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A Global Study of Vitamin D Status and Parathyroid Function in Postmenopausal Women with Osteoporosis: Baseline Data from the Multiple Outcomes of Raloxifene Evaluation Clinical Trial

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ABSTRACT

Vitamin D deficiency leads to secondary hyperparathyroidism, increased bone turnover, and bone loss and, when severe, to osteomalacia. Vitamin D deficiency is common in elderly people, especially the institutionalized. The definition of vitamin D deficiency is hampered by the fact that large interlaboratory differences exist in assays for serum 25-hydroxyvitamin D (25OHD), the main circulating metabolite. The international Multiple Outcomes of Raloxifene Evaluation study, a large prospective intervention trial in postmenopausal women with osteoporosis, offered the opportunity to compare vitamin D status and parathyroid function throughout many countries over the world.

For this study, baseline data were available from 7564 postmenopausal women from 25 countries on 5 continents. All women had osteoporosis, *i.e.* bone mineral density (BMD) at femoral neck or lumbar spine was lower than *t*-score −2.5, or they had 2 vertebral fractures. Serum 25OHD was measured by RIA, and serum PTH was measured by immunoradiometric assay. BMD was measured by dual x-ray absorptiometry. The mean (±SD) serum 25OHD was 70.8 ± 30.9 nmol/L. A low serum 25OHD (<25 nmol/L) was observed in 4.1% of all women in the Multiple Outcomes of Raloxifene Evaluation study, ranging from 0% in south east Asia (very few patients) to 8.3% in southern Europe. Serum 25OHD was between 25–50 nmol/L in 24.3% of the women. Serum 25OHD showed a significant seasonal relationship, with lower values in all regions in winter. Serum PTH correlated negatively with serum 25OHD ($r = -0.25$; $P < 0.001$). This significant negative correlation was observed in all regions. When serum 25OHD was less than 25, 25–50, or more than 50 nmol/L, respectively, mean serum PTH levels were 4.8, 4.1, and 3.5 pmol/L, respectively (by ANOVA, $P < 0.001$). Similarly, mean alkaline phosphatase levels were 83.7, 79.1, and 75.7 U/L ($P < 0.001$), respectively, with increasing serum 25OHD. The effect of serum 25OHD on BMD was only significant for the BMD of the trochanter where a serum 25OHD level less than 25 nmol/L was associated with a 4% lower BMD. After 6 months of treatment with vitamin D_3 (400–600 IU/day) and calcium (500 mg/day), serum 25OHD increased from 70.8 ± 29.8 to 92.3 ± 28.6 nmol/L. Serum PTH decreased significantly after 6 months of treatment, and this decrease depended on baseline serum 25OHD. When baseline serum 25OHD was less than 25, 25–50, or more than 50 nmol/L, respectively, serum PTH decreased by 0.8, 0.5, or 0.2 pmol/L, respectively ($P < 0.001$).

In conclusion, serum 25OHD was less than 25 nmol/L in 4% of the women, and this was associated with a 30% higher serum PTH. In 24% of the women serum 25OHD was between 25–50 nmol/L, associated with a 15% higher level of serum PTH compared with women with a serum 25OHD greater than 50 nmol/L. A low serum 25OHD level was also associated with higher serum alkaline phosphatase and lower BMD of the trochanter. Treatment with vitamin D_3 and calcium increased serum 25OHD and decreased serum PTH significantly; the effect was greater for lower baseline serum 25OHD. (*J Clin Endocrinol Metab* **86:** 1212–1221, 2001)

VITAMIN D DEFICIENCY, when prolonged and severe, can lead to osteomalacia, characterized by insufficient mineralization of the newly formed bone matrix, the osteoid (1). Less severe vitamin D deficiency, also called vitamin D insufficiency, causes secondary hyperparathyroidism, increased bone turnover, and bone loss mainly from cortical sites such as the femoral neck (2–7). Vitamin D deficiency has been implicated as a cause of hip fractures. Supplementation of elderly people with vitamin D improves vitamin D status, decreases synthesis of PTH, and increases the bone mineral density (BMD) of the lumbar spine and hip (8–10). In addition, vitamin D and calcium supplementation have been demonstrated to decrease the incidence of hip and other nonspine fractures (11, 12).

Vitamin D status depends on latitude, as vitamin D_3 is synthesized in the skin under the influence of UV irradiation from the sun mainly during spring and summer (13, 14). The diet, especially fatty fish, also contains vitamin D_3, and some foods, mainly dairy products, are fortified with vitamin D. Elderly people do not often go out into the sunshine, and the diet cannot adequately compensate for this. Vitamin D deficiency is common in elderly people, and the incidence may vary from 5–25% in independent elderly to 60–80% in institutionalized elderly depending on latitude, nutrition, sup-

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plementation, and definition (4, 8, 15, 16). Opinions with regard to the definition of vitamin D deficiency and adequate vitamin D status vary widely (6–8, 14, 17–20).

