



University
of Glasgow

El-Fakhri, N., McDevitt, H., Shaikh, M.G., Halsey, C., and Ahmed, S.F. (2014) *Vitamin D and its effects on glucose homeostasis, cardiovascular function and immune function*. Hormone Research in Paediatrics . ISSN 1663-2818

Copyright © 2014 The Authors

<http://eprints.gla.ac.uk/93353/>

Deposited on: 01 May 2014

Vitamin D and Its Effects on Glucose Homeostasis, Cardiovascular Function and Immune Function

N. El-Fakhri^a H. McDevitt^{a,b} M.G. Shaikh^a C. Halsey^c S.F. Ahmed^a

^aSchool of Medicine, University of Glasgow, Royal Hospital for Sick Children, ^bNeonatal Unit, Southern General Hospital, and ^cInstitute for Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK

Key Words

Vitamin D · Extraskelatal benefits · Immune function · Cardiovascular function · Glucose homeostasis

Abstract

In recent years there has been increasing interest in the non-skeletal effects of vitamin D. It has been suggested that vitamin D deficiency may influence the development of diabetes, cardiovascular dysfunction and autoimmune diseases. This review focuses on the current knowledge of the effects of vitamin D and its deficiency on cardiovascular function, glucose homeostasis and immune function, with a particular focus on children. Although, there is good evidence to show that there is an association between vitamin D deficiency and an abnormality of the above systems, there is little evidence to show that vitamin D supplementation leads to an improvement in function, especially in childhood.

© 2014 S. Karger AG, Basel

Vitamin D Overview

Most plants and animals that are exposed to sunlight have the ability to produce vitamin D. In humans, the active vitamin D metabolite, 1,25-dihydroxyvitamin D (1,25(OH)₂D), has been well recognized for its role in calcium and phosphate homeostasis [1]. However, intensive

research over the last two decades has indicated that vitamin D may also be a critical modulator of several non-skeletal systems and related diseases. Vitamin D refers to two biological precursors – ergocalciferol (D₂) and cholecalciferol (D₃). Vitamin D₃ constitutes around 80–90% of the circulating metabolites and is synthesized mainly in the skin by the action of ultraviolet (UV) light (280–315 nm). Vitamin D₃ can also be obtained exogenously from animal sources such as fish oils or fortified dairy products and vitamin supplements. Sun-dried mushrooms, UV-B irradiation of the yeast sterol ergosterol, as well as vitamin supplements are considered as main sources of vitamin D₂ [2]. Vitamin D (D₂, D₃) has no biological activity without a two-step hydroxylation process. The first step, in the liver, requires P450 enzymes such as CYP2R1 and CYP27A1 (25-hydroxylases) to form the major circulating form 25(OH)D. The second step, in the kidneys, requires the P450 enzyme, CYP27B1 (1 α ,25-hydroxylase) to form the main active metabolite – 1,25(OH)₂D or calcitriol. The second hydroxylation reaction is stimulated mainly by parathyroid hormone (PTH), and inhibited by calcium, phosphate and fibroblast growth factor-23 (FGF-23) [3]. The biological action of 1,25(OH)₂D is mediated through the vitamin D receptors (VDRs) and this receptor as well as CYP27B1 are expressed widely in several tissues [4] (fig. 1).

Vitamin D deficiency has been defined by the Institute of Medicine (IOM) as a measured serum 25(OH)D of <30 nmol/l (12 ng/ml), vitamin D insufficiency when the se-

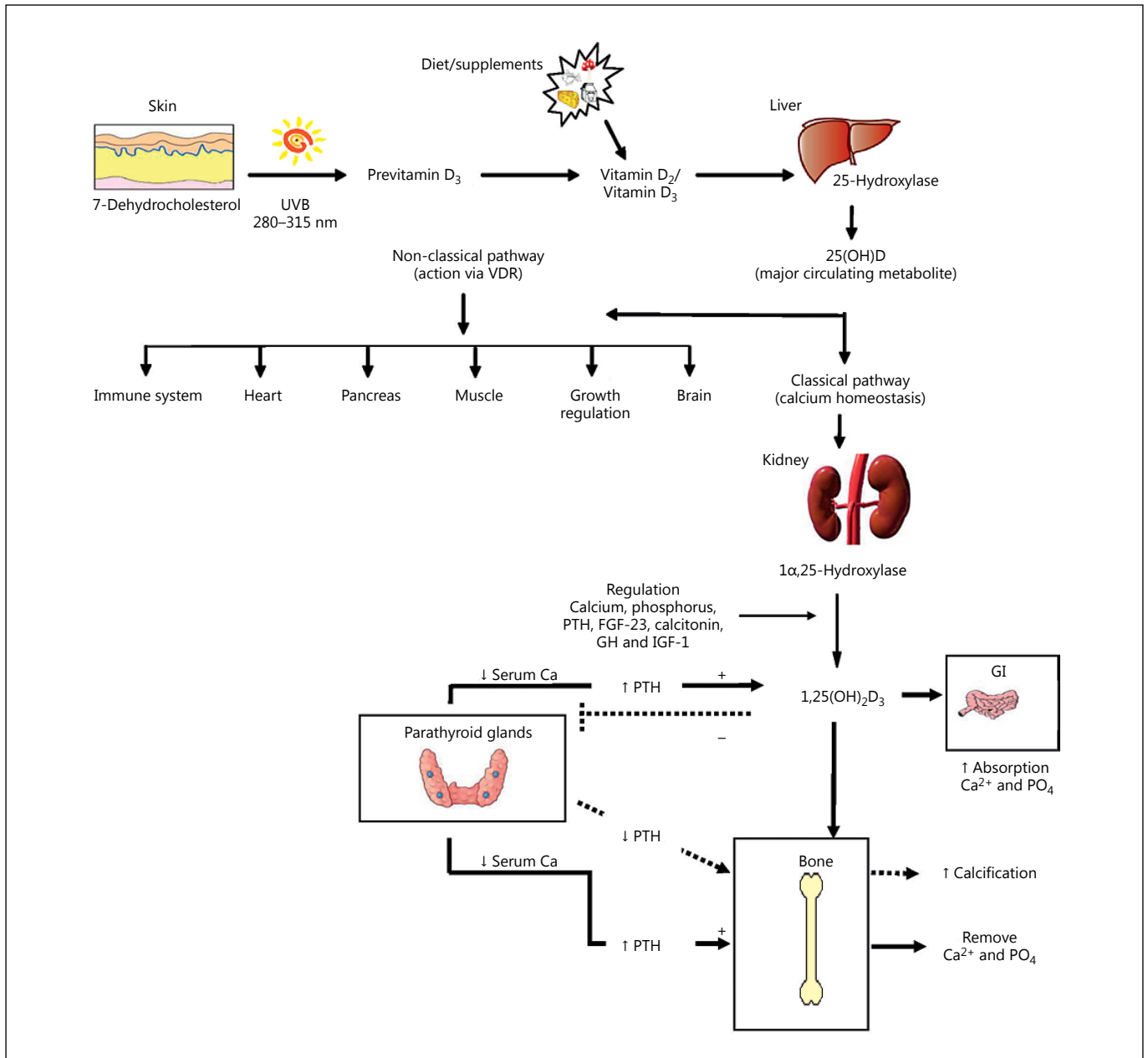


Fig. 1. Photochemical synthesis of vitamin D and main target tissues. Classical pathway of vitamin D and calcium homeostasis. A drop in the serum calcium stimulates an increase in the secretion of PTH and mobilizes further calcium from the bone. PTH increases the synthesis of $1,25(\text{OH})_2\text{D}$ in the kidney, which, in turn,

stimulates the mobilization of calcium from bone and intestine and regulates the synthesis of PTH by negative feedback. GH = Growth hormone; IGF-1 = insulin-like growth factor-1; GI = gastrointestinal.

rum $25(\text{OH})\text{D}$ is 30 to <50 nmol/l (12 to <20 ng/ml) and vitamin D sufficiency is defined at $25(\text{OH})\text{D}$ levels equal to 50 nmol/l (20 ng/ml) [5]. There are a number of guidelines which have been published over the last decade to evaluate, manage and prevent vitamin D deficiency [6–8].

However, there is little consensus on the threshold which reflects biological vitamin D sufficiency at the end-organ level. In addition, there is substantial uncertainty about the extraskeletal benefits of vitamin D supplementation, especially in those who have relatively mild vitamin D

Table 1. Summary of studies reporting association between 25(OH)D and glucose homeostasis in fasted state (boys and girls)

Reference	Age, years	BMI	n	Method	25(OH)D, nmol/l	Association with glucose homeostasis	Adjusted for variable	Comment
Reinehr et al. [36]	12.1±2.4	27.7±3.8	133	glucose, insulin	50	no	BMI	longitudinal study (1 year)
Smotkin-Tan-gorra et al. [37]	12.9±5.5	32.3±6.4	217	glucose, insulin	55.2% <50, 44.8% ≥50	no	no	retrospective study
Delvin et al. [155]	9, 13, 16	20.1±4.2 (boys), 20.4±4.5 (girls)	1,745	glucose, insulin	45.9±13 (boys), 45.9±12.2 (girls)	yes	age, sex, BMI, smoking, income, activity	–
Ford et al. [156]	12–17 (range)	–	1,941	glucose, insulin, HbA1C	59	yes	age, sex, BMI, ethnicity, activity, vitamin intake, HDL	association with insulin resistance in selected subgroups
Kelly et al. [157]	11±4	2.1(–1.2, 4.1) (median (min, max))	85	glucose, insulin, HbA1C	59±32	yes	age, sex, season, ethnicity, BMI, puberty	correlation between HOMA and race, sex, season disappears after adjustment to puberty and BMI-Z
Olson et al. [39]	6–16 (range)	99.2 (percentile for age)	411	glucose, insulin, OGTT, HbA1C	49±17.8	yes	age, BMI	correlation exists only after adjustment; no correlation with HbA1C
Roth et al. [40]	11.9±2.7	SDS-BMI; 20% (non-obese), 80% (obese)	156	glucose, insulin, HbA1C	39.4±6.6	yes	age, sex, BMI	no impact of adiposity on study result
Poomthavorn et al. [38]	11.2±2.6	28.6±4.8	150	OGTT (obese), glucose (non-obese), insulin	70.4	no	no	subjected to selection bias as recruited from obesity clinic
Nsiah-Kumi et al. [41]	10.8±0.3	77.0±1.7 (percentile for age and sex)	198	glucose, insulin, 2 h blood glucose	42.4 (16.9, 99.8) (median (min, max))	yes	BMI	–

OGTT = Oral glucose tolerance test; HbA1C = glycosylated haemoglobin; BMI = body mass index; BMI-SDS = body mass index-standard deviation score. Data are shown as mean (SD), unless indicated otherwise.

deficiency [6, 9]. In this review, PubMed and the Web of Knowledge were used to identify studies that explored a link between vitamin D, glucose homeostasis and cardiovascular and immune function in children. Studies conducted within the last 7 years, which involved large paediatric samples and those reported in English, were selected and are summarized in tables 1–3 as appropriate.

