Putting cardiovascular disease and vitamin D insufficiency into perspective

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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 as 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 whereas 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...
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. 2005; 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).

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 (Baadenkopf 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; Barendgolts 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).

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

<table>
<thead>
<tr>
<th>Stages of vitamin D status</th>
<th>25(OH)D concentrations (nmol/l)</th>
<th>Biochemical and clinical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>0–25</td>
<td>Severe hyperparathyroidism, Ca malabsorption, rickets, osteomalacia, myopathy</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>&gt; 25–50</td>
<td>Mild hyperparathyroidism, low intestinal Ca absorption rates, reduced bone mineral density, subclinical myopathy</td>
</tr>
<tr>
<td>Hypovitaminosis D</td>
<td>&gt; 50–70 to 100</td>
<td>Low body stores of vitamin D, slightly elevated PTH levels</td>
</tr>
<tr>
<td>Adequacy</td>
<td>70–100 to 250</td>
<td>No disturbances of vitamin D-dependent functions</td>
</tr>
<tr>
<td>Toxicity</td>
<td>&gt; 250</td>
<td>Intestinal Ca hyperabsorption, hypercalcaemia</td>
</tr>
</tbody>
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PTH, parathyroid hormone.
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 mg/d (Zittermann, 2003a). 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 levels 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, 2003b). 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, 2003a). There is thus no risk for human adults to develop vascular calcification as a result of vitamin D intoxication.

![Figure 1. Hypothetical associations between vitamin D insufficiency and CVD. MGP, matrix Gla protein; PTH, parathyroid hormone; RAS, renin–angiotensin system.](https://doi.org/10.1079/BJN20051544)
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 occurs in combination with osteoprotic 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 × PO4 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 impair, 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 D3 was associated with a 70% lower risk of death from CVD when compared with a group of 1α-hydroxyvitamin D3 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
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 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 (Enquelslassie 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. 3. Mean circulating 25-hydroxyvitamin D levels in children, adolescents, and adults according to geographic latitude ($r = -0.68$; $P<0.01$). (1) Children, Lishares 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, Lamborg-Allardt et al. 2001; (15) adolescents, Lehtonen-Vermoa et al. 1999; (16) adults, Vik et al. 1980.](https://www.cambridge.org/core/core_ip_address: 54.70.40.11, on 16 Sep 2018 at 00:09:58, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms . https://doi.org/10.1079/BJN20051544)
Urbanisation is associated with an increased mortality from IHD (Enterline et al. 1997). 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 were observed in elderly subjects with low vitamin D status throughout the year, despite marked seasonal fluctuations in daily sunshine (Goswami et al. 2000).

Urbanisation is associated with an increased mortality from IHD (Enterline et al. 1997). 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). 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 ν.
68 nmol/l; 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 per-
formed 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 D₃ 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)
designed to compare 3-monthly injections of a depot sol-
tion 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 Bergh 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 ν.
120 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. Epide-
miological data indicate that geographic latitude, altitude,
season, and the place of residence (rural or urban) are all associ-
ated with CVD mortality. Until now, no sufficient explanations
for a common origin of these associations were available. How-
ever, 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 hypo-
thesis 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 interven-
tion 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 ill-
nesses, 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 rec-
ommendation 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 car-
diovascular risk markers and CVD mortality.

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Vitamin D and cardiovascular disease


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