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Prevalence of Subclinical Vitamin D Deficiency in Different European Countries

S. H. Scharla

Klinikum Berchtesgadener Land, Schönau am Königssee, Germany

Introduction

Long-lasting and severe vitamin D deficiency leads to osteomalacia, a metabolic bone disease characterized by typical biochemical abnormalities (low serum concentrations of calcium and phosphate, increased activity of alkaline phosphatase). Bone histology shows decreased mineralization of bone matrix, increased osteoid volume and decreased bone formation. Vitamin D deficiency can be confirmed by measuring the serum concentration of 25-hydroxyvitamin D (25(OH)D), which is the major circulating metabolite bound with high affinity to a binding protein (DBP) and representing the storage form of vitamin D. In patients with osteomalacia, serum 25(OH)D levels are usually below 5 ng/ml and often undetectable.

In contrast, patients with primary osteoporosis usually have serum concentrations of calcium and phosphate within the normal range, and alkaline phosphatase is rarely elevated. Therefore, in the opinion of many authors vitamin D deficiency is not an important pathogenetic factor for the development of osteoporosis.

However, growing evidence demonstrates that moderately low levels of vitamin D can already have unfavorable effects on calcium homeostasis leading to bone loss, even if osteomalacia is not present. Barger-Lux and coworkers [1] showed that 25(OH)D contributes to the stimulation of enteral calcium absorption explaining the secondary increase in parathyroid hormone resulting from vitamin D deficiency, although 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D) levels may still be normal. A vitamin D status insufficient to maintain physiologic calcium homeostasis, but not resulting in overt osteomalacia, is called vitamin D insufficiency or subclinical vitamin D deficiency.

Vitamin D insufficiency is a common problem especially in Europe (for reasons explained below), and therefore this paper will review the vitamin D status in different European countries.

Correspondence and offprint requests to: Dr Stephan H. Scharla, Klinikum Berchtesgadener Land, Malterhöh 1, D-83471 Schönau am Königssee, Germany.

Definition of 'Subclinical' Vitamin D Deficiency

An early sign of vitamin D insufficiency is the secondary increase in the serum concentration of parathyroid hormone, which may still be within the 'upper normal range'. Several investigators have demonstrated an inverse relationship between serum 25(OH)D and intact parathyroid hormone [2]. A recent Dutch study found that 25(OH)D concentrations below 12 ng/ml (= 30 nmol/l) result in secondary hyperparathyroidism and decreased bone mineral density at the proximal femur [3]. A threshold of 12 ng/ml to define vitamin D insufficiency has also been proposed by others [4]. McKenna [5] used a threshold of 25 nmol/l (= 10 ng/ml), which is very similar.

A different approach to define subclinical vitamin D deficiency has been described by Bouillon and coworkers [6] using a vitamin D challenge test: if in the absence of histologic or biochemical signs of vitamin D deficiency a rapid (but usually transient) increase in serum 1,25-$(OH)_2$D is observed after supplementation with physiologic amounts of vitamin D or 25(OH)D, then one may conclude that the preexisting substrate availability was insufficient for optimal 1,25-$(OH)_2$D production, which is normally well feedback regulated [7]. If the serum concentration of 25(OH)D is above 10–15 ng/ml, then 1,25-$(OH)_2$D does not increase after vitamin D challenge, thus defining the lower limit of physiologically normal 25(OH)D levels. This agrees well with the above-mentioned threshold for secondary hyperparathyroidism.

Factors Influencing Vitamin Status in Different European Populations

Skin synthesis under the influence of ultraviolet light (290–315 nm) and dietary intake are the main sources of vitamin D. Relevant amounts of vitamin D are found in sea fish, egg yolk, butter and some mushrooms [8]. Therefore, vitamin D supply can be expected to be good in populations with regular consumption of sea fish and dairy products, such as Scandinavia or the Netherlands.

However, nutritional vitamin D supply will be low in non-coastal areas such as continental Europe. Supplementation of food with vitamin D is not common in Europe with the exception of some Scandinavian countries. This is in contrast to the USA, where milk is fortified with vitamin D. Older women in the USA exhibit a good correlation between milk intake and serum 25(OH)D levels [9]. This explains the low prevalence of vitamin D deficiency even in the elderly US population [10], which is in contrast to the high prevalence in Europe (see below).

