirmed hypertension and plasma 25(OH)D concentrations amongst elderly men. *J Intern Med* 2011; **269**: 211-218 [DOI: 10.1111/j.1365-2796.2010.02309.x]
110 **Bhandari SK**, Pashayan S, Liu ILA, Rasgon SA, Kujubu DA, Tom TY, Sim JJ. 25-Hydroxyvitamin D Levels and Hypertension Rates. *J Clin Hypertens* 2011; 13: 170-177 [DOI: 10.1111/j.1751-7176.2010.00408.x]
111 **Pacifico L**, Anania C, Osborn JF, Ferraro F, Bonci E, Olivero E, Chiesa C. Low 25(OH)D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents. *Eur J Endocrinol* 2011; **165**: 603-611 [PMID: 21753070 DOI: 10.1530/EJE-11-0545]
112 **Williams DM**, Fraser A, Lawlor DA. Associations of vitamin D, parathyroid hormone and calcium with cardiovascular risk factors in US adolescents. *Heart* 2011; **97**: 315-320 [PMID: 21193684 DOI: 10.1136/hrt.2010.203224]
113 **Forrest KY**, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res* 2011; **31**: 48-54 [PMID: 21310306 DOI: 10.1016/j.nutres.2010.12.001]
114 **Bischoff-Ferrari HA**, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006; **84**: 18-28 [PMID: 16825677]
115 **Dorjgochoo T**, Ou Shu X, Xiang YB, Yang G, Cai Q, Li H, Ji BT, Cai H, Gao YT, Zheng W. Circulating 25-hydroxyvitamin D levels in relation to blood pressure parameters and hypertension in the Shanghai Women's and Men's Health Studies. *Br J Nutr* 2012; **108**: 449-458 [PMID: 22365135 DOI: 10.1017/S0007114511005745]
116 **Hollis BW**. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr* 2005; **135**: 317-322 [PMID: 15671234]
117 **World Health Organization and Food and Agricultural Organization of the United Nations**. Vitamin and Mineral requirements in Human Nutrition. Geneva: WHO, 2004
118 **Sakamoto R**, Jaceldo-Siegl K, Haddad E, Oda K, Fraser GE, Tonstad S. Relationship of vitamin D levels to blood pressure in a biethnic population. *Nutr Metab Cardiovasc Dis* 2013; **23**: 776-784 [PMID: 22770642 DOI: 10.1016/j.numecd.2012.04.014]
119 **Caro Y**, Negrón V, Palacios C. Association between vitamin D levels and blood pressure in a group of Puerto Ricans. *P R Health Sci J* 2012; **31**: 123-129 [PMID: 23038884]
120 **Parikh S**, Guo DH, Pollock NK, Petty K, Bhagatwala J, Gutin B, Houk C, Zhu H, Dong Y. Circulating 25-hydroxyvitamin D concentrations are correlated with cardiometabolic risk among American black and white adolescents living in a year-round sunny climate. *Diabetes Care* 2012; **35**: 1133-1138 [PMID: 22410810 DOI: 10.2337/dc11-1944]
121 **Sabanayagam C**, Shankar A, Somasundaram S. Serum vitamin D level and prehypertension among subjects free of hypertension. *Kidney Blood Press Res* 2012; **35**: 106-113 [PMID: 21934326 DOI: 10.1159/000330716]
122 **van Ballegooijen AJ**, Snijder MB, Visser M, van den Hurk K, Kamp O, Dekker JM, Nijpels G, Stehouwer CD, Henry RM, Paulus WJ, Brouwer IA. Vitamin D in relation to myocardial structure and function after eight years of follow-up: the Hoorn study. *Ann Nutr Metab* 2012; **60**: 69-77 [PMID: 22343754 DOI: 10.1159/000336173]
123 **Skaaby T**, Husemoen LL, Pisinger C, Jørgensen T, Thuesen BH, Fenger M, Linneberg A. Vitamin D status and changes in cardiovascular risk factors: a prospective study of a general population. *Cardiology* 2012; **123**: 62-70 [PMID: 22986625 DOI: 10.1159/000341277]