Recently, vitamin D status has been defined as adequate when the serum PTH concentration is not elevated and when vitamin D supplementation does not decrease serum PTH (7, 17). This has led to the conclusion that serum 25OHD should be higher than estimated previously, and that the vitamin D requirement in the elderly may be 400–800 IU/day or even more (20, 21). Precise definitions and consensus are hampered by the fact that there are large interlaboratory differences in assays for serum 25OHD (22). Several studies have compared vitamin D status in different populations and geographical regions (15, 23–25). These comparisons are complicated by differences in assays, except in one European study with a central laboratory (25). Another confounder is the dietary calcium intake, which influences serum PTH. The increase in serum PTH in the case of low serum 25OHD may be less prominent when calcium intake is high (26).

The international Multiple Outcomes of Raloxifene Evaluation (MORE) study, a large prospective intervention trial of women with postmenopausal osteoporosis, offers the opportunity to compare vitamin D status and parathyroid function in postmenopausal women throughout many countries throughout the world, as biochemical measurements were performed in a central laboratory facility. This may help to define more precisely the borderline between vitamin D deficiency and a vitamin D-replete state.

Subjects and Methods

The study was performed on the baseline data of the MORE study, a multicenter study on the effects of raloxifene (27) on BMD and fracture incidence in postmenopausal women (28). The total study population of MORE consisted of 7705 postmenopausal women. For this study, baseline values were available from 7564 women, aged 31–80 yr (mean, 66.5 yr), from 25 countries on 5 continents. Subjects were at least 2 yr postmenopausal or, in case of hysterectomy, had serum FSH levels greater than 30 IU/L and serum estradiol levels less than 73 pmol/L. The women had osteoporosis according to WHO criteria, *i.e.* BMD at the femoral neck or lumbar spine in substudy I patients was lower than *t*-score −2.5. The substudy II patients had, in addition, one moderate (25% height loss) or two mild (20% height loss) vertebral fractures in the presence of low BMD (*t*-score, less than −2.5) or at least two moderate vertebral fractures regardless of BMD. Women with a history of metabolic bone disease other than osteoporosis, substantial postmenopausal symptoms, malignancy, or recent treatment for osteoporosis (with exception of calcium and vitamin D supplements) were excluded. In addition, patients with systemic glucocorticoid therapy for more than 1 month within the preceding year, antiepileptic drugs, pharmacological doses of vitamin D, endocrine diseases requiring therapy (except for diabetes mellitus type 2 or hypothyroidism), serum creatinine levels greater than 225 μmol/L, active renal lithiasis, abnormal liver function tests, and consumption of more than 4 alcoholic drinks/day were excluded. Women with stable diabetes or hypothyroidism were included. The protocol was approved by the ethical review board at each center, and all women gave written informed consent in accordance with the Declaration of Helsinki. The women were enrolled between November 1994 and August 1995 at 180 centers in 25 countries (22 in the northern and 3 in the southern hemisphere; see list of centers at the end of the article). Fasting blood samples were obtained at baseline, and after centrifugation the serum samples were kept frozen until analysis. Fasting blood samples were again obtained after 6 months of treatment with vitamin D_3 (400–600 IU/day), calcium (500 mg/day), and either placebo or raloxifene. The 6-month data of the placebo group are included in this paper. The 6-month data of the raloxifene groups are not included, because this drug can also influence PTH secretion (29). Serum 25OHD was measured by RIA (INCSTAR Corp., Stillwater, MN) with an interassay coefficient of variation (CV) between 9.8–12.2%. For the purpose of this study, serum 25OHD was measured in 31 participants of the MORE study with the Incstar RIA (Covance laboratory) and Nichols CPB (Academic Hospital Vrije Universiteit) with very similar results: 88.3 ± 24.6 and 88.6 ± 27.1 nmol/L, respectively. This enables comparison of the data from the present study with those from the recent interlaboratory comparative study of 25OHD measurements (22). Serum PTH concentrations were measured by an immunoradiometric assay (INCSTAR Corp.). The interassay CV was 10.2–11.5%. Serum alkaline phosphatase concentrations were assessed by photometric measurement (at 405 nm) of the change in *p*-nitrophenol overtime (Sigma, St. Louis, MO). The interassay CV ranged from 2.5–5.7%. The assays were performed in two laboratories: Covance Indianapolis and Covance Geneva. All assays were calibrated toward Indianapolis. The data were classified according to conventional geographical regions, which do not exactly match latitude. For the classification of serum 25OHD, the limits were 50 nmol/L (20 ng/mL), which is the reference limit for vitamin D insufficiency in a recent study from the U.S. (17), and 25 nmol/L (10 ng/mL), which is near the reference limit for vitamin D deficiency in some studies from Europe (7, 8, 23, 30) (see also *Discussion*).

