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Sun deprivation, vitamin D insufficiency, coronary heart disease, and diabetes mellitus: A point of concern

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Abstract

This review summarises available evidence for an association of low vitamin D status with chronic diseases, such as cardiovascular disease (CVD), congestive heart failure (CHF), and diabetes mellitus. Human vitamin D status primarily depends on skin exposure to the ultraviolet B (UVB) spectrum of the sunlight. Sun-deprived lifestyle is associated with low vitamin D status and high morbidity for CVD and diabetes mellitus. Experimental data have demonstrated the essential role of the vitamin D hormone calcitriol for vascular health and insulin secretion. Several retrospective studies already indicate that calcitriol and other active vitamin D analogues reduce all-cause and cardiovascular mortality in specific patients groups. In addition, vitamin D status is low in groups with a high cardiovascular morbidity risk such as elderly people and immobilized subjects. Meanwhile, the first large observational studies indicate an association between low vitamin D status and an increased risk for CVD and type 2 diabetes in the general population. CVD is also a major risk factor for CHF. Up to 50% of end-stage CHF patients have very low calcitriol concentrations. In these patients, calcitriol is an independent predictor of survival. Importantly, there is evidence that CHF patients and healthy subjects differ during earlier periods of their lives with regard to life style factors that are associated with risk of a low vitamin D status. Available data point to the importance of preventive strategies to improve vitamin D status in early periods of life. Such strategies should

include adequate daily oral vitamin D intake and/or regular moderate solar ultraviolet B exposure.

Vitamin D physiology

Sunlight is the major provider of vitamin D for humans. The ultraviolet B (UVB) spectrum of the sunlight [290-315 nm] induces skin synthesis of vitamin D. Food is a second source of vitamin D, but only a few foods such as eel, herring, and salmon are good vitamin D sources. Consequently, cutaneously synthesized vitamin D usually contributes 80-90% to human vitamin D supply. Season, daytime, geographical latitude, and altitude are important predictors of environmental UVB radiation. In the human body, cutaneously synthesized or orally ingested vitamin D are metabolized by a hepatic hydroxylase into 25-hydroxyvitamin D (25(OH)D) and by a renal 1α -hydroxylase into vitamin D hormone 1,25 dihydroxyvitamin D (calcitriol) (Figure 1). This step is under control of the parathyroid hormone (PTH). Beside the kidney, calcitriol is also produced by local 1α -hydroxylases in various extra-renal tissues. Here, calcitriol plays an important autocrine role, which has just been realized during recent years.

Circulating 25(OH)D is the standard for determining vitamin D status. Vitamin D status can be categorized as follows: < 25 nmol/l for deficiency, 25-49.9 nmol/l for insufficiency, 50-74.9 nmol/L for borderline status, and ≥ 75 nmol/l for normal status (1). In case of vitamin D deficiency/insufficiency, renal synthesis of calcitriol becomes substrate dependent, i.e. dependent on the circulating 25(OH)D concentration (2). Extra-renal calcitriol production also depends on the level of circulating 25(OH)D (3). But uptake of 25(OH)D into those extra-renal tissues/cells that are able to produce calcitriol by themselves such as monocytes is also limited by low circulating calcitriol levels (4). Data indicate that low serum concentrations of 25(OH)D and calcitriol can both lead to insufficient calcitriol synthesis in extra-renal tissues. Results are of clinical importance, since locally produced calcitriol can suppress cellular synthesis of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α and interleukin-6 (5). They play a critical role in several chronic diseases (see below).

Vitamin D and Cardiovascular Disease (CVD)

CVD is one of the major life-threatening diseases in Western societies and has emerged a major cause of death worldwide (6). Tobacco consumption, elevated LDL-cholesterol levels, low HDL-cholesterol concentrations, high blood pressure and elevated blood glucose levels are causally linked risk factors of

