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Review article

Putting cardiovascular disease and vitamin D insufficiency into perspective

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The aetiology of CVD is still not completely understood. The present review article summarises data supporting the hypothesis that an insufficient vitamin D status may contribute to the worldwide high prevalence of CVD. Human vitamin D status primarily depends on skin exposure to the UVB spectrum of the sunlight. Epidemiological data indicate that geographic latitude, altitude, season, and the place of residence (urban or rural) are associated with CVD mortality. Interestingly, all these factors also have an influence on human UVB exposure and thus on vitamin D status. Several mechanisms might be responsible for a protective role of vitamin D in CVD. 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, and the action of vitamin D as a negative endocrine regulator of the renin–angiotensin system. The first intervention trials indicate that vitamin D may suppress cardiovascular risk markers. However, more controlled clinical trials are needed to investigate whether optimal oral vitamin D supplementation is able to reduce CVD morbidity and mortality.

Cardiovascular disease: Vitamin D: Parathyroid hormone: Inflammation: Cytokines

CVD is one of the major life-threatening diseases in Western societies. For example, annual death rates in males and females caused by CVD are 37 and 41 %, respectively in the USA and 40 and 52 %, respectively in Germany (Federal Statistical Office, 2003). During the last few decades, CVD has emerged a major cause of death worldwide. In 1990, the developing countries contributed 63 % of world mortality due to CVD (Murray & Lopez, 1997). In 2020, 76 % of an estimated 25 million deaths will occur in economically developing countries (Yusuf *et al*. 2001).

Over the past five decades the prevalence of CVD has steadily increased in many African countries, with hypertension as the most common cause of CVD by far (Akinkugbe, 1990; Muna, 1993). The prevalence of hypertension has almost doubled in Northern India as well over 30 years (Ahlawat *et al*. 2002). Moreover, it is estimated that by the year 2020 CHD will be the leading cause of premature death in India whereof the urban Indians are worst affected compared with the rural dwellers (Ramchandran *et al*. 2001). In developing countries, unadjusted mortality of IHD will be 120 % higher in women and 137 % in men in the year 2020 compared with the year 1990 (Yusuf *et al*. 2001).

There is now general agreement that tobacco consumption, elevated LDL-cholesterol levels, low HDL-cholesterol concentrations, high blood pressure and elevated blood glucose levels are causally linked risk factors of CVD. Physical inactivity, obesity, diet and low socio-economic status are thought to be predisposing risk factors which work, at least in part, through an impact on other risk factors that act directly. These factors predispose to develop syndrome X, which is characterised by obesity, hypertension, dyslipoproteinaemia, and disturbed glucose tolerance. Recently, some evidence has been provided for an association between syndrome X and its risk factors with a low vitamin D status (Lind *et al*. 1995; Boucher, 1998; Chiu *et al*. 2004). Some other factors such as elevated prothrombotic factors, markers of infection and inflammation, elevated homocysteine, elevated lipoprotein (a) and some psychological factors show associations with CVD (Yusuf *et al*. 2001). Nevertheless, the aetiology of CVD is far from clear (Yancy *et al*. 2003). There are still several paradoxes in the pathogenesis of CVD that cannot be sufficiently explained; the French paradox indicates that mortality from CVD is relatively low in France despite a high intake of saturated fatty acids (Renaud & de Lorgeril, 1992). The Italian paradox indicates that a population with a high prevalence of cigarette smoking has a low CVD mortality rate (Grimes *et al*. 2000). The Northern Ireland paradox indicates that a population with a high incidence of CVD does not have the expected risk indicators (Evans *et al*. 1995). The Albanian paradox indicates that a population of low socio-economic status has a low CVD mortality (Gjonca & Bobak, 1997). The Indian paradox indicates that CVD mortality rate in urban populations is higher compared with rural populations despite a very low fat intake (Singh *et al*. 1998). All these paradoxes support

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CRP, C-reactive protein; PTH, parathyroid hormone.

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the assumption that one or more important factors in the aetiology of CVD are currently unknown.

There is increasing evidence that a low vitamin D status may be an important and hitherto neglected factor in the pathogenesis of CVD (see later). Therefore, the present review article summarises data supporting the hypothesis that an insufficient vitamin D status may contribute to the high and worldwide increasing prevalence of CVD.

Vitamin D physiology

Sunlight is the major provider of vitamin D for man. The UVB spectrum of sunlight (290–315 nm) induces skin synthesis of vitamin D (Holick, 2002). Food is a second source of vitamin D, but only a few foods such as eel, herring and salmon are good vitamin D sources. They contain between 16 and 27 μg vitamin D per 100 g edible portion (Souci *et al*. 1994). Only in a few parts of Europe are some foods such as margarine, vegetable oil, milk, cereals, breakfast beverages and breads fortified with vitamin D (Lips *et al*. 1996). They are usually enriched with not more than 10 μg vitamin D per 100 g edible portion. Over the counter supplements can contain up to 25 μg vitamin D per tablet. Nevertheless, cutaneously synthesised vitamin D usually contributes 80–90 % to human vitamin D supply (Glerup *et al*. 2000; Heaney *et al*. 2003). Season, daytime, geographic latitude, and altitude are important predictors of environmental UVB radiation (Holick, 2002). Factors that influence environmental UVB radiation can thus be used as vitamin D surrogates (Grant, 2003), especially when large population groups with similar cultural background and lifestyle are compared with each other.

