REVIEW ARTICLE

The role of vitamin D deficiency in cardiovascular disease: where do we stand in 2013?

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Abstract The high worldwide prevalence of vitamin D deficiency is largely the result of low sunlight exposure with subsequently limited cutaneous vitamin D production. Classic manifestations of vitamin D deficiency are linked to disturbances in bone and mineral metabolism, but the identification of the vitamin D receptor in almost every human cell suggests a broader role of vitamin D for overall and cardiovascular health. The various cardiovascular protective actions of vitamin D such as anti-diabetic and anti-hypertensive effects including renin suppression as well as protection against atherosclerosis and heart diseases are well defined in previous experimental studies. In line with this, large epidemiological studies have highlighted vitamin D deficiency as a marker of cardiovascular risk. However, randomized controlled trials (RCTs) on vitamin D have largely failed to show its beneficial effects on cardiovascular diseases and its conventional risk factors. While most prior vitamin D RCTs were not designed to assess cardiovascular outcomes, some large RCTs have been initiated to evaluate the efficacy of vitamin D supplementation on cardiovascular events in the general population. When considering the history of previous disappointing vitamin RCTs in general populations, more emphasis should be placed on RCTs among severely vitamin D-deficient populations who would most likely benefit from vitamin D treatment. At present, vitamin D deficiency can only be considered a cardiovascular risk marker, as vitamin D supplementation with doses recommended for osteoporosis treatment is neither proven to be beneficial nor harmful in cardiovascular diseases.

Keywords Vitamin D · Cardiovascular · Epidemiology · 25(OH)D

Introduction

Vitamin D was initially described by McCollum in 1922 as a substance capable of curing rickets (Holick 1994). It was

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originally classified as a vitamin and given that it was the fourth known vitamin, it was named "vitamin D". Based on our current knowledge, however, vitamin D should rather be re-classified as a pro-hormone since its biologically most active metabolite, i.e., 1,25-dihydroxyvitamin D (1,25[OH]2D), is per definition a steroid hormone (Holick 2007). The receptor required for its endocrine function, i.e., the vitamin D receptor (VDR), is expressed in almost all human cells and regulates hundreds of genes, i.e., approximately three percent of the human genome (Bouillon et al. 2008). It is therefore tempting to speculate that vitamin D deficiency may have widespread adverse health consequences.

While effects of vitamin D are historically known to be relevant to bone and mineral diseases, accumulating data suggest that vitamin D might also play a role in various extra-skeletal diseases including auto-immune and infectious diseases, cancer, neuropsychological and cardiovascular diseases (CVD) (Holick 2007; Pludowski et al. 2013; Souberbielle et al. 2010; Muscogiuri et al. 2012; Brouwer-Brolsma et al. 2013). In this narrative review, we aim to provide a general up-to-date overview of the role of vitamin D in CVD. Following a brief outline on basic vitamin D metabolism and classic vitamin D effects, we will cover the various study types relating vitamin D to CVD and its risk factors. While the general topic of our review, in our opinion, cannot be adequately addressed by a systematic approach in a single journal article, we put particular emphasis on recent findings, existing systematic reviews and meta-analyses reporting on specific research questions regarding vitamin D and CVD. In addition to the potential benefits of vitamin D in CVD, we also provide a summary of the existing literature on the possible adverse consequences of vitamin D. Finally, we discuss our personal expectations for the future development and finish this review with our conclusions on the current implications regarding vitamin D and CVD for research and clinical practice.

Basic vitamin D metabolism

The chemical structure of vitamin D is a secosteroid. It has several isoforms with two major forms: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Its metabolism is unique since vitamin D can be derived from endogenous production in the skin as well as from dietary intake (Holick 2007). Cutaneous production requires ultraviolet-B (UV-B) radiation of the skin to convert the precursor 7-dehydrocholesterol, a liver-derived product, to previtamin D_3 and finally to vitamin D_3. Natural foods also contain vitamin D_3 (e.g., fatty fish) or vitamin D_2 (e.g., yeast or mushrooms). Additional sources for vitamin D_3 or vitamin

D_2 are supplements and food fortification that has been introduced, for instance, in the US or in Finland (Black et al. 2012). The main source for vitamin D is sunlight (UV-B)-induced production in the skin that accounts for approximately 80% of vitamin D (MacDonald et al. 2011). This classic view of sunlight-induced vitamin D production as the major source of vitamin D has, however, been partially challenged by recent investigations suggesting that all source basal vitamin D inputs, in particular of undocumented food sources, might play a greater role than previously recognized (Heaney et al. 2013a). There is ongoing discussion on whether vitamin D_3 supplementation is superior compared to vitamin D_2 supplementation in raising the main circulating vitamin D metabolite 25-hydroxyvitamin D (25[OH]D) (Tripkovic et al. 2012). Some organizations and experts alike prefer the use of vitamin D_3 rather than vitamin D_2. Though since both isoforms are further converted to vitamin D metabolites that are considered to exert almost identical biological activities, the term vitamin D (meaning vitamin D_3 and/or D_2) will be used throughout the manuscript, unless otherwise stated, Vitamin D itself exerts no relevant effects unless it is further converted to its biologically active metabolites. Formation of the most active vitamin D metabolite 1,25-dihydroxyvitamin D (1,25[OH]2D), i.e., the "vitamin D hormone" calcitriol, requires two hydroxylation steps: the first one in the liver is catalyzed by 25-hydroxylase to form 25(OH)D, and the second one mainly takes place in the kidneys (proximal tubule cells) to form 1,25(OH)2D. This latter reaction is catalyzed by the enzyme 1-alpha-hydroxylase. The kidneys are the major site for the synthesis of circulating 1,25(OH)2D, but it has been demonstrated that several extra-renal tissues also express 1-alpha-hydroxylase (Höbaus et al. 2013). While kidney-derived 1,25(OH)2D circulates in the bloodstream to exert its endocrine functions, locally produced extra-renal 1,25(OH)2D does not significantly contribute to serum concentrations of 1,25(OH)2D. This in turn supports the concept that locally produced 1,25(OH)2D exerts its effects in an autocrine or paracrine manner (Peterlik and Cross 2009; Höbaus et al. 2013). A main difference between the renal and extra-renal 1-alpha-hydroxylases is that the activity of renal 1-alpha-hydroxylase is tightly controlled by parameters of mineral metabolism (e.g, stimulation by PTH or inhibition by fibroblast growth factor-23 [FGF-23]). Hence, circulating serum levels of 1,25(OH)2D are strongly influenced by renal 1-alpha-hydroxylase activity and are not a reliable indicator of whole body vitamin D status. In contrast, 25(OH)D levels are considered the most appropriate parameter for classification of vitamin D status, since the activity of 25-hydroxylase is primarily dependent on the supply of vitamin D. 25(OH)D is the major circulating vitamin D metabolite with serum levels up to ~1,000-fold higher than 1,25(OH)2D and has a significantly longer

half-life (~3 weeks) compared to vitamin D or 1,25(OH)2D (a few hours for both). A general consensus has therefore been reached that 25(OH)D concentrations should be measured to assess vitamin D status (Holick 2007; Souberbielle et al. 2010; Ross et al. 2011). Similar to other steroid hormones, vitamin D metabolites are mainly transported in the circulation bound to its carrier, i.e, the vitamin D-binding protein (DBP). Only very small fractions of vitamin D metabolites circulate in completely unbound (free) forms or are bound to other carriers (e.g, lipoproteins). At present, laboratory methods measure and report the sum of all vitamin D metabolites, e.g, total 25(OH)D serum levels. It should, however, be noted that some, but not all, studies suggest that the free (unbound) fraction of 25(OH)D could be of high biological relevance and may be worth measuring or estimating using DBP concentrations (Powe et al. 2011; Dastani et al. 2013; Bhan et al. 2012). It must also be noted that the measurement of 25(OH)D is not straightforward and several studies have reported on significant assay and laboratory differences (Carter 2012). It is therefore important to standardize 25(OH)D measurements, which is the aim of the Vitamin D Standardization Program (VDSP) (Sempos et al. 2012; Schmid et al. 2013). Institutions working on the VDSP include the NIH Office of Dietary Supplements (ODS) in collaboration with the CDC National Center for Environmental Health (NCEH), the National Institute of Standards and Technology (NIST), and Ghent University (Sempos et al. 2012; Cashman et al. 2013).