The BMDs of the lumbar spine, femoral neck, and trochanter were measured by dual energy x-ray absorptiometry as previously reported (28). A control reading facility provided correction factors to adjust for intersite differences, longitudinal drifts, and manufacturer differences.

For statistical analysis, *t* tests were used to compare mean values of serum 25OHD, PTH, and alkaline phosphatase by season. In the northern hemisphere, winter was defined as October through March, and summer as April through September, whereas in the southern hemisphere, it was the reverse. A one-way ANOVA was performed to compare the mean values of serum PTH, alkaline phosphatase, and BMD according to different 25OHD levels. Pairwise comparisons with adjustment for multiple comparisons (Bonferroni) were also made if the one-way ANOVA was significant. Fisher's exact test and the χ^2 test of association were used to determine whether significant associations between vitamin D deficiency and other factors, such as substudy, hemisphere, and season, existed. Pearson correlation coefficients were calculated between serum 25OHD and PTH as well as other biochemical markers. Changes in serum 25OHD and PTH according to baseline serum 25OHD were tested with the Kruskal-Wallis test.

Results

Baseline results were available from 7564 women. The mean serum 25OHD concentration of the whole study population was 70.8 ± 30.9 nmol/L. Table 1 shows the mean serum 25OHD concentration classified according to country, region, and level (<25, 25–50, and >50 nmol/L) among osteoporotic women participating in the MORE study. It should be noted that the prevalence of serum 25OHD below 25 nmol/L differed widely by country and region ($P < 0.01$), being more common in Southern Europe and some countries of Central Europe (Poland, Slovakia, and Slovenia). The country differences are not explained by seasonal and/or age differences in recruitment of the participants. The season- and age-adjusted mean values for different regions are significantly different ($P < 0.01$). The prevalence of low serum 25OHD (<25 nmol/L) and the mean serum 25OHD concentration according to region are shown in Fig. 1, A and B. Serum 25OHD did not show a significant correlation with latitude on a global scale. However, within Europe there was an unexpected significant positive correlation between serum 25OHD and latitude (Fig. 2). The distribution of serum 25OHD levels (<25, 25–50, or >50 nmol/L) was not different in patients with or without vertebral fractures.

The serum concentrations of 25OHD and PTH are presented according to geographical region and season in Table 2. Serum 25OHD was higher in summer than in winter in

TABLE 1. Serum 25OHD and prevalence of serum 25OHD less than 25, 25–50, or greater than 50 nmol/L according to country

Region	Country	Latitude	n	Age (yr)	25OHD (nmol/L)	Vitamin D status		
						% <25 nmol/L	% 25–50 nmol/L	% >50 nmol/L
Northern Europe	Denmark	56	258	68.1 ± 6.2	75.0 ± 30.7	5.0	18.2	76.7
	Finland	60–64	139	65.9 ± 6.0	71.2 ± 26.1	2.9	19.4	77.7
	Norway	59–70	848	67.3 ± 5.9	89.6 ± 29.3	0.1	8.5	91.4
	Sweden	57–62	125	68.2 ± 5.9	86.0 ± 26.8	0.8	5.6	93.6
	Total		1370	67.4 ± 6.0	84.7 ± 29.9	1.4	11.2	87.5
Central Europe	Austria	48	23	67.5 ± 6.8	80.4 ± 43.1	4.4	17.4	78.3
	Belgium	51	262	65.5 ± 7.4	69.2 ± 33.9	4.6	30.5	64.9
	Czech Republic	50	55	62.3 ± 6.5	58.9 ± 30.8	7.3	43.6	49.1
	France	44–50	58	66.6 ± 6.6	67.1 ± 41.4	10.3	27.6	62.1
	Germany	48–53	31	63.9 ± 7.7	57.7 ± 28.9	6.5	41.9	51.6
	Netherlands	52	345	67.6 ± 6.3	70.3 ± 34.9	5.8	25.8	68.4
	Poland	51	152	64.6 ± 5.6	55.2 ± 33.5	12.5	45.4	42.1
	Slovakia	49	17	64.2 ± 9.2	50.2 ± 34.4	17.7	35.3	47.1
	UK	50–57	253	67.1 ± 6.7	64.8 ± 28.9	6.3	32.8	60.9
	Total		1196	66.2 ± 6.8	65.9 ± 33.9	6.9	32.1	61.0
Southern Europe	Hungary	47	187	62.1 ± 7.8	64.0 ± 29.6	2.7	34.8	62.6
	Italy	38–45	200	62.6 ± 6.5	55.9 ± 28.6	12.5	33.5	54.0
	Israel	32	79	67.0 ± 6.6	72.7 ± 27.7	1.3	16.5	82.3
	Slovenia	46	31	63.7 ± 7.7	53.3 ± 30.8	22.6	29.0	48.4
	Spain	37–43	132	64.1 ± 7.9	59.9 ± 34.5	10.6	31.1	58.3
	Total		629	63.3 ± 7.4	61.1 ± 30.6	8.3	31.0	60.7
North America	Canada	44–54	425	65.4 ± 6.9	76.3 ± 30.3	2.6	15.8	81.7
	U.S.A.	25–47	3149	67.1 ± 7.3	68.4 ± 28.3	3.5	25.8	70.7
	Total		3574	66.9 ± 7.3	69.4 ± 28.7	3.4	24.6	72.0
Latin America	Argentina	35	402	65.7 ± 7.3	61.5 ± 28.9	6.5	35.3	58.2
	Mexico	20	89	65.7 ± 7.4	66.8 ± 26.6	2.3	28.1	69.7
	Total		491	65.7 ± 7.3	62.5 ± 28.5	5.7	34.0	60.3
South East Asia	Singapore	1	51	65.8 ± 6.8	80.4 ± 15.5	0.0	0.0	100.0
Pacific Rim	Australia	20–38	190	67.5 ± 6.8	82.7 ± 32.0	1.1	16.3	82.6
	New Zealand	37–43	63	66.4 ± 7.1	64.5 ± 28.8	1.6	42.9	55.6
	Total		253	67.2 ± 6.8	78.1 ± 32.1	1.2	22.9	75.9
Total			7564	66.5 ± 7.1	70.8 ± 30.9	4.1	24.3	71.7