In the human body, vitamin D is metabolised by a hepatic hydroxylase into 25-hydroxyvitamin D (25(OH)D). Circulating 25(OH)D is the hallmark for determining vitamin D status that is deficiency, insufficiency, hypovitaminosis, adequacy, and toxicity (Table 1). Deficiency is characterised by nutrient depletion that leads to severe clinical symptoms. In the insufficient stage, pathophysiological biochemical alterations can be observed. Severe clinical signs are usually not present. Hypovitaminosis (or suboptimal nutrient supply) characterises a stage where the body stores of a nutrient are already unphysiologically low. Only minor functional alterations are seen in this stage. In the stage of adequacy, no disturbances of the nutrient-dependent body functions occur, while toxicity is due to nutrient-dependent adverse reactions. 25(OH)D is metabolised by a renal 1α-hydroxylase into the vitamin D hormone calcitriol (1,25 dihydroxyvitamin D). This step is under control of parathyroid hormone (PTH). However, PTH levels correlate better with 25(OH)D concentrations than they do with calcitriol (Zittermann *et al*. 2003). Circulating calcitriol levels are usually homeostatically regulated. Even vitamin D intoxication is associated with physiological serum calcitriol levels (but with markedly elevated 25(OH)D levels). 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 been realised during recent years. Local calcitriol production depends on the level of circulating 25(OH)D. Vitamin D receptors have been identified in several tissues, among them heart muscle cells and blood vessels (Simpson & Weishaar, 1988; Davies & Hruska, 2001). Circulating calcitriol is an important regulator of systemic Ca metabolism and also of the intracellular Ca metabolism of various tissues. Calcitriol is also known as a regulator of the cellular production of pro-inflammatory and anti-inflammatory cytokines, a mechanism that may be important in the prevention of CVD (see later).

Table 1. Stages of vitamin D status according to circulating 25-hydroxyvitamin D (25(OH)D) concentrations (Vieth *et al.* 2003; Zittermann, 2003*a*; Lips, 2005)

Stages of vitamin D status	25(OH)D concentrations (nmol/l)	Biochemical and clinical symptoms
Deficiency	0–25	Severe hyperparathyroidism, Ca malabsorption, rickets, osteomalacia, myopathy
Insufficiency	> 25–50	Mild hyperparathyroidism, low intestinal Ca absorption rates, reduced bone mineral density, subclinical myopathy
Hypovitaminosis D	> 50–70 to 100	Low body stores of vitamin D, slightly elevated PTH levels
Adequacy	70–100 to 250	No disturbances of vitamin D-dependent functions
Toxicity	> 250	Intestinal Ca hyperabsorption, hypercalcaemia

PTH, parathyroid hormone.

Vitamin D and vascular calcification

Vascular calcification has been clearly defined as a risk factor for cardiovascular mortality in the general population and is a frequent finding in patients with CVD. Almost all angiographically atherosclerotic lesions are calcified (Honye *et al*. 1992). The presence of Ca within coronary vasculature is associated with an increased risk of myocardial infarction (Baedenkopf *et al*. 1964) and poorer 5-year survival (Margolis *et al*. 1980). It has recently been hypothesised that atherosclerotic plaque calcification is an active, regulated process (Doherty & Detrano, 1994). In several studies, a significant association has also been reported between vascular calcification and osteoporosis (Dent *et al*. 1968; Fujita *et al*. 1984; Banks *et al*. 1994; Barengolts *et al*. 1998). Data indicate an inverse relationship between the amount of vascular and skeletal Ca (Moon *et al*. 1992). The mechanism of this relationship is largely unclear at present. In two human populations at high and moderate risk for IHD, serum levels of the vitamin D hormone calcitriol were inversely correlated with the extent of vascular calcification (Watson *et al*. 1997). Although circulating calcitriol levels are usually homeostatically regulated, there is evidence from some epidemiological studies that low circulating 25(OH)D levels can obviously lead to low calcitriol levels (Bouillon *et al*. 1987; Docio *et al*. 1998; Zittermann *et al*. 2000, 2003), probably as a result of a substrate deficiency for the renal 1α-hydroxylase. In addition, vitamin D supplementation has been demonstrated to increase serum calcitriol levels (Pfeifer *et al*. 2001).

Several mechanisms might be responsible for a protective effect of calcitriol on atherosclerotic lesions and vascular calcification (Fig. 1). First, vascular smooth muscle cells express vitamin D receptors. Calcitriol inhibits proliferation of these cells by an acute influx of Ca into the cells (Davies & Hruska, 2001). Second, matrix Gla protein has been shown to be a strong inhibitor of vascular calcification (Schurgers *et al*. 2001). Matrix Gla protein is synthesised by chondrocytes and vascular smooth muscle cells (Luo *et al*. 1997; Shanahan & Weissberg, 1998).