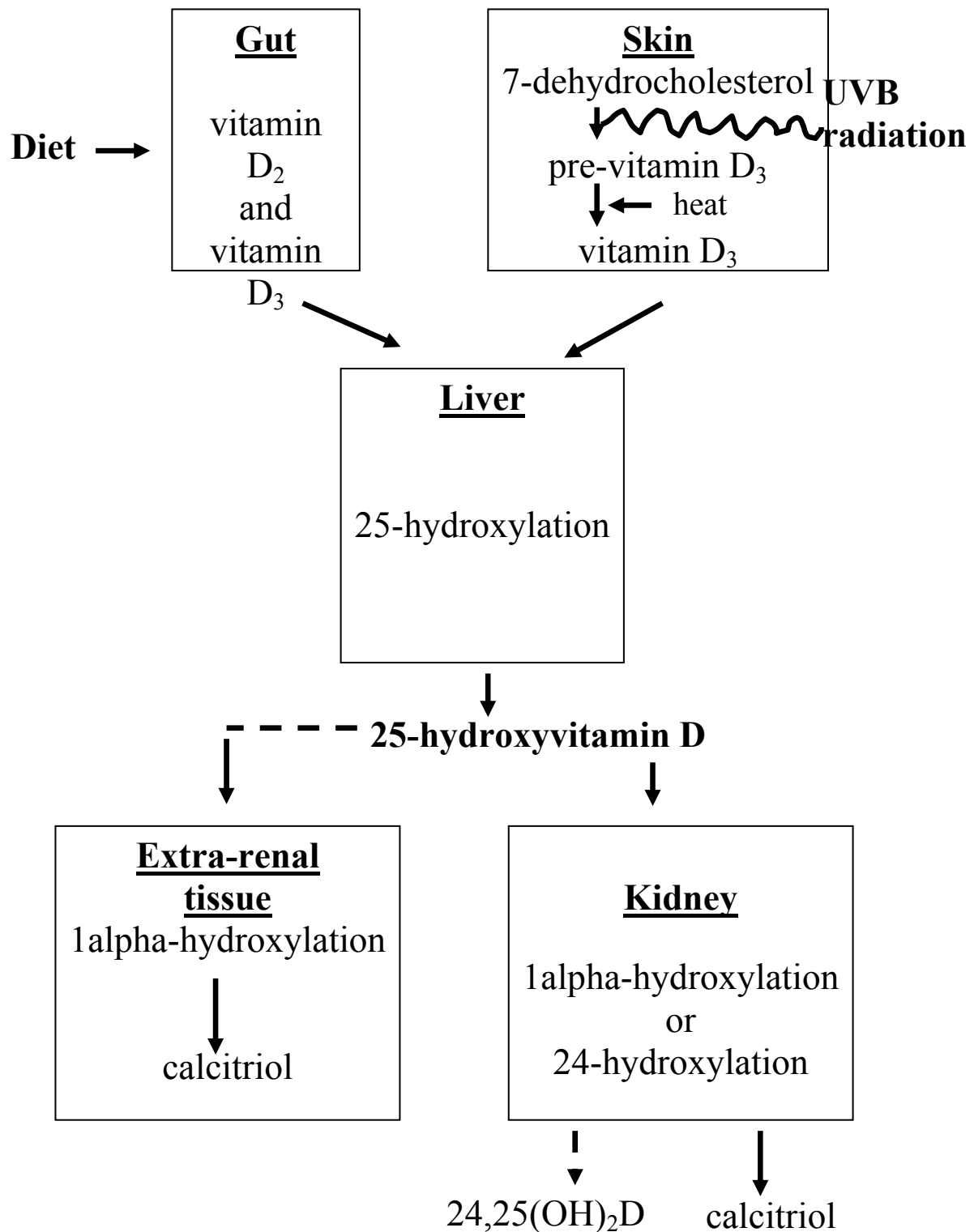


Figure 1. Vitamin D metabolism in the human body. UVB ultraviolet B radiation (290-315 nm) ; 24,25(OH)₂D, 24,25-dihydroxyvitamin D.

CVD. Physical inactivity, obesity, diet and low socio-economic status are predisposing risk factors. Some other factors such as elevated prothrombotic factors and markers of infection and inflammation also show associations with

CVD (6). There is now increasing evidence that a low vitamin D status may be an additional important and hitherto neglected factor in the pathogenesis of CVD. Indicators for vitamin D status such as geographic latitude, altitude, season, and the place of residence (urban/rural) are inversely associated with CVD mortality in the general population (7). Especially when large population groups with similar cultural background and lifestyle are compared with each other, indicators for vitamin D status can reliably be used to estimate vitamin D status (8). There is an inverse association between 25(OH)D levels and geographic latitude in children, adolescents, and young adults (7). Since the development of CVD may last years or even decades, it is understandable that CVD mortality is generally higher in European countries of northern latitude than in European countries of more southern latitude (7). Further evidence for a causal link between a latitude-associated risk factor such as vitamin D and CVD comes from the British Regional Heart Study, a prospective investigation of ischemic heart disease (IHD) among 7735 men aged 40-59 years (9). This study has demonstrated a twofold higher risk of a major IHD event per 1000 men per year in Scotland compared with the South of England, while those men recruited in the Midlands, Wales and the North of England experienced intermediate rates. This geographic gradient was also found for internal and international immigrants indicating that the place of residence was a more important determinant of the risk of a major IHD event than the place of birth. Recently, data from the 1958 British Birth Cohort demonstrated that the prevalence of 25(OH)D concentrations <40 nmol/l were twice as likely in Scottish participants as in those from other parts of Great Britain (i.e, England and Wales) (10). Generally, hypovitaminosis D was frequent in this study cohort, especially during the winter and spring, when 25(OH)D concentrations <25 , <40 , and <75 nmol/L were found in 15.5%, 46.6%, and 87.1% of participants, respectively. The proportions were 3.2%, 15.4%, and 60.9%, respectively, during the summer and fall.