While our understanding of vitamin D transport, cellular uptake or intracellular concentrations, and metabolism is still in its infancy, it is clear that VDR activation is required to exert vitamin D effects on gene regulation. The affinity of the VDR is much higher for 1,25(OH)2D than for 25(OH)D, which underscores why many authors consider 1,25(OH)2D as the active vitamin D hormone. As a steroid hormone receptor, the VDR is mainly located in an intracellular manner, but cell-membrane bound forms of the VDR have also been described suggesting some additional non-genomic effects (Bouillon et al. 2008). The classic pathway does, however, indicate that 1,25(OH)2D binds to the intracellular VDR and activates this receptor, followed by dimerization of the VDR and the retinoid X receptor (RXR). This VDR–RXR complex translocates to the nucleus where it binds to so-called vitamin D regulatory elements on the DNA. In concert with some interactions of the VDR/RXR complex with other regulatory factors, hundreds of genes are either up-regulated or down-regulated as a consequence of VDR activation (Bouillon et al. 2008). Degradation of vitamin D metabolites is initiated by 24-hydroxylation and results in the formation of, e.g, 24,25-dihydroxyvitamin D (24,25[OH]2D) or 1,24,25-dihydroxyvitamin D (1,24,25[OH]3D). These are known to be less active vitamin D metabolites that are further metabolized to calcitroic acid, which is then excreted via the urine (Reddy and Tserng 1989). While high levels of 1,25(OH)2D and subsequent VDR activation stimulate 24-hydroxylases in a regulatory loop, there remain some gaps in the literature regarding the biological meaning of many of the formed vitamin D metabolites (e.g, 24,25(OH)2D, 3-epimers and others) (Bailey et al. 2013; Jones et al. 2012).

Classic effects of vitamin D

Vitamin D has an established role in the regulation of bone and mineral metabolism (Bouillon et al. 2008; Holick 2007). Its effects on calcium metabolism by stimulation of calcium absorption in the gut ensure an adequate calcium supply required for physiologic bone mineralization. A hallmark of vitamin D deficiency is therefore an increase in parathyroid hormone (PTH) levels because PTH is synthesized in the parathyroid glands in response to low serum calcium. PTH effects on, for example, bone and kidneys are subsequently required to increase and maintain serum calcium concentrations within the normal range.

Overt vitamin D deficiency can therefore lead to rickets in children and osteomalacia in adults (Holick 2007; Lips 2001). These diseases are characterized by bone mineralization defects in addition to clinical symptoms such as proximal muscle weakness or bone pain (Lips 2001). Hence, vitamin D supplementation is recommended throughout the first year(s) of life in order to prevent rickets. Public health authorities base their dietary intake recommendations for vitamin D on doses that are considered to be sufficient to avoid osteomalacia or rickets (Ross et al. 2011). Beyond this, large RCTs and meta-analyses have shown that vitamin D supplementation reduce fractures and to some extent falls (Ross et al. 2011; Holick et al. 2011; Bischoff-Ferrari et al. 2012; Bischoff-Ferrari et al. 2009). Against this background, vitamin D supplementation is considered an integral part of the treatment of patients with osteoporosis. However, at present there is no consensus on the cutoff values for vitamin D deficiency. Suggested cutoffs for vitamin D deficiency according to 25(OH)D serum concentrations are <12 ng/mL (multiply by 2.496 to convert ng/mL to nmol/L), <20, and <30 ng/mL. A particularly hot debate is ongoing as to whether levels of 20 or 30 ng/mL can be considered sufficient (Holick et al. 2012; Rosen et al. 2012). In this context, it should be acknowledged that not all studies and meta-analyses have shown significant vitamin D effects on fractures and falls, so questions still remain regarding musculoskeletal vitamin D effects. These include, for example, the precise pathophysiological mechanisms, the optimal doses, and the impact of concomitant calcium supplementation (Ross et al. 2011; Holick

et al. 2011; Brouwer-Brolsma et al. 2013). Important data for clinicians were derived from an individual patient data meta-analysis showing that vitamin D doses ranging from approximately 800–2,000 International Units (IU) per day (1 IU is equal to 0,025 µg vitamin D) are effective for the prevention of fractures (Bischoff-Ferrari et al. 2012).

Experimental studies

Numerous experimental animal and cell culture studies have been performed on the involvement of vitamin D in CVD (Bouillon et al. 2008). The main findings of these investigations are summarized in this chapter. The starting point for these experimental studies was the identification of the VDR in cells of the vessel wall and the heart (Bouillon et al. 2008; Schnatz et al. 2012; Chen et al. 2008).

Knockout models

Knockout models for the VDR yield various pathologies, in particular regarding bone and mineral metabolism (Bouillon et al. 2008). With regard to the cardiovascular system, the VDR knockout mice develop a phenotype with arterial hypertension and myocardial hypertrophy (Bouillon et al. 2008). Additional features of these animals are increased thrombogenicity and overexpression of renin (Bouillon et al. 2008). Similar phenotypes were observed in knockout models for 1-alpha-hydroxylase (Zhou et al. 2008). Most notably, inhibition of the renin angiotensin aldosterone system (RAAS) prevented the cardiovascular damage in these experimental models suggesting that renin overexpression may play a crucial role. Considering that a general VDR knockout mouse may not be the best model to study specific effects of VDR on cardiovascular health, a cardiomyocyte selective knockout model was created (Chen et al. 2011). In this mouse model, bone and mineral metabolism were normal, but myocardial hypertrophy still occurred suggesting a specific effect of VDR activation on the heart (Chen et al. 2011).

Atherosclerosis

Several cell culture studies have shown that VDR activation may inhibit various steps in the pathogenesis of atherosclerosis. In detail, it has been shown that vitamin D is able to inhibit macrophage to foam cell formation, as well as suppressing the expression of endothelial adhesion molecules and smooth muscle cell proliferation (Bouillon et al. 2008; Riek et al. 2013; Weng et al. 2013). In animal studies, vitamin D deficiency was associated with accelerated atherosclerosis and lower VDR expression in coronary arteries correlated with a greater atherosclerotic plaque size

(Schnatz et al. 2012; Weng et al. 2013). It has also been shown that VDR activation in macrophages inhibits atherosclerosis in mice by suppressing the local renin angiotensin aldosterone system (RAAS) (Szeto et al. 2012).