The latitudes are those of the participating centers in the countries.

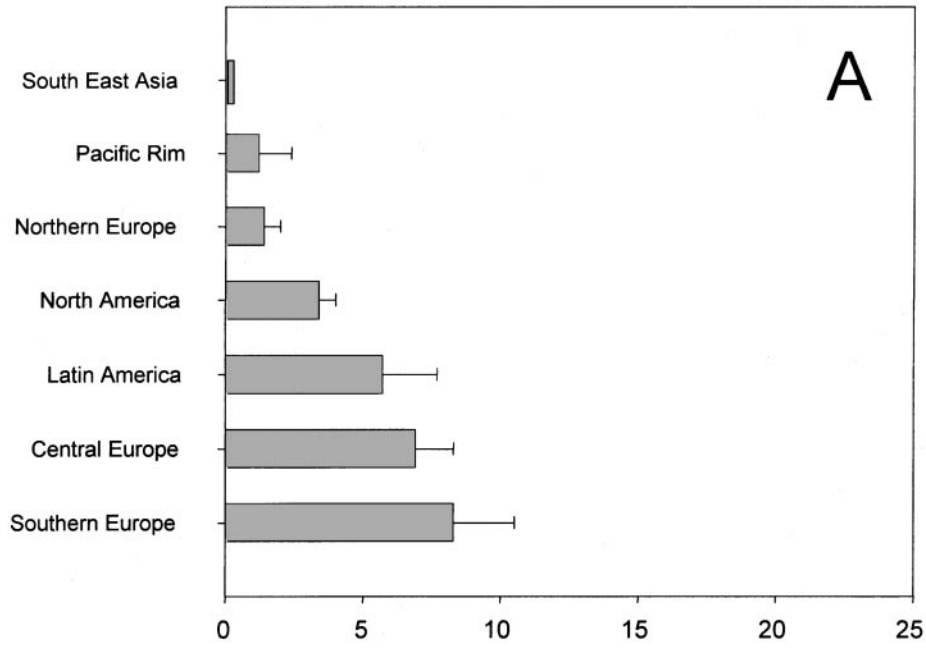
most countries. A low serum 25OHD level (<25 nmol/L) was observed in 3% of participants in summer and 5.1% of participants in winter ($P < 0.001$) Serum PTH showed a less consistent picture, with few differences between summer and winter. BMD of the femoral neck, trochanter, and lumbar spine did not show significant seasonal differences (data not shown).

Serum PTH and alkaline phosphatase levels and BMDs of femoral neck, trochanter, and lumbar spine are presented according to serum 25OHD levels in Table 3. It is apparent that higher serum concentrations of PTH and alkaline phosphatase were associated with lower serum 25OHD concentrations, especially when serum 25OHD was lower than 25 nmol/L. The effect of vitamin D deficiency on BMD was small and not significant, except for BMD of the trochanter, where a serum 25OHD level below 25 nmol/L was associated with a 4% lower BMD. A low, but very significant, negative correlation existed between serum 25OHD and serum PTH ($r = -0.25$; $P < 0.001$). This correlation was significant in all regions, even in countries near the equator (Singapore; $r = -0.39$; $P < 0.01$).