Meanwhile, the first large observational studies have investigated the association of serum 25(OH)D with CVD risk factors. Results from the Third National Health and Nutrition Examination Survey revealed mean 25(OH)D levels of 75 nmol/l in US adults. Levels of 25(OH)D are lower in elderly persons (≥ 60 years), racial/ethnic minorities such as Blacks and Hispanics, and participants with obesity, hypertension, and diabetes mellitus (11). In that study, the adjusted prevalence of hypertension, and high serum triglyceride levels was significantly higher in the first than in the fourth quartile of serum 25(OH)D levels (odds ratios 1.30 and 1.47, respectively). In a representative sample of German adults, mean 25(OH)D levels were lower than in US adults and were only 45 nmol/l in men and women. Women with lower 25-hydroxyvitamin D levels were more likely to have hypertension and CVD. Among men, adjusted prevalence of hypertension decreased significantly per 10 nmol/l increase in serum 25(OH)D levels (odds ratio 0.97) (12).

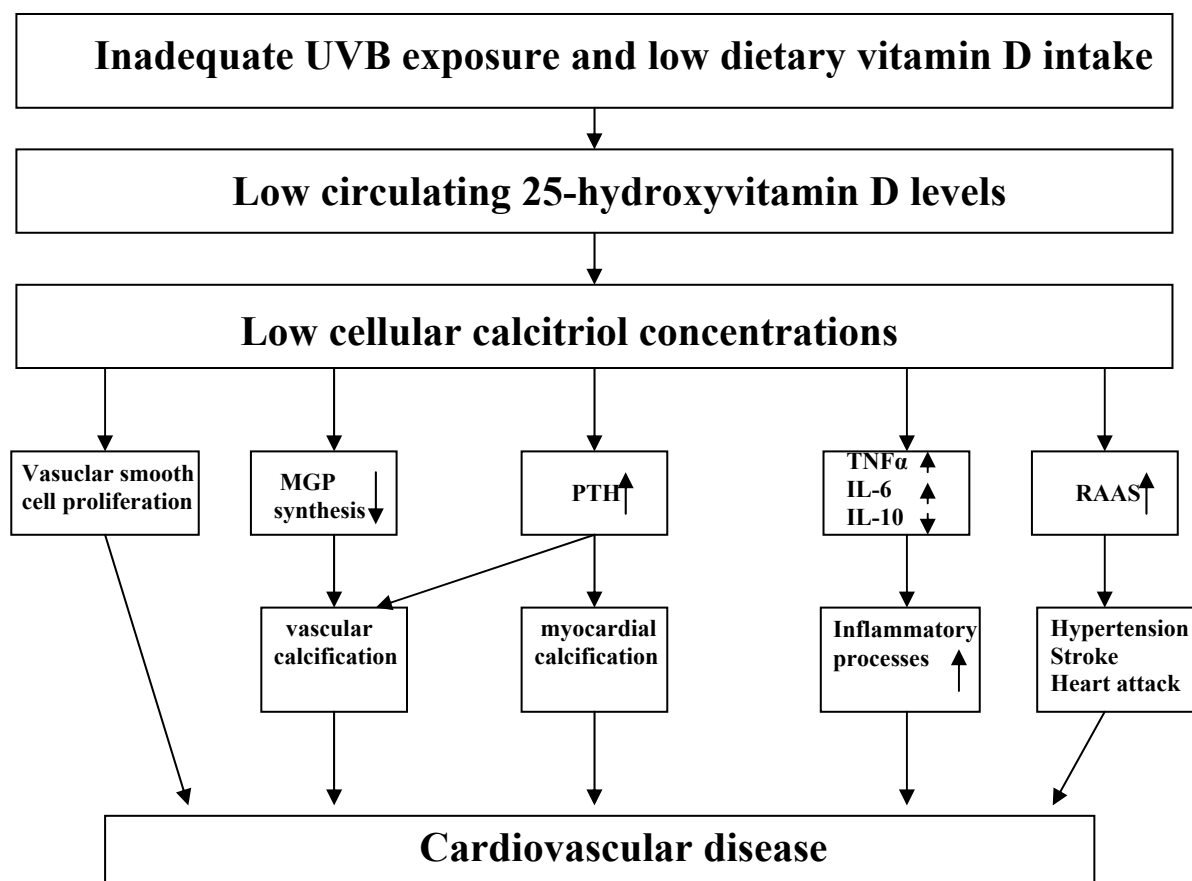


Figure 2. Hypothetical associations between vitamin D insufficiency and CVD. MGP, matrix Gla protein; PTH, parathyroid hormone; RAAS, renin–angiotensin–aldosterone system. With permission from Zittermann et al., 2005 (7).

There is now increasing evidence that the vitamin D hormone calcitriol exerts important physiological actions in the vasculature (Figure 2). These mechanisms include the inhibition of vascular smooth muscle proliferation, the suppression of vascular calcification, the down regulation of pro-inflammatory cytokines, the up regulation of anti-inflammatory cytokines, the action of vitamin D as a negative endocrine regulator of the renin–angiotensin system, and the inhibition of vascular calcification (2,7). Vascular calcification is an important risk factor for CVD mortality in the general population and is a frequent finding in patients with CVD (7). Data from two human populations at high and moderate risk for ischemic heart disease indicate an inverse association of serum calcitriol levels with vascular calcification (13).