Heart diseases

Myocardial hypertrophy is accompanied by an increased expression of the VDR in the heart (Chen et al. 2008). This may be a beneficial adaptive mechanism when considering that VDR activation has been shown to exert antihypertrophic and antiproliferative effects on cardiomyocytes (Pilz et al. 2010a). In addition, vitamin D downregulates various genes that are involved in the development of myocardial hypertrophy (Pilz et al. 2010a). VDR effects are also involved in the regulation of calcium flux of cardiomyocytes and have been implicated in the maintenance of diastolic function (Green et al. 2006). Accumulating evidence also indicates that vitamin D may play a role in the regulation of myocardial extracellular matrix turnover and may protect against cardiac fibrosis (Gardner et al. 2013; Pilz et al. 2010a).

CVD risk factors

Numerous experimental studies have reported that vitamin D may exert beneficial effects on almost all cardiovascular risk factors.

VDR activation has been shown to suppress the expression of renin (Li 2011; Vaidya and Williams 2012). This is of particular interest since the RAAS is a major regulator of blood pressure, and plasma renin concentrations are a cardiovascular risk marker (Tomaschitz et al. 2010, 2011). Other proposed antihypertensive effects of vitamin D include anti-inflammatory properties such as suppression of nuclear-factor-κB (NF-κB), renoprotective actions, direct effects on the vasculature as well as regulation of calcium homeostasis including suppression of PTH, which may itself contribute to high blood pressure (Dusso and Tokumoto 2011; Kienreich et al. 2013).

Several but not all experimental studies have demonstrated that VDR activation stimulates insulin secretion and protects against beta-cell dysfunction (Pilz et al. 2013a). Vitamin D regulation of calcium homeostasis may be of relevance in beta-cell function as insulin secretion is a calcium-dependent process (Pilz et al. 2013a). Other suggested anti-diabetic effects include improved peripheral insulin resistance, anti-inflammatory actions, and stimulation of osteocalcin, a bone marker with putative effects on insulin secretion and insulin sensitivity (Pilz et al. 2013a). Various other effects of vitamin D on cardiovascular risk factors including blood lipids, inflammation, and oxidative stress have also been characterized in experimental studies

as reviewed elsewhere (Bouillon et al. 2008; Muscogiuri et al. 2012; Beveridge and Witham 2013; Gardner et al. 2013; Pilz et al. 2013a; Kienreich et al. 2013).

Sunlight exposure and cardiovascular risk

In 1981, Robert Scragg reported on the seasonality of CVD with an increased incidence in winter and a lower incidence in summer. He hypothesized that more sunlight (UV-B) exposure with subsequent increased vitamin D synthesis in the skin might be a possible explanation for the seasonal differences in CVD incidence (Scragg 1981). Subsequent studies have confirmed that UV exposure is inversely associated with cardiovascular risk and mortality (Zittermann and Gummert 2010; Yang et al. 2011). Several reasons may account for these observations but these reports fit well to the hypothesis that sunlight-induced vitamin D production may protect against CVD. This is reinforced by data showing that the prevalence of arterial hypertension or type 1 diabetes is lowest in sunny countries, but gradually increases when moving away from the equator (Mohr et al. 2008; Rostand 1997). Similar data related to latitude have been reported for altitude showing that higher altitude with a more intense UV-B radiation is associated with a lower cardiovascular risk (Zittermann and Gummert 2010). A few clinical studies have evaluated effects of UV radiation on CVD risk factors with mixed results regarding blood pressure (Krause et al. 1998; Scragg et al. 2011). Interestingly, a high UV-B exposure has also been identified as a possible protective factor against developing heart failure (Zittermann et al. 2007). When discussing the aforementioned studies on UV exposure and cardiovascular risk, it should be acknowledged that sunlight exposure can raise 25(OH)D concentrations up to levels that are equivalent to a daily vitamin D supplementation of 10,000 IU per day (Holick 2007). Further, it should be noted that UV exposure exerts some direct, vitamin D independent effects that may be beneficial for cardiovascular health and include an increase in the vasodilator nitric oxide (NO) (Feelisch et al. 2010).

Vitamin D genetics and CVD

Several studies evaluated associations of the single-nucleotide polymorphisms (SNPs) of the VDR and of enzymes of the vitamin D metabolism with CVD and its risk factors. Despite some significant associations between certain SNPs and CVD and/or its risk factors, the majority of the studies reported a lack of significant findings (Shen et al. 2010; Jorde et al. 2012a; Kühn et al. 2013; Wilke et al. 2009; Li et al. 2013; Trummer et al. 2013). This is in line with data from patients with hereditary 1,25(OH)2D-resistant

rickets (HVDRR) who did not exhibit major cardiovascular pathologies (Tiosano et al. 2011). Of note, however, is a large meta-analysis of prospective studies showing that the association between 25(OH)D and multiple outcomes (i.e, hip fracture, myocardial infarction, cancer or death) is modified by a certain SNP of the VDR (Levin et al. 2012).

Our understanding on vitamin D metabolism and its related genetic background was significantly improved by a large genome-wide association study (GWAS) (Wang et al. 2010a, b). That study aimed to identify genetic loci that are associated with 25(OH)D serum levels. Four genetic loci were identified in that study related to the enzyme for 7-dehydrocholesterol synthesis in the liver, the DBP, the 24-hydroxylase, and the 1-alpha-hydroxylase (Wang et al. 2010a, b). This GWAS was not only important for the characterization of a genetic predisposition for higher or lower 25(OH)D levels but also opened the door to perform so-called Mendelian Randomization (MR) studies. The MR approach uses the genetic determinants for 25(OH)D levels as an instrument to study associations with disease outcomes. Assuming that the inherited SNPs related to 25(OH)D levels are not significantly related to confounding factors, MR permits investigators to address research questions with an evidence level that is considered approximate to the results achieved by RCTs (Verduijn et al. 2010; Berry et al. 2012). One important question addressed by a MR study was the link between obesity and 25(OH)D. In a large meta-analysis, Vimaleswaran et al. (2013) demonstrated that the genetic determinants of 25(OH)D are not related to body mass index (BMI). By contrast, the genetic determinants for BMI were significantly associated with lower 25(OH)D concentrations. This so-called bi-directional MR study came therefore to the conclusion that a higher BMI seems to lower 25(OH)D levels but not vice versa (Vimaleswaran et al. 2013).

Accumulating evidence suggests that some of the proposed beneficial effects of vitamin D on common chronic diseases could be mediated by microRNAs (Salic and De Windt 2012; Ha 2011). MicroRNAs are small non-coding RNAs that can regulate gene expression on a post-transcriptional level by binding messengerRNAs (mRNAs) (Salic and De Windt 2012; Ha 2011). This in turn leads to mRNA degradation or translation inhibition. Apart from their role in regulating gene expression, microRNAs are also released into the circulation and have been found to be associated with various chronic diseases. At present, there is intensive research ongoing to explore the diagnostic and therapeutic potential of microRNAs. To this end, it should be noted that vitamin D effects seem to participate and interact with the function and regulation of microRNAs (Giangreco and Nonn 2013; Jorde et al. 2012b; Alvarez-Díaz et al. 2012). Currently, however, our knowledge on vitamin D and microRNAs is still in its infancy. There are

only very limited data on alterations in circulating microR-NAs that are induced by vitamin D supplementation as part of a large clinical RCT (Giangreco and Nonn 2013; Jorde et al. 2012b; Alvarez-Díaz et al. 2012).