124 **Kruger IM**, Kruger MC, Doak CM, Schutte AE, Huisman HW, Van Rooyen JM, Schutte R, Malan L, Malan NT, Fourie CM, Kruger A. The association of 25(OH)D with blood pressure, pulse pressure and carotid-radial pulse wave velocity in African women. *PLoS One* 2013; **8**: e54554 [PMID: 23355878 DOI: 10.1371/journal.pone.0054554]
125 **Lee JH**, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2008; **52**: 1949-1956 [PMID: 19055985 DOI: 10.1016/j.jacc.2008.08.050]
126 **Ke L**, Graubard BI, Albanes D, Fraser DR, Weinstein SJ, Virtamo J, Brock KE. Hypertension, pulse, and other cardiovascular risk factors and vitamin D status in Finnish men. *Am J Hypertens* 2013; **26**: 951-956 [PMID: 23598420 DOI: 10.1093/ajh/hpt051]
127 **Orwoll E**, Nielson CM, Marshall LM, Lambert L, Holton KF, Hoffman AR, Barrett-Connor E, Shikany JM, Dam T, Cauley JA. Vitamin D deficiency in older men. *J Clin Endocrinol Metab* 2009; **94**: 1214-1222 [PMID: 19174492 DOI: 10.1210/jc.2008-1784]
128 **Fiscella K**, Winters P, Tancredi D, Franks P. Racial disparity in blood pressure: is vitamin D a factor? *J Gen Intern Med* 2011; **26**: 1105-1111 [PMID: 21509604 DOI: 10.1007/s11606-011-1707-8]
129 **Forman JP**, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 2007; **49**: 1063-1069 [PMID: 17372031 DOI: 10.1161/HYPERTENSIONAHA.107.087288]
130 **Thomas MK**, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS. Hypovitaminosis D in medical inpatients. *N Engl J Med* 1998; **338**: 777-783 [PMID: 9504937 DOI: 10.1056/NEJM199803193381201]
131 **Forouhi NG**, Luan J, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990-2000. *Diabetes* 2008; **57**: 2619-2625 [PMID: 18591391 DOI: 10.2337/db08-0593]
132 **Forman JP**, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young

women. *Hypertension* 2008; **52**: 828-832 [PMID: 18838623 DOI: 10.1161/HYPERTENSIONAHA.108.117630]
133 **Anderson JL**, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, Lappé DL, Muhlestein JB. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol* 2010; **106**: 963-968 [PMID: 20854958 DOI: 10.1016/j.amjcard.2010.05.027]
134 **Griffin FC**, Gadegbeku CA, Sowers MR. Vitamin D and subsequent systolic hypertension among women. *Am J Hypertens* 2011; **24**: 316-321 [PMID: 21088670 DOI: 10.1038/ajh.2010.226]
135 **Margolis KL**, Martin LW, Ray RM, Kerby TJ, Allison MA, Curb JD, Kotchen TA, Liu S, Wassertheil-Smoller S, Manson JE. A prospective study of serum 25-hydroxyvitamin D levels, blood pressure, and incident hypertension in postmenopausal women. *Am J Epidemiol* 2012; **175**: 22-32 [PMID: 22127681 DOI: 10.1093/aje/kwr274]
136 **Wang L**, Ma J, Manson JE, Buring JE, Gaziano JM, Sesso HD. A prospective study of plasma vitamin D metabolites, vitamin D receptor gene polymorphisms, and risk of hypertension in men. *Eur J Nutr* 2013; **52**: 1771-1779 [PMID: 23262750 DOI: 10.1007/s00394-012-0480-8]
137 **Lind L**, Lithell H, Skarfors E, Wide L, Ljunghall S. Reduction of blood pressure by treatment with alphacalcidol. A double-blind, placebo-controlled study in subjects with impaired glucose tolerance. *Acta Med Scand* 1988; **223**: 211-217 [PMID: 3281411]
138 **Pan WH**, Wang CY, Li LA, Kao LS, Yeh SH. No significant effect of calcium and vitamin D supplementation on blood pressure and calcium metabolism in elderly Chinese. *Chin J Physiol* 1993; **36**: 85-94 [PMID: 8198625]
