

## Hypovitaminosis D in an Italian population of healthy subjects and hospitalized patients

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The present study aimed to investigate the prevalence and seasonal variation of hypovitaminosis D (defined as serum 25-hydroxyvitamin D level below 30 nmol/l) among healthy subjects and hospitalized patients living in central Italy. We studied 297 subjects, 131 in February 1997 and 166 in July 1997, subdivided into four groups: (a) young healthy blood donors; (b) healthy postmenopausal women; (c) inpatients with various medical diseases and (d) inpatients engaged in long-term rehabilitation programmes because of various neurological disorders. In all subjects and patients serum levels of 25-hydroxyvitamin D were measured by radioimmunoassay. We found a significant seasonal variation ( $P < 0.0001$ ) of serum 25-hydroxyvitamin D levels, mean values being higher in summer in all groups, except in patients with a longer hospitalization time (group (d)). In each group, a significantly higher prevalence of hypovitaminosis D was found in winter compared with summer time ( $P < 0.001$ ), being unexpectedly high in postmenopausal women (winter 32% and summer 4.5%); furthermore, in both seasons, inpatients were characterized by the highest incidences of hypovitaminosis, particularly those in group (d) (winter 82.3% and summer 57.8%). The results of the present study emphasize the importance of 25-hydroxyvitamin D measurement, and the need to increase vitamin D intake in Italy; foodstuff fortification and supplement use must be considered in order to prevent negative effects of vitamin D deficiency on skeletal integrity.

### Vitamin D: Skeletal integrity: Hypovitaminosis D

In recent years, a growing interest has developed in the role of the vitamin D–endocrine system interaction in the pathogenesis of bone loss and osteoporosis. While it is well known that severe and protracted vitamin D deficiency leads to osteomalacia, the impact and consequences on bone remodelling of subclinical vitamin D deficiency remain controversial (Parfitt *et al.* 1982; Woitge *et al.* 1998).

Sunlight exposure and diet are the main determinants of vitamin D status, but each is greatly influenced by a variety of factors such as age, race, geographical location, seasons and use of sunscreen (Fraser, 1995). As a consequence, epidemiological studies on vitamin D status, usually defined by the amount of circulating 25-hydroxyvitamin D (25(OH)D) (Hollis, 1996), have shown marked differences between countries. In fact, the prevalence of hypovitaminosis D is lower in North America where sunshine exposure is adequate and the food is vitamin D-fortified, and higher in most European countries, independent of

geographical location (McKenna, 1992; van der Wielen *et al.* 1995; Chapuy *et al.* 1997). Nevertheless, it has been demonstrated that vitamin D deficiency (defined as a serum 25(OH)D level below 30 nmol/l) is very common worldwide in the elderly (McKenna, 1992; Keane *et al.* 1995; van der Wielen *et al.* 1995; Chapuy *et al.* 1996, 1997; Jacques *et al.* 1997), especially if hospitalized (Goldray *et al.* 1989) and/or institutionalized (Komar *et al.* 1993; Gloth *et al.* 1995; Liu *et al.* 1997). This may occur as a result of low dietary intake that is not compensated for by an adequate exposure to sunlight. Moreover, the decline of renal function with age can lead to reduced serum levels of 1,25-dihydroxyvitamin D and impaired intestinal Ca absorption (Akeson *et al.* 1997), even if this finding is not universally recognized (Sherman *et al.* 1990). Vitamin D deficiency, through secondary hyperparathyroidism, could play a significant role in decreasing femoral bone density and increasing bone fragility and fracture risk in the elderly (Quesada-Gomez

**Abbreviation:** 25(OH)D, 25-hydroxyvitamin D.

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*et al.* 1996). Moreover, it has been demonstrated that an adequate vitamin D status is important in the maintenance of bone density even in peri- and postmenopausal women (Villareal *et al.* 1991; Khaw *et al.* 1992). Therefore, estimation of vitamin D status is clearly relevant in order to understand better its influence on bone turnover and bone loss.

Few studies have been carried out in Italy in order to evaluate the prevalence of hypovitaminosis D. Recent data reports a high prevalence of vitamin D deficiency among free-living postmenopausal women from the area of Milan (Bettica *et al.* 1997), confirming previous results on elderly subjects with chronic diseases or living in areas of northern Italy with short periods of sunlight (Rossini *et al.* 1990).

The aim of the present study was to investigate the prevalence and seasonal variation of hypovitaminosis D in free-living normal subjects and hospitalized patients from the area of Rome, in central Italy.