Vitamin D and cardiovascular risk factors

Many observational studies have evaluated the relationship between vitamin D status and cardiovascular risk factors by utilizing serum levels of 25(OH)D. Most of these studies found that vitamin D deficiency was associated with an adverse cardiovascular risk profile. While this would support an involvement of vitamin D in CVD, such findings should be interpreted with caution: (1) observational studies cannot prove causality; (2) reverse causation may explain the observed associations (i.e, that an underlying disease may lead to vitamin D deficiency and not vice versa); (3) as sunlight-induced vitamin D production and nutrition are sources for vitamin D, it cannot be ruled out that residual confounding may exist (e.g, unmeasured or unknown lifestyle factors related to less sunlight exposure or unhealthy diet that may be the driving factors explaining the link between vitamin D deficiency and cardiovascular risk factors). Current available data from randomized controlled trials (RCTs) on vitamin D supplementation and cardiovascular risk factors are less in favor of significant effects of vitamin D on cardiovascular risk factors. This in turn may suggest that observational results in this field could be significantly influenced by unconsidered or unmeasured confounding factors. In this chapter, we briefly summarize the current literature on vitamin D and CVD risk factors by presenting observational and RCT data for each cardiovascular risk factor.

Obesity

It is well established that a higher BMI is associated with lower 25(OH)D levels (Earthman et al. 2012; Vanlint 2013). A biologically plausible and widely accepted explanation for this relationship is that vitamin D, as a fat-soluble vitamin, is trapped in adipose tissue (Earthman et al. 2012). Another factor suggested to contribute to this association is that obese individuals, due to socio-psychological factors (e.g. social physique anxiety), tend to avoid exposing their skin to sunlight in public areas. According to some experimental data suggesting VDR activation in adipose tissue may facilitate weight loss, it has been hypothesized that vitamin D deficiency could also partially contribute to obesity (Earthman et al. 2012; Vanlint 2013). Nevertheless, this hypothesis has not been consistently supported by epidemiological studies. The present available evidence is in clear favor of the concept that obesity contributes to

vitamin D deficiency and not vice versa. This finding has clinical implications since the treatment and prevention of obesity has the potential to improve vitamin D status. In line with this, several studies have shown that weight loss is accompanied by an increase in 25(OH)D levels (Rock et al. 2012; Earthman et al. 2012; Vanlint 2013).

Arterial hypertension

Meta-analyses of cross-sectional and longitudinal studies have shown that vitamin D deficiency is a risk factor for higher blood pressure and arterial hypertension (Burgaz et al. 2011; Kunutsor et al. 2013). In 283,537 individuals from the general population, the relative risk (with 95% CIs) for incident arterial hypertension was 0.70 (0.58–0.86) in the highest compared with the lowest 25(OH)D tertile (Kunutsor et al. 2013). RCTs on vitamin D supplementation and blood pressure are already available, but these trials have produced mixed results, some showing a marginally significant blood pressure reduction following vitamin D supplementation and others reporting no relevant effect (Kienreich et al. 2013). Whereas various vitamin D RCTs reported on blood pressure as a secondary outcome, there are only a handful of trials that addressed the blood pressure effects of vitamin D as the primary study aim (Kienreich et al. 2013). In 102 hypertensive patients who were randomly allocated to either 3,000 IU vitamin D daily or placebo during winter, there was no significant effect on blood pressure in the entire cohort (Larsen et al. 2012). In a subgroup analysis of the same study restricted to patients with 25(OH)D less than 32 ng/mL, 24-h systolic and diastolic blood pressure decreased significantly by 3 and 4 mm Hg, respectively, in the intervention group compared with the placebo group (Larsen et al. 2012). In 159 older patients with isolated systolic blood pressure and 25(OH)D concentrations below 30 ng/mL, there was no significant blood pressure effect of 100,000 IU vitamin D every 3 months for 1 year (Witham et al. 2013). Strengths of this trial were the long treatment period and the availability of 24-h ambulatory blood pressure measurements, whereas a possible limitation might have been the relatively small increase in 25(OH)D (i.e, 8 ng/mL, in the treatment compared with the placebo group) (Witham et al. 2013). In the largest published study addressing the effects of vitamin D on blood pressure as a primary end point, 283 black participants were randomized in a 4-arm RCT to receive either placebo, 1,000, 2,000, or 4,000 IU vitamin D per day for 3 months (Forman et al. 2013). Main finding of this trial was that each additional vitamin D dose of 1,000 IU per day resulted in a decrease in systolic blood pressure of −1.4 mm Hg, while there was no relevant effect on diastolic blood pressure (Forman et al. 2013). It was further calculated that each increase in 25(OH)D concentrations

of 1 ng/mL resulted in a decrease in systolic blood pressure of −0.2 mm Hg. Taken together, there appear to be no major effects, albeit vitamin D supplementation may have low-to-moderate effects on reducing systolic blood pressure. Further studies on the role of vitamin D toward arterial hypertension are warranted in particular as even minor reductions in systolic blood pressure (as shown by Forman et al. 2013) could have significant public health ramifications at a population level.

Diabetes mellitus

Cross-sectional and prospective studies have largely shown that low levels of 25(OH)D are associated with insulin resistance and type 2 diabetes mellitus (O'Hartaigh et al. 2013; Pilz et al. 2012a, 2013a). Meta-analyses of epidemiological studies indicate that vitamin D deficiency is an independent risk factor for type 2 diabetes mellitus (Song et al. 2013; Afzal et al. 2013). It is important to point out the finding of an epidemiological study showing that the association between 25(OH)D and insulin resistance (as well as blood pressure) is nonlinear with strong correlations at certain values within the vitamin D deficiency range but no association for 25(OH)D values above 32–36 ng/mL (Heaney et al. 2013b). Vitamin D RCTs have, with only rare exceptions, failed to show beneficial effects of vitamin D supplementation on glucose homeostasis or incident diabetes mellitus (Pilz et al. 2013a). Reviewing the current available literature, we propose that there is likewise no relevant effect of vitamin D on glucose metabolism in the general population, or among individuals at high risk of diabetes mellitus (Pilz et al. 2013a; Davidson et al. 2013). Of note is a RCT in 109 prediabetic individuals with 25(OH)D levels below 30 ng/mL (Davidson et al. 2013). That RCT failed to show any relevant benefits of high-dose vitamin D supplementation over 1 year on glucose metabolism (Davidson et al. 2013). Considering that some other RCTs reported an improved glucose metabolism after vitamin D supplementation in patients with diabetes mellitus, it remains unclear whether vitamin D can improve glucose control in diabetic patients (Pilz et al. 2013a). It must, however, be acknowledged that the majority of RCTs conducted in diabetic patients were unable to show beneficial effects of vitamin D supplementation on glycemic control (Pilz et al. 2013a; Breslavsky et al. 2013).

Meta-analyses of observational studies have shown that vitamin D deficiency during pregnancy is also an independent risk factor for gestational diabetes (Aghajafari et al. 2013; Poel et al. 2012). Some, but not all, studies in pregnant women have shown improved glycemic control with vitamin D supplementation but further studies are still needed (Soheilykhah et al. 2013; Wagner et al. 2013). One such promising study is the "DALI: Vitamin D and lifestyle

intervention for gestational diabetes mellitus (GDM) prevention" study (Jelsma et al. 2013). A particular aim of that ongoing study in 880 pregnant women is to evaluate whether vitamin D supplementation is effective for the prevention of gestational diabetes mellitus (Jelsma et al. 2013).