139 **Scragg R**, Khaw KT, Murphy S. Effect of Winter Oral Vitamin-D-3 Supplementation on Cardiovascular Risk-Factors in Elderly Adults. *Eur J Clin Nutr* 1995; **49**: 640-646
140 **Krause R**, Bühring M, Hopfenmüller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. *Lancet* 1998; **352**: 709-710 [PMID: 9728997 DOI: 10.1016/S0140-6736(05)60827-6]
141 **Pfeifer M**, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001; **86**: 1633-1637 [PMID: 11297596]
142 **Sugden JA**, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. *Diabet Med* 2008; **25**: 320-325 [PMID: 18279409 DOI: 10.1111/j.1464-5491.2007.02360.x]
143 **Alborzi P**, Patel NA, Peterson C, Bills JE, Bekele DM, Bunaye Z, Light RP, Agarwal R. Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: a randomized double-blind pilot trial. *Hypertension* 2008; **52**: 249-255 [PMID: 18606901 DOI: 10.1161/HYPERTENSIONAHA.108.113159]
144 **Margolis KL**, Ray RM, Van Horn L, Manson JE, Allison MA, Black HR, Beresford SA, Connelly SA, Curb JD, Grimm RH, Kotchen TA, Kuller LH, Wassertheil-Smoller S, Thomson CA, Torner JC. Effect of calcium and vitamin D supplementation on blood pressure: the Women's Health Initiative Randomized Trial. *Hypertension* 2008; **52**: 847-855 [PMID: 18824662 DOI: 10.1161/HYPERTENSIONAHA.108.114991]
145 **Nagpal J**, Pande JN, Bhartia A. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. *Diabet Med* 2009; **26**: 19-27 [PMID: 19125756 DOI: 10.1111/j.1464-5491.2008.02636.x]
146 **Daly RM**, Nowson CA. Long-term effect of calcium-vitamin D(3) fortified milk on blood pressure and serum lipid concentrations in healthy older men. *Eur J Clin Nutr* 2009; **63**: 993-1000 [PMID: 19156159 DOI: 10.1038/ejcn.2008.79]
147 **Hilpert KF**, West SG, Bagshaw DM, Fishell V, Barnhart L, Lefevre M, Most MM, Zemel MB, Chow M, Hinderliter AL, Kris-Etherton PM. Effects of Dairy Products on Intracellular Calcium and Blood Pressure in Adults with Essential Hypertension. *J Am Coll Nutr* 2009; **28**: 142-149
148 **Witham MD**, Dove FJ, Sugden JA, Doney AS, Struthers AD. The effect of vitamin D replacement on markers of vascular health in stroke patients - a randomised controlled trial. *Nutr Metab Cardiovasc Dis* 2012; **22**: 864-870 [PMID: 21194910 DOI: 10.1016/j.numecd.2010.11.001]
149 **Witham MD**, Dove FJ, Dryburgh M, Sugden JA, Morris AD, Struthers AD. The effect of different doses of vitamin D(3) on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia* 2010; **53**: 2112-2119 [PMID: 20596692]
150 **Judd SE**, Raiser SN, Kumari M, Tangpricha V. 1,25-dihydroxyvitamin D3 reduces systolic blood pressure in hypertensive adults: a pilot feasibility study. *J Steroid Biochem Mol Biol* 2010; **121**: 445-447 [PMID: 20420907 DOI: 10.1016/j.jsbmb.2010.04.013]
151 **Scragg R**, Wishart J, Stewart A, Ofanoa M, Kerse N, Dyall L, Lawes CM. No effect of ultraviolet radiation on blood pressure and other cardiovascular risk factors. *J Hypertens* 2011; **29**: 1749-1756 [PMID: 21720260 DOI: 10.1097/HJH.0b013e328349666d]
152 **Salehpour A**, Shidfar F, Hosseinpanah F, Vafa M, Razaghi M, Hoshiarrad A, Gohari M. Vitamin D3 and the risk of CVD in overweight and obese women: a randomised controlled trial. *Br J Nutr* 2012; **108**: 1866-1873 [PMID: 22317756 DOI: 10.1017/S0007114512000098]