The strongest evidence for a role of vitamin D in the pathogenesis of CVD comes from patients with end-stage renal disease (ESRD). ESRD is frequently associated with vascular calcification (14). Patients with ESRD have an excess prevalence of coronary artery disease. Coronary artery disease is the major factor in the pathogenesis of CVD and accounts for almost 50% of deaths among ESRD patients in the United States (15). Patients with end-stage kidney

disease often have low serum calcitriol concentrations (16). Two very large retrospective studies in Japanese and US ESRD patients have shown that vitamin D receptor (VDR) activators (calcitriol and paricalcitol) provide a 20% and 24% survival advantage, respectively, over no VDR activator therapy (17,18). In particular, CVD mortality was significantly lower in the vitamin D group compared to the non-vitamin D group (18). In the very large study of Teng et al (18), all-cause mortality was approximately 2.3 times higher in dialysis patients not treated with vitamin D compared to patients treated with active vitamin D during the first year of follow-up (1-year mortality rates of approximately 26% and 11%, respectively). In a small cohort of Japanese ESRD patients, the use of 1α -hydroxyvitamin D₃ was associated with a 70% lower risk of death from cardiovascular disease when compared with a group of 1α -hydroxyvitamin D₃ non-users. The median intake of 1α -vitamin D was 0.5 $\mu\text{g}/\text{day}$ for a median follow-up of 61 months (19). Note that mild renal impairment, insufficient 25(OH)D levels, and secondary hyperparathyroidism are common in elderly people, e.g. in residents of aged-care facilities (20). However, the consequences of these pathophysiological alterations on vascular calcification and CVD mortality have not been studied yet.

Recently, results from the Women's Health Initiative study on CVD events have been published (21). No significant differences were observed for myocardial infarction, CVD death, stroke, ischemic attack, and hospitalization rate for heart failure in the group supplemented with 1,000 mg calcium and 10 μg vitamin D daily compared with the placebo group. However, this investigation has several shortcomings concerning its calcium/vitamin D study arm. First, participants received a low daily vitamin D dose of only 10 μg . It is now clear that this amount is not sufficient to achieve a meaningful increase in circulating 25(OH)D levels (22). Second, no measurements of serum 25(OH)D and/or calcitriol levels are available. It may be that the vitamin D dose was too low to influence circulating calcitriol concentrations. It may also be that baseline 25(OH)D concentrations were already sufficient enough to produce adequate amounts of calcitriol. Third, the Women's Health Initiative study was performed in outpatient subjects during 7 years of follow-up. Note that the reliability of results from a randomised controlled trial might suffer if other sources of the study medication are available (23). Since skin synthesis of vitamin D usually contributes 80-90% to human vitamin D supply, outdoor activities may have had a far greater impact on vitamin D status in both study groups than the study medication. Thus, well designed prospective, randomised trials concerning the effect of vitamin D on CVD are still warranted.

Vitamin D and Congestive Heart Failure

Congestive heart failure (CHF) is a cardiac dysfunction syndrome of high prevalence in developed countries. Approximately five million Americans and ten million Europeans suffer from CHF (24, 25). The clinical syndrome of CHF is characterized by reduced left ventricular ejection fraction (LVEF) and low cardiac output, leading to dyspnea and fatigue at rest or with exertion, ankle swelling and pulmonary edema. CHF is associated with an activation of the renin-angiotensin-aldosterone-system (RAAS), resulting in fluid retention and hypertension. CHF patients also have elevated levels of pro-inflammatory cytokines such as TNF- α and interleukin-6 (Figure 3).