Serum 25OHD and serum PTH were again assessed at 6 months after the baseline visit after supplementation with vitamin D_3 (400–600 IU/day) and calcium (500 mg/day), as described in the MORE protocol (28). In the placebo group (2529 women), serum 25OHD increased from 70.8 ± 29.8 nmol/L at baseline to 92.3 ± 28.6 nmol/L after 6 months ($P < 0.001$), and serum PTH decreased from 3.7 ± 1.6 pmol/L at baseline to 3.4 ± 1.5 pmol/L after 6 months of treatment ($P < 0.001$). The changes in serum 25OHD and serum PTH after 6 months of treatment according to baseline serum 25OHD in the placebo group are presented in Table 4. The increase in serum 25OHD and the decrease in serum PTH after treatment were greater when baseline serum 25OHD was lower ($P < 0.001$).

Discussion

This is to our knowledge the first study to compare globally vitamin D status and parathyroid function among postmenopausal women with osteoporosis enrolled in one double blind, randomized, controlled clinical trial using a central laboratory facility. As expected, a large global variation in vitamin D status was observed, with the prevalence of low serum 25OHD (<25 nmol/L) ranging from 0–22%. The prevalence of these low levels was lowest in Singapore, Australia, New Zealand, and (surprisingly) northern Europe. The highest prevalence of low serum 25OHD was observed in coun-



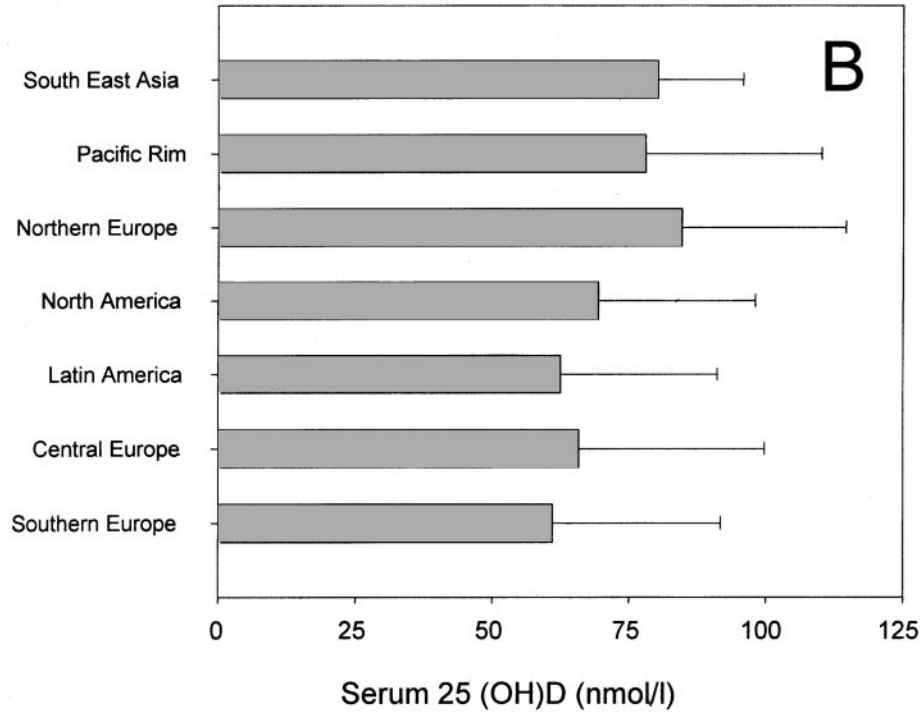


FIG. 1. A, Prevalence (percentage) of low serum 25OHD (<25 nmol/L) in 7564 postmenopausal women according to region. B, Mean serum 25OHD concentration (±SD) in 7564 postmenopausal women according to region. A significant association between serum 25OHD and regions was observed ($P < 0.01$).

tries of central and southern Europe (>10% in France, Italy, Spain, Poland, Slovakia, and Slovenia). The regional classification used was based on practical grounds. It is not a perfect one, as there is an overlap in latitudes between different regions. The classification of serum 25OHD levels (<25, 25–50, and >50 nmol/L) is arbitrary, but can be justified by the increase in serum PTH levels (5, 8) in the case of a low serum 25OHD and the suppression of serum PTH by vitamin D supplementation (17) (see below). One should bear in mind that this is not a population-based study, and