Some, but not all studies, have shown that low 25(OH)D concentrations are a risk factor for type 1 diabetes mellitus (Munger et al. 2013; Thorsen et al. 2013; Chakhtoura and Azar 2013). RCTs with active or natural vitamin D on the preservation of beta-cell function in type 1 diabetic patients yielded inconsistent results, but it has been documented that vitamin D supplementation increases regulatory T cells, which are considered to protect against autoimmune diseases (Chakhtoura and Azar 2013; Bock et al. 2011; Prietl et al. 2010). While primary prevention studies are not available, it has been observed in Finland that vitamin D supplementation during childhood is associated with a significantly reduced risk to develop type 1 diabetes later in life (Hyppönen et al. 2001). This finding has been confirmed in a meta-analysis of existing studies on vitamin D intake during early life and subsequent risk of type 1 diabetes (Dong et al. 2013).

Lipids

Observational studies have, by the majority, revealed that low 25(OH)D concentrations are associated with higher triglycerides and total cholesterol but lower levels of HDL-cholesterol and apolipoprotein A-1 (Ponda et al. 2012; Jorde and Grimnes 2012). Data from RCTs showed mixed results but largely failed to demonstrate relevant effects of vitamin D supplementation on lipids (Zittermann et al. 2011a). A meta-analysis including 1,346 study participants derived from 12 clinical trials showed no significant effect of vitamin D on total cholesterol, HDL-cholesterol or triglycerides, but a marginally significant increase in LDL-cholesterol (Wang et al. 2012a, b). This modest increase in LDL-cholesterol post vitamin D supplementation could not be confirmed in a RCT of 305 postmenopausal women, and separately, in a retrospective cohort analysis when lipid profiles of patients with 25(OH)D levels below 20 ng/mL and an increase to ≥30 ng/mL during follow-up were analyzed (Wood et al. 2012; Ponda et al. 2012). Hence, the current literature does not support a relevant effect of vitamin D supplementation on blood lipids but further RCTs are required before drawing firm conclusions.

Parathyroid hormone (PTH)

PTH can also be considered a cardiovascular risk factor because PTH receptors are expressed in the cardiovascular system, and epidemiological studies have shown that

higher PTH levels, even in the absence of chronic kidney disease (CKD), are a significant risk factor for CVD and mortality (van Ballegooijen et al. 2013a; van Ballegooijen et al. 2013b; Fitzpatrick et al. 2008; Pilz et al. 2010b; Hagström et al. 2009). Considering that high PTH levels are a biochemical sign of overt vitamin D deficiency, it is reasonable to speculate that PTH could partially mediate the effects of vitamin D deficiency on the cardiovascular system.

Inflammation and other cardiovascular risk factors

Vitamin D influences the innate and adaptive immune system and may play a role in autoimmunity and infectious diseases (Hewison 2012; Pludowski et al. 2013). Immune effects of vitamin D and their potential impact on inflammation are also relevant to the pathogenesis of CVD (Querfeld 2013). Associations between vitamin D deficiency and markers of inflammation (e.g, C-reactive protein) have been observed in some but not all epidemiological studies (Murr et al. 2012; Querfeld 2013). Results from vitamin D RCTs are also equivocal; some report vitamin D treatment exerts beneficial effects on inflammatory parameters, while others report no effect (Schleithoff et al. 2006; Alvarez et al. 2013; Abou-Raya et al. 2013; Grossmann et al. 2012; Beilfuss et al. 2012; Wood et al. 2012). Considering the accumulating trial reports on vitamin D effects on inflammation in combination with experimental data on this topic, it seems likely that vitamin D supplementation may exert some effects on inflammatory processes. Whether these anti-inflammatory effects of vitamin D are of clinical relevance, and in which populations, remains to be elucidated. Inflammation and/or acute stress *per se* may also have an impact on vitamin D status and could potentially contribute to lowering 25(OH)D levels, probably by modulating vitamin D metabolism (Quraishi and Camargo 2012; Reid et al. 2011). With reference to this, it has also been hypothesized that RAAS activity and VDR activation may counteract each other in a feedback relationship mediated in part by inflammatory processes (Ferder et al. 2013). Foremost, a single-center, open-label, blinded end point trial in 101 heart failure patients reported a significant reduction in renin levels after vitamin D supplementation at a daily dose of 2,000 IU for 6 weeks (Schroten et al. 2013).

Observational and some interventional studies suggest that vitamin D may exert anti-oxidative properties, but the overall evidence is still inconclusive (Nair-Shalliker et al. 2012; Nikooyeh et al. 2013; Asemi et al. 2013; Gradinaru et al. 2012). Low testosterone levels, which are considered a cardiovascular risk factor, have also been associated with a poor vitamin D status but further studies are needed to clarify this relationship (Wehr et al. 2010, 2013; Lerchbaum et al. 2012; Pilz et al. 2011a).

Vitamin D and CKD

Vitamin D treatment is widely used in CKD patients (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group 2009). We therefore pay particular attention to clinical data and treatment modalities of vitamin D in these patients. Vitamin D deficiency is very common in patients suffering from CKD. In the German Diabetes Dialysis Study (4D Study), more than 70 percent of diabetes dialysis patients had 25(OH)D concentrations below 20 ng/mL (Drechsler et al. 2010). Factors contributing to this high prevalence of vitamin D deficiency in CKD include limited sunlight access and impaired vitamin D synthesis in the skin of uremic patients (Doorenbos et al. 2009), malnutrition and loss of vitamin D metabolites during dialysis as well as via urine (Chen et al. 1992). The latter process may be due to reduced tubular reabsorption of the 25(OH)D in patients with proteinuria because albumin and the DBP-25(OH)D complex compete for binding to the megalin receptor of the proximal tubular cells which is required for tubular reabsorption (Dusso and Tokumoto 2011). Low 25(OH)D levels in CKD are frequently accompanied by inadequate low 1,25(OH)2D levels. Reduced renal 1-alpha-hydroxylase activity may contribute to these relatively low 1,25(OH)2D levels, but some studies suggest that increased 24-hydroxylation may also significantly decrease 1,25(OH)2D levels in renal failure (Helvig et al. 2010). Apart from this, FGF-23 is secreted by osteocytes in response to high phosphate levels in CKD and reduces 1,25(OH)2D levels by inhibition of 1-alpha-hydroxylase activity (Quarles 2012).

As in the general population, low 25(OH)D levels are a risk marker for adverse health outcomes including mortality and CVD (Drechsler et al. 2011; Pilz et al. 2011b, c; Drechsler et al. 2010). Similar data were also obtained for low 1,25(OH)2D (Wolf et al. 2007). Considering that 1,25(OH)2D is usually not measured in clinical routine, there are only few data available on 1,25(OH)D and adverse outcomes, but accumulating evidence suggests that circulating 1,25(OH)2D might also be related to cardiovascular risk and mortality, even in the absence of significant CKD (Zittermann et al. 2009; Pilz et al. 2008). Future research should therefore put more emphasis on the relationship between circulating 1,25(OH)2D and cardiovascular risk (Zittermann et al. 2012a). Apart from this, it should be mentioned that several, but not all, studies reported that low 25(OH)D levels are also a risk factor for albuminuria, declining glomerular filtration rate (GFR) or CKD itself (de Boer et al. 2011, 2012; Damasiewicz et al. 2013). A role of vitamin D deficiency in the development of (renal) anemia has also been hypothesized (Icardi et al. 2013). Whether vitamin D is beneficial or harmful with regard to vascular calcification is at present unclear. It is also of interest to

note that in 16,268 adults of the general population, there was no significant association between 25(OH)D levels and kidney stones (Tang et al. 2012). Considering that vitamin D supplementation did not significantly increase urinary calcium excretion in patients with a history of kidney stones, it has been suggested that even in these patients vitamin D supplementation is not contraindicated (Leaf et al. 2012).