Link between Vitamin D and Glucose Homeostasis – Putative Mechanisms

Evidence for an association between vitamin D and glucose homeostasis was first raised in reports of lower serum 1,25(OH)D level in diabetic rats compared to the

control animals, and restoration of 1,25(OH)D to a normal level after insulin treatment [10]. Coexisting hypovitaminosis D and abnormal glucose metabolism has also been reported in patients with type 2 diabetes mellitus (T2DM) compared to healthy controls [11] and a possible link with vitamin D was also raised when a seasonal variation in plasma glucose and insulin was observed in normal individuals [12].

There were several suggested biological mechanisms by which vitamin D may contribute to the development of T2DM. This evidence includes the presence of VDRs and the expression of 1 α -hydroxylase enzymes in the pancreatic β cell along with the existence of a vitamin D response element in the human insulin gene promoter [13–15]. In accordance with this finding, a significant

Table 2. Summary of studies reporting association between 25(OH)D and cardiovascular (CV) risk factors in children (boys and girls)

Reference	Age, years	BMI	n	Outcome assessed	25(OH)D, nmol/l	Association with CV risk factors	Adjusted for variable	Comment
Smotkin-Tangorra et al. [37]	12.9±5.5	32.3±6.4	217	BP, lipids	55.2% <50, 44.8% ≥50	yes	no	vitamin D insufficiency associated with ↑BMI, ↑SBP, ↓HDL-C
Reis et al. [82]	12–19	17.6 (≥95th percentile)	3,528	BP, lipids	61.9	yes	age, gender, race, income, activity, BMI	positive association with BP even after adjustment
Delvin et al. [155]	9, 13, 16	20.1±4.2 (boys), 20.4±4.5 (girls)	1,745	lipids	45.9±12.2 (boys), 45.9±13 (girls)	yes	age, sex, BMI, smoking, income, activity	positive association only present in girls
Dong et al. [91]	16.3±1.4	61.6±33.4 (percentile)	23 (study) 21 (control)	BP, adiposity, arterial stiffness	33.4	yes	age, sex	16-week randomized control trial of 2,000 IU daily 25(OH)D supplementation
Pacifico et al. [83]	11.5 (lowest), 11.2 (middle), 11 (highest)	24 (lowest), 22 (middle), 21 (highest)	452	BP, lipids, endothelial dysfunction	29.9 (lowest), 54.9 (middle), 89.8 (highest) (median)	yes	age, sex, Tanner stage, BMI	data divided according to serum 25(OH)D tertiles; an association with BP and lipids
Patange et al. [158]	14.7±2.6	23.6±7.5	34	arterial compliance, left ventricular mass, diastolic function	38.21±23.41	yes	–	subjects had chronic renal disease; vitamin D deficiency associated with ↑ left ventricular mass and diastolic dysfunction
Nsiah-Kumi et al. [41]	10.8±0.3	77.0±1.7 (percentile for age and sex)	198	BP, lipids, hsCRP	42.4 (16.9, 99.8) (median (min, max))	yes	BMI	–

BMI = Body mass index; BP = blood pressure; hsCRP = high-sensitivity C-reactive protein. Data are shown as mean (SD), unless indicated otherwise.

reduction in the insulin secretion in VDR mutant mice has been observed [16] and the human insulin gene has been shown to be transcriptionally activated by 1,25(OH)₂D₃ [17]. Vitamin D may influence insulin secretion indirectly through its role in the regulation of calcium flux through the cell membrane combined with its role in the synthesis and regulation of calbindin, a vitamin D-dependent Ca-binding protein in pancreatic β cells [18]. Vitamin D may also protect β cells from fatal immune attacks, or programmed cell death either directly or through its effect on various components of innate and adaptive immune system at different levels (as discussed later). It has been reported that 1,25(OH)₂D₃ may counteract apoptotic pathways and the inflammatory effect induced by cytokines through inactivation of NF-κB antiapoptotic protein and suppression of Fas receptor expression [19, 20].

Another possible mechanism explaining the involvement of vitamin D in the pathogenesis of T2DM is the role of hypovitaminosis D in enhancing insulin resistance at the target tissues [21, 22]. The presence of the VDR in extraskeletal target sites, such as skeletal muscle, together with the upregulation of insulin receptors (INS-R) after 1,25-hydroxyvitamin D₃ treatment appears to support this hypothesis [23]. Elevated PTH has also been suggested as a modulator for both insulin sensitivity and secretion status by affecting glucose uptake and inhibiting insulin transport signalling in the target tissues primarily by increasing intracellular calcium concentration [24]. Chronic inflammation may worsen insulin resistance and vitamin D may influence the inflammatory reaction through several mechanisms including modulation of the release of inflammatory cytokines such as tumour necrosis factor-α (TNF-α), reg-

Table 3. Summary of studies reporting association between 25(OH)D and immunity in children (boys and girls)

Reference	Age	n	25(OH)D, nmol/l	Outcome assessed	Association with outcome	Comment
<i>Observational studies</i>						
Wright et al. [159]	16 years (median)	38	44.9	severity of SLE	yes	25(OH)D lower in SLE patients (African origin & obese) compared with control (36.8 vs. 9.2%, $p < 0.001$)
Peroni et al. [160]	5.6 years	37	92.1±39.1 (mild AD), 68.6±21.4 (moderate), 51.1±14.7 (sever AD)	severity of AD	yes	25(OH)D higher in mild AD compared with moderate and severe AD ($p < 0.05$)
Greer et al. [161]	10.1±0.9 years	56	81.4 (T1DM), 70.5 (newly diagnosis)	T1DM	yes	25(OH)D lower in children with T1DM compared with controls [mean (95% CI) = 78.7 nmol/l (71.8–85.6) vs. 91.4 nmol/l (83.5–98.7), $p = 0.02$]
Allen et al. [162]	12.7±0.7 months	928	–	infantile food allergy	yes	infants of Australian parents with 25(OH)D ≤50 nmol/l were more likely to be allergic to peanuts (aOR, 11.51; 95% CI 2.01–65.79; $p = 0.006$) and/or EGG (aOR, 3.79; 95% CI 1.19–12.08; $p = 0.025$)
<i>Interventional studies</i>						
Manaseki-Holland et al. [153]	13.18±9.1 years	224	–	reduction of pneumonia attack	yes	children received 100,000 IU vitamin D ₃ along with AB; decreased risk of repeat episode in treatment group (92/204; 45%) compared with control (122/211; 58%)
Camargo et al. [152]	10.1±0.9 years	143	17.47	ARIs attack in winter	yes	children received milk fortified with 300 IU of vitamin D ₃ ; reduction in ARIs attack in treatment group comparing with control (aOR 0.52 (95% CI 0.31–0.89))
Manaseki-Holland et al. [154]	1–11 months (range)	1,487	–	incidence of pneumonia	no	children received 100,000 IU vitamin D ₃ every 3 months for 18 months; no effect of vitamin D on the frequency of pneumonia episodes

SLE = Systemic lupus erythematosus; AD = atopic dermatitis; AB = antibiotics; ARIs = respiratory infections; T1DM = type 1 diabetes mellitus; aOR = Adjusted odds ratio. Data are shown as mean (SD), unless indicated otherwise.

ulation of the activity of NF-κB, regulation of genes encoding pro-inflammatory cytokines and downregulation of Toll-like receptor (TLR)2 and TLR4 expression [25–27]. Figure 2 illustrates the putative role of vitamin D on insulin synthesis, release and β-cell function.

Link between Vitamin D and Glucose Homeostasis – Evidence from Observational Studies

In a cross-sectional study, Orwoll et al. [28] reported no relationship between serum 25(OH)D, fasting or post-challenge glucose and insulin secretion. However, the indirect method for measuring insulin level and unadjusted results for confounders may have had an impact on the study outcome. A positive association between 25(OH)D and insulin secretion has been reported in both glucose-intolerant East London women of South Asian origin [29] and healthy Caucasian elderly men [30]. These studies were performed using an oral glucose

tolerance test and have been further supported by other studies which used a hyperglycaemic clamp technique [31, 32].

Indeed, most of the available cross-sectional studies, including a large data from the National Health and Nutrition Examination Survey (NHANES), support an inverse relationship between serum 25(OH)D and glycaemia and insulin resistance. However, the result from this survey was applied only to particular ethnic groups, non-Hispanic White and Mexican-American but not non-Hispanic Black [33]. Prospective studies assessing the association between 25(OH)D and diabetes risks are very limited. A negative association between basal serum concentration of 25(OH)D level and future hyperglycaemia and insulin resistance has been found in one prolonged study conducted over a 10-year period [34]. A recent systematic review and meta-analysis showed that each 10-nmol/l increase in 25(OH)D levels was associated with a 4% lower risk of T2DM. In addition, the relative risk of T2DM was 0.62 (95% CI 0.54–0.70) when com-