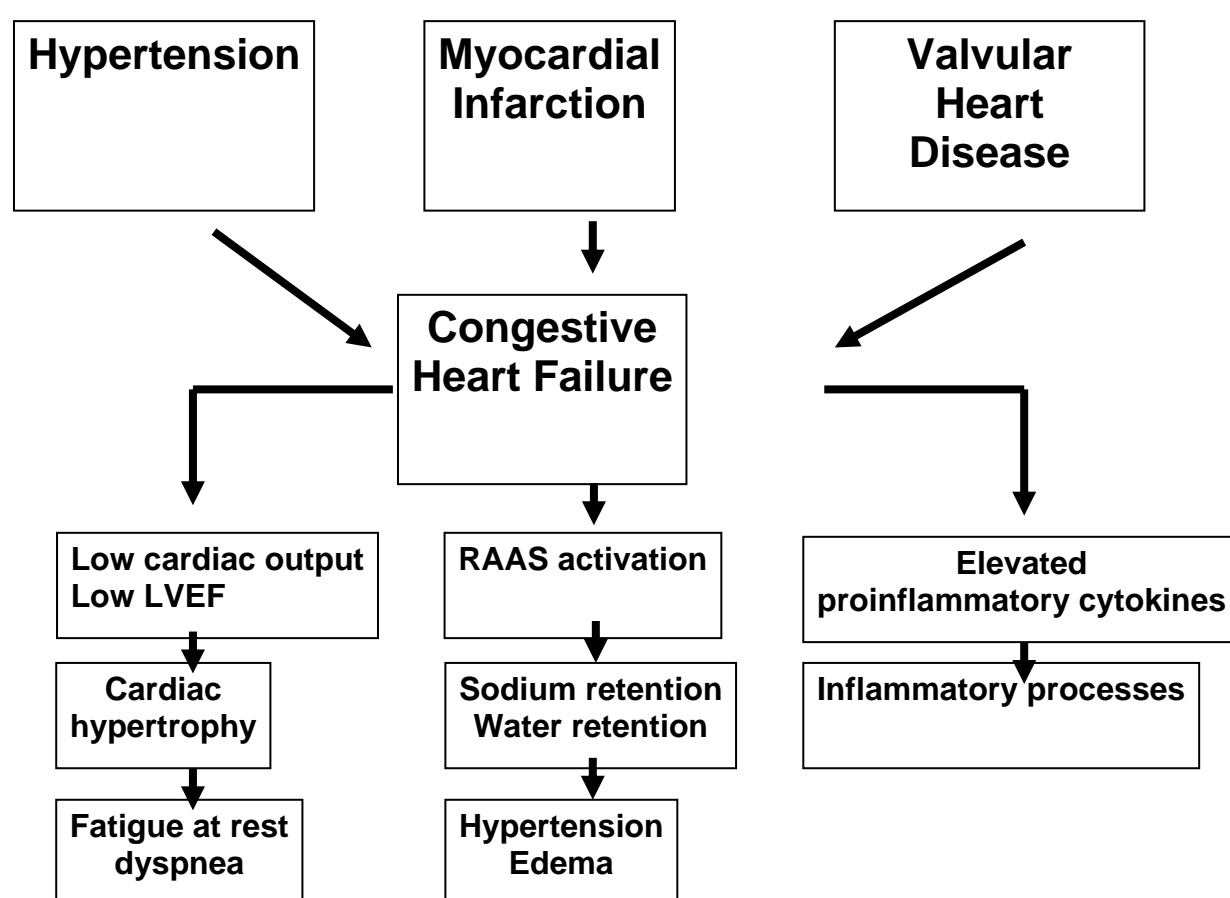


Figure 3. Simplified scheme of the etiology and pathophysiological consequences of congestive heart failure. LVEF, left ventricular ejection fraction; RAAS, renin-angiotensin-aldosterone system.

Optimal medical treatment can significantly reduce mortality in CHF patients (26). Despite evidence-based advances in the medical treatment of CHF over the past 15 years (25) survival rate 5 years after the first diagnosis of CHF is, however, still only 35-50% (27,28). Of those with advanced disease, the 1-year

mortality may exceed 50 percent (29). Cardiac transplantation is the ultimate therapeutic treatment option in end-stage heart failure.

The etiology of CHF is unclear at present. In the general population, CHF is associated with hypertension, coronary and valvular cardiovascular disease (Figure 3). Based on population attributable risks, hypertension has the greatest impact, accounting for 39% of CHF events in men and 59% in women. Myocardial infarction also has a high attributable risk in men (34%) and women (13%). Valvular heart disease only accounts for 7-8% of CHF (30). We have recently hypothesized that a low vitamin D status may contribute to the etiology of CHF (31). Increasing evidence from clinical and experimental trials supports this assumption. Vitamin D receptor knockout mice develop typical signs of CHF such as cardiac hypertrophy, over-stimulation of the RAAS system, high blood pressure, and increased levels of atrial natriuretic peptide (32-34). In experimental animals with hyperaldosteronism, calcitriol and dietary calcium and magnesium supplements can prevent both oxidative stress and an increase in cytosolic free ionized calcium (35). These pathophysiological alterations are typical findings in CHF (35,36). Calcitriol acts as negative endocrine regulator of the RAAS (37). Calcitriol treatment was shown to reduce plasma renin activity, angiotensin II levels, blood pressure, and myocardial hypertrophy (38,39). In VDR receptor knockout mice, the developing hypertension can be corrected by angiotensin converting enzyme inhibitors and angiotensin I receptor antagonists (37).

Very low concentrations of calcitriol (< 37 pmol/l) have been found in approximately 20% of CHF patients (40). Generally, calcitriol levels are lowest in those CHF patients with early onset of the disease (31). In urgent/high urgent candidates for cardiac transplantation, approximately 40% of the patients have frankly low calcitriol concentrations (41). A high percentage of end-stage CHF patients suffer from cachexia (42). Interestingly, vitamin D depleted experimental animals also have lower body weights compared to vitamin D repleted animals (43). Anemia is another complication in end-stage CHF patients (44). In chronic diseases which are associated with a high risk for calcitriol deficiency such as end-stage renal disease (45), calcitriol administration is able to improve hemoglobin concentrations (46,47). Together, data indicate that calcitriol deficiency may be responsible for various symptoms that are observed in CHF patients.