Vitamin D intervention studies have a long-standing history in nephrology. It must be differentiated between "natural vitamin D therapy" (vitamin D_3 or vitamin D_2), which is usually used to treat vitamin D deficiency in non-CKD patients, and active vitamin D treatment with 1,25(OH)2D or its analogs. Evidently, the risk of side effects (i.e, hypercalcemia or hyperphosphatemia) is significantly higher with active vitamin D treatment, which is also more expensive than "natural" vitamin D.

In CKD, the best-known effect of vitamin D is the reduction in PTH, which is achieved by both active and "natural" vitamin D (Jean et al. 2009; Kandula et al. 2011). This has been demonstrated in a recent meta-analysis of RCTs (Kandula et al. 2011) and is remarkable because "natural" vitamin D has previously been considered ineffective in end-stage CKD due to reduced 1-alpha-hydroxylase activity. Consistently, in some RCTs, natural vitamin D significantly increased 1,25(OH)2D (Jean et al. 2009; Kandula et al. 2011). Interestingly, the vitamin D analog paricalcitol could significantly reduce albuminuria in patients with diabetic nephropathy who were already treated with renin angiotensin aldosterone system inhibitors (de Zeeuw et al. 2010). This has been confirmed in a meta-analysis of 9 paricalcitol intervention studies among 832 patients (Cheng et al. 2012). With reference to the heart, a recent multicenter RCT was unable to document any significant effect of paricalcitol on left ventricular mass or diastolic dysfunction (Thadhani et al. 2012). A post hoc analyses of that PRIMO study, however, showed that paricalcitol reduced the left atrial volume index significantly and attenuated an increase in brain natriuretic peptide (BNP), suggesting some beneficial effects on the heart (Tamez et al. 2012). Finally, in observational studies, the prescription of active vitamin D analogs (i.e. 1,25(OH)2D or its analogs such as paricalcitol) was associated with improved survival (Nigwekar and Thadhani 2013; Kalantar-Zadeh et al. 2010).

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines 25(OH)D concentrations should be measured in CKD patients at stage 3 to 5D (i.e, GFR < 60 ml/min/m^2) and be normalized by natural vitamin D treatment (Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group 2009). Active vitamin D treatment should only be used in the event that despite correction of vitamin D deficiency PTH is progressively rising and remains consistently above the normal

range. In CKD patients stage 5D (dialysis patients), it is recommended to aim for PTH levels in the range of twofold to ninefold higher than the upper limit of the reference range. Dose titration for active vitamin D treatment is mainly done by measuring PTH concentrations.

Data on natural vitamin D supplementation and cardiovascular risk in CKD patients are limited so far and inconclusive (Alvarez et al. 2012, 2013). Accumulating evidence does however suggest that natural vitamin D supplementation in CKD may reduce albuminuria (Molina et al. 2013).

Vitamin D and atherosclerosis

Endothelial dysfunction

Observational studies have largely shown that vitamin D deficiency is associated with endothelial dysfunction. In 554 healthy adults, there was a significant inverse association between 25(OH)D, endothelial dysfunction, and arterial stiffness (Al Mheid et al. 2011). This is in line with data from 280 patients with type 2 diabetes mellitus showing that 25(OH)D concentrations are associated with brachial flow-mediated dilation (FMD) and circulating endothelial progenitor cell (EPC) numbers (Yiu et al. 2011).

RCTs of vitamin D supplementation for correcting endothelial dysfunction have produced mixed results. In 45 African-American adults, 60,000 IU vitamin D monthly for 16 weeks improved FMD (Harris et al. 2011). By contrast, in 100 patients with type 2 diabetes mellitus, there was no significant effect of a daily vitamin D supplementation of 5,000 IU over 12 weeks on brachial artery FMD, circulating levels of EPCs, and brachial-ankle pulse wave velocity (Yiu et al. 2013). In another RCT in 62 vitamin D-deficient patients with peripheral artery disease, there was also no significant effect of a single oral dose of 100,000 IU vitamin D on endothelial function and arterial stiffness (Stricker et al. 2012). In 58 stroke patients, a single dose of 100,000 IU vitamin D resulted in a significant improvement in FMD after 8 weeks that was no longer significant after 16 weeks (Witham et al. 2012). Hence, it is still unclear whether vitamin D exerts clinically relevant effects on endothelial function.

Carotid intima media thickness (IMT)

Observational studies on vitamin D status and carotid IMT showed controversial results. Some studies demonstrate that low 25(OH)D levels are associated with higher carotid IMT, whereas others did not report on any such association. In 654 community-dwelling older adults there was a significant inverse association between 25(OH)D and internal carotid IMT, but not with common carotid IMT

(Reis et al. 2009). Further, carotid IMT and carotid plaques were measured at baseline and after a median follow-up of 9.4 years in 3,251 participants of the Multi-Ethnic Study of Atherosclerosis (Blondon et al. 2013). In that study, there was no significant association between 25(OH)D or PTH with carotid IMT or carotid plaques, neither in cross-sectional nor in prospective analyses (Blondon et al. 2013). Similarly, there was no significant association between 25(OH)D and carotid IMT in 1,193 participants with type 1 diabetes (Sachs et al. 2013). There are no relevant data on vitamin D RCTs and carotid IMT but the overall evidence argues against a significant relationship between vitamin D status and carotid IMT.

Peripheral artery disease

In 4,839 participants of the National Health and Nutrition Examination Survey (NHANES), the prevalence of patients with peripheral artery disease was significantly increased at lower 25(OH)D concentrations (Melamed et al. 2008a). Most of the studies in this field support a link between low vitamin D status and increased risk of peripheral artery disease, but there are no RCTs addressing whether vitamin D supplementation has significant effects on clinical endpoints related to peripheral artery disease (Chua et al. 2011).

Coronary artery disease (CAD)

Data on atherosclerosis of the coronary arteries (i.e, CAD) have partially but not consistently shown that low 25(OH)D levels are associated with coronary heart disease. In 130 patients with acute ST-segment elevation myocardial infarction (STEMI), there was no relationship between 25(OH)D and the angiographic severity of CAD (Goleniewska et al. 2013). There was also no significant and independent association between 25(OH)D and the presence of CAD in 2,015 patients referred for coronary angiography (Murr et al. 2012). By contrast, in 1,000 older men and women, vitamin D deficiency was identified as an independent marker for the presence of CAD (Lim et al. 2012). Another study in 100 patients undergoing coronary angiography revealed a significant relationship between vitamin D deficiency and both the presence and severity of CAD (Syal et al. 2012). Serum levels of 25(OH)D were also significantly lower in patients with type 2 diabetes mellitus and microalbuminuria who suffered from asymptomatic CAD when compared with controls without CAD (Joergensen et al. 2012). Interestingly, vitamin D deficiency in patients with type 1 diabetes was also a significant predictor of the prevalence and development of coronary artery calcification, a marker of coronary artery plaque burden (Young et al. 2011). These data are, however, in contrast to a study in 650 Amish adults which showed no association between

25(OH)D and coronary artery calcification (Michos et al. 2009). Data on coronary heart disease events, in particular myocardial infarction, are outlined further in the paragraph on vitamin D and cardiovascular events.