### Materials and methods

We studied 297 subjects in total, 131 in February and 166 in July 1997. The subjects were recruited from the following four groups: (a) young healthy blood donors (February, *n* 47, mean age 35.1 (SD 10.5) years and July, *n* 41, mean age 34.9 (SD 9.52) years); (b) healthy postmenopausal women (February, *n* 25, mean age 62.28 (SD 6.59) years and July, *n* 22, mean age 62.36 (SD 10.41) years); (c) inpatients with various medical diseases (February, *n* 42, mean age 69.60 (SD 9.93) years, mean hospitalization time 15.73 (SD 22.53) d and July, *n* 46, mean age 61.6 (SD 14.7) years, mean hospitalization time 10.9 (SD 8.9) d); (d) inpatients engaged in long-term rehabilitation programmes because of various neurological disorders (February, *n* 17, mean age 73.76 (SD 4.41) years, mean hospitalization time 47.18 (SD 24.23) d and July, *n* 45, mean age 74.7 (SD 7.7) years, mean hospitalization time 61.0 (SD 32.2) d). In group (d), during the month of July, we also studied twelve patients, mean age 39.75 (SD 19.0)

years, mean hospitalization time 475.5 (SD 402.0) d (range 205–1330 d), whose diagnosis was a vegetative state (awake coma) secondary to a traumatic or anoxic encephalopathy. Informed consent was obtained from all eligible subjects or their relatives. Healthy blood donors and postmenopausal women were not taking any drug known to interfere with vitamin D metabolism, while patients were included in the study independently of diseases and/or medication use.

There was no significant seasonal difference in mean age between groups. However, in patients admitted to a general hospital (group (c)) mean age was higher in winter ( $P < 0.005$ ). There was no seasonal difference in mean hospitalization time between the two groups of inpatients ((c) and (d)).

In all subjects and patients serum levels of 25(OH)D were measured by radioimmunoassay (Incstar Co., Stillwater, MN, USA) (Hollis *et al.* 1993). The assay consists of a two-step procedure: the first step involves a rapid extraction of 25(OH)D and other hydroxylated metabolites with acetonitrile; following extraction, the treated sample is then assayed using an equilibrium radioimmunoassay procedure, based on an antibody with specificity to 25(OH)D. In our laboratory the intra- and interassay CV were 8.1 and 10.2 % respectively.

### Statistical methods

Data are presented as means and standard deviations. Correlations between variables were tested using linear regression analysis. Means were compared using Student's *t* test for two groups or one-way ANOVA for more groups.

### Results

Table 1 shows mean values of serum 25(OH)D levels obtained for each group both in winter and in summer time; no data were collected during February for patients with awake coma and thus they were excluded from inferential statistics. The ANOVA showed significant differences of 25(OH)D concentrations between groups

**Table 1.** Seasonal variation of serum 25-hydroxyvitamin D levels (nmol/l) in healthy subjects and hospitalized patients

(Mean values and standard deviations)

Time of study ...	February		July	
	Mean	SD	Mean	SD
Young blood donors	61.2 ( <i>n</i> 47)	25.2	120.3*** ( <i>n</i> 41)	32.1
Postmenopausal women	45.9 ( <i>n</i> 25)	28.5	90.1*** ( <i>n</i> 22)	49.6
Inpatients with medical diseases	27.2 ( <i>n</i> 42)	17.8	65.5*** ( <i>n</i> 46)	45.5
Inpatients engaged in long-term rehabilitation programmes	22.5 ( <i>n</i> 17)	11.9	31.1 ( <i>n</i> 45)	21.5
Inpatients with awake coma			62.9 ( <i>n</i> 12)	25.8

Mean values were significantly different from those for subjects studied in February: \*\*\* $P < 0.0001$ .

**Table 2.** Prevalence of hypovitaminosis D (%) in summer and winter time in healthy subjects and hospitalized patients

Time of year ...	February	July
Young blood donors	14.6	0.0
Postmenopausal women	32.0	4.5
Inpatients with medical conditions	71.4	29.8
Inpatients engaged in long-term rehabilitation programmes	82.3	57.8

( $P < 0.0001$ ), both in February and in July. Significant seasonal variations ( $P < 0.0001$ ) of serum 25(OH)D levels were also found for each group, mean values being higher in summer; only patients with longer hospitalization time (group (d)) showed no seasonal variation of mean 25(OH)D levels.

The prevalence of hypovitaminosis D (defined as a serum 25(OH)D level below 30 nmol/l) in both winter and summer time is shown in Table 2. For each group a significantly higher prevalence of hypovitaminosis D was found in winter time compared with summer time ( $P < 0.001$ ), the percentage being unexpectedly high in postmenopausal women (32 %); moreover, in both seasons, inpatients were found to be at high risk of hypovitaminosis D, particularly those with long-term hospitalization (group (d)).

Furthermore, we found significant negative correlation between the length of hospitalization and serum 25(OH)D levels both in summer ( $n 91$ ,  $r -0.363$ ,  $P < 0.001$ ) and in winter ( $n 59$ ,  $r -0.236$ ,  $P < 0.01$ ). A significant linear negative correlation was found between age and serum levels of 25(OH)D, both in February ( $n 131$ ,  $r -0.454$ ,  $P < 0.0001$ ) and in July ( $n 154$ ,  $r -0.625$ ,  $P < 0.0001$ ).