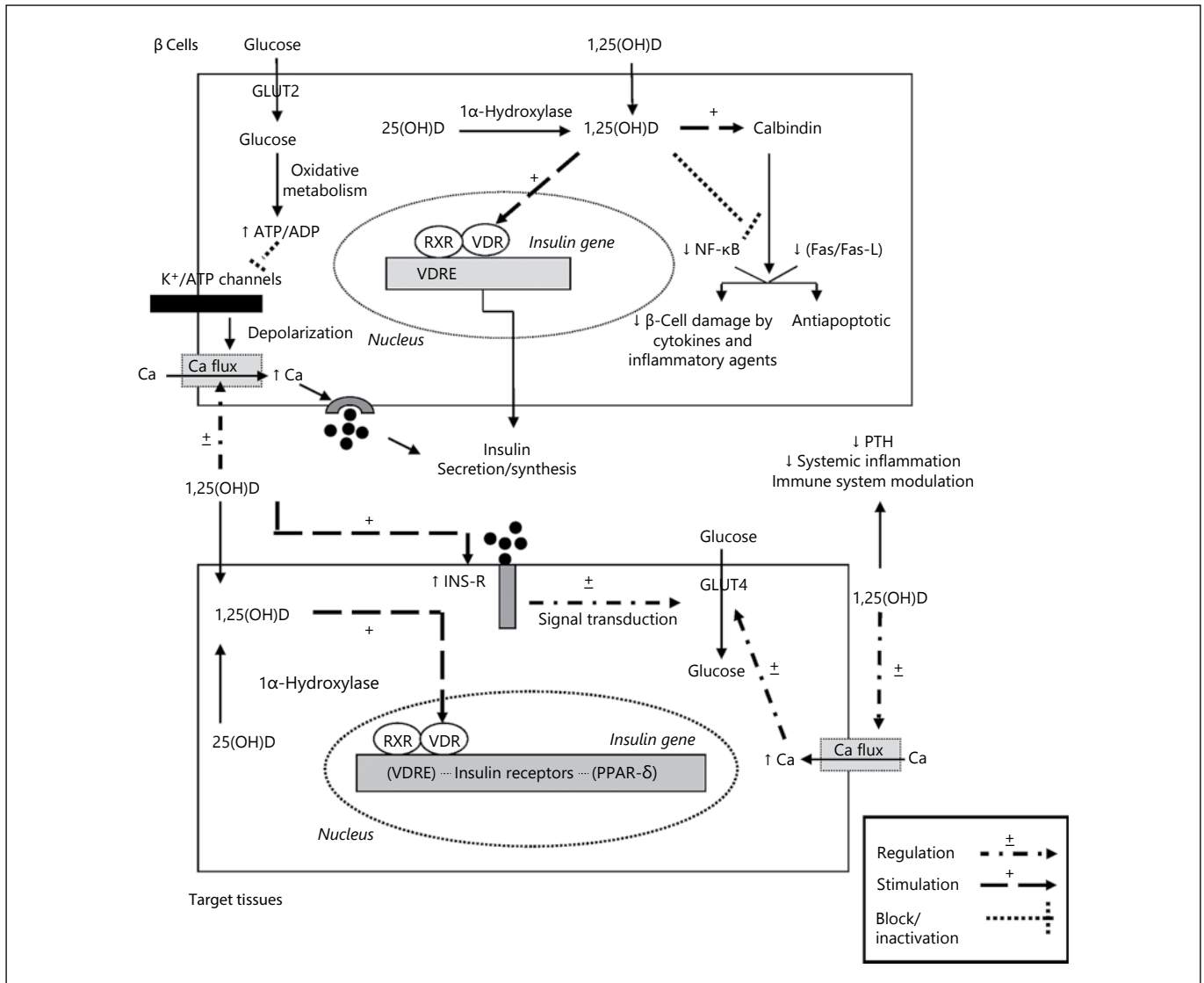


Fig. 2. Vitamin D and its role in glucose homeostasis and pancreatic beta-cell function. *Beta cells* (above): Source of 1,25(OH)D includes the circulation or the pancreatic β cells. I. 1,25(OH)D up-regulated insulin gene transcription via VDR binding which lead to more insulin synthesis. II. Vitamin D improves insulin secretion and glucose tolerance also through indirect regulation of intracellular calcium through increasing the ATP/ADP ratio resulting in closure of the plasma membrane ATP-gated channels and depolarization of the cell leading to exocytosis of insulin-containing secretory granules. III. Modulation of cytokine secretion and

apoptotic pathways occurs through interaction with VDRE in cytokine genes, inactivation of NF- κ B and suppression of Fas receptor. IV. Upregulation of calbindin may also protect against cytokine-induced apoptosis by increasing intracellular free calcium. *Target tissues* (below): I. Vitamin D stimulates the expression of insulin receptors and signalling transduction, resulting translocation of GLUT4 to the membrane and glucose transport in peripheral tissues. II. Vitamin D causes activation of peroxisome proliferator-activated receptor (PPAR- δ), a transcription factor implicated in the regulation of fatty acid metabolism.

paring the highest to the lowest category of 25(OH)D levels [35].

Based on the available observational studies, little is known about the association between insulin sensitivity/resistance, glucose intolerance and vitamin D deficiency

in the paediatric population. Three studies have failed to find any association between vitamin D and insulin resistance in obese children [36–38]. Other studies report an inverse association between hypovitaminosis D and measures of insulin resistance and glycaemia in obese chil-

dren [39–41]. Table 1 summarizes some of the recent studies that have investigated the association of 25(OH)D with glucose homeostasis in children.

In summary, observational studies investigating an association between vitamin D status, as indicated by 25(OH)D levels and glycaemia, diabetic risk and β -cell function have been performed in multiple cohorts. Despite the overall view in favour of a negative impact of hypovitaminosis D on glucose homeostasis and β -cell function, the available literature demonstrates inconsistent results. There are several possible explanations for this variation including differences in study design, subject characteristics, study population, confounders and techniques used to assess glucose homeostasis and β -cell function.

Link between Vitamin D and Glucose Homeostasis – Evidence from Interventional Studies

A possible association between vitamin D and insulin secretion was raised in interventional studies over three decades ago [29, 42, 43]. On the other hand, other studies did not find any effect of vitamin D supplementation [44–46]. Grimnes et al. [47] could not find any effect of 6 months of 20,000 IU vitamin D₃ administered orally twice a week to a healthy Caucasian cohort who had vitamin D levels lower than 40.3 ± 12.8 nmol/l on both insulin sensitivity and secretion. This was consistent with another study which showed that the injection of two doses of 100,000 IU vitamin D₃ did not lower fasting glucose or insulin sensitivity in a Caucasian cohort [48]. However, these results could not be applied to other ethnic populations as shown by the study which involved South Asian participants and demonstrated a significant effect of the administration of 4,000 IU vitamin D₃ for 6 months to decrease fasting glucose and increase insulin sensitivity in vitamin D-deficient and insulin-resistant South Asian women [49]. Mitri et al. [50] designed the short-term Calcium and Vitamin D for Diabetes Mellitus (CaDDM) 2 by 2 factorial, double-masked, placebo-controlled trial, which looked at the effect of vitamin D and calcium supplementation alone or in combination on pancreatic β -cell function, insulin sensitivity and glucose tolerance in 92 mainly Caucasian, obese and glucose-tolerant adults. Study participants were divided into four groups; one of them taking 2,000 IU vitamin D₃ for 16 weeks. The deposition index which was used as an indication for pancreatic β -cell function was measured. The results from this study showed a significant increase in deposition index in the vitamin D supplement group and improve-

ment in pancreatic β -cell function by 15–30% with a tendency to decrease the rise in the measure of glycaemia. A recent double-blind, placebo-controlled trial of obese vitamin D-deficient adolescents aged 9–19 years failed to find any significant effect of 6 months' supplementation of 4,000 IU vitamin D on BMI, inflammatory markers, fasting glucose and insulin [51].

In conclusion, results from interventional studies show some degree of inconsistency with heterogeneity of techniques, study designs, subject characteristics and the therapeutic regimen. Most of the available studies used indirect methods to measure the effect of vitamin D on insulin sensitivity. Basal vitamin D levels were not available for most of the studies and there was no universal threshold to define vitamin D deficiency, insufficiency or sufficiency.

Link between Vitamin D and Cardiovascular Function – Putative Mechanisms

Seasonal variation of cardiovascular disease was observed many years ago, with higher mortality from ischaemic heart disease occurring in winter [52]. A linear relationship between mortality from ischaemic heart disease and higher latitude has been reported as well, with decreasing mortality with residence within increasing proximity to the equator [53]. Results of several clinical and epidemiological studies have linked low vitamin D status to cardiovascular risk factors such as hypertension, diabetes, obesity and elevated blood cholesterol level [54, 55].

Vitamin D may affect cardiovascular health through many mechanisms. These include downregulation of PTH [56], suppression of the renin-angiotensin-aldosterone system [57], regulation of vascular smooth muscle and cardiomyocyte proliferation and hypertrophy [58, 59], enhancement of endothelial cell-derived vascular vasodilatation [60], regulation of coagulation [61], modulation of inflammatory markers [62] and metalloproteinase-9 (MMP-9) [63], as well as improved insulin sensitivity and secretion [64] (fig. 3).

Chronic vitamin D deficiency leads to overproduction of PTH, mainly due to decreased intestinal calcium absorption and increased calcium mobilization from bone. Overproduction of PTH can have several cardiovascular consequences including left ventricular hypertrophy (LVH), valvular calcification, myocardial calcification, cardiac arrhythmia and arterial hypertension [65, 66]. The renin-angiotensin system (RAS) is known to play a vital role in controlling blood pressure, intravascular vol-

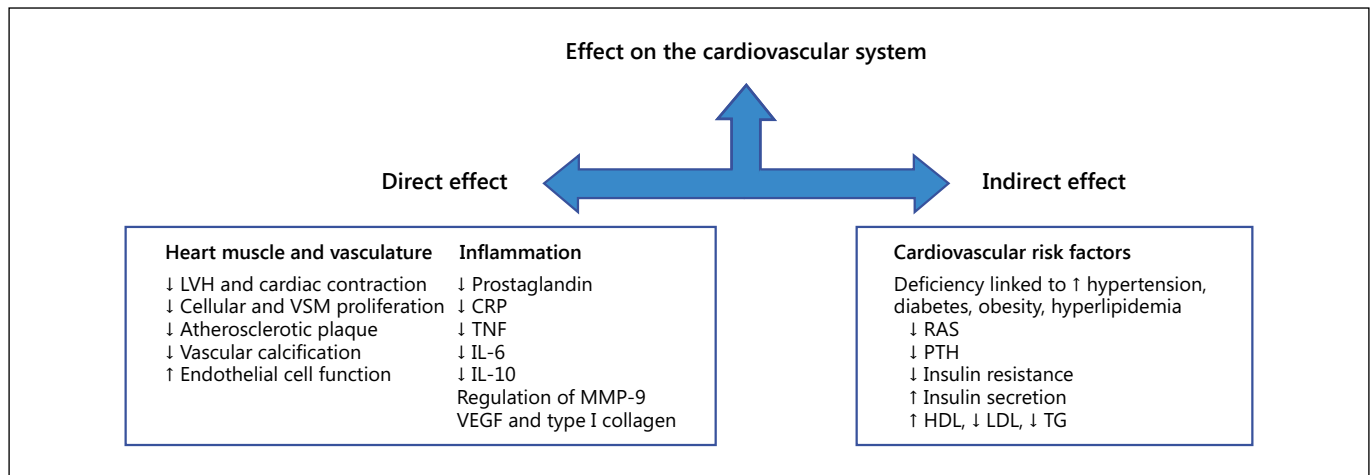


Fig. 3. Potential role of vitamin D on cardiovascular system. VSM = Vascular smooth muscle; CRP = C-reactive protein; VEGF = vascular endothelial growth factor; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

ume and electrolyte balance. Low vitamin D levels up-regulate the renin-angiotensin-aldosterone system, increase inflammation and cause endothelial dysfunction. Genetic disruption of the VDR in mice results in over-stimulation of the RAS, leading to high blood pressure and cardiac hypertrophy [67]. Similarly, in humans, recent studies have reported an inverse association between 1,25(OH)₂D₃ level, renin activity and blood pressure in both normal and hypertensive human subjects [68, 69].