Skin synthesis of vitamin D cannot compensate for low nutritional intake, because Europe is located at high latitude reaching from 40° N (Madrid, Spain) to 60° N (Oslo, Norway). Webb and coworkers [11] in the USA demonstrated that in Boston (latitude 42° N) photosynthesis of previtamin D is nearly impossible during the winter months (November through February), and in Edmonton (latitude 52° N) vitamin D synthesis is impaired from October through March. From this it is obvious that vitamin D deficiency may occur even in southern Europe, but can present a severe problem in northern Europe. However, populations in southern Europe usually have more skin pigmentation, which counteracts the larger amount of sunlight in this area. Melanin pigmentation decreases the efficiency of the photosynthesis of vitamin D. The ability of skin to produce vitamin D also decreases with age, contributing to lower vitamin D levels in the elderly.

Studies Investigating Vitamin D Status in Selected Subjects from Different Countries

It is well known that elderly people in Europe, especially nursing home residents, often suffer from vitamin D insufficiency and even osteomalacia. An early study by Corless and coworkers [12] in England demonstrated vitamin D insufficiency (25(OH)D < 15 ng/ml) in all geriatric females, who stayed for a long period in hospital. Ninety percent of the subjects had severe vitamin D deficiency (25(OH)D < 5 ng/ml) [12]. Similar results were reported in a more recent Finnish study investigating 55 geriatric long-term nursing home residents, which found low 25(OH)D serum levels (< 10 ng/ml) in all subjects [13]. A high prevalence of vitamin D insufficiency is also found in geriatric patients in Germany [14,15], France [16], and Switzerland [17].

However, vitamin D insufficiency is not restricted to hospitalized elderly people. A Dutch investigation found vitamin D insufficiency (defined by 25(OH)D concentrations < 8 ng/ml) in 16% of the healthy elderly population, and vitamin D insufficiency in 60% of people experiencing a hip fracture [18–20]. In German patients with hip fracture vitamin D insufficiency occurred in 69% of the women and 55% of the men. All patients had been ambulatory before the fracture event [21]. In northern Italy there is also a high prevalence of low vitamin D status in postmenopausal women. According to a new study [22], 38.5% of all women (mean age 59 years, range 41–80 years) had 25(OH)D serum concentrations below 12 ng/ml during winter/spring (December through May), and 12.5% of the women still had low levels during summer/autumn (June through November). However, this study did not observe a population-based sample, but 570 consecutive women referred to a clinic for an osteoporosis investigation.

Vitamin D insufficiency may occur even in adolescents. Guillemant and coworkers [23] studied seasonal variations of serum levels of 25(OH)D and parathyroid hormone in male adolescents (age from 13 years 6 months to 15 years 9 months) from a horse-riding school in the north of Paris (49° N). Serum 25(OH)D concentrations were 29.96 ± 7.46 ng/ml in September and 6.61 ± 2.04 ng/ml in March. In March all adolescents had subclinical vitamin D deficiency (25(OH)D < 12 ng/ml) and increased parathyroid hormone (still within the normal range).

In 1992 McKenna [5] published a review dealing with reports on vitamin D status from 1971 to 1990. In total, 117 studies of vitamin D status from 27 regions were taken into account: 34 studies on the elderly alone, 42 on young adults alone, and 41 on both. The studies were grouped according to geographic regions (North America, Scandinavia and Central/Western Europe). To control for seasonal variations, analyses were performed separately for late winter (January–March), late spring (April–June), late summer (July–September), and late autumn (October–December). In young adults, no significant difference was found between American and Scandinavian regions. However, European values were significantly lower compared with Scandinavia and North America during winter, spring and autumn. Summer values of serum 25(OH)D were not different between the regions. In healthy elderly, trends were similar to those of younger adults but not as marked, with European values being lower compared with Scandinavia or North America in spring and autumn. In institutionalized elderly, again the European values were lower than both Scandinavian and North American values, and Scandinavian values were lower than North American values.

The prevalence of vitamin D insufficiency was very low in North America, reached about 4–9% of young adults in Scandinavia, and was > 40% in young adults in Western/Central Europe during winter. Regarding the healthy elderly population, in North America and Scandinavia nearly 25% of subjects have low values in the winter but less than 5% have low levels throughout the remainder of the year. In Western/Central Europe, the frequency of vitamin D insufficiency ranges from 8% to 60% [5].

