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Sun, vitamin D, and cardiovascular disease

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ABSTRACT

Globally, cardiovascular disease (CVD) is the number one cause of death, being responsible for approximately 30% of deaths worldwide. Urbanization and a westernized lifestyle are thought to play a major role in the development of CVD. There is accumulating evidence that vitamin D is a nonclassical risk factor for CVD. The active vitamin D metabolite, 1,25-dihydroxyvitamin D, which is synthesized from its precursor 25-hydroxyvitamin D (25[OH]D), down-regulates several negative and up-regulates various protective pathways in the heart and vasculature. First randomized trials demonstrate that vitamin D supplementation leads to vasodilatation and suppresses cardiovascular risk markers such as triglycerides and the inflammation marker tumor necrosis factor-α.

Solar UV-B radiation is the major source of vitamin D for humans. Consequently, the vitamin D status is largely influenced by season, geographic latitude, daily outdoor activities, and the percentage of body surface exposed to solar UV-B. A significant proportion of individuals in Europe and North America have vitamin D concentrations in the deficiency range (25[OH]D < 25 nmol/l). Available data indicate that low solar UV-B exposure and/or low 25(OH)D concentrations are associated with an increased risk of CVD. Large nonrandomized studies indicate that CVD mortality is more than twice as high in older individuals with deficient 25(OH)D concentrations compared with those individuals who have adequate 25(OH)D concentrations (>75 nmol/l). Together, experimental and epidemiological evidence does support a plausible role for improving vitamin D status in CVD prevention in the population at large. Nevertheless, future randomised clinical trials are needed to evaluate whether vitamin D is effective with respect to primary, secondary, and/or tertiary prevention of CVD.

1. Introduction

Globally, cardiovascular disease (CVD) is the number one cause of death. In 2005, CVD was responsible for approximately 30% of deaths worldwide. CVD includes various illnesses such as coronary artery disease (CAD), peripheral arterial disease, cerebrovascular disease such as stroke, and congestive heart failure. Lifestyle factors such as westernized diets and physical inactivity in concert with an increasing life expectancy are thought to play a major role in the development of CVD [1]. From the year 1990 to the year 2020, the numbers of CAD related deaths will double in the male population and will increase by 80% in the female population [2]. With respect to cerebrovascular disease, mortality in females and males will increase by 78% and 106%, respectively, during the aforementioned time period. The continued worldwide rise in CVD morbidity and mortality is accompanied by the increasing process of urbanization [2,3]. Until recently [4], little attention has been paid to the fact that vitamin D deficiency may play a pivotal role in the development of CVD and that urbanization may contribute to the problem of vitamin D deficiency. In contrast, it has already been known for several decades that urbanization was a major risk factor for severe vitamin D deficiency in infants during the 18th and 19th century in North America and Europe. This problem has disappeared in the 20th century after it became obvious that rickets, a bone disease caused by vitamin D deficiency, can be prevented by regular supplementation of infants with vitamin D and/or by the exposure of children to artificial UV-B irradiation. It is now becoming increasingly clear that in adults, inadequate solar UV-B exposure and a lack of vitamin D is very prevalent throughout the world [5]. Evidence is accumulating that vitamin D deficiency contributes to CVD morbidity and mortality (see below).

2. Sun, vitamin D metabolism, and vitamin D status

Solar UV-B radiation is the major source of vitamin D for humans, whereas dietary vitamin D is a second, less important source. Once in the circulation, vitamin D is metabolized by a hepatic hydroxylase into 25-hydroxyvitamin D (25[OH]D) and by a

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renal 1α-hydroxylase into the vitamin D hormone 1,25-dihydroxyvitamin D. The latter step is under control of parathyroid hormone (PTH). However, in case of vitamin D deficiency/insufficiency, renal synthesis of 1,25-dihydroxyvitamin D becomes substrate dependent, i.e. dependent on the circulating 25(OH)D concentration [6]. The vitamin D receptor (VDR) is nearly ubiquitously expressed, and almost all cells respond to 1,25-dihydroxyvitamin D exposure; about 3% of the human genome is regulated, directly and/or indirectly, by the vitamin D endocrine system [7]. Consequently, 1,25-dihydroxyvitamin D influences many physiological processes, including muscle function, cardiovascular homeostasis, nervous function, and the immune response [8]. 1,25-dihydroxyvitamin D is also produced by local 1α-hydroxylases from its precursor 25(OH)D in various extra-renal cells, including the gastrointestinal tract, skin, vasculature, myocardium, and placenta [9,10]. Vitamin D status can be assessed by using the following cut-offs of serum 25(OH)D:<25 nmol/l for deficiency (divide by 2.5 to convert into ng/ml), 25–49.9 nmol/l for insufficiency, 50 to 75–99.9 nmol/l for hypovitaminosis, ⩾100 to 250–500 nmol/l for normal status, and ⩾250–500 nmol/l for intoxication (Table 1). Although there is still some debate on how to classify vitamin D status, the vast majority of vitamin D researchers agree that 25(OH)D levels below 50 nmol/l are insufficient.