Vitamin D has been recognized as a powerful modulator which can inhibit various inflammatory mediated processes such as atherosclerosis, myocardial infarction and blood clot formation. Vitamin D deficiency is reported to induce atherosclerosis [70] and enhance tissue plasminogen activator secretion in experimental animals [71]. It has been shown to reduce MMP-9 secretion [63].

Vitamin D through its VDR in heart muscle has been suggested to exert a direct role on the heart muscle and to regulate the cardiomyocyte cell cycle [72]. Vitamin D has been shown to suppress cardiac cell proliferation and to maintain structure and function of cardiac cells directly through anti-inflammatory, antifibrotic and antiapoptotic mechanisms [73, 74].

Link between Vitamin D and Cardiovascular – Evidence from Observational Studies

The NHANES in the United States, which involved >16,600 subjects, showed a strong and independent association between low vitamin D and angina, myocardial

infarction and stroke [75]. Marniemi et al. [76] also found that both low vitamin D intake and low serum levels of 1,25(OH)₂D predicted acute myocardial infarction and stroke after a 10-year follow-up in an elderly population-based survey. Using data from the (NHANES) 2001–2004 study population which included 2,609 hypertensive adults, a linear inverse association between 25(OH)D concentration and cardiovascular mortality (p = 0.010) has been suggested, a hazard ratio of 3.2 (95% CI 1.14–8.99) in the first quartiles (<17 ng/ml), compared with the highest 25(OH)D quartile (≥29 ng/ml) [77]. The association between low levels of vitamin D and hypertension has been studied and reported extensively. A cross-sectional study which involved 2,722 adults recruited from California has reported an increased prevalence of hypertension with serum levels of 25(OH)D <100 nmol/l, with an even higher prevalence (52%) when serum 25(OH)D falls <38 nmol/l [78].

Results from prospective studies showed mixed results. One study found a twofold increase in the incidence of myocardial infarction in vitamin D-deficient healthy men after a 10-year follow-up period, even after controlling for factors known to be associated with coronary artery disease [79]. However, another study did not find any significant difference in the prevalence of cardiovascular events between vitamin D deficiency and sufficiency after a 4.4-year follow-up of 813 elderly men who had osteoporotic fractures [80]. There is less evidence from paediatric studies of the association between vitamin D deficiency and cardiovascular risk factors. One recent systematic review which looked at the asso-

ciation between 25(OH)D and cardiometabolic risk factors did not find sufficient evidence to support this association [81]. Most of the reviewed cross-sectional studies found an inverse relationship between systolic blood pressure and vitamin D [82, 83]. Severe nutritional vitamin D deficiency has been reported as one of the aetiological factors in the development of dilated cardiomyopathy and significant improvement with subsequent vitamin D and calcium supplementation [84, 85]. Table 2 summarizes some of the recent studies that have been conducted in children.

Collectively, current evidence from observational studies supports the role of hypovitaminosis D in the development and/or progression of cardiovascular disease in the adult population. There is insufficient evidence available to conclude whether or not vitamin D status in childhood significantly alters cardiovascular risk in adulthood.

Link between Vitamin D and Cardiovascular – Evidence from Interventional Studies

There remains some uncertainty regarding the benefit of vitamin D supplementation. A single oral dose of 100,000 IU vitamin D₃ has been shown to increase the serum level of 25(OH)D in vitamin D-deficient patients with peripheral artery diseases, without any significant effect on endothelial function, arterial stiffness, coagulation and inflammation markers [86]. Another study involving 78 Scottish adults showed a significant effect of single high dose of 100,000 IU vitamin D₂ in improving endothelial function in patients with T2DM and low serum 25-hydroxyvitamin D levels during winter [87]. The Women's Health Initiative trial failed to find any difference on cardiovascular disease outcome over a 7-year follow-up period of 36,282 post-menopausal women treated with both 400 IU of vitamin D and 1 g calcium daily compared to placebo. However, Hsia et al. [88] and others [89] found an overall trend towards a favourable effect of taking vitamin D to reduce total cardiovascular mortality and cancer. A meta-analysis conducted to summarize the available randomized trials assessing the relationship between vitamin D and cardiovascular outcomes was unable to find any significant effect of vitamin D on total mortality from cardiovascular disease (relative risk (RR) 0.96; 95% CI 0.93–1.00; $p = 0.08$), myocardial infarction (RR 1.02; 95% CI 0.93–1.13; $p = 0.64$) or stroke (RR 1.05; 95% CI 0.88–1.25; $p = 0.59$). Additionally, there were no significant changes in the other cardiometabolic risk factors such as blood pressure, lipids and blood glucose [90].

Studies examining the effect of vitamin D supplementation on cardiovascular events in children are scarce. The first randomized controlled trial involved a 16-week administration of either 2,000 or 400 IU vitamin D₃ in 44 healthy African-American youths aged 14–18 years and found that the administration of vitamin D can counteract the progression of aortic stiffness and there was also a negative association between adiposity and vitamin D level in the treatment group [91]. One study of 14 post-menarcheal obese females, who had been treated for vitamin D deficiency, did not find an association between vitamin D level and blood pressure but reported a beneficial effect of vitamin D on glucose homeostasis. This study also indicated one possible adverse effect of vitamin D on specific ethnic groups as shown by a positive association between vitamin D and lipid profile and alanine transaminase in African-Americans [92].

In summary, current evidence from interventional studies does not clearly support the use of vitamin D supplementation in protecting against cardiovascular disease [93, 94]. Therefore, large clinical trials with robust follow-up are still needed. There also remains a need for assessment of the effect of childhood vitamin D status on cardiovascular disease in adulthood [85].

Immune Function and Its Links to Vitamin D Deficiency – Putative Mechanisms

An immunoregulatory role for vitamin D was suggested several decades ago when sunshine was shown to increase resistance to infections in experimental animals [95]. The effect of seasons and/or latitude on vitamin D status has been discussed extensively [96] and vitamin D and/or UV radiation has long been advocated as a cure for various illnesses and infections [97]. The evidence for vitamin D as a modulator of immune responses is reviewed below.

Physical Barrier and Innate Immunity

Innate immunity provides the first defence against external challenges. The first component of the innate immune system consists of a combination of physical and chemical barriers. Expression of VDR and 1 α -hydroxylase by epithelial cells in the respiratory passages, skin, gut and urogenital system suggests that vitamin D may be involved in preservation of barrier integrity and maintaining intracellular functions [98, 99]. Its role in maintaining barrier functions is also supported by the observation that

vitamin D upregulates genes which encode junctional proteins between epithelial cells, such as tight junctions (e.g. occludin), gap junctions (e.g. connexin 43) and adherens junctions (e.g. E-cadherin) [100–102]. However, more research is needed to fully understand the role of vitamin D in this area.

The second level of innate immunity is production of antimicrobial peptides (AMPs) such as α -defensins, β -defensins and cathelicidin. Vitamin D stimulates human AMP expression in different epithelial tissues such as bronchial [103], urogenital [104], and skin [105] and also in myeloid cells [106]. Aside from their direct microbicidal role, AMPs modulate many other immune processes, including mast cell degranulation, stimulation of cytokine and chemokine production, cell differentiation, vascular permeability, wound healing and the process of antigen presentation [107–110].

Finally, vitamin D has been suggested to play a vital role at the third level of defence which is the specific immune response, mainly through its effect on the recruitment of phagocytic cells, promotion of healing and initiation of inflammatory responses [111, 112] as discussed below.

Antigen Presentation and Adaptive Immunity

Vitamin D has been suggested to differentially affect dendritic cell (DC) subsets to enable more tolerogenic responses, and thereby promote the development of regulatory T cells (Tregs) [113, 114]. While leaving plasmacytoid DCs unaffected, $1,25(\text{OH})_2\text{D}_3$ can block myeloid DC maturation, causing reduced expression of MHC class II, and co-stimulatory molecules [115]. Both macrophages and DCs express increasing levels of 1α -hydroxylase during maturation into antigen-presenting cells (APCs). In DCs, the outcome of this is that both vitamin D and its metabolite (25-OHD_3) are able to suppress the differentiation and function of these cells. When the APCs mature, their ability to produce active vitamin D is increased but they express less VDRs. The vitamin D from mature APCs has been suggested to act in a paracrine fashion on neighbouring immature APCs to trigger more antigen presentation, whilst the ability of mature APCs to decrease VDR expression prevents overstimulation [116].

T cells also express the VDR and appears to be a direct target of vitamin D [117]. T cells were traditionally divided into T-helper (Th) cells ($\text{CD}4^+$) – responsible for regulating T- and B-cell responses and cytotoxic T cells ($\text{CD}8^+$) – capable of killing target cells such as virally infected cells or tumour cells. More recently, additional subsets have been identified including Tregs and several functionally distinct

Th cell subsets including Th1, Th2 and Th17 cells. Tregs are crucial for the maintenance of immunological self-tolerance, whilst the Th cell subsets secrete different patterns of cytokines resulting in distinct immune responses. An imbalance in the Th1/Th2 immune response has been implicated in the pathogenesis autoimmune disorders [118]. Vitamin D suppresses effector T-cell function, influences Th subsets, and stimulates Tregs [119, 120]. Th cells have been found to be a main target of vitamin D [121] which inhibits production of Th1-related cytokines such as $\text{TNF-}\alpha$ and $\text{IFN-}\gamma$, whilst promoting Th2 cytokines such as interleukin (IL)-4 and IL-5 [122, 123]. However, other studies could not confirm these findings [124]. Th17 cells are a recently discovered subset of Th cells, which are thought to be important in the pathogenesis of autoimmune diseases such as multiple sclerosis and rheumatoid arthritis. Vitamin D also downregulates Th17-secreted cytokines such as IL-17 and IL-21 [124, 125]. Therefore, vitamin D deficiency may promote autoimmune diseases through both direct and indirect roles in regulating Th1/Th17 and Treg function in addition to skewing cytokine production towards a Th2 phenotype [118].