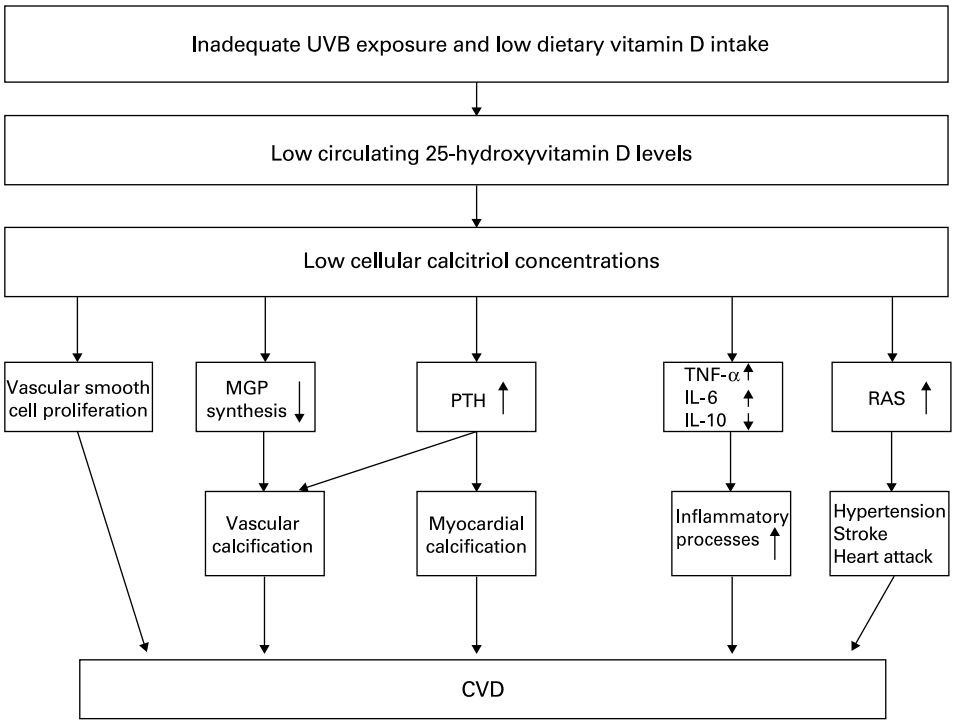

Fig. 1. Hypothetical associations between vitamin D insufficiency and CVD. MGP, matrix Gla protein; PTH, parathyroid hormone; RAS, renin–angiotensin system.

Synthesis of the Matrix is rapidly and dramatically increased by calcitriol (Fraser *et al*. 1988). Gla protein-deficient mice show massive calcification of the main arteries and die within 8 weeks after birth due to rupture of the aorta (Luo *et al*. 1997). Third, a lack of calcitriol results in an increase in serum PTH levels. Excess PTH levels may at least in part promote CVD by increased cardiac contractility, chronic atherosclerosis via insulin resistance, Ca and phosphate deposition in vessel walls, chronic myocardial calcification, and chronic heart valve calcification (Rostand & Drueke, 1999). Fourth, experimental studies have shown that calcitriol dose-dependently suppresses the release of the pro-inflammatory cytokines TNF-α and IL-6 (Muller *et al*. 1992). There is now increasing evidence that inflammatory processes play an important role in the development of a vascular insult (Mendall *et al*. 1997; van Lente, 2000). IL-6 and TNF-α are chief physiological stimulants of C-reactive protein (CRP), which can serve as an indicator of inflammatory processes. In contrast to its effects on pro-inflammatory cytokines, calcitriol up regulates synthesis of the anti-inflammatory cytokine IL-10 (Canning *et al*. 2001). Interestingly, serum concentrations of IL-10 and 25(OH)D are both higher in infants born during the summer half-year compared with infants born during the winter half-year (Zittermann *et al*. 2004). IL-10 deficiency is associated with severe atherosclerosis in experimental animals (Mallat *et al*. 1999). Fifth, calcitriol is a negative endocrine regulator of the renin–angiotensin system, in fact, independently of Ca metabolism (Li *et al*. 2002). Neuroendocrine mechanisms such as the renin–angiotensin system induce the progression of IHD. The renin–angiotensin system plays a central role in the regulation of blood pressure, electrolyte, and volume homeostasis. Inappropriate stimulation of the renin–angiotensin system has been associated with hypertension, heart attack, and stroke. Calcitriol treatment reduces blood pressure, plasma renin activity, and angiotensin II levels (Kimura *et al*. 1999). Clinical studies have revealed an inverse relationship between inadequate sunlight exposure or low serum levels of calcitriol and blood pressure and/or plasma renin activity (Kimura *et al*. 1999; Li *et al*. 2002). UVB radiation leading to 25(OH)D-serum concentrations >100 nmol/l was shown to lower blood pressure in patients with mild essential hypertension (Rostand, 1997; Krause *et al*. 1998). Moreover, supplementation with vitamin D leads to a lower blood pressure as well (Pfeifer *et al*. 2001).