Vitamin D and heart failure

Numerous observational studies have shown that patients with heart failure frequently suffer from vitamin D deficiency (Zittermann et al. 2003; Pilz et al. 2010a; Gardner et al. 2013). Considering that heart failure leads to limited physical performance and probably low sunlight exposure, it is difficult to disentangle the true cause and effect relationship in observational studies. Echocardiographic examinations with prospective data have failed to show significant associations between 25(OH)D and left ventricular structure and function (van Ballegooijen et al. 2013c; Fall et al. 2012; van Ballegooijen et al. 2012). Only a few intervention studies have evaluated the effects of vitamin D on myocardial function. In a RCT in 123 patients with heart failure, there was no significant effect of vitamin D supplementation (2,000 IU per day over 9 months) on parameters of myocardial function, but there was a significant improvement in the cytokine profile (Schleithoff et al. 2006). In a RCT of 105 vitamin D-deficient patients with congestive heart failure, vitamin D supplementation with 100,000 IU vitamin D did not improve functional capacity or quality of life, but resulted in a significant decrease in B-type natriuretic peptide, a marker of heart failure and high cardiovascular risk (Witham et al. 2010a). In an uncontrolled trial in 100 heart failure patients, vitamin D supplementation for 4 months was associated with reduced levels of pro-brain natriuretic peptide and improvements in NYHA class as well as 6-min walking distance (Amin et al. 2013). B-type natriuretic peptide levels were also significantly lowered following vitamin D supplementation in a RCT in 61 patients with type 2 diabetes mellitus (Witham et al. 2010b). These findings are fitting with data from an observational study of 3,005 heart failure patients in whom vitamin D supplementation was associated with improved survival (Gotsman et al. 2012). In addition, there exist case reports on heart failure in vitamin D deficient rickets with significant improvement of myocardial function after calcium plus vitamin D supplementation in affected children (Maiya et al. 2008). Nevertheless, it remains to be determined, whether vitamin D supplementation has beneficial effects on the myocardium.

Vitamin D and cerebrovascular events

Meta-analyses of prospective studies have clearly shown that low 25(OH)D concentrations are a risk factor for

stroke (Brøndum-Jacobsen et al. 2013; Chowdhury et al. 2012; Sun et al. 2012). In the largest meta-analysis including 58,384 participants and 2,644 events, the multivariate adjusted odds ratio (with 95% CIs) for ischemic stroke was 1.54 (1.43–1.65) in the lowest compared with the highest 25(OH)D quartile (Brøndum-Jacobsen et al. 2013). In sensitivity analyses of prospective general population studies, the hazard ratio for ischemic stroke remained significant with 1.46 (1.35–1.58). Apart from this, vitamin D deficiency is also an independent predictor of short-term mortality and poor functional outcome in stroke patients (Tu et al. 2013). While vitamin D deficiency is thus an established risk factor for cerebrovascular events, all of the previous vitamin D RCTs failed to show any significant reduction in stroke incidence (Kienreich et al. 2013). In light of this point, it must be taken into consideration that none of the published vitamin D RCTs was designed to evaluate vitamin D effects on stroke incidence so that final conclusions cannot be drawn (Hsia et al. 2007; Trivedi et al. 2003; Avenell et al. 2012). From a clinical perspective, it must be considered that stroke patients are at particularly high risk of osteoporosis, fractures and falls, thereby supporting the need for a sufficient vitamin D status among these individuals (Pilz et al. 2011d). Given that 25(OH)D crosses the blood–brain barrier, it has been suggested that VDR activation may also exert some neuroprotective effects that may be beneficial in stroke patients (Pilz et al. 2011d). It is therefore of interest to note that 25(OH)D levels are low in dementia (Annweiler et al. 2013; Llewellyn et al. 2010). Whether this reflects a causal relationship in the direction that vitamin D deficiency contributes to cognitive decline warrants large RCTs (Soni et al. 2012).

Vitamin D and cardiovascular events

Many prospective studies have largely but not consistently shown that low 25(OH)D levels are associated with an increased incidence rate of cardiovascular events (Pilz et al. 2011e; Karakas et al. 2013; Giovannucci et al. 2008; Wang et al. 2008; Schierbeck et al. 2012). Regarding specific cardiovascular events, vitamin D deficiency turned out as a risk factor for myocardial infarction and heart failure, but there are also data on a particular strong association with sudden cardiac death (SCD) (Pilz et al. 2008; Deo et al. 2011). In a meta-analysis including 65,994 study participants and 6,123 cardiovascular events, it was shown that there exists a generally linear and inverse association between 25(OH)D and cardiovascular risk for 25(OH)D levels ranging from 8 to 24 ng/mL (Wang et al. 2008). Insufficient data exist for the association between 25(OH)D and cardiovascular risk for 25(OH)D levels above 24 ng/mL (Wang et al. 2008). Further, vitamin D deficiency is also associated with poor

outcomes of patients with acute coronary syndromes or myocardial infarction (Ng et al. 2013; Correia et al. 2013).

A possible interaction of 25(OH)D and race has been suggested by data from 6,436 participants of the Multi-Ethnic Study of Atherosclerosis who were followed up for a median of 8.5 years (Robinson-Cohen et al. 2013). In that study low 25(OH)D was an independent risk factor for coronary heart disease events in participants who were white or Chinese, but not black or Hispanic. Similar data were obtained for the association between 25(OH)D and stroke risk (Michos et al. 2012). Hence, further studies are needed to evaluate whether there exists a significant racial difference for the relationship between 25(OH)D and cardiovascular risk.

Individual intervention studies and meta-analysis of RCTs failed to show significant effects of vitamin D supplementation on cardiovascular events (Mao et al. 2013; Wang et al. 2010a, b). These results argue against major beneficial, but also harmful effects of vitamin D supplementation on cardiovascular risk. However, several points need to be considered when interpreting these findings. First, none of the previous vitamin D RCTs was designed to evaluate cardiovascular events. Second, the vitamin D doses used were relatively low and frequently calcium was given at the same time. Third, study participants were included regardless of their vitamin D status.

Vitamin D and mortality

When reviewing data on vitamin D and CVD, it is also of interest to briefly describe the existing literature on vitamin D and mortality, as CVDs are the major cause of death. Observational studies have largely, but not always, shown that low 25(OH)D levels are an independent risk factor for mortality. Indeed, this has been documented in the general population (Schöttker et al. 2013; Melamed et al. 2008b), and also in different patient populations such as CKD patients (Pilz et al. 2011b), patients suffering from CVD (Zittermann et al. 2013a), patients with liver diseases (Putz-Bankuti et al. 2012), patients with type 2 diabetes mellitus and the metabolic syndrome (Thomas et al. 2012), cancer patients (Pilz et al. 2013b) or nursing home residents (Pilz et al. 2012b). The notion that low 25(OH)D is an independent risk factor for mortality has previously been confirmed in a large meta-analysis (Zittermann et al. 2012b). The optimal 25(OH)D concentrations associated with the lowest mortality risk in that study ranged from 30 to 35 ng/mL. While some studies showed that mortality risk is not only increased at very low 25(OH)D levels but also at high 25(OH)D levels in the sense of a U- or J-shaped curve, there was no significantly increased risk of mortality in the meta-analysis by Zittermann et al. It must, however, be

noted that sufficient data are not available to draw firm conclusions on the relationship between 25(OH)D and mortality at concentrations above approximately 45–50 ng/mL. In line with data from the general population, it has also been demonstrated in a meta-analysis that low 25(OH)D is associated with increased mortality in patients with CKD (Pilz et al. 2011c). As magnesium is important for vitamin D metabolism and transport, it has been argued that the association between 25(OH)D and mortality may be modified by magnesium intake (Deng et al. 2013).