Finally, a number of reports indicate that vitamin D can inhibit the generation of memory B cells from naive B cells, inhibit B-cell proliferation, induce apoptosis and suppress immunoglobulin secretion and maintain the development and function of natural killer cells [126, 127]. Figure 4 shows the potential role of vitamin D in the different components of the immune system.

Link between Vitamin D and Immune Function – Evidence from Observational Studies

Clinical associations between the prevalence of immune-related illness and vitamin D deficiency have been reported widely in the literature. Results from most observational studies report an inverse relationship between vitamin D status and the risk of acute respiratory tract infection, tuberculosis and pneumonia in both paediatric and adult populations [128–131]. In addition, there is a strong association between vitamin D and the prevalence of oral [132, 133], gastrointestinal [134], urinary tract [104] and ocular infections [135]. The impact of vitamin D on several dermatological conditions such as wound healing, psoriasis, atopic dermatitis and acne has been also has been reported [136–140]. Finally, several autoimmune diseases such as inflammatory bowel diseases, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes mellitus and rheumatoid arthritis have been re-

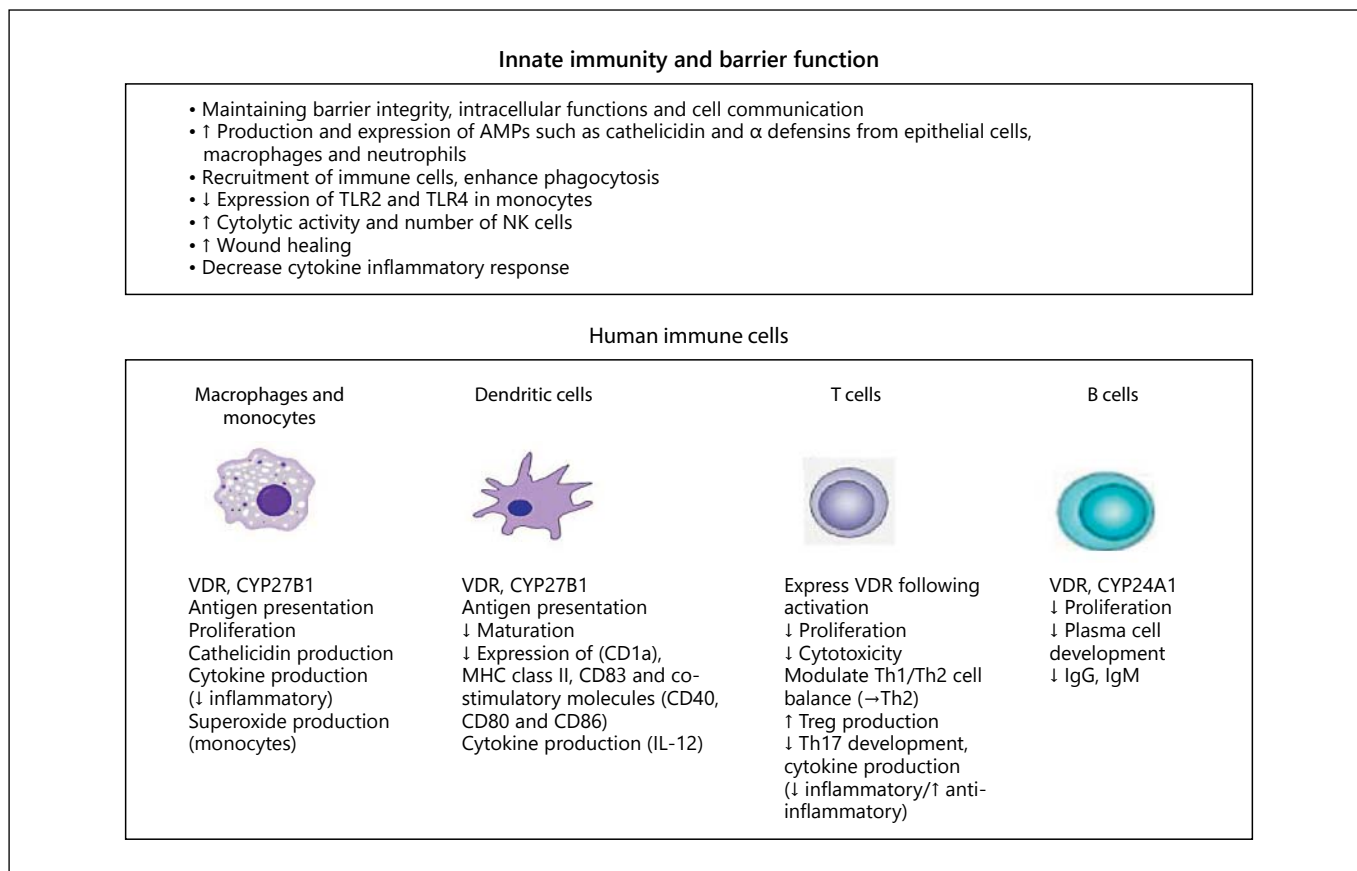


Fig. 4. Modulation of different components of the immune system. Potential action of systemic or locally synthesized vitamin D on different components of immune system and immune-cell types. NK cells = Natural killer cells; CYP27B1 (25-hydroxyvitamin D₃-1α-hydroxylase) = cytochrome P450 enzyme that catalyzes the

conversion of 25-hydroxyvitamin D₃ (25(OH)D) to 1α,25-dihydroxyvitamin D₃ (1,25(OH)₂D); MHC class II = major histocompatibility complex *class II* molecules; Treg = forkhead box protein 3 (FOXP3)⁺ Treg cells; IgG = immunoglobulin G; IgM = immunoglobulin M.

viewed. Again, significant associations between a low vitamin D and the prevalence autoimmune disorders were reported [141–144].

Link between Vitamin D and Immune Function – Evidence from Interventional Studies

Despite these strong observational and theoretical links between vitamin D and immune system disorders, interventional studies looking at the therapeutic effect of vitamin D supplementation show conflicting results. In a randomized double-blind study, 4,000 IU of vitamin D₃ daily for 1 year in patients with an immune disorder and frequent attacks of acute respiratory tract infection showed a 23% decrease in the number of attacks and 60% reduction of antibiotic use [145]. However, in another

trial using healthy adults, administration of vitamin D did not affect the severity or prevalence of acute respiratory tract infection [146, 147]. In one study, high-dose vitamin D supplementation was reported to accelerate clinical and radiological improvement in pulmonary tuberculosis patients [148]. However, others reported no effect [149]. A recent systematic review of randomized, placebo double-blind trials assessing the beneficial of vitamin D administration in patients with multiple sclerosis was unable to reach a verdict with no significant effect seen in 4 out of 5 available trials [150]. Although there are limited studies looking at the effect of vitamin D intervention in children, most publications show a beneficial effect of vitamin D supplementation on reducing acute respiratory tract infections [151, 152]. A randomized controlled trial looking at the effect of 100,000 IU of vitamin D supplementation in South Asian children with pneumonia

showed a reduced number of repeat attacks in the vitamin D group (58%; RR 0.78; 95% CI 0.64–0.94; $p = 0.01$) [153]. However, supplementation with the same dose once every 3 months for a period of 18 months did not reduce the prevalence of pneumonia in high-risk South Asian infants [154]. Table 3 summarizes some of recent clinical studies which have been conducted in children.

In summary, scientific studies support an important role for vitamin D in many aspects of the immune response. Clinical evidence from observational studies shows a strong correlation between vitamin D deficiency and development of various immune and infectious diseases.

Conclusion

The numbers of reports that highlight possible therapeutic actions of vitamin D have increased over the last decade. Initial observational studies have indicated that vitamin D deficiency may be associated with impairment in glucose homeostasis, increase cardiovascular risk and immune dysfunction. However, interventional studies have been inconsistent and there is a need for more detailed and larger-scale studies to clarify the therapeutic benefit of vitamin D in these important clinical areas.

References

- Holick MF: Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006;116:2062–2072.
- Holick MF: Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.
- Henry HL: Regulation of vitamin D metabolism. *Best Pract Res Clin Endocrinol Metab* 2011;25:531–541.
- Nagpal S, Na SQ, Rathnachalam R: Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev* 2005;26:662–687.
- Institute of Medicine (IOM): Dietary Reference Intakes for Calcium and Vitamin D. Washington, The National Academies Press, 2011.
- Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM: Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:1911–1930.
- Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA: The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53–58.
- Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M: Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics* 2008;122:398–417.
- Rosen CJ, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Manson JE, Mayne ST, Ross AC, Shapses SA, Taylor CL: IOM committee members respond to endocrine society vitamin D guideline. *J Clin Endocrinol Metab* 2012;97:1146–1152.
- Schneider LE, Schedl HP, McCain T, Haussler MR: Experimental diabetes reduces circulating 1,25-dihydroxyvitamin D in rat. *Science* 1977;196:1452–1454.
- Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E: Serum 25-hydroxyvitamin D₃ levels decreased in impaired glucose-tolerance and diabetes-mellitus. *Diabetes Res Clin Pract* 1995;27:181–188.
- Behall KM, Scholfield DJ, Hallfrisch JG, Kelsay JL, Reiser S: Seasonal variation in plasma glucose and hormone levels in adult men and women. *Am J Clin Nutr* 1984;40:1352–1356.
- Bland R, Markovic D, Hills CE, Hughes SV, Chan SLF, Squires PE, Hewison M: Expression of 25-hydroxyvitamin D₃-1 α -hydroxylase in pancreatic islets. *J Steroid Biochem Mol Biol* 2004;89–90:121–125.
- Johnson JA, Grande JP, Roche PC, Kumar R: Immunohistochemical localization of the 1,25(OH)₂D₃ receptor and calbindin D-28k in human and rat pancreas. *Am J Physiol* 1994;267:E356–E360.
- Maestro B, Davila N, Carranza MC, Calle C: Identification of a vitamin D response element in the human insulin receptor gene promoter. *J Steroid Biochem Mol Biol* 2003;84:223–230.
- Zeitz U, Weber K, Soegiarto DW, Wolf E, Balling R, Erben RG: Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. *FASEB J* 2003;17:509–511.
- Maestro B, Molero S, Bajo S, Davila N, Calle C: Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D₃. *Cell Biochem Funct* 2002;20:227–232.
- Lee S, Clark SA, Gill RK, Christakos S: 1,25-Dihydroxyvitamin-D₃ and pancreatic β -cell function: vitamin-D receptors, gene expression, and insulin secretion. *Endocrinology* 1994;134:1602–1610.
- Riachy R, Vandewalle B, Conte JK, Moerman E, Sacchetti P, Lukowiak B, Gmyr V, Boucke-nooghe T, Dubois M, Pattou F: 1,25-Dihydroxyvitamin D₃ protects RINm5F and human islet cells against cytokine-induced apoptosis: implication of the antiapoptotic protein A20. *Endocrinology* 2002;143:4809–4819.
- Riachy R, Vandewalle B, Moerman E, Belaich S, Lukowiak B, Gmyr V, Muharram G, Conte J, Pattou F: 1,25-Dihydroxyvitamin D₃ protects human pancreatic islets against cytokine-induced apoptosis via down-regulation of the Fas receptor. *Apoptosis* 2006;11:151–159.
- Kawashima H, Castro A: Effect of 1 α -hydroxyvitamin D₃ on the glucose and calcium-metabolism in genetic obese mice. *Res Commun Chem Pathol Pharmacol* 1981;33:155–161.
- Zhou QG, Hou FF, Guo ZJ, Liang M, Wang GB, Zhang X: 1,25-Dihydroxyvitamin D improved the free fatty-acid-induced insulin resistance in cultured C2C12 cells. *Diabetes Metab Res Rev* 2008;24:459–464.
- Maestro B, Campion J, Davila N, Calle C: Stimulation by 1,25-dihydroxyvitamin D₃ of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. *Endocr J* 2000;47:383–391.
- McCarty MF: Vitamin D, parathyroid hormone, and insulin sensitivity. *Am J Clin Nutr* 2004;80:1451–1452.
- Sadeghi K, Wessner B, Laggner U, Ploder M, Tamandl D, Friedl J, Zugel U, Steinmeyer A, Pollak A, Roth E, Boltz-Nitulescu G, Spittler A: Vitamin D₃ down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. *Eur J Immunol* 2006;36:361–370.
- Baker RG, Hayden MS, Ghosh S: NF- κ B, inflammation, and metabolic disease. *Cell Metab* 2011;13:11–22.
- Teegarden D, Donkin SS: Vitamin D: Emerging new roles in insulin sensitivity. *Nutr Res Rev* 2009;22:82–92.
- Orwoll E, Riddle M, Prince M: Effects of vitamin D on insulin and glucagon secretion in non-insulin-dependent diabetes-mellitus. *Am J Clin Nutr* 1994;59:1083–1087.
- Boucher BJ, Mannan N, Noonan K, Hales CN, Evans SJ: Glucose intolerance and impairment of insulin secretion in relation to vitamin-D deficiency in East London Asians. *Diabetologia* 1995;38:1239–1245.