Some may argue that high doses of oral vitamin D can induce severe vascular calcification in animals (Spiess, 1932; Hass *et al*. 1958; Kent *et al*. 1958; Shi-Kuang *et al*. 1976; Atkinson *et al*. 1994). In animals, vitamin D is known to cause calcification of the artery media in as little as 3 to 4 d (Takeo *et al*. 1989). However, in several of these animal studies, very high amounts of vitamin D have been used (oral bolus of up to 7·5–12·5 mg vitamin D; Takeo *et al*. 1989; Price *et al*. 2000). Mean oral vitamin D intake in Western countries is currently only 3–5 μg/d (Zittermann, 2003*a*). Recently performed controlled studies in human subjects have demonstrated that vitamin D intakes up to 100 μg/d do not lead to hypercalcaemia and do not lead to circulating 25(OH)D concentrations above 200 nmol/l (Heaney *et al*. 2003; Vieth *et al*. 2004), a level that is regarded as safe (Table 1). In contrast, available data indicate that a daily vitamin D intake of 1 μg/kg body weight is necessary to achieve circulating 25(OH)D levels of 100 nmol/l in the absence of skin exposure to UVB radiation (Heaney *et al*. 2003; Zittermann, 2003*b*). Consequently, modern adults are not consuming physiologically meaningful amounts of vitamin D through foods or vitamin pills (Vieth, 2002). It should also be mentioned that exposure of the human body to the UVB spectrum of the sunlight cannot lead to vitamin D intoxication (Zittermann, 2003*a*). There is thus no risk for human adults to develop vascular calcification as a result of vitamin D intoxication.

Vascular calcification may not only be the result of intestinal Ca hyperabsorption in combination with hypercalcaemia after oral intake of supraphysiological dosages of vitamin D, but may also occur as a result of an unphysiological mobilisation of skeletal Ca stores. However, no data are available that vascular calcification, which occur in combination with osteoporotic Ca loss from bone, is due to hypercalcaemia. Therefore, presently unknown mechanisms may exist which may lead to vascular calcification. Consequently, the above-mentioned animal studies do not contradict the assumption that an insufficient vitamin D status may promote vascular calcification. There is now increasing evidence that the high prevalence of CVD in renal failure is at least in part associated with low levels of vitamin D metabolites. Patients with end-stage renal failure have an excess prevalence of coronary artery disease. Coronary artery disease is the major factor in the pathogenesis of cardiac disease and accounts for almost 50 % of deaths among end-stage renal disease patients in the USA (Stack & Bloembergen, 2001). An elevated Ca × PO_4 product (>72) and high serum P concentrations (>65 mg/l) significantly increase the mortality risk, most probably as a result of cardiovascular complications (Block *et al.* 1998). In renal failure, a disturbed vitamin D metabolism is a frequent finding. When renal function impairs, the serum concentrations of calcitriol are reduced (Juttmann *et al.* 1981). Generally, there is an association between the decrease in creatinine clearance and the fall in serum calcitriol levels in patients with chronic renal failure (Ishimura *et al.* 1999). Activity of renal 1α-hydroxylase is attenuated in chronic renal failure due to phosphate load as well as to the decreased number of viable nephrons (Fukagawa & Kurokawa, 2005). There is also some evidence from clinical studies that low 25(OH)D availability can contribute to the low calcitriol levels in renal failure (Halloran *et al.* 1984). In chronic renal failure, the secretion of PTH is stimulated by several factors, primarily hypocalcaemia and reduced production of calcitriol. Moreover, resistance to physiological concentrations of calcitriol may develop during the early phase of chronic renal failure (Fukagawa & Kurokawa, 2005). Therefore, chronic renal failure results in high circulating PTH levels (>6·8 pmol/l) caused by secondary hyperparathyroidism (Rostand & Drueke, 1999; Davies & Hruska, 2001). However, treatment of secondary hyperparathyroidism with vitamin D and Ca is often complicated in these patients by hypercalcaemia and hyperphosphataemia. Therefore, vitamin D analogues have been developed and have been successfully used to treat these patients (Block *et al.* 2004).

In a recent review, several alterations which are associated with vitamin D depletion, such as reduced cardiac inotrophy, enhanced heart weight, increased myocardial collagen content, and increased vascular smooth muscle cell proliferation, have been made responsible for the enhanced risk of CVD in chronic renal failure (Rostand & Drueke, 1999). Moreover, it has been assumed by these authors that the accompanying PTH excess may impair intracellular Ca metabolism of the cardiomyocyte and may promote chronic atherosclerosis.

In line with the earlier experimental and observational studies in renal failure, it has recently been demonstrated in a cohort of Japanese end-stage renal disease patients that the use of 1α-hydroxyvitamin D_3 was associated with a 70 % lower risk of death from CVD when compared with a group of 1α-hydroxyvitamin D_3 non-users. The median intake of 1α-vitamin D was 0·5 μg/d for a median follow-up of 61 months (Shoji *et al.* 2004).