Meta-analyses of RCTs on vitamin D supplementation have established that vitamin D treatment is associated with a moderate but statistically significant reduction in overall mortality (Bjelakovic et al. 2011; Rejnmark et al. 2012). A Cochrane meta-analysis based on 74,789 study participants reported a 6% mortality reduction in vitamin D_3 treatment (Bjelakovic et al. 2011). It was estimated that 161 individuals must be treated with vitamin D_3 for approximately 2 years to prevent one premature death (Bjelakovic et al. 2011). Similar results were reported by another individual patient data meta-analysis (Rejnmark et al. 2012). That study showed, however, that mortality reduction was only achieved with combined calcium plus vitamin D supplementation. The interpretation of these findings is obviously not straightforward and there remain several open questions as to the optimal vitamin D dose and the combined supplementation of calcium.

Vitamin D and calcium

Clinical studies on bone health suggest interactions of vitamin D and calcium (Lips 2012). While calcium and vitamin D seem to act in concert to exert beneficial skeletal effects, there are accumulating data suggesting that calcium supplementation may slightly increase cardiovascular risk (Bolland et al. 2011; Reid 2013; Uusi-Rasi et al. 2013; Zittermann et al. 2011b; Heaney et al. 2012). In detail, it has been demonstrated in meta-analyses of RCTs that calcium supplementation is associated with a significantly elevated risk of myocardial infarction (Reid 2013; Bolland et al. 2011). This is of particular concern since many RCTs were performed with the combination of both vitamin D and calcium and are thus hard to interpret. Obviously, calcium supplementation may contribute to calcification of vascular smooth muscle cells and alters their gene expression toward a more osteoblastic phenotype (Reid 2013). There is currently an ongoing discussion on whether the effects of calcium supplementation related to improved bone health outweigh adverse cardiovascular effects or vice versa (Reid 2013; Heaney et al. 2012; Uusi-Rasi et al. 2013). In addressing this issue, it has been calculated that "treating 1,000 people with calcium supplements for 5 years would

cause additional 14 myocardial infarctions, 10 strokes and 13 deaths, while preventing 26 fractures" (Reid 2013; Bolland et al. 2011). Finally, there is evidence that the combined intake of calcium plus vitamin D intake may decrease the drug compliance compared to intake of vitamin D alone (Autier et al. 2012).

Vitamin D toxicity

In humans, vitamin D doses up to 10,000 IU per day have not been associated with significant adverse effects (Hathcock et al. 2007; Zittermann et al. 2013b). This appears biologically plausible since the capacity of the body to produce vitamin D in the skin is approximately equivalent to an oral intake of 10,000 IU per day and there is no known case of acute vitamin D intoxication caused by sunlight exposure (Holick 2007). Some health authorities, in particular those who set vitamin D intake levels for the general population, are more conservative and consider 4,000 IU vitamin D per day as absolutely safe, i.e., as the tolerable upper intake level (EFSA 2012; Ross et al. 2011). Acute vitamin D intoxication, which is characterized by hypercalcemia, can, however, occur if 25(OH)D levels rise above approximately 150–200 ng/mL (Zittermann et al. 2013b). Clinical features of acute vitamin D intoxication include hypercalciuria, with its possible consequences of dehydration and acute renal failure as well as calcifications of the vessels or the kidneys. Such high levels of 25(OH)D can only be achieved by extreme overdosing of vitamin D, in particular if one considers that the relationship between vitamin D intake and the 25(OH)D concentration becomes flat at higher doses (Cashman et al. 2011). Hence, in the absence of extremely rare conditions such as granulomatous diseases (e.g, sarcoidosis) in which extrarenal 1-alpha-activity is increased, commonly used vitamin D doses are extremely unlikely to cause acute intoxication or hypercalcemia. We have, however, only sparse data available on long term safety with currently no compelling evidence that high-dose vitamin D supplementation exerts clinically relevant harmful or beneficial effects on cardiovascular risk factors (Jorde et al. 2013; Davidson et al. 2013).

Expectations for the future of vitamin D

Some large vitamin D RCTs in the general older population have just started within the last few years and will probably be finished in 2017–2020 (Kupferschmidt 2012). On the background of previous experience with other vitamins, it seems very unlikely that these vitamin D RCTs will reveal significant benefits of vitamin D supplementation (Pilz et al. 2012c). Such considerations are supported

by the fact that hardly any drug reduces clinical endpoints when given to unselected individuals of the older population. Other, probably more serious issues with the ongoing large vitamin D RCTs are that they mainly use single vitamin D doses for everyone, allow vitamin D supplementation in addition to the study drugs in the placebo group, and do not select individuals on the basis of low 25(OH)D levels. This latter point is of particular concern because the results from epidemiological studies and meta-analyses draw a relatively clear picture on the association between 25(OH)D and outcomes such as mortality or CVD. Depending on the study and outcome of interest, the risk of adverse events associated with vitamin D deficiency was only visible at relatively low 25(OH)D levels and thus in only a certain proportion of the analyzed patient populations. On the other hand, several studies suggest a U-shaped association between 25(OH)D and outcomes with some indications for a possible risk increase at very high 25(OH)D levels. Thus, a logical design for a vitamin D RCT would be to include participants with very low 25(OH)D levels and with the intention to supplement vitamin D doses to achieve optimal levels without overtreatment to very high and putative harmful 25(OH)D concentrations. Such RCTs are therefore still necessary, but the time frame to obtain sufficient funding for vitamin D trials may close within the next few years if negative results of large ongoing vitamin D RCTs reduce the interest for research and clinical applications of vitamin D.

Conclusions

Experimental and cell culture studies have clearly shown that VDR activation exerts various beneficial effects on the cardiovascular system. This is in line with the findings from large epidemiological studies that highlight a significant association between vitamin D deficiency and various cardiovascular risk factors such as arterial hypertension and diabetes mellitus. Moreover, meta-analyses of prospective studies revealed that low 25(OH)D levels are an independent risk marker for future cardiovascular events and mortality. By contrast, the results from RCTs on vitamin D treatment and cardiovascular risk are inconsistent, and consequently, we are unable to draw firm conclusions regarding effects of vitamin D on cardiovascular risk. We therefore have to wait for results of large vitamin D RCTs to assess cardiovascular endpoints. Such studies are currently ongoing but they aim to evaluate whether vitamin D supplementation is effective among generally healthy older adults. Looking at the history of other studies in unselected individuals from general populations it is likely that these studies will not show significant effects. If this is the case, there only remains a small time frame within the next few

years to perform additional RCTs to address the question whether severely vitamin D-deficient individuals benefit from vitamin D treatment.

In conclusion, vitamin D deficiency is indeed a cardiovascular risk factor, but vitamin D supplementation with commonly used doses as recommended for osteoporosis treatment is neither proven to be beneficial nor harmful in CVD.

Conflict of interest   None.

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