- 30 Baynes KCR, Boucher BJ, Feskens EJ, Kromhout D: Vitamin D, glucose tolerance and insulinaemia in elderly men. *Diabetologia* 1997; 40:344–347.
- 31 Chiu KC, Chu A, Go VL, Saad MF: Hypovitaminosis D is associated with insulin resistance and β -cell dysfunction. *Am J Clin Nutr* 2004; 79:820–825.
- 32 Kamycheva E, Jorde R, Figenschau Y, Haug E: Insulin sensitivity in subjects with secondary hyperparathyroidism and the effect of a low serum 25-hydroxyvitamin D level on insulin sensitivity. *J Endocrinol Invest* 2007;30:126–132.
- 33 Scragg R, Sowers M, Bell C: Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004;27:2813–2818.
- 34 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.
- 35 Song Y, Wang L, Pittas AG, Del Gobbo LC, Zhang C, Manson JE, Hu FB: Blood 25-hydroxyvitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care* 2013;36:1422–1428.
- 36 Reinehr T, de Sousa G, Alexy U, Kersting M, Andler W: Vitamin D status and parathyroid hormone in obese children before and after weight loss. *Eur J Endocrinol* 2007;157:225–232.
- 37 Smotkin-Tangorra M, Purushothaman R, Gupta A, Nejadi G, Anhalt H, Ten S: Prevalence of vitamin D insufficiency in obese children and adolescents. *J Pediatr Endocrinol Metab* 2007;20:817–823.
- 38 Poomthavorn P, Saowan S, Mahachoklertwattana P, Chailurkit L, Khlairit P: Vitamin D status and glucose homeostasis in obese children and adolescents living in the tropics. *Int J Obes* 2012;36:491–495.
- 39 Olson ML, Maalouf NM, Oden JD, White PC, Hutchison MR: Vitamin D deficiency in obese children and its relationship to glucose homeostasis. *J Clin Endocrinol Metab* 2012; 97:279–285.
- 40 Roth CL, Elfers C, Kratz M, Hoofnagle AN: Vitamin D deficiency in obese children and its relationship to insulin resistance and adipokines. *J Obes* 2011;2011:495101.
- 41 Nsiah-Kumi PA, Erickson JM, Beals JL, Ogle EA, Whiting M, Brushbreaker C, Borgeson CD, Qiu F, Yu F, Larsen JL: Vitamin D insufficiency is associated with diabetes risk in native American children. *Clin Pediatr (Phila)* 2012;51:146–153.
- 42 Gedik O, Akalin S: Effects of vitamin-D deficiency and repletion on insulin and glucagon secretion in man. *Diabetologia* 1986;29:142–145.
- 43 Inomata S, Kadowaki S, Yamatani T, Fukase M, Fujita T: Effect of $1\alpha(\text{OH})$ -vitamin D₃ on insulin-secretion in diabetes mellitus. *Bone Miner* 1986;1:187–192.
- 44 Ljunghall S, Lind L, Lithell H, Skarfors E, Selinus I, Sorensen OH, Wide L: Treatment with 1α -hydroxycholecalciferol in middle-aged men with impaired glucose-tolerance – a prospective randomized double-blind-study. *Acta Med Scand* 1987;222:361–367.
- 45 Nyomba BL, Auwerx J, Bormans V, Peeters TL, Pelemans W, Reynaert J, Bouillon R, Vantrappen G, De Moor P: Pancreatic-secretion in man with subclinical vitamin-D deficiency. *Diabetologia* 1986;29:34–38.
- 46 Zofkova I, Stolba P: Effect of calcitriol and trifluoperazine on glucose stimulated β -cell function in healthy humans. *Exp Clin Endocrinol* 1990;96:185–191.
- 47 Grimnes G, Figenschau Y, Almas B, Jorde R: Vitamin D, insulin secretion, sensitivity, and lipids results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique. *Diabetes* 2011;60: 2748–2757.
- 48 Tai K, Need AG, Horowitz M, Chapman IM: Glucose tolerance and vitamin D: effects of treating vitamin D deficiency. *Nutrition* 2008; 24:950–956.
- 49 Von Hurst PR, Stonehouse W, Coad J: Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomised, placebo-controlled trial. *Br J Nutr* 2010;103:549–555.
- 50 Mitri J, Dawson-Hughes B, Hu FB, Pittas AG: Effects of vitamin D and calcium supplementation on pancreatic β -cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr* 2011;94:486–494.
- 51 Belenchia AM, Tosh AK, Hillman LS, Peterson CA: Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. *Am J Clin Nutr* 2013;97:774–781.
- 52 Rose G: Cold weather and ischaemic heart disease. *Br J Prev Soc Med* 1966;20:97–100.
- 53 Fleck A: Latitude and ischemic heart disease. *Lancet* 1989;1:613.
- 54 Martins D, Wolf M, Pan D, Zadsir 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.
- 55 Awad AB, Alappat L, Valerio M: Vitamin D and metabolic syndrome risk factors: evidence and mechanisms. *Crit Rev Food Sci Nutr* 2012;52:103–112.
- 56 Anderson JL, Vanwoerkom RC, Horne BD, Bair TL, May HT, Lappe DL, Muhlestein JB: Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: dependent or independent risk factors? *Am Heart J* 2011;162:331–339.
- 57 Li YC, Kong J, Wei MJ, Chen ZF, Liu SQ, Cao LP: $1,25$ -Dihydroxyvitamin D₃ is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002;110:229–238.
- 58 O’Connell TD, Berry JE, Jarvis AK, Somerman MJ, Simpson RU: $1,25$ -Dihydroxyvitamin D₃ regulation of cardiac myocyte proliferation and hypertrophy. *Am J Physiol* 1997; 272:H1751–H1758.
- 59 Carthy EP, Yamashita W, Hsu A, Ooi BS: $1,25$ -Dihydroxyvitamin D₃ and rat vascular smooth muscle cell growth. *Hypertension* 1989;13:954–959.
- 60 Borges ACR, Feres T, Vianna LM, Paiva TB: Effect of cholecalciferol treatment on the relaxant responses of spontaneously hypertensive rat arteries to acetylcholine. *Hypertension* 1999;34:897–901.
- 61 Ohsawa M, Koyama T, Yamamoto K, Hiro-sawa S, Kamei S, Kamiyama R: $1\alpha,25$ -Dihydroxyvitamin D₃ and its potent synthetic analogs downregulate tissue factor and upregulate thrombomodulin expression in monocytic cells, counteracting the effects of tumor necrosis factor and oxidized LDL. *Circulation* 2000;102:2867–2872.
- 62 Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W: Independent association of low serum 25-hydroxyvitamin D and $1,25$ -dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008;168: 1340–1349.
- 63 Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, Aganna E, Price CP, Boucher BJ: Circulating MMP-9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? *QJM* 2002;95:787–796.
- 64 Alvarez JA, Ashraf A: Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. *Int J Endocrinol* 2010; 2010:351385.
- 65 Andersson P, Rydberg E, Willenheimer R: Primary hyperparathyroidism and heart disease – a review. *Eur Heart J* 2004;25:1776–1787.
- 66 Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE: Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995;47:186–192.
- 67 Xiang W, Kong J, Chen SC, Cao LP, Qiao GL, Zheng W, Liu WH, Li XM, Gardner DG, Li YC: Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. *Am J Physiol Endocrinol Metab* 2005;288:E125–E132.
- 68 Resnick LM, Muller FB, Laragh JH: Calcium-regulating hormones in essential hypertension – relation to plasma-renin activity and sodium-metabolism. *Ann Intern Med* 1986; 105:649–654.