Epidemiological data on cardiovascular disease and vitamin D surrogates

Geographic latitude and cardiovascular disease

Fig. 2 shows the relationship between death rates from IHD and geographic latitude in males and females from different European countries. Geographic latitude of the countries were adopted from Grimes *et al.* (2000) and IHD death rates were obtained from the Global Cardiovascular Infobase of the WHO Collaborating Centre on Surveillance of CVD (Global Cardiovascular Infobase, 2003). Data indicate an increase in IHD with the increase in geographic latitude. Fleck (1989) has reported a similar correlation coefficient (r 0·58) between IHD mortality rate of males and geographic latitude for several European and Western countries. Data are in gross agreement with the observation that environmental UVB radiation is absent from November until February at the geographic latitude of 40°N and from October until March at the geographic latitude of 50°N or 60°N, while there is environmental UVB radiation throughout the year at the geographic latitude of 30°N or closer to the equator (Holick, 2002). Moreover, available data from America and Europe indicate

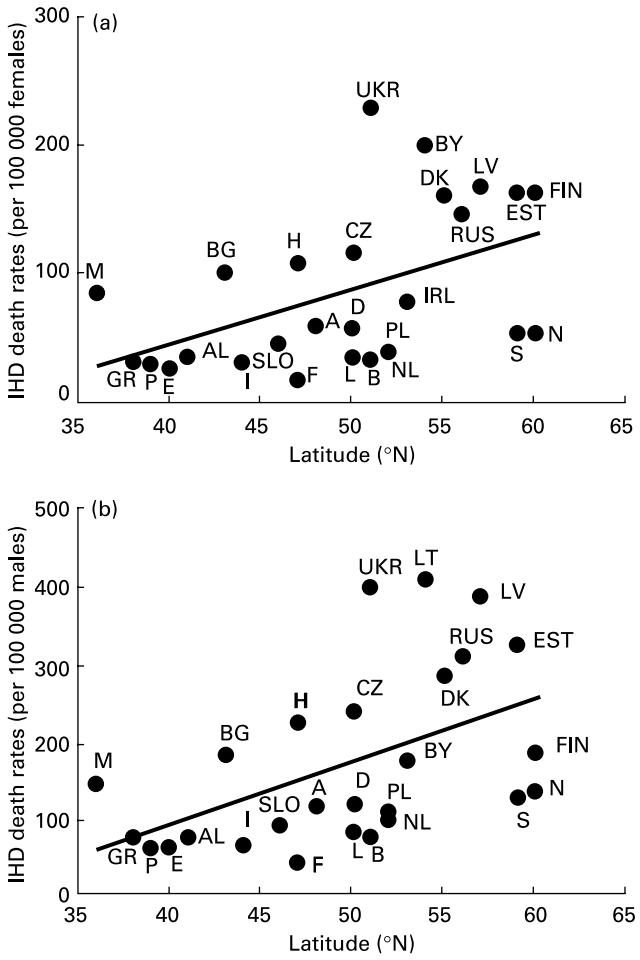

Fig. 2. Associations between geographic latitude and IHD death rates in (a) females (r 0·49; $P<0·01$) and (b) males (r 51; $P<0·01$) of different European countries. A, Austria; AL, Albania; B, Belgium; BG, Bulgaria; BY, Belarus; CZ, Czech; D, Germany; DK, Denmark; E, Spain; EST, Estonia; F, France; FIN, Finland; GR, Greece; H, Hungary; I, Italy; L, Luxembourg; LT, Luthuania; LV, Latvia; M, Malta; N, Norway; NL, Netherlands; P, Portugal; PL, Poland; S, Sweden; SLO, Slovenia; RUS, Russia; UKR, Ukraine.

that the winter values of serum 25(OH)D are higher in healthy subjects who live at lower latitudes compared with subjects living at higher latitudes (Fig. 3). The data in Fig. 3 show an inverse association (r −0·68; $P<0·01$) between latitude and serum 25(OH)D levels. 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 IHD among 7735 men aged 40–59 years (Elford *et al*. 1989). This study has demonstrated a two-fold 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.

Altitude and cardiovascular disease

Mortimer *et al*. (1977) have shown a serial decline in mortality from IHD for males in the US state New Mexico with higher altitudes. An increase of 1000 m (3280 feet) in the altitude of residence was associated with a 28 % decrease in IHD mortality rates. Moreover, a statistical evaluation of different areas of the USA revealed an inverse association in death rates from IHD with altitude for men and women (Gordan & Danner, 1977). According to sex and age group, correlation coefficients for death rates with altitude were between −0·209 and −0·375 ($P=0·001–0·0014$). Associations were lowest in middle-aged females and were highest in elderly men. It is well known that