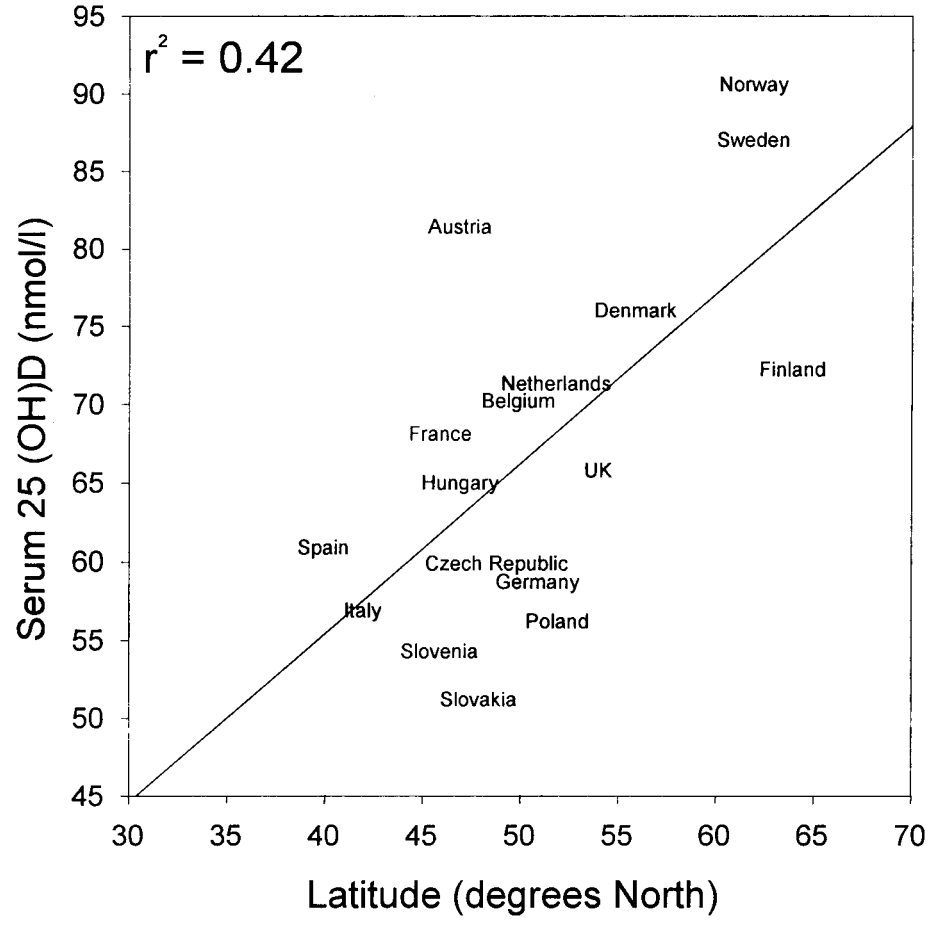


FIG. 2. Relationship between the serum 25OHD concentration and northern latitude in Europe. The relationship was very significant ($P < 0.001$).

TABLE 2. Serum concentration of 25OHD and PTH according to region and season

Region	n		Serum 25 OHD (nmol/L)		PTH (pmol/L)	
	Summer	Winter	Summer	Winter	Summer	Winter
Northern Europe	726	624	85.7 ± 29.9	83.6 ± 30.0[a]	3.4 ± 1.5	3.6 ± 2.0[b]
Central Europe	556	619	71.3 ± 35.5	59.5 ± 30.7[c]	3.4 ± 1.5	3.5 ± 1.5
Southern Europe	247	363	63.8 ± 30.2	57.7 ± 31.3[b]	3.8 ± 1.6	3.7 ± 1.7
North America	1717	1771	72.2 ± 28.5	66.2 ± 28.5[c]	3.8 ± 1.6	3.8 ± 1.7
Latin America	317	164	71.9 ± 30.1	57.9 ± 26.4[c]	4.0 ± 1.8	4.0 ± 2.2
South East Asia	49		79.7 ± 15.3		3.5 ± 1.1	
Pacific Rim	199	53	104.0 ± 32.9	71.4 ± 28.3[c]	3.3 ± 1.2	3.6 ± 2.0[d]

[a] $P = 0.13$.
[b] $P < 0.05$.
[c] $P < 0.001$.
[d] $P = 0.09$.

TABLE 3. Serum PTH and alkaline phosphatase and bone mineral density (BMD) of femoral neck, trochanter, and lumbar spine according to vitamin D status (serum 25OHD)

Serum 25OHD (nmol/L)	n	PTH (pmol/L)	Alkaline phosphatase (U/L)	BMD		
				Femoral neck (g/cm²)	Trochanter (g/cm²)	Lumbar spine (g/cm²)
<25	297	4.8 ± 2.2	83.7 ± 27.4	0.61 ± 0.08	0.53 ± 0.09	0.80 ± 0.13
25–50	1721	4.1 ± 1.8	78.8 ± 23.0	0.62 ± 0.08	0.55 ± 0.08	0.82 ± 0.14
>50	4982	3.5 ± 1.5	74.9 ± 20.5	0.62 ± 0.08	0.55 ± 0.08	0.82 ± 0.13
P value, by ANOVA		0.0001	0.0001	NS	0.0001	NS

the results should not be generalized to all postmenopausal women. Another limitation is the small sample size for some countries. In the case of vitamin D deficiency, as in Slovakia and Slovenia, this should await confirmation from larger studies.