End-stage CHF patients who did not survive a follow-up period of 1-year had significantly lower calcitriol levels and higher concentrations of the pro-inflammatory parameters C-reactive peptide (CRP) and interleukin 6 compared to survivors. In patients in the lowest calcitriol tertile (< 43 pmol/l) mortality risk was 2.4 times higher compared with patients in the highest calcitriol tertile (> 73 pmol/l). The associations of calcitriol with mortality remained significant after adjustment for potential confounders (41). Even after cardiac

transplantation, low circulating calcitriol concentrations are a risk factor for survival: Kaplan-Meier survival rates were 96.7% in the patients in the highest calcitriol tertile, 87.8% in the patients in the intermediate tertile, and 67.8% in the patients in the lowest calcitriol tertile. Of various risk factors, circulating calcitriol remained the only independent risk factor in multivariate Cox regression analysis (unpublished own data). The life-saving effects of calcitriol in cardiac transplant recipients can be at least in part explained by the immunomodulatory properties of calcitriol leading to fewer severe rejections and infections.

In CHF patients, low levels of the calcitriol substrate 25(OH)D are frequently found (31). In addition, a high percentage of CHF patients have secondary hyperparathyroidism. The low 25(OH)D concentrations may at least in part be due to disease-related limited mobility leading to low UVB-induced skin synthesis of vitamin D (40). In addition, there is also evidence from a case controlled study that vitamin D associated lifestyle factors are already low before the onset of the disease (48) indicating that vitamin D insufficiency/deficiency is an important cause and not the result of CHF. An improvement in vitamin D status can influence several risk factors for CHF, such as hypertension and pro-inflammatory cytokines. It has been demonstrated that regular exposure to UVB radiation but not to UVA radiation increases circulating 25(OH)D above a level of 100 nmol/l and significantly reduces blood pressure by approximately 6 mmHg in hypertensive patients with initial 25(OH)D levels of 26 nmol/l within an intervention period of 6 weeks (49). In another study (50), elderly women were supplemented with calcium and 20 µg vitamin D₃ daily or with calcium alone. Initial 25(OH)D levels in the 2 study groups were 24.6 and 25.7 nmol/l, respectively. Compared with calcium supplementation alone, supplementation with vitamin D₃ and calcium resulted in an increase in serum 25(OH)D of 20 nmol/l ($P < 0.01$), a decrease in serum PTH of 17% ($P < 0.05$), a decrease in systolic blood pressure of 9.3% ($P < 0.025$), and a decrease in heart rate of 5.4% ($P < 0.025$). A daily supplement of 50 µg vitamin D in combination with 500 mg calcium resulted in an increase in serum 25(OH)D levels of 60 nmol/l in CHF patients, whereas the increase in TNF- α was blunted compared to calcium supplementation only (51).

Vitamin D and Diabetes Mellitus

Physical inactivity in combination with energy-rich diets is driving a global pandemic of type 2 diabetes. The prevalence of type 2 diabetes worldwide is set to increase from its present level of 150 million, to 225 million by the end of the decade and to as many as 300 million by 2025. Shocking as they are, these figures represent only clinically diagnosed diabetes and many cases of diabetes remain undiagnosed and untreated. In addition, up to one-quarter of western

populations have impaired glucose tolerance or the metabolic syndrome, which are considered to represent pre-diabetes states. Type 2 diabetes is appearing increasingly in children and adolescents, and the frequency of diagnosis of pediatric type 2 diabetes is increasing faster than that of type 1 diabetes in some areas (52). The high co-morbidity and prevalence of concomitant diseases such as hypertension and dyslipidemia in diabetic patients cause the high risk of developing secondary, cost intensive, and for the patient often disastrous late complications (53). Similar to type 2 diabetes, vitamin D deficiency is becoming pandemic (54). Low vitamin D status and type 2 diabetes are prevalent in similar population groups such as elderly people, obese people, physically inactive people, and dark skinned people living in Europe and North America (2,55).