One can conclude that vitamin D status in Scandinavia is much better than in Western and Central Europe, which is in good accord with a more recent population-based study ([24], see below). This may be unexpected, because sunlight exposure is much lower in Scandinavia than Central Europe. However, the percentage of people taking vitamin D supplements is rather high in

Scandinavia, and some countries such as Norway have fortification of food (e.g., addition of vitamin D to margarine).

Population-Based Studies

Van der Wielen and coworkers [24] reported the results of the SENECA study, which is an investigation of the diet and health of elderly people from 19 towns in 11 European countries. Participating countries were Greece, Portugal, Italy, Spain, France, Switzerland, Hungary, Belgium, Netherlands, Denmark and Norway. In each country, towns with a population size of 10 000–20 000 and a socioeconomic structure comparable to the country or the region as a whole were selected. In each town, random samples of the residents were stratified for age and sex, whereby the age range was between 71 years and 76 years. The collection of blood samples was done during January, February and March. Determination of 25(OH)D was done at a single center using a competitive binding assay. Mean 25(OH)D serum concentrations ranged from 10 ng/ml (Greece) to 24 ng/ml (Switzerland) in men and from 8.4 ng/ml (Greece, Spain) to 19 ng/ml (Norway) in women. Subclinical vitamin D deficiency (25(OH)D < 12 ng/ml) was much more frequent in Mediterranean countries (prevalence up to 83% in Greek women) than in northern Europe (18% in Norway) (Fig. 1). One factor associated with better vitamin D status was increased fish consumption, but the main reasons for the relative good vitamin D status in Scandinavian countries are probably fortification of food and a higher percentage of people taking vitamin D supplements.

Chapuy and coworkers [25] investigated vitamin D status and bone turnover in elderly women selected from a population-based sample in France. Elderly ambulatory women from the general community were recruited by mailing from electoral lists as participants of the EPIDOS INSERM Merck study, a prospective multicentric study on risk factors for hip fracture. Among the EPIDOS population 445 women (mean age 80 years) were randomly selected. Women taking vitamin D tablets, women with previous fractures or institutionalized women were excluded. Blood samples were taken at the end of winter (between February 15 and March 15). The mean 25(OH)D levels were 17 ± 10 ng/ml (42.5 ± 25 nmol/l), and 39% of these healthy ambulatory elderly women had vitamin D insufficiency with 25(OH)D levels < 12 ng/ml. The elderly women with vitamin D insufficiency had increased parathyroid hormone levels above the normal range (69 ± 34 pg/ml). Biochemical markers of bone turnover were increased in comparison with a control group of younger women.

In a further study, Chapuy and coworkers [26] looked at the vitamin D status of a middle-aged general adult urban population in nine geographic regions of France. The study was conducted within the framework of the French SUVIMAX project, a large interventional epidemiologic study. Of 15 000 volunteers, 765 men aged 45–65 years and 804 women aged 35–60 years were randomly selected from 20 French cities in nine geographic regions whose latitude varies from 43° N to 51° N. All blood samples were taken between November and April. There was no effect of age and sex on 25(OH)D levels, but there was a significant influence of latitude and sunshine on vitamin D status, with mean 25(OH)D levels ranging from 38 ± 15 ng/ml (94 ± 38 nmol/l) in the South-West to 17 ± 8 ng/ml (43 ± 21 nmol/l) in the North. Surprisingly, vitamin D insufficiency (25(OH)D < 12 ng/ml) was found in 14% of this healthy urban population, and was even present in the Mediterranean coast region (7%). This study also investigated the relation between vitamin D status and parathyroid hormone, proving a significant negative correlation between intact parathyroid hormone (iPTH) and 25(OH)D values. Interestingly, above 25(OH)D levels of 31.2 ng/ml (78 nmol/l) iPTH reached a plateau. In other words, below this 25(OH)D threshold iPTH starts to increase in the sense of secondary hyperparathyroidism.