The prevalence of low serum 25OHD levels observed in

TABLE 4. Absolute changes in serum 25OHD and serum PTH after 6-month treatment with vitamin D_3 (400–600 IU/day) and calcium (500 mg/day) according to the baseline serum 25OHD concentration

Baseline serum 25OHD (nmol/L)	n	Changes after 6 months	
		Serum 25OHD (nmol/L)	Serum PTH (pmol/L)
<25	93	+58.4 ± 32.2	−0.8 ± 1.8
25–50	614	+39.4 ± 25.4	−0.5 ± 1.5
>50	1822	+13.5 ± 29.6	−0.2 ± 1.2
P		<0.001	<0.001

All data are from the placebo group (not treated with raloxifene).

this study cohort was generally lower than that reported in healthy adult and elderly subjects in previous studies (4, 7, 8, 15). In contrast to the 5% prevalence of serum 25OHD levels less than 25 nmol/L observed globally during the winter months in the present study, 25–50% of the healthy elderly in the U.S. and Europe, respectively, are reported to have these low levels during the winter months (4, 5, 7, 8, 15, 25). The women enrolled in this clinical trial were fairly healthy and free of diseases other than osteoporosis. In addition, volunteers for clinical trials may be more conscious about their health than the general population. Both of these factors may have contributed to the lower overall prevalence of vitamin D deficiency observed in this study compared with previous studies.

Consistent with previous assessments of vitamin D in various countries, the prevalence of low serum 25OHD levels was lower in countries of North America and northern Europe than in those of central and southern Europe (15, 25). The often practiced fortification of dairy products with vitamin D (400 IU/quart) in North American countries is probably responsible for much of this difference (16). The widespread consumption of fatty fish provides an excellent source of dietary vitamin D for residents of northern Europe (31) and may explain the lower prevalence of vitamin D deficiency in this region compared with central and southern Europe.

Serum 25OHD levels exhibit a marked seasonal variation in different regions of the world, being lowest during the winter months and peaking in late summer (32–35). Consistent with these data, the global prevalence of low serum 25OHD was higher during the winter than during the summer months in the present study.

Given that sunshine exposure is the most important source of vitamin D, one should expect that vitamin D status depends upon geographic location relative to the equator, with vitamin D status being better in residents closer to the equator compared with those living at higher latitudes. Such a relationship was reported for the general adult urban population living in various regions of France (7). However, when considering all countries represented in this study, there was no apparent relationship between either serum 25OHD levels or the prevalence of low levels (<25 nmol/L) and latitude of the country of origin. In contrary to what should be expected, a positive relationship was observed between northern latitude and serum 25OHD levels in Europe, *i.e.* the prevalence of low serum 25OHD levels tended to decrease with increasing northern latitude. Similar results were reported for women participating in the SENECA study, a nutrition study in elderly men and women from 11 European countries in which low serum 25OHD was most prevalent in Italy and Spain, followed by Hungary, Switzerland, and France and was least prevalent in Denmark and Norway (25). These data suggest that although the influence of sunlight exposure is detectable when comparing vitamin D status within countries between the winter and summer months, these differences in vitamin D status may be overwhelmed by the influences of vitamin D fortification policies, dietary habits, and the use of vitamin D supplements. Inhabitants of southern Europe stay out of direct sunlight (25). In addition, time spent outdoors, clothing habits, and skin type and pigmentation may influence differences in vitamin D status between countries (13, 14).

Vitamin D deficiency is associated with secondary hyperparathyroidism. A negative correlation between serum PTH and serum 25OHD levels has been reported by many investigators (5, 7, 8). A negative correlation was observed in all global regions in our study. As shown in Table 3, the mean serum PTH level was 30% higher in women with low serum 25OHD (<25 nmol/L) than in women with higher serum 25OHD (>50 nmol/L). This confirms previous observations in elderly people in Lyon, Amsterdam, and Boston (10–12). Serum PTH shows an inverse seasonal variation, with maximal values at the end of winter and a nadir at the end of summer, when serum 25OHD is at its maximum (34). In this study a seasonal variation in serum PTH was not observed in most regions, which may be explained by the fact that most samples were obtained between January and July.