The molecular mechanisms that might explain how vitamin D may prevent diabetes have recently been reviewed by Mathieu et al. (56). Obviously, the cytokine TNF- α is an important risk factor for type 2 diabetes. In healthy subjects, plasma levels of this cytokine are inversely related to glucose oxidative metabolism and whole glucose disposal (57). In Indian people, not only the plasma concentrations of TNF- α but also the risk for diabetes are markedly higher in urban than in rural population groups (58). Interestingly, 25(OH)D concentrations are lowest in Indians who live in urban areas (59,60). Experimental studies have demonstrated that a reduction in vitamin D activity can result in both insulin resistance and reduced insulin secretion (61). Mathieu et al. (56) have summarized available evidence from several small clinical trials and case reports until 2004 that provide evidence for a preventive effect of vitamin D against diabetes mellitus. Meanwhile, various large observational studies have been performed supporting the assumption that vitamin D can prevent type 2 diabetes in the general population. In postmenopausal women, glucose was found to be highly significantly related to body mass index and 25(OH)D but only just significant to age. Higher fasting glucose levels were found in those with serum 25(OH)D up to 40 nmol/l than in those with 25(OH)D above 40 nmol/l. The difference in fasting serum glucose was still significant if those with 25(OH)D below 80 nmol/l were compared with those with 25(OH)D above 80 nmol/l (62). In a Californian study with glucose-tolerant young subjects whose 25(OH)D levels ranged between 6 and 200 nmol/l, 25(OH)D showed an independent negative relation with plasma glucose at fasting, 90 min, and 120 min during an oral-glucose-tolerance-test (63). Moreover, there was also an independent positive correlation between 25(OH)D and insulin sensitivity index (calculated by dividing the average glucose infusion rate during the last hour of each clamp process [$\mu\text{mol/L} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$] by the average plasma insulin concentration (pmol/L) during the same interval). Results from the Third National Health and Nutrition Examination Survey in US adults revealed lower levels of 25(OH)D participants with obesity and diabetes mellitus (11). In that study, the adjusted prevalence of diabetes mellitus was significantly higher in the first than in the fourth quartile of serum 25(OH)D

levels (odds ratio 1.98). In a representative sample of German adults (12), men with lower 25(OH)D levels were more likely to have insulin-treated diabetes mellitus. Adjusted prevalence of insulin-treated diabetes mellitus decreased significantly per 10 nmol/l increase in serum 25(OH)D levels (odds ratio 0.67). Among women, non-insulin-treated diabetes mellitus was associated with lower serum 25-hydroxyvitamin D levels (12). In the 1958 British Birth Cohort, 25(OH)D was < 75 nmol/l in 80% of the obese subjects (BMI \geq 30 kg/m²) versus 68% of the other subjects (64). Serum 25(OH)D decreased and hemoglobin A_{1C} increased by increasing BMI. There was a nonlinear association between 25(OH)D and hemoglobin A_{1C}: a steep linear decrease in hemoglobin A_{1C} by 25(OH)D until 65 nmol/l and only smaller decreases with further increases. After adjustment for multiple potential confounders, mean percent change in hemoglobin A_{1C} by 10 nmol/l increase in 25(OH)D was -0.21 for BMI < 25 kg/m², -0.25 for BMI 25-29.9 kg/m², -0.65 for BMI 30-34.9 kg/m², and -1.37 for BMI \geq 35 kg/m². A systematic review concerning the role of vitamin D and calcium in glucose homeostasis came to the conclusion that observational studies show a relatively consistent association between low vitamin D status and prevalent type 2 diabetes or metabolic syndrome. Results revealed a type 2 prevalence of 0.36 (0.16-0.80) among non-Blacks for highest vs. lowest 25-hydroxyvitamin D (65). The Nurses' Health Study assessed vitamin D and calcium intake every 2-4 years in approximately 84,000 women who had no history of diabetes. During 20 years of follow-up, 4,843 incident cases of type 2 diabetes were recorded. A combined daily intake of > 1,200 mg calcium and > 20 μ g vitamin D was associated with a 33% lower risk of type 2 diabetes compared with an intake of < 600 mg and 10 μ g calcium and vitamin D (66). Recently, an ancillary analysis using existing data in archived samples from a completed double-blind, parallel-group, single center, randomized, controlled 3-year clinical trial on the effect of calcium (500 mg) and vitamin D (17.5 μ g) in Caucasian adults without diabetes was published (67). Among participants with high fasting glucose at baseline, those who took combined calcium/vitamin D supplements had a lower rise in fasting blood glucose at 3 years compared with those on placebo (0.4 mg/dl versus 6.1 mg/dl, respectively; P=0.042) and a better insulin sensitivity (estimated by homeostasis model assessment of insulin resistance). For the participants with normal fasting glucose, there was no difference in the change in fasting plasma glucose or insulin sensitivity between the two treatment arms.