The author of the present paper has investigated vitamin D status in the normal population of southern

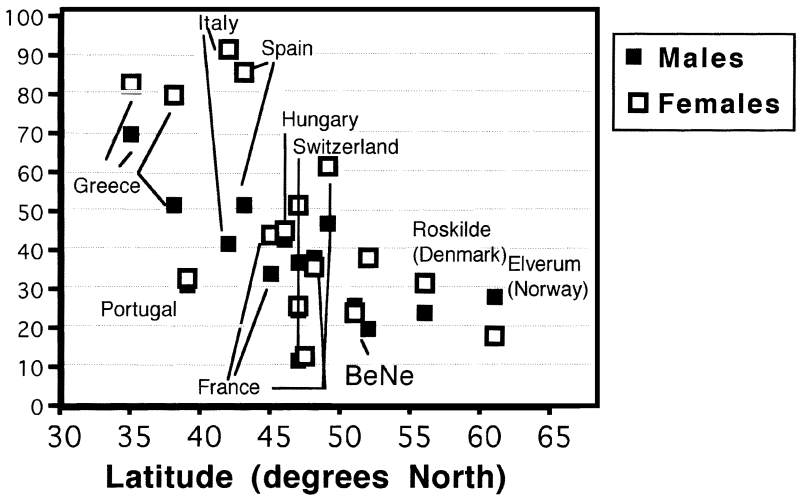

Fig. 1. The percentage of the healthy elderly population with subclinical vitamin D deficiency (25-hydroxyvitamin D serum concentration below 12 ng/ml) is plotted against the latitude (degrees North) of the respective home towns. Countries are indicated in the figure (*BeNe*, Belgium/Netherlands). It is obvious that the prevalence of subclinical vitamin D deficiency is higher in Southern Europe as compared with Scandinavia. (Modified from van der Wielen et al. [24].

Germany aged between 50 years and 80 years [27]. Vitamin D status was assessed in 415 inhabitants of a small town in southern Germany who were participating in the European study on vertebral osteoporosis (EVOS). The subjects (50–80 years) had been recruited using the city register of inhabitants to obtain a population-based sample stratified for age and sex. Each person presented on a single day, and data collection consisted of a standardized medical history, determination of the body mass index, non-fasting blood sampling, collection of a spot urine specimen, and bone mineral density measurement. The serum was stored frozen at –80° C until determination. The serum concentration of 25(OH)D was determined with a commercial radioimmunoassay employing ^{125}I-25-OH-vitamin D as tracer (25(OH)D RIA Kit, Incstar, Stillwater, MN). This radioimmunoassay is based on the method published by Hollis and coworkers [28]. Serum 25(OH)D concentrations were not different in women and men [29], but there was a pronounced seasonal variation (Fig. 2). In late summer the 25(OH)D concentration (mean ± SD) was 28 ± 11 ng/ml in men and 27 ± 9 ng/ml in women, whereas in late winter the concentrations were 18 ± 9 ng/ml in men and 16 ± 9 ng/ml in women. There was a moderate decrease in 25(OH)D concentrations with age, which was more pronounced in females in winter (Figs 3, 4). Forty percent of the women and 30% of the men had subclinical vitamin D deficiency in winter [30].

The same study demonstrated an association between low vitamin D status and increased bone resorption (reflected by urinary excretion of collagen crosslinks,

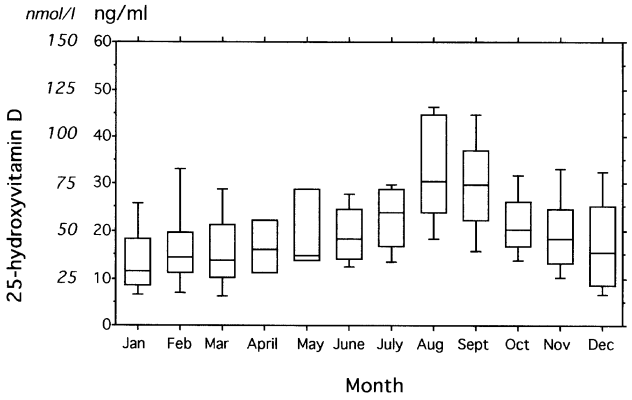

Fig. 2. Seasonal variation of 25-hydroxyvitamin D serum concentration in the average German population (age 50–80 years). The data are shown in the form of a box-plot diagram. The *crossbar* in the box represents the median; 50% of all values lie within the box; the *small vertical bars* indicate the range between the 10% and the 90% percentiles. (From Scharla and Scheidt-Nave [30].