Secondary hyperparathyroidism is associated with increased bone turnover and bone loss, which is mainly cortical, but also may be trabecular (1, 3, 35–37). In an earlier study in Amsterdam, a positive correlation was observed between serum 25OHD and BMD of the femoral neck in elderly women, compatible with a bone deficit of 5–10% when the serum 25OHD level was 20 or 10 nmol/L, respectively (5). In the present study, BMD of the hip was similar in women with low or high serum 25OHD levels. There was evidence for high bone turnover in women with low serum 25OHD levels, as alkaline phosphatase was higher with low serum 25OHD than with high serum 25OHD. The differences in BMD according to vitamin D status were small and only significant for the trochanter, compatible with a bone deficit of 4% in women with low serum 25OHD levels (<25 nmol/L) compared with the other groups (serum 25OHD, >25 nmol/L).

Last decades, several attempts have been made to define vitamin D deficiency. A definition based on the lower reference limit in healthy adults is not satisfactory because it depends on sunshine exposure, clothing habits, skin pigmentation, use of sunblocks, and diet (13, 14, 38). The existence of secondary hyperparathyroidism could be another way to define vitamin D deficiency (5, 7, 17, 39), but the increase in serum PTH usually is small and in the normal range in mild degrees of vitamin D deficiency, also called vitamin D insufficiency (6). In elderly people in Amsterdam, the negative relationship between serum PTH and serum 25OHD only was significant when serum 25OHD was lower than 30 nmol/L (5). In normal French adults, serum PTH

started to increase when serum 25OHD was lower than 78 nmol/L (7). In Boston, the seasonal variation in serum PTH disappeared when serum 25OHD was higher than 90 nmol/L (40). These different borderlines may be partly explained by interlaboratory differences in assays for serum 25OHD (22). Another modifying factor of the relationship between serum PTH and serum 25OHD is the calcium intake. The 24-h pattern of PTH secretion decreases markedly after an increase in calcium intake (41). Calcium intake is relatively low in France (7, 11) and high in The Netherlands (4, 5), and this may influence the serum 25OHD level at which serum PTH starts to increase (26). According to a recent study from the U.S., 8 weeks of treatment with vitamin D (50,000 IU/week) and calcium (1000–1500 mg/day) caused a significant decrease in serum PTH when baseline serum 25OHD was lower than 50 nmol/L, but serum PTH did not decrease with higher serum 25OHD levels (17). This limit for vitamin D insufficiency was used in our classification. However, arguments may exist to set this limit higher (7, 18–20, 40).

What are the therapeutic implications of vitamin D deficiency in postmenopausal women? Treatment with vitamin D_3 (400–800 IU/day) in institutionalized elderly adequately increases serum 25OHD and suppresses serum PTH about 15–30% (8, 42). In elderly women in Amsterdam, a vitamin D_3 supplement of 400 IU/day decreased serum PTH by 15% and increased BMD of the femoral neck by 2.2% after 2 yr (10). However, in that study vitamin D supplementation had no effect on the incidence of hip and other osteoporotic fractures (43). A greater suppression of serum PTH (up to 50%) and a larger increase in BMD of the hip (up to 6%) have been observed in elderly women during combined treatment with vitamin D_3 and calcium, and this caused a significant decrease of the incidence of hip and other peripheral fractures in elderly French women in nursing homes (11). Similar results were reported from elderly women in Boston (12).

In this study serum 25OHD increased, on the average, 21 nmol/L after supplementation with vitamin D_3 and calcium. The increase was much more when the baseline serum 25OHD level was lower than 25 nmol/L and, on the contrary, was rather small when the baseline serum 25OHD level was higher than 50 nmol/L. A similar observation was made in the vitamin D supplementation study in Amsterdam (10), where the increase in serum 25OHD showed a negative correlation with baseline serum 25OHD ($r = -0.47$; $P < 0.001$; Ooms, M. E., personal communication). It is uncertain how many women in this study would profit from vitamin D treatment. The higher serum PTH in the groups with serum 25OHD levels below 25 and 25–50 nmol/L and the greater decrease in serum PTH in these groups after treatment suggest that at least these groups might profit from vitamin D supplementation.

The MORE trial was not designed to investigate the consequences of vitamin D deficiency and secondary hyperparathyroidism and the effects of vitamin D supplementation. We used a serum 25OHD level of 50 nmol/L as the limit for sufficiency in our classification based on one high dose supplementation study (17). Other investigators have advocated higher desired serum 25OHD levels up to 100 nmol/L (18–20) with potential benefits for the prevention of osteoporosis, osteoarthritis, some cancers, multiple sclerosis, and hypertension (18–20). Large scale trials are needed to explore possible preventive effects of various doses of vitamin D supplementation on osteoporosis and other chronic diseases in the elderly.

In conclusion, serum 25OHD was lower than 50 nmol/L in 28.4% of the postmenopausal women participating in the MORE trial, and this was associated with a relatively higher serum PTH. Low levels of serum 25OHD (<25 nmol/L) were most frequent in some countries of central and southern Europe. Treatment with vitamin D_3 and calcium increased serum 25OHD and decreased serum PTH significantly, and the effect was greater for lower baseline serum 25OHD.

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