The importance of solar UV-B exposure for human vitamin D status is underscored by several findings: first, 25(OH)D levels show seasonal fluctuations in Europe and North America with the lowest values observed in winter [12]. This is due to the fact that solar UV-B radiation is not sufficient for significant vitamin D production in the skin at geographic latitude of 40°N from November until February and at latitude of 50°N from October until April [13]. Second, dark skinned US Americans have far lower 25(OH)D levels than white Americans [14]. Third, women who completely avoid sun exposure have 25(OH)D levels in the deficiency range [15]. Fourth, blood 25(OH)D levels are lower within a country in geographical regions of low solar UV-B radiation compared with regions of higher solar UV-B radiation [16]. Finally, indoor workers who spend only 25 min daily outdoor have deficient 25(OH)D levels [17].

Diet contributes only a small percentage to vitamin D supply. It has been calculated that 1 μg vitamin D increases circulating 25(OH)D levels by 1 nmol/l [18]. In Germany, for example, mean daily vitamin D intake in adults is only 1–3 μg (1 μg is equivalent to 40 international units) [19,20]. In the United States, mean daily vitamin D intake is 9.3 μg [21]. The higher vitamin D intake in the United States compared with Germany is at least in part due to vitamin D fortification of milk, some juices and cereals, and the more frequent use of vitamin D supplements.

Worldwide, mean 25(OH)D concentrations are 54 nmol/l [22]. In Europe, mean concentrations are only 45 nmol/l [23]. More than 40% of young European adults and between 8% and 60% of healthy elderly persons have deficient 25(OH)D levels during the winter season [17]. In North America, there is evidence that the vitamin D status in the general population declined from 1988 to 1994 until 2000–2004 [24].

An important risk factor for an inadequate vitamin D status is the worldwide process of urbanization in concert with a westernized lifestyle. Urbanization often leads to insufficient outdoor activities and is associated with highly polluted air in some cities [4]. An additional reason for inadequate vitamin D status may involve indoor exposures to UV-A passing through windows, which can break down vitamin D in the blood, whereas windows effectively block UV-B passage [25]. It has also been hypothesized that vitamin D may be removed from the skin by washing [26].

3. Seasonal, latitudinal, and altitudinal differences in CVD

Excess winter mortally is a well-known worldwide phenomenon. The amplitude of seasonal fluctuations in mortality rhythm is highest at latitudes of 30–50° North or South and is low or absent near the equator or in subpolar regions [27]. In moderate climates, the amplitude of annual mortality rhythm is up to 20%. Seasonality of deaths is mostly due to increased cardiovascular and respiratory mortality during winter. Several possible biologic and environmental explanations for this seasonal effect have been postulated, among them changes in ambient temperature [28]. Nevertheless, winter temperature and climate differences cannot sufficiently explain excess winter mortality. It has also been assumed that variations in solar UV-B radiation and a lack of vitamin D in winter might contribute to the seasonality of heart failure and total cardiovascular deaths [4,29,30]. The vitamin D hypothesis is in line with the fact that in contrast to seasonal variations in 25(OH)D levels in individuals living in Central Europe, no meaningful annual variations in 25(OH)D levels have been observed in healthy elderly Scandinavians (geographic latitude: 55–70°N) and in subjects living near the equator [17,31]. Similar to CAD, other arterial thrombotic complications such as stroke have shown seasonal variations [32,33]. The risk of thromboembolic events is greater in the winter months than in the summer months [34,35]. No plausible explanation has yet been given for these findings. In a recent cohort study, 40,000 Swedish women were followed for a mean of 11 years [36]. Seventy-four percent answered a questionnaire at baseline and provided detailed information on their sun exposure habits. During follow-up, 313 thromboembolic events occurred. Women who sunbathed during the summer, on winter vacations, or when abroad, or used a tanning bed, were at 30% lower risk of thromboembolic events than those who did not. Besides seasonal variations in vitamin D status and cardiovascular events, a relation of geographic latitude with vitamin D status and CAD events has also been observed. In Scotland, the percentage of blood 25(OH)D levels below 40 nmol/l are twice as high compared with England and Wales [8]. Similarly, the rate of CAD events is 100% higher in Scotland compared with the South of Great Britain [37]. Very recently, a Swiss study demonstrated that

Table 1
Vitamin D status classified according to circulating 25-hydroxyvitamin D concentrations (modified from Ref. [11]).

	25-Hydroxyvitamin D (nmol/l)	Clinical/biochemical alterations
Deficiency	<25	Rickets, osteomalacia, myopathy, calcium malabsorption, severe hyperparathyroidism, low 1,25-dihydroxyvitamin D concentrations, impaired immune and cardiac function?
Insufficiency	25–49.9	Reduced bone mineral density, impaired muscle function, low intestinal calcium absorption rates, elevated PTH levels, slightly reduced 1,25-dihydroxyvitamin D levels
Hypovitaminosis D	50 to 75–99.9	Low bodily stores of vitamin D, slightly elevated PTH levels
Adequacy	100 to 250–500	No disturbances of vitamin D-dependent functions
Intoxication	>250–500	Soft tissue calcification, intestinal calcium hyperabsorption, hypercalcemia

Abbreviation: PTH, parathyroid hormone.