153 **Gepner AD**, Ramamurthy R, Krueger DC, Korcarz CE, Binkley N, Stein JH. A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. *PLoS One* 2012; **7**: e36617 [PMID: 22586483 DOI: 10.1371/journal.pone.0036617]
154 **Wood AD**, Secombes KR, Thies F, Aucott L, Black AJ, Mavroeidi A, Simpson WG, Fraser WD, Reid DM, Macdonald HM. Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. *J Clin Endocrinol Metab* 2012; **97**: 3557-3568 [PMID: 22865902 DOI: 10.1210/jc.2012-2126]
155 **Larsen T**, Mose FH, Bech JN, Hansen AB, Pedersen EB. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. *Am J Hypertens* 2012; **25**: 1215-1222 [PMID: 22854639 DOI: 10.1038/ajh.2012.111]
156 **Zhu W**, Cai D, Wang Y, Lin N, Hu Q, Qi Y, Ma S, Amarasekara S. Calcium plus vitamin D3 supplementation facilitated fat loss in overweight and obese college students with very-low calcium consumption: a randomized controlled trial. *Nutr J* 2013; **12**: 8 [PMID: 23297844 DOI: 10.1186/1475-2891-12-8]
157 **Forman JP**, Scott JB, Ng K, Drake BF, Suarez EG, Hayden DL, Bennett GG, Chandler PD, Hollis BW, Emmons KM, Giovannucci EL, Fuchs CS, Chan AT. Effect of vitamin D supplementation on blood pressure in blacks. *Hypertension* 2013; **61**: 779-785 [PMID: 23487599 DOI: 10.1161/HYPERTENSIONAHA.111.00659]
158 **Witham MD**, Price RJ, Struthers AD, Donnan PT, Messow CM, Ford I, McMurdo ME. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. *JAMA Intern Med* 2013; **173**: 1672-1679 [PMID: 23939263 DOI: 10.1001/jamainternmed.2013.9043]
159 **Pittas AG**, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, Lichtenstein AH, Lau J, Balk EM. Systematic review: Vitamin D and cardiometabolic outcomes. *Ann Intern Med* 2010; **152**: 307-314 [PMID: 20194237 DOI: 10.7326/0003-4819-152-5-201003020-00009]
160 **Witham MD**, Nadir MA, Struthers AD. Effect of vitamin D

on blood pressure: a systematic review and meta-analysis. *J Hypertens* 2009; **27**: 1948-1954 [PMID: 19587609 DOI: 10.1097/HJH.0b013e32832f075b]
161 **Wu SH**, Ho SC, Zhong L. Effects of vitamin D supplementation on blood pressure. *South Med J* 2010; **103**: 729-737 [PMID: 20622727 DOI: 10.1097/SMJ.0b013e3181e6d389]
162 **Burgaz A**, Orsini N, Larsson SC, Wolk A. Blood 25-hydroxyvitamin D concentration and hypertension: a meta-analysis. *J Hypertens* 2011; **29**: 636-645 [PMID: 21191311 DOI: 10.1097/HJH.0b013e32834320f9]
163 **Kunutsor SK**, Apekey TA, Steur M. Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants. *Eur J Epidemiol* 2013; **28**: 205-221 [PMID: 23456138 DOI: 10.1007/s10654-013-9790-2]
164 **Melamed ML**, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008; **168**: 1629-1637 [PMID: 18695076 DOI: 10.1001/archinte.168.15.1629]
165 **Wang TJ**, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; **117**: 503-511 [PMID: 18180395 DOI: 10.1161/CIRCULATIONAHA.107.706127]
166 Vitamin D and Omega-3 Hypertension Trial (VITAL Hypertension). ClinicalTrials.gov. Available from: URL: http://clinicaltrials.gov/ct2/results?term=vitamin D AND hypertension&type=Intr&pg=1.
167 **Adams JS**, Hewison M. Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. *Arch Biochem Biophys* 2012; **523**: 95-102 [PMID: 22446158 DOI: 10.1016/j.abb.2012.02.016]

P- Reviewers: Wang M, Wolin MS **S- Editor**: Song XX
L- Editor: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com