Considerations for prevention

There is now increasing evidence from large observational studies that low 25(OH)D levels are associated with various chronic diseases, such as CVD, CHF, and diabetes mellitus. Since skin synthesis of vitamin D contributes approximately 80-90% to human vitamin D status, insufficient skin exposure to

UVB radiation is the major reason for the low vitamin D status. Generally, low 25(OH)D levels also affect serum calcitriol levels. Calcitriol is the only vitamin D metabolite with known physiologic actions. In elderly vitamin D-deficient patients and in immobilized subjects, measures that result in a meaningful rise in serum 25(OH)D, such as supplementation with approximately 25 µg 25-hydroxyvitamin D for 2 weeks or mobilisation after 14 weeks of bedrest, also increase plasma calcitriol very rapidly (68,69). Moreover, children and young adults with insufficient 25(OH)D levels in winter (mean levels of 30 and 32 nmol/l, respectively) show a significant increase in serum calcitriol in summer in parallel with a rise in serum 25(OH)D (70,71). On the other hand, serum calcitriol remained constant in subjects with initial serum 25(OH)D of approximately 50 nmol/l, despite a marked rise in serum 25(OH)D following vitamin D supplementation (72). Together, data indicate that a substrate-dependent reduction in serum calcitriol levels may occur if the circulating serum 25(OH)D level falls below 30-40 nmol/l. These associations are not linear but are more pronounced if 25(OH)D levels fall below 25 nmol/l (2). The dependency of circulating calcitriol on substrate availability is used as one rationale among others to consider 25(OH)D levels below 25 nmol/l as deficient and 25(OH)D levels between 25 and 50 nmol/l as insufficient. Theoretically, vitamin D status could also be categorized according to serum 25(OH)D levels by an alternative approach using functional biochemical parameters such the vitamin D-induced suppression of pro-inflammatory cytokines. As outlined before, calcitriol can suppress pro-inflammatory cytokines such as interleukin-6 and TNF- α in vitro. These cytokines are elevated in various chronic diseases such as the diseases described in this article and seem to contribute to the etiology of the diseases. Although some prospective, randomized trials demonstrate that vitamin D can suppress pro-inflammatory cytokines, results are conflicting however. Timms et al. (73) compared 3-monthly injections of a depot solution of cholecalciferol at high (1250 µg) or low (12.5 µg) dosage on serum CRP levels over 1 year. The dosages were equivalent to approximately 14 µg and 0.14 mg vitamin D daily. Initial 25(OH)D levels were 21.8 nmol/l in the high-dose vitamin D group and 20.7 nmol/l in the low-dose vitamin D group. Mean CRP levels decreased by 40% in the high-dose vitamin D group and by only 5% in the low-dose vitamin D group. The mean increase in serum 25(OH)D levels during the study period was, however, very similar in both groups (16.7 and 12.3 nmol/l), indicating that changes in serum 25(OH)D levels could not solely be responsible for the markedly decreased circulating CRP levels in the high-dose vitamin D group. In a study of van den Berghe et al. (74), patients with prolonged critical illness received different amounts of vitamin D during the first 10 days after intensive care unit admission (5.5 versus 12.0 µg daily). Initial 25(OH)D levels of patients at intensive care admission were 27.3 nmol/l. Serum concentrations of 25(OH)D in the high-dose vitamin D group were higher than in the low-dose group only on days 2, 6 and 7 (approximately 5 nmol/l). Elevated CRP levels decreased significantly with time in the intensive

care unit in both study groups. However, the fall in CRP was significantly more pronounced in the high-dose vitamin D group compared with the low-dose group between days 3 and 7. Likewise, interleukin-6 levels decreased in the high-dose vitamin D group, whereas they remained unaltered in the low-dose group. As mentioned before, a daily supplement of 50 µg vitamin D in combination with 500 mg calcium resulted in an increase in serum 25(OH)D levels of 60 nmol/l in CHF patients, whereas the increase in TNF-α was blunted compared to calcium supplementation only (51). However, the vitamin D effects on TNF-α were small and plasma calcitriol concentrations did not change significantly. Moreover, clinical outcome parameters were not influenced by vitamin D supplementation. Taken together, no clear dose response curve can be obtained from the available prospective studies. There is also some evidence that pro-inflammatory cytokines are able to suppress serum calcitriol (75). This means that inflammatory processes are not only the result of low calcitriol levels but probably contribute to the low calcitriol concentration in chronic diseases with elevated pro-inflammatory cytokines. Thus, patients may enter a *circulus vitiosus*. In patients with elevated pro-inflammatory cytokine levels, the interpretation of vitamin D status according to serum 25(OH)D categories may thus be useless. In this case, administration of calcitriol itself instead of an improvement of serum 25(OH)D levels may be a better strategy. Consequently, 25(OH)D categories may only be useful in healthy or apparently healthy subjects. This points to the importance of preventive strategies to improve vitamin D status in early periods of life. Such strategies include regular oral supplementation with vitamin D, food fortification, regular solar ultraviolet B exposure, or regular use of sunbeds. With regard to oral vitamin D intake, a daily amount of approximately 50 µg seem to be necessary to achieve 25(OH)D concentrations in the adequate range in the absence of UVB exposure (22). Concerning daily UVB exposure, adequate 25(OH)D levels can most probably be obtained by a daily dose of 0.25 MED (mean erythemal dose) to approximately 25% of the body surface (2).

Due to the pandemic of vitamin D deficiency and chronic diseases, such as CVD, CHF, and diabetes mellitus, large prospective, randomised trials are urgently needed. These studies should investigate the effects of a meaningful increase in 25(OH)D levels on long-term clinical outcome parameters.

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