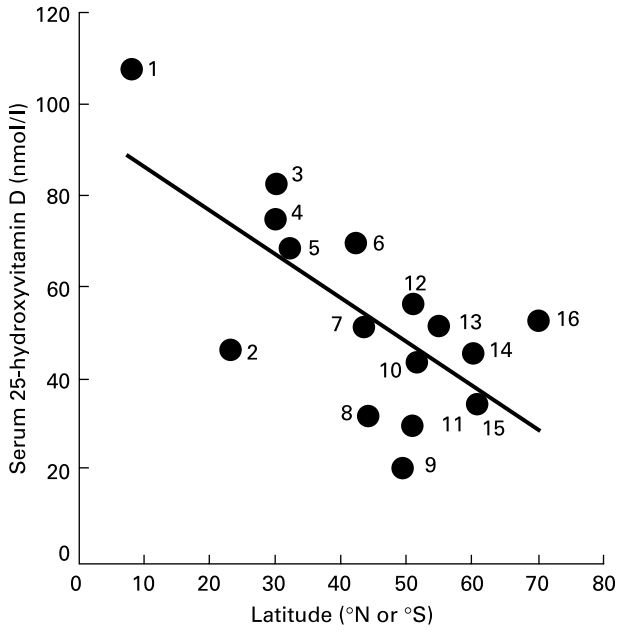

Fig. 3. Mean circulating 25-hydroxyvitamin D levels in children, adolescents, and adults according to geographic latitude (r −0·68; $P<0·01$). (1) Children, Linhares *et al.* 1984; (2) male adults, Goswami *et al.* 2000; (3) male adolescents and adults, Looker *et al.* 2002; (4) female adolescents and adults, Looker *et al.* 2002; (5) male adults, Looker *et al.* 2002; (6) adolescents and adults, Tangpricha *et al.* 2002; (7) adults, Vieth *et al.* 2001; (8) children, Docio *et al.* 1998; (9) adolescents, Guillement *et al.* 2001; (10) children, Zittermann, 1987; (11) adults, Zittermann *et al.* 1998; (12) adults, Rucker *et al.* 2002; (13) children, Davies *et al.* 1999; (14) adults, Lamberg-Allardt *et al.* 2001; (15) adolescents, Lehtonen-Veromaa *et al.* 1999; (16) adults, Vik *et al.* 1980.

intensity of UVB increases exponentially with altitude. The increase is 4 % per 305 m (1000 feet) at an altitude close to sea level and is 8–10 % per 305 m (1000 feet) at an altitude above 2420 m (8000 feet). In early spring, UVB intensity at sea level is only 60 % UVB intensity at an altitude of 2580 m (8500 feet), indicating that skin synthesis of vitamin D can be more effective in late winter (and probably also in late autumn) at higher altitude compared with sea level (Rigel *et al*. 1999). In line with altitude-associated IHD mortality rates in the USA, relatively low mortality rates of IHD have also been reported for subjects living in Alpine European regions of high altitude (Scragg, 1981). Interestingly, hypertension is also less common or less severe at higher altitudes (Hultgren, 1970). Controlled clinical studies have 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 also significantly reduces blood pressure by approximately 6 mmHg in hypertensive patients within an intervention period of 6 weeks (Krause *et al*. 1998).

Seasonality of cardiovascular disease

Some studies have evaluated the effect of season on CVD deaths. In Scotland, IHD mortality rates showed a nadir in summer (Douglas *et al*. 1991). Scottish death rates of IHD in summer were approximately 30 % lower compared with winter (Douglas *et al*. 1991). Moreover, a large evaluation of all IHD deaths in Scotland between 1962 and 1971 also showed a winter peak and a summer nadir in male and female IHD deaths (Douglas *et al*. 1995). Grimes *et al*. (1996), using data from the 1992 National British Household Survey, found an inverse correlation of −0·85 ($P<0·001$) between sunshine per year and IHD death rate per 100 000 males within the seventeen regions of that study. When the data were evaluated according to the 200 districts of that study, the correlation coefficient was −0·59 ($P<0·001$) between sunshine per year and IHD death rate per 100 000 males. The reported data fit well together with results on vitamin D status of healthy subjects living at geographic latitudes between 40°N and 60°N, for instance in North America and Europe. These subjects have seasonal fluctuations in circulating 25(OH)D levels. Concentrations of 25(OH)D are higher in summer than in winter (Fig. 4). Moreover, data indicate that in many Western countries a large part of the population have 25(OH)D levels in the insufficiency range (<50 nmol/l), especially during wintertime. Some epidemiological studies have also demonstrated seasonal variations for circulating calcitriol levels in children and young adults with a peak in summer and a nadir in winter (Docio *et al*. 1998; Zittermann *et al*. 1998).

Seasonality of CVD has also been observed in the Southern hemisphere. An Australian study has demonstrated that coronary events were 20–40 % more likely to occur in winter and spring than at other times of the year (Enquselassie *et al*. 1993). In some of the earlier studies lower temperature was associated with coronary death. It should be mentioned, however, that mean annual temperatures are also low in Alpine regions of relatively low IHD mortality, indicating that ambient temperature is not a major factor in the pathogenesis of CVD. More than two decades ago, Scragg (1981, 1982) had already suggested that seasonal variations in UVB radiation and in body levels of vitamin D are responsible for the seasonality of CVD. Recently, a circa-annual rhythm has been described not only for serum 25(OH)D concentrations but also for serum PTH levels in Central Europe