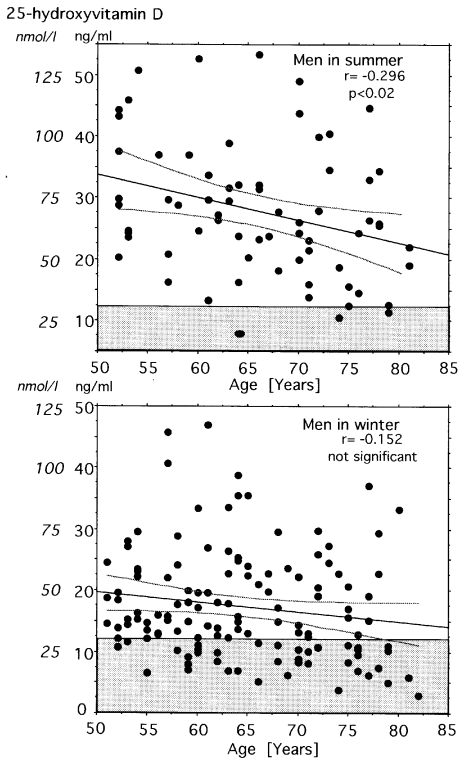

Fig. 3. Distribution of 25-hydroxyvitamin D serum concentration in German men according to age. The range of subclinical vitamin D deficiency (25-hydroxyvitamin D <12 ng/ml) is indicated as a *shaded area.* The data are shown separately for the summer season (May through October) and the winter season (November through April). Statistical evaluation was done by linear regression analysis. (From Scharla and Scheidt-Nave [30].

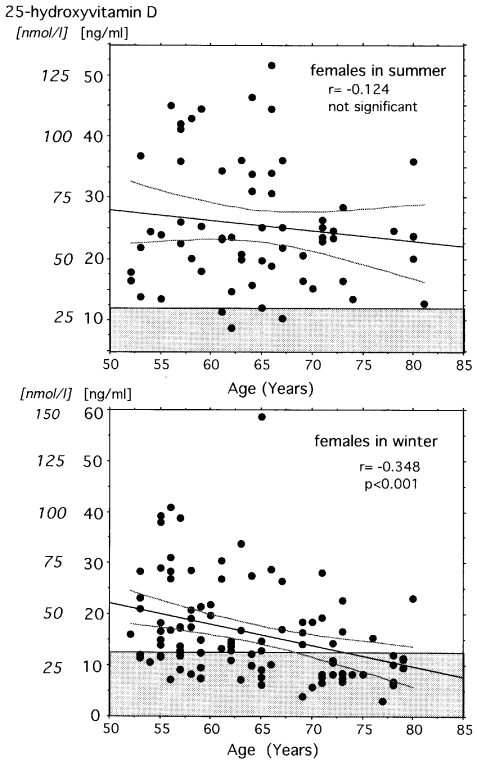

Fig. 4. Distribution of 25-hydroxyvitamin D serum concentration in German women according to age. The range of subclinical vitamin D deficiency (25-hydroxyvitamin D <12 ng/ml) is indicated as a *shaded area.* The data are shown separately for the summer season (May through October) and the winter season (November through April). Statistical evaluation was done by linear regression analysis. (From Scharla and Scheidt-Nave [30].

pyridinoline) in women. To obtain this relationship, subjects taking any medication influencing bone metabolism were excluded [27]. In addition, low 25(OH)D concentrations were also associated with lower bone mineral density at the femoral neck in women. This relationship was more pronounced and independent of age when the data obtained in summer were evaluated. This could mean that sun exposure during summer resulting in improved vitamin D status during this season is important for maintaining bone mass, independently of vitamin D status in the late winter.

Conclusions

The European population is at high risk for vitamin D insufficiency, because the continent is located at high latitude leading to restricted ultraviolet light exposure. In addition, the nutritional supply of vitamin D is low in most countries and fortification of food is done only in few countries, mostly in Northern Europe. Addition of vitamin D to margarine is compulsory in Norway, Denmark, the Netherlands, Belgium and Portugal. Accordingly, the percentage of people taking vitamin D supplements is higher in Northern Europe compared with Southern Europe. This explains why vitamin D insufficiency is more prevalent in Southern Europe (reaching up to 90% in healthy elderly women during winter in Greece, Italy and Spain). Darker skin pigmentation and cultural habits such as clothing and avoidance of outdoor activities may contribute to vitamin D insufficiency in Mediterranean countries. However, the findings from North America and Scandinavia demonstrate that food fortification and intake of vitamin supplements are able to improve vitamin D status even in absence of sufficient sunlight exposure.

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