## Discussion

To our knowledge, this is the first study assessing vitamin D status in a sample of both adult general population and hospitalized patients living in central Italy. Epidemiological studies investigating the importance of hypovitaminosis D in Italy are few. In fact, in the SENECA study (van der Wielen *et al.* 1995), data regarding Italy are not representative, because only twenty-five subjects were enrolled. Other studies carried out in northern Italy have demonstrated that, especially in winter, the prevalence of hypovitaminosis D is unexpectedly high, not only in elderly people with chronic disease (Rossini *et al.* 1990) but also in free-living postmenopausal women (Bettica *et al.* 1997).

As previously reported (Chapuy *et al.* 1983; Tsai *et al.* 1987), serum 25(OH)D concentrations progressively decrease with advancing age independently of season. Moreover, we found a progressive significant decrease in mean values of serum 25(OH)D among groups examined, both in February and in July. This finding, among other factors, can be partly ascribed to the progressive increase of mean age observed from group (a) to group (d). In this context it is important to emphasize that we found an unexpectedly high mean value of 25(OH)D (62.9 (SD 25.8) nmol/l; range 18.52–90.22 nmol/l) in the twelve patients with vegetative state, despite being characterized

by the longer hospitalization time. This finding confirms that ageing is one of the main determinants of vitamin D status, because patients with awake coma were much younger than other inpatients. However, the better dietary intake in these patients, whose enteral nutrition included multivitamin solutions, should also be taken into account; indeed, such solutions contain at least 3.0–4.5 µg vitamin D daily, which is approximately the amount recently recommended as an adequate intake for people aged 19–50 years (Utiger, 1998).

As in previous reports (Juttman *et al.* 1981; Krall *et al.* 1989; Woitge *et al.* 1998), we also found a significant seasonal variation in serum 25(OH)D levels ( $P < 0.0001$ ) in both healthy young subjects and postmenopausal women, with higher values in summer. In patients admitted to a general hospital we still found a seasonal variation of vitamin D, with lower mean values of 25(OH)D in February compared with July. This finding, in our opinion, could partly be ascribed to the younger mean age of these patients studied in summer; alternatively, since their period of hospitalization was very short, we should consider these patients as being more representative of the general population, at least as far as lifestyle features are concerned. Conversely, in longstay patients (group (d)) the lack of sunshine exposure resulted in no seasonal variation of 25(OH)D levels. This finding is in disagreement with results reported in residents of long-term care facilities (Liu *et al.* 1997). This discrepancy could be ascribed to the different characteristics of patients examined, including affecting diseases, medications used and limitation in mobility with rare outdoor exposure.

The prevalence of hypovitaminosis D (defined as a serum 25(OH)D level below 30 nmol/l) is reported in Table 2. The choice of 30 nmol/l as a cut-off value for defining hypovitaminosis is in agreement with the threshold considered in several studies carried out in different European countries (van der Wielen *et al.* 1995; Chapuy *et al.* 1996, 1997; Lips *et al.* 1996). A greater percentage of prevalence would have been obtained if the hypovitaminosis was defined at a higher threshold as has been recently suggested (Malabanan *et al.* 1998). The results are unexpected, especially as far as the healthy population is concerned; interestingly, in postmenopausal women the high percentage of hypovitaminosis D in winter (about 32 %) was the same as that reported recently in free-living postmenopausal women from the area of Milan (Bettica *et al.* 1997). This finding is intriguing, because in northern Italy the supply of sunshine is limited to a shorter period of the year compared with the centre of the country. One possible explanation might be that as dairy products are not fortified with vitamin D and the use of nutritional supplements is uncommon in Italy, estimated vitamin D intake (about 3–5 µg/d) is below the amount recommended (10 µg/d) (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 1997). We can hypothesize that other physiological and/or lifestyle characteristics may influence serum 25(OH)D concentrations (Chapuy *et al.* 1996).

All hospitalized patients, both in summer and in winter, are characterized by the highest prevalence of hypovitaminosis D, especially the older patients. Medical inpatients may be at risk for vitamin D deficiency,

especially residents of nursing homes and elderly people (Goldray *et al.* 1989; Komar *et al.* 1993; Gloth *et al.* 1995; Chapuy *et al.* 1996). However, the results of our study clearly demonstrate that younger patients admitted to a general hospital for various medical diseases also exhibit a high prevalence of hypovitaminosis D, reaching 72% in winter. This finding is in agreement with results recently reported in the USA (Shane *et al.* 1997; Thomas *et al.* 1998), demonstrating that the problem of vitamin D deficiency in patients needing admission to hospital is more widespread than previously appreciated.

In the group of patients engaged in long-term rehabilitation programmes we found the highest prevalence of hypovitaminosis D, ranging from 57.8% in summer to 82.3% in winter. The older age, the presence of neurological disease causing reduced mobility and/or the requirement of anti-convulsant-drug therapy are probably responsible for an increased risk of vitamin D deficiency in this group of inpatients.

In conclusion, the results of the present study clearly provide evidence of the impact of hypovitaminosis D on medical practice in our country and underline the importance of serum 25(OH)D measurement. Foodstuff fortification and supplement use must be considered in order to prevent the negative effect of vitamin D deficiency on skeletal integrity.

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