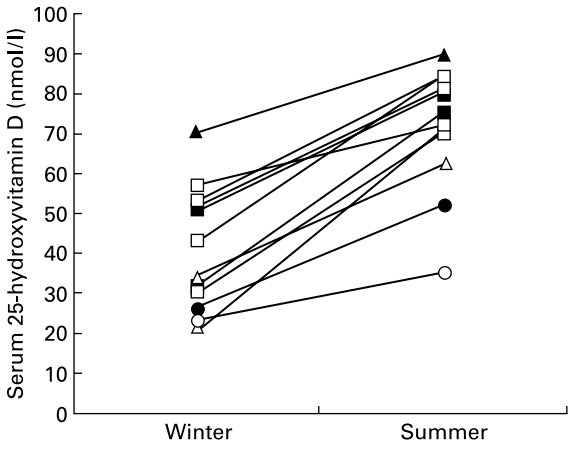

Fig. 4. Mean circulating concentrations of 25-hydroxyvitamin D in newborns (●–●), children (■–■), adolescents (Δ–Δ), adults (□–□), elderly subjects (○–○) and a mixed group of adolescents and adults (▲–▲) according to season (Vik *et al.* 1980; Zittermann, 1987; Hegarty *et al.* 1994; Docio *et al.* 1998; Zittermann *et al.* 1998, 2004; Davies *et al.* 1999; Lehtonen-Veromaa *et al.* 1999; Vieth *et al.* 2001; Rucker *et al.* 2002; Tangpricha *et al.* 2002).

(Woitge *et al.* 2000). The investigators could also demonstrate that a daily vitamin D supplement of 12·5 μg was able to blunt the PTH peak in winter during the second year of that study. In the supplemented group, the rhythm-adjusted annual mean PTH levels fell by approximately 12 % during the second study year, but remained unchanged in a control group (Meier *et al.* 2004). Interestingly, high PTH levels are a risk factor for IHD in the general population. In a Norwegian study, the highest PTH quartile (>3·50 pmol/l in men and >3·30 pmol/l in women) predicted IHD, with odds ratios of 1·70 for men and 1·73 for women, *v.* the lowest PTH quartile (<1·90 pmol/l for men and <1·80 pmol/l for women) (Kamycheva *et al.* 2004). Recently performed investigations have demonstrated that 25(OH)D is the major predictor of serum PTH levels in healthy adults (Pepe *et al.* 2005). Moreover, no cases of secondary hyperparathyroidism (PTH levels >6·8 pmol/l) are seen in elderly subjects with 25(OH)D levels above 100 nmol/l (Gomez-Alonso *et al.* 2003).

Keeping in mind that insufficient 25(OH)D levels can lead to hyperparathyroidism and that local calcitriol production depends on circulating 25(OH)D levels, it is interesting that high PTH levels induce IL-6 production (Mitnick *et al.* 2001), whereas low calcitriol concentrations induce synthesis of IL-6 and TNF-α (Muller *et al.* 1992). These two cytokines are the chief physiological stimulants of the hepatic production of acute-phase reactants such as fibrinogen and CRP (Heinrich *et al.* 1990). Higher blood pressure, an enhanced blood viscosity, increased fibrinogen levels, and higher CRP levels can all contribute to the increased risk of CVD in winter compared with summer (Frohlich *et al.* 1997; Mendall *et al.* 1997; Crawford *et al.* 2000; Mavri *et al.* 2001). Thus, a decreased vitamin D production leading to high PTH levels might at least in part be responsible for the wintertime increases in fibrinogen and CRP, which are both important cardiovascular risk factors (Ridker *et al.* 2000).

Urban and rural differences in cardiovascular disease

Urbanisation is associated with an increased mortality from IHD (Enterline *et al.* 1960). The prevalence of risk factors for CVD and also of disease rates is higher in urban than in rural communities in India (Gupta *et al.* 1996, 1997) and China (Anonymous, 1992). Moreover, studies in African countries have shown that coronary artery disease is more prevalent in urban than in rural dwellers (Muna, 1993). In addition, a study in South America demonstrated that among isolated island dwellers, hypertension was not detectable and blood pressure was comparable in 60- and 20–30-year-old subjects whereas the prevalence of hypertension was 10·7 % in the urban population, and exceeded 45 % in those subjects over 60 years of age (Hollenberg *et al.* 1997).

As mentioned earlier, IHD mortality will increase by 120–137 % in developing countries from 1990 until 2020. This increase is paralleled by a doubling of the percentage of individuals living in urban settings (Yusuf *et al.* 2001). It is well known that low environmental UVB irradiation due to urbanisation was a major risk factor for severe vitamin D deficiency in infants during the 18th and 19th centuries in North America and Europe. At the turn of the 20th century, for example, rickets was rampant among the poor children living in the industrialised and polluted northern cities of the USA (Rajakumar, 2003). This problem has disappeared in the 20th century by regular supplementation of infants with vitamin D and/or with the exposure of children to artificial UVB irradiation. It is important to mention that at latitudes of approximately 25–60° North or South, synthesis of vitamin D is only possible between 10.00 hours and 18.00 hours, with a maximal capacity at 12.00–14.00 hours (Holick, 2002). Therefore, low outdoor activities of urban children and adults during the daytime can increase the risk of developing vitamin D insufficiency or even deficiency. Indeed, there is evidence that vitamin D levels are markedly lower in individuals working indoors, characterised by a sedentary lifestyle and spending most of their leisure-time activity at home compared with those working outside such as farmers and spending much time doing outdoor activities (Chapuy *et al.* 1996). In a recent European study, middle-aged urban dwellers had only modest seasonal variations in circulating 25(OH)D levels and a high percentage of subjects had low vitamin D status throughout the year, despite marked seasonal fluctuations in daily sunshine (Bhattoa *et al.* 2004). The prevalence of 25(OH)D levels below 50 nmol/l during spring, summer, autumn, and winter was 71, 46·3, 49·4, and 56·7 %, respectively. Even in a sunny country such as Lebanon, low 25(OH)D levels (<25 nmol/l) were observed in 72·8 % of a middle-aged group of adults. In a multiple linear regression analysis, circulating 25(OH)D levels were inversely related to urban dwelling in the group of male adults (r −0·57; P<0·001). This association was weaker in female adults (r −0·27; P=0·002), whereas inadequate vitamin D intake and the style of clothing were more important than urban or rural dwelling (Gannage-Yared *et al.* 2000). Very low mean 25(OH)D levels of 8 nmol/l in winter and 18 nmol/l in summer were observed in Indian physicians and nurses who lived in the city of Delhi and had a daily sun exposure of only 25 min. In contrast, Indian soldiers with a daily sun exposure of 370 min had a mean 25(OH)D level of 47 nmol/l in winter (Goswami *et al.* 2000).