- 69 Lind L, Hanni A, Lithell H, Hvarfner A, Sorensen OH, Ljunghall S: Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. *Am J Hypertens* 1995;8:894–901.
- 70 Weng S, Sprague JE, Oh J, Riek AE, Chin K, Garcia M, Bernal-Mizrachi C: Vitamin D deficiency induces high blood pressure and accelerates atherosclerosis in mice. *PLoS One* 2013;8:e54625.
- 71 Puri S, Bansal DD, Uskokovic MR, MacGregor RR: Induction of tissue plasminogen activator secretion from rat heart microvascular cells by $1,25(\text{OH})_2\text{D}_3$. *Am J Physiol Endocrinol Metab* 2000;278:E293–E301.
- 72 O'Connell TD, Berry JE, Jarvis AK, Somerman MJ, Simpson RU: $1,25$ -Dihydroxyvitamin D_3 regulation of cardiac myocyte proliferation and hypertrophy. *Am J Physiol* 1997;272:H1751–H1758.
- 73 Nibbelink KA, Tishkoff DX, Hershey SD, Rahman A, Simpson RU: $1,25(\text{OH})_2$ -vitamin D_3 actions on cell proliferation, size, gene expression, and receptor localization, in the HL-1 cardiac myocyte. *J Steroid Biochem Mol Biol* 2007;103:533–537.
- 74 Bae S, Singh SS, Yu H, Lee JY, Cho BR, Kang PM: Vitamin D signaling pathway plays an important role in the development of heart failure after myocardial infarction. *J Appl Physiol* 2013;114:979–987.
- 75 Kendrick J, Targher G, Smits G, Chonchol M: 25 -Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. *Atherosclerosis* 2009;205:255–260.
- 76 Marniemi J, Alanen E, Impivaara O, Seppanen R, Hakala P, Rajala T, Ronnema T: Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. *Nutr Metab Cardiovasc Dis* 2005;15:188–197.
- 77 Zhao G, Ford ES, Li C, Croft JB: Serum 25 -hydroxyvitamin D levels and all-cause and cardiovascular disease mortality among US adults with hypertension: the NHANES linked mortality study. *J Hypertens* 2012;30:284–289.
- 78 Bhandari SK, Pashayan S, Liu ILA, Rasgon SA, Kujubu DA, Tom TY, Sim JJ: 25 -hydroxyvitamin D levels and hypertension rates. *J Clin Hypertens (Greenwich)* 2011;13:170–177.
- 79 Giovannucci E, Liu Y, Hollis BW, Rimm EB: 25 -Hydroxyvitamin D and risk of myocardial infarction in men – a prospective study. *Arch Intern Med* 2008;168:1174–1180.
- 80 Messenger W, Nielson CM, Li H, Beer T, Barrett-Connor E, Stone K, Shannon J: Serum and dietary vitamin D and cardiovascular disease risk in elderly men: a prospective cohort study. *Nutr Metab Cardiovasc Dis* 2012;22:856–863.
- 81 Dolinsky DH, Armstrong S, Mangarelli C, Kemper AR: The association between vitamin D and cardiometabolic risk factors in children: a systematic review. *Clin Pediatr (Phila)* 2013;52:210–223.
- 82 Reis JP, von Muehlen D, Miller ER III, Michos ED, Appel LJ: Vitamin D status and cardiometabolic risk factors in the United States adolescent population. *Pediatrics* 2009;124:E371–E379.
- 83 Pacifico L, Anania C, Osborn JF, Ferraro F, Bonci E, Olivero E, Chiesa C: Low $25(\text{OH})\text{D}_3$ levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents. *Eur J Endocrinol* 2011;165:603–611.
- 84 Kosecik M, Ertas T: Dilated cardiomyopathy due to nutritional vitamin D deficiency rickets. *Pediatr Int* 2007;49:397–399.
- 85 Olgun H, Ceviz N, Ozkan B: A case of dilated cardiomyopathy due to nutritional vitamin D deficiency rickets. *Turk J Pediatr* 2003;45:152–154.
- 86 Stricker H, Bianda FT, Guidicelli-Nicolosi S, Limoni C, Colucci G: Effect of a single, oral, high-dose vitamin D supplementation on endothelial function in patients with peripheral arterial disease: a randomised controlled pilot study. *Eur J Vasc Endovasc Surg* 2012;44:307–312.
- 87 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.
- 88 Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M: Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 2007;115:846–854.
- 89 LaCroix AZ, Kotchen J, Anderson G, Brzyski R, Cauley JA, Cummings SR, Gass M, Johnson KC, Ko M, Larson J, Manson JE, Stefanick ML, Wactawski-Wende J: Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. *J Gerontol A Biol Sci Med Sci* 2009;64:559–567.
- 90 Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Hazem A, Erwin PJ, Hensrud DD, Murad MH, Montori VM: Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96:1931–1942.
- 91 Dong Y, Stallmann-Jorgensen IS, Pollock NK, Harris RA, Keeton D, Huang Y, Li K, Bassali R, Guo D-H, Thomas J, Pierce GL, White J, Holick MF, Zhu H: A 16-week randomized clinical trial of 2,000 international units daily vitamin D_3 supplementation in black youth: 25 -hydroxyvitamin D, adiposity, and arterial stiffness. *J Clin Endocrinol Metab* 2010;95:4584–4591.
- 92 Ashraf AP, Alvarez JA, Gower BA, Saenz KH, McCormick KL: Associations of serum 25 -hydroxyvitamin D and components of the metabolic syndrome in obese adolescent females. *Obesity* 2011;19:2214–2221.
- 93 Souberbielle J-C, Body J-J, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, Bischoff-Ferrari HA, Cavalier E, Ebeling PR, Fardellone P, Gandini S, Gruson D, Guerin AP, Heickendorff L, Hollis BW, Ish-Shalom S, Jean G, von Landenberg P, Largura A, Olsson T, Pierrot-Desseilligny C, Pilz S, Tincani A, Valcour A, Zittermann A: Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. *Autoimmun Rev* 2010;9:709–715.
- 94 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.
- 95 Ross JR, Robertson EC, Tisdall FF: Effect of sunshine through window glass and fresh air on resistance to infection – experiments on animals. *Am J Dis Child* 1933;45:81–95.
- 96 Holick MF: Environmental factors that influence the cutaneous production of vitamin D. *Am J Clin Nutr* 1995;61:638S–645S.
- 97 Chan TY: Vitamin D deficiency and susceptibility to tuberculosis. *Calcif Tissue Int* 2000;66:476–478.
- 98 Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, Bissonnette M, Li YC: Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am J Physiol Gastrointest Liver Physiol* 2008;294:G208–G216.
- 99 Yin Z, Pintea V, Lin Y, Hammock BD, Watsky MA: Vitamin D enhances corneal epithelial barrier function. *Invest Ophthalmol Vis Sci* 2011;52:7359–7364.
- 100 Clairmont A, Tessmann D, Stock A, Nicolai S, Stahl W, Sies H: Induction of gap junctional intercellular communication by vitamin D in human skin fibroblasts is dependent on the nuclear vitamin D receptor. *Carcinogenesis* 1996;17:1389–1391.
- 101 Gniadecki R, Gajkowska B, Hansen M: $1,25$ -Dihydroxyvitamin D_3 stimulates the assembly of adherens junctions in keratinocytes: involvement of protein kinase C. *Endocrinology* 1997;138:2241–2248.
- 102 Palmer HG, Gonzalez-Sancho JM, Espada J, Berciano MT, Puig I, Baulida J, Quintanilla M, Cano A, de Herreros AG, Lafarga M, Munoz A: Vitamin D_3 promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of β -catenin signaling. *J Cell Biol* 2001;154:369–387.
- 103 Yim S, Dhawan P, Ragnauth C, Christakos S, Diamond G: Induction of cathelicidin in normal and CF bronchial epithelial cells by $1,25$ -dihydroxyvitamin D_3 . *J Cyst Fibros* 2007;6:403–410.
- 104 Hertting O, Holm A, Luthje P, Brauner H, Dyrdak R, Jonasson AF, Wiklund P, Chromek M, Brauner A: Vitamin D induction of the human antimicrobial peptide cathelicidin in the urinary bladder. *PLoS One* 2010;5:e15580.