Many cities in developing countries are highly polluted. A higher degree of air pollution that contains ozone also leads to an efficient atmospheric absorption of UVB photons, thereby reducing the skin photosynthesis of vitamin D (Holick, 1995; Mims, 1996). For example, Delhi is one of the most polluted cities in the world. Children living in a downtown area of Delhi have significantly lower mean 25(OH)D concentrations than

those living in less polluted area on the outskirts of the city (29 *v.* 68 nmol/1; Agarwal *et al*. 2002). Interestingly, Indians from urban slums and also from an urban middle-class residential area have markedly higher circulating levels of IL-6 and TNF-α than rural village populations (Yudkin *et al*. 1999).

Intervention trials with vitamin D

Some supplementation studies with vitamin D have been performed where cardiovascular risk markers have been assessed. In a study of Scragg *et al.* (1995) using a single oral dose of 2·5 mg vitamin D_3 given in the winter to elderly individuals re-studied at about 5 weeks later in January and February, neither blood pressure nor serum cholesterol concentrations were altered. In that study, the increase of the serum 25(OH)D levels was only 18 nmol/l. The study of Timms *et al*. (2002) was designed to compare 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 μg 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*. (2003), patients with prolonged critical illness received different amounts of vitamin D during the first 10 d after intensive care unit admission (5·5 *v.* 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, IL-6 levels decreased in the high-dose vitamin D group, whereas they remained unaltered in the low-dose group. In a study of Pfeifer *et al*. (2001), elderly women were supplemented with Ca and 20 μg vitamin D daily or with Ca alone. Initial 25(OH)D levels in the two study groups were 24·6 and 25·7 nmol/l, respectively. Compared with Ca, supplementation with vitamin D and Ca resulted in an increase in serum 25(OH)D of 72 % ($P<0·01$), 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 % ($P<0·025$).

Conclusions

The aetiology of CVD is still not completely understood. Epidemiological data indicate that geographic latitude, altitude, season, and the place of residence (rural or urban) are all associated with CVD mortality. Until now, no sufficient explanations for a common origin of these associations were available. However, all these environmental factors share the common possession that they have an influence on human UVB exposure and therefore also on human vitamin D status. Moreover, the vitamin D hypothesis of the aetiology of CVD is in line with the high prevalence of CVD in obese and elderly individuals and the low prevalence of CVD in physically active individuals, since vitamin D status is inversely related to body weight (Wortsman *et al*. 2000; Arunabh *et al*. 2003) and age (McKenna, 1992; Passeri *et al*. 2003), and is positively related to the level of physical activity (Zittermann *et al*. 2000). There are several mechanisms that might explain the association between vitamin D status and CVD, among them an effect of vitamin D on inflammation markers. The first intervention trials indicate that oral vitamin D supplementation may be able to improve inflammation parameters.

Recently, it has been stated that for the defence of chronic illnesses, such as CVD, urban planning for health needs to be strengthened, and that cities and towns should be turned into safe places for pedestrians, cyclists, and children in order to encourage regular physical activity (Anonymous, 2004). This recommendation is exactly what is also necessary to improve vitamin D status of urban dwellers. Nevertheless, it is questionable whether all individuals who are at risk for low UVB exposure such as indoor workers, veiled women, and elderly individuals are able to adequately increase their skin synthesis of vitamin D. Therefore, it is necessary to provide optimal amounts of oral vitamin D to these groups. Intakes that are needed to maintain adequate circulating 25(OH)D levels range between 50 and 100 μg daily (Heaney *et al*. 2003; Vieth *et al*. 2004) and can only be achieved by supplementation or food fortification. Some of the above-mentioned earlier vitamin D studies on serum cytokines have used dosages which were not adequate to achieve physiological circulating 25(OH)D levels. In future, more controlled clinical trials are needed to investigate whether optimal oral vitamin D supplementation is able to reduce cardiovascular risk markers and CVD mortality.

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