- 105 Weber G, Heilborn JD, Jimenez CIC, Hammarsojo A, Torma H, Stahle M: Vitamin D induces the antimicrobial protein hCAP18 in human skin. *J Invest Dermatol* 2005;124:1080–1082.
- 106 Gombart AF, Borregaard N, Koeffler HP: Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D₃. *FASEB J* 2005;19:1067–1077.
- 107 Aung G, Niyonsaba F, Ushio H, Kajiwara N, Saito H, Ikeda S, Ogawa H, Okumura K: Catestatin, a neuroendocrine antimicrobial peptide, induces human mast cell migration, degranulation and production of cytokines and chemokines. *Immunology* 2011;132:527–539.
- 108 Chertov O, Michiel DF, Xu LL, Wang JM, Tani K, Murphy WJ, Longo DL, Taub DD, Oppenheim JJ: Identification of defensin-1, defensin-2, and CAP37/azurocidin as T-cell chemoattractant proteins released from interleukin-8-stimulated neutrophils. *J Biol Chem* 1996;271:2935–2940.
- 109 Zughaier SM, Shafer WM, Stephens DS: Antimicrobial peptides and endotoxin inhibit cytokine and nitric oxide release but amplify respiratory burst response in human and murine macrophages. *Cell Microbiol* 2005;7:1251–1262.
- 110 Lai Y, Li D, Li C, Muehleisen B, Radek KA, Park HJ, Jiang Z, Li Z, Lei H, Quan Y, Zhang T, Wu Y, Kotol P, Morizane S, Hata TR, Iwatsuki K, Tang C, Gallo RL: The antimicrobial protein REG3A regulates keratinocyte proliferation and differentiation after skin injury. *Immunity* 2012;37:74–84.
- 111 Zhang J-Z, Maruyama K, Ono I, Kaneko F: Production and secretion of platelet-derived growth factor AB by cultured human keratinocytes: regulatory effects of phorbol 12-myristate 13-acetate, tretinoin, 1,25-dihydroxyvitamin D₃, and several cytokines. *J Dermatol (Tokyo)* 1995;22:305–309.
- 112 Chandra G, Selvaraj P, Jawahar MS, Banurekha VV, Narayanan PR: Effect of vitamin D₃ on phagocytic potential of macrophages with live mycobacterium tuberculosis and lymphoproliferative response in pulmonary tuberculosis. *J Clin Immunol* 2004;24:249–257.
- 113 Adorini L, Penna G: Induction of tolerogenic dendritic cells by vitamin D receptor agonists. *Handb Exp Pharmacol* 2009;188:251–273.
- 114 Ferreira GB, van Etten E, Verstuyf A, Waer M, Overbergh L, Gysemans C, Mathieu C: 1,25-Dihydroxyvitamin D₃ alters murine dendritic cell behaviour in vitro and in vivo. *Diabetes Metab Res Rev* 2011;27:933–941.
- 115 Penna G, Adorini L: 1 α ,25-Dihydroxyvitamin D₃ inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T-cell activation. *J Immunol* 2000;164:2405–2411.
- 116 Hewison M, Zehnder D, Chakraverty R, Adams JS: Vitamin D and barrier function: a novel role for extrarenal 1 α -hydroxylase. *Mol Cell Endocrinol* 2004;215:31–38.
- 117 Von Essen MR, Kongsbak M, Schjerling P, Olgaard K, Odum N, Geisler C: Vitamin D controls T-cell antigen receptor signaling and activation of human T cells. *Nat Immunol* 2010;11:344–349.
- 118 Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HFJ, O'Garra A: 1 α ,25-Dihydroxyvitamin D₃ has a direct effect on naive CD4⁺ T cells to enhance the development of Th2 cells. *J Immunol* 2001;167:4974–4980.
- 119 Baeke F, Korf H, Overbergh L, Verstuyf A, Thorrez L, Van Lommel L, Waer M, Schuit F, Gysemans C, Mathieu C: The vitamin D analog, TX527, promotes a human CD4⁺CD25^{high}CD27^{low} regulatory T-cell profile and induces a migratory signature specific for homing to sites of inflammation. *J Immunol* 2011;186:132–142.
- 120 Prietl B, Pilz S, Wolf M, Tomaschitz A, Obermayer-Pietsch B, Graninger W, Pieber TR: Vitamin D supplementation and regulatory T cells in apparently healthy subjects: vitamin D treatment for autoimmune diseases? *Isr Med Assoc J* 2010;12:136–139.
- 121 Mosmann TR, Coffman RL: Th1 and Th2 cells different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 1989;7:145–173.
- 122 Mahon BD, Gordon SA, Cruz J, Cosman F, Cantorna MT: Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. *J Neuroimmunol* 2003;134:128–132.
- 123 Staeva-Vieira TP, Freedman LP: 1,25-Dihydroxyvitamin D₃ inhibits IFN- γ and IL-4 levels during in vitro polarization of primary murine CD4⁺ T cells. *J Immunol* 2002;168:1181–1189.
- 124 Higashimoto Y, Ohata M, Nishio K, Iwamoto Y, Fujimoto H, Uetani K, Suruda T, Nakamura Y, Funasako M, Saijo N: 1 α ,25-Dihydroxyvitamin D₃ and all-*trans*-retinoic acid inhibit the growth of a lung cancer cell line. *Anticancer Res* 1996;16:2653–2659.
- 125 Chang SH, Chung Y, Dong C: Vitamin D suppresses Th17 cytokine production by inducing C/EBP homologous protein (CHOP) expression. *J Biol Chem* 2010;285:38751–38755.
- 126 Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE: Modulatory effects of 1,25-dihydroxyvitamin D₃ on human B cell differentiation. *J Immunol* 2007;179:1634–1647.
- 127 Cantorna MT, Zhao J, Yang L: Symposium 3: Vitamin D and immune function: from pregnancy to adolescence vitamin D, invariant natural killer T cells and experimental autoimmune disease. *Proc Nutr Soc* 2012;71:62–66.
- 128 Camargo CA Jr, Ingham T, Wickens K, Thadhani R, Silvers KM, Epton MJ, Town GI, Pattermore PK, Espinola JA, Crane J: Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics* 2011;127:E180–E187.
- 129 Muhe L, Lulseged S, Mason KE, Simoes EAF: Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. *Lancet* 1997;349:1801–1804.
- 130 Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamaki H, Ylikomi T: An association of serum vitamin D concentrations <40 nmol/l with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr* 2007;86:714–717.
- 131 Gibney KB, MacGregor L, Leder K, Torresi J, Marshall C, Ebeling PR, Biggs BA: Vitamin D deficiency is associated with tuberculosis and latent tuberculosis infection in immigrants from sub-Saharan Africa. *Clin Infect Dis* 2008;46:443–446.
- 132 Ulitsky A, Ananthakrishnan AN, Naik A, Skaros S, Zadornova Y, Binion DG, Issa M: Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. *J Parenter Enteral Nutr* 2011;35:308–316.
- 133 McDermott AM: The role of antimicrobial peptides at the ocular surface. *Ophthalmic Res* 2009;41:60–75.
- 134 Carretero M, Escamez MJ, Garcia M, Duarte B, Holguin A, Retamosa L, Jorcano JL, del Rio M, Larcher F: In vitro and in vivo wound healing-promoting activities of human cathelicidin LL-37. *J Invest Dermatol* 2008;128:223–236.
- 135 Di Nardo A, Yamasaki K, Dorschner RA, Lai Y, Gallo RL: Mast cell cathelicidin antimicrobial peptide prevents invasive group A streptococcus infection of the skin. *J Immunol* 2008;180:7565–7573.
- 136 Kaur I, Saraswat A, Kumar B: Comparison of calcipotriol and coal tar in conjunction with sun exposure in chronic plaque psoriasis: a pilot study. *J Dermatol* 2001;28:448–450.
- 137 Howell MD, Jones JF, Kisich KO, Streib JE, Gallo RL, Leung DYM: Selective killing of vaccinia virus by IL-37: vimplications for eczema vaccinatum. *J Immunol* 2004;172:1763–1767.
- 138 Asgari MM, Tang J, Warton ME, Chren M-M, Quesenberry CP Jr, Bikle D, Horst RL, Orentreich N, Vogelmann JH, Friedman GD: Association of prediagnostic serum vitamin D levels with the development of basal cell carcinoma. *J Invest Dermatol* 2010;130:1438–1443.
- 139 Cantorna MT, Mahon BD: Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *Exp Biol Med* 2004;229:1136–1142.
- 140 Cutolo M, Pizzorni C, Sulli A: Vitamin D endocrine system involvement in autoimmune rheumatic diseases. *Autoimmun Rev* 2011;11:84–87.
- 141 Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, Ascherio A: Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004;62:60–65.

- 142 Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, Gilkeson GS: Vitamin D deficiency in systemic lupus erythematosus. *Autoimmun Rev* 2006;5:114–117.
- 143 Stene LC, Jøner G: Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. *Am J Clin Nutr* 2003;78:1128–1134.
- 144 Jahnsen J, Falch JA, Mowinckel P, Aadland E: Vitamin D status, parathyroid hormone and bone mineral density in patients with inflammatory bowel disease. *Scand J Gastroenterol* 2002;37:192–199.
- 145 Bergman P, Norlin A-C, Hansen S, Rekha RS, Agerberth B, Bjorkhem-Bergman L, Ekstrom L, Lindh JD, Andersson J: Vitamin D₃ supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study. *BMJ open* 2012;2:e001663.
- 146 Murdoch DR, Slow S, Chambers ST, Jennings LC, Stewart AW, Priest PC, Florkowski CM, Livesey JH, Camargo CA Jr, Scragg R: Effect of vitamin D₃ supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. *JAMA* 2012;308:1333–1339.
- 147 Avenell A, Cook JA, MacLennan GS, Macpherson GC: Vitamin D supplementation to prevent infections: a sub-study of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing* 2007;36:574–577.
- 148 Salahuddin N, Ali F, Hasan Z, Rao N, Aqeel M, Mahmood F: Vitamin D accelerates clinical recovery from tuberculosis: results of the SUCCINCT study (Supplementary Cholecalciferol in Recovery from Tuberculosis). A randomized, placebo-controlled, clinical trial of vitamin D supplementation in patients with pulmonary tuberculosis'. *BMC Infect Dis* 2013;13:22.
- 149 Wejse C, Gomes VF, Rabna P, Gustafson P, Aaby P, Lisse IM, Andersen PL, Glerup H, Sodemann M: Vitamin D as supplementary treatment for tuberculosis a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2009;179:843–850.
- 150 Pozuelo-Moyano B, Benito-Leon J, Mitchell AJ, Hernandez-Gallego J: A systematic review of randomized, double-blind, placebo-controlled trials examining the clinical efficacy of vitamin D in multiple sclerosis. *Neuroepidemiology* 2013;40:147–153.
- 151 Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H: Randomized trial of vitamin D supplementation to prevent seasonal influenza a in school children. *Am J Clin Nutr* 2010;91:1255–1260.
- 152 Camargo CA Jr, Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, Sumberzul N, Rich-Edwards JW: Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics* 2012;130:E561–E567.
- 153 Manaseki-Holland S, Qader G, Masher MI, Bruce J, Mughal MZ, Chandramohan D, Walraven G: Effects of vitamin D supplementation to children diagnosed with pneumonia in Kabul: a randomised controlled trial. *Trop Med Int Health* 2010;15:1148–1155.
- 154 Manaseki-Holland S, Maroof Z, Bruce J, Mughal MZ, Masher MI, Bhutta ZA, Walraven G, Chandramohan D: Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superior trial. *Lancet* 2012;379:1419–1427.
- 155 Delvin EE, Lambert M, Levy E, O'Loughlin J, Mark S, Gray-Donald K, Paradis G: Vitamin D status is modestly associated with glycemia and indicators of lipid metabolism in French-Canadian children and adolescents. *J Nutr* 2010;140:987–991.
- 156 Ford ES, Zhao G, Tsai J, Li C: Associations between concentrations of vitamin D and concentrations of insulin, glucose, and HbA_{1c} among adolescents in the United States. *Diabetes Care* 2011;34:646–648.
- 157 Kelly A, Brooks LJ, Dougherty S, Carlow DC, Zemel BS: A cross-sectional study of vitamin D and insulin resistance in children. *Arch Dis Child* 2010;96:447–452.
- 158 Patange AR, Valentini RP, Gothe MP, Du W, Pettersen MD: Vitamin D deficiency is associated with increased left ventricular mass and diastolic dysfunction in children with chronic kidney disease. *Pediatr Cardiol* 2013;34:536–542.
- 159 Wright TB, Shults J, Leonard MB, Zemel BS, Burnham JM: Hypovitaminosis D is associated with greater body mass index and disease activity in pediatric systemic lupus erythematosus. *J Pediatr* 2009;155:260–265.
- 160 Peroni DG, Piacentini GL, Cametti E, Chinnellato I, Boner AL: Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. *Br J Dermatol* 2011;164:1078–1082.
- 161 Greer RM, Portelli SL, Hung BS, Cleghorn GJ, McMahon SK, Batch JA, Conwell LS: Serum vitamin D levels are lower in Australian children and adolescents with type 1 diabetes than in children without diabetes. *Pediatr Diabetes* 2013;14:31–41.
- 162 Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, Martin P, Matheson M, Lowe A, Robinson M, Tey D, Osborne NJ, Dang T, Tan HTT, Thiele L, Anderson D, Czech H, Sanjeevan J, Zurzolo G, Dwyer T, Tang MLK, Hill D, Dharmage SC: Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *J Allergy Clin Immunol* 2013;131:1109–1116.