# Vitamin D inadequacy: the Italian picture

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**Summary**

**Numerous epidemiological studies have assessed the prevalence of low serum 25-hydroxyvitamin D concentrations and have indicated that vitamin D inadequacy is a common problem in Italy, particularly in elderly women, and not only in inpatients with chronic disease or institutionalised subjects. There are important seasonal fluctuations in subjects living at home. Lower educational level, living in central Italy, smoking, and low intake of dairy products are associated with increased risk of vitamin D inadequacy.**
**European and International studies have confirmed the high incidence of hypovitaminosis D in Italy, that appears unexpectedly more common than in northern European countries.**
**Also, in Italy there is evidence that concentrations of 25-hydroxyvitamin D below 30 nmol/L is associated with secondary hyperparathyroidism, increased bone turnover, decreased bone mineral density at the hip, higher hip fracture prevalence, reduced muscular function and disability.**
**The frequent finding of a high prevalence of vitamin D deficiency, in spite of the large amount of scientific data regarding the important role in the pathogenesis of skeletal and non-skeletal diseases, indicates that the treatments used up to now are insufficient or inadequate. A population-based strategy to correct this condition and new treatment methods with vitamin D that guarantee a better and long term compliance appear urgent. Preliminary experiences are heartening.**

*KEY WORDS: vitamin D, hip fracture, osteoporosis, PTH.*

## Introduction

The standard method used to assess vitamin D status is the measurement of 25-hydroxyvitamin D (25OHD) serum concentration, the major circulating metabolite of vitamin D. Opinions regarding the optimal concentration of serum 25OHD vary widely. Generally in Italian studies a cut-off of 30 nmol/L has been used because concentrations of 25OHD below 30 nmol/L were associated with secondary hyperparathyroidism, increased bone turnover, and decreased bone mineral density at the hip, even if many recent studies have shown that serum concentrations of at least 50-75 nmol/L are necessary to maximize intestinal calcium absorption and minimize perturbations in parathyroid hormone (PTH), calcium, and phosphorus homeostasis.
Numerous epidemiological studies have assessed the prevalence of low serum 25OHD concentrations and have indicated that vitamin D inadequacy is a common problem worldwide. Differences in the prevalence of vitamin D inadequacy have been related to a variety of factors, including physiological changes with age, race, body mass index, sun exposure, latitude, and dietary vitamin D intake.
Several studies have compared vitamin D status in different populations and geographical regions, but these comparisons are frequently complicated by differences in assays.
Here we review the available data on the prevalence and consequences of hypovitaminosis D (defined as serum 25OHD level below 30 nmol/L) in Italy and some of the strategies for its prevention.

## Italian epidemiological studies on prevalence of hypovitaminosis D

The first evidence of vitamin D inadequacy in Italy was reported in 1990 (Table I) (1). We measured the serum levels of 25OHD in 660 subjects (441 females and 249 males) aged 62 ± 19 years (range 20-95 years). The study includes 369 unselected healthy subjects (group A), 211 inpatients with different chronic diseases (group B) and 80 persons living in a narrow valley with only a few hours of sunlight per day (group C).
The lowest values of 25OHD were observed during the winter season and the highest in late spring or summer. In winter, values of 25OHD lower than 30 nmol/L were found in 45% of group A, 67% of group B and 85% of group C. The prevalence of hypovitaminosis D increased with aging, with seasonal fluctuations in elderly subjects living at home in contrast with institutionalised patients (Figure 1). Therefore, it appeared that the incidence of hypovitaminosis D in northern Italy is unexpectedly high, particularly, but not only, in elderly subjects with chronic diseases or living in areas with short periods of sunlight. Because of the correlation found between hypovitaminosis D and long bone fractures, a prophylactic administration of vitamin D supplements was recommended in most elderly people.
Between October 1995 and September 1996, five hundred and seventy postmenopausal women from the Milan area who were referred to outpatient clinics for an osteoporosis investigation were included in the study of Bettica et al. (2). All the women were healthy, were not taking any medication known to influence bone metabolism and were engaged in normal physical activity. Average age and years since menopause were 59.2 ± 7.7 years (range 41-80 years) and 11.3 ± 8.8 years (range 0.5-51 years), respectively. In the whole population mean values of serum 25OHD were 46 ± 21 nmol/L. The Authors found a significant ($p < 0.001$) seasonal variation for both 25OHD and PTH; in particular, 25OHD was lowest in March-April and highest in September-October, while an inverse fluctuation was seen for PTH. Moreover, the regression line for 25OHD shows that reduced serum levels of vitamin D can be found during about half the year (December-May). Considering a serum 25OHD level of 30 nmol/L as a cut-off for hypovita-

Table I - Italian epidemiological studies on prevalence of hypovitaminosis D.

| Authors (year of pubblication) | Study population | N° | Mean age (yr) (SD) | Vitamin D deficiency (< 30 nmol/L) (%) | |
|---|---|---|---|---|---|
| | | | | Summer | Winter |
| Rossini et al. (1990) | Healthy subjects | 369 | 50 (16) | 15 | 45 |
| | Inpatients with different chronic diseases | 211 | 64 (17) | 52 | 67 |
| | Persons living in areas with short periods of sunlight | 80 | 68 (8) | 27 | 85 |
| Bettica et al. (1999) | Postmenopausal women referred to an osteoporosis center | 570 | 59 (8) | 13 | 39 |
| Romagnoli et al. (1999) | Young healthy blood donors | 88 | 35 (10) | 0 | 15 |
| | Healthy postmenopausal women | 47 | 62 (10) | 5 | 32 |
| | Inpatients with various medical diseases | 88 | 66 (14) | 30 | 71 |
| | Inpatients engaged in long-term rehabilitation programmes | 62 | 74 (7) | 58 | 82 |
| Carnevale et al. (2001) | Young healthy subjects | 90 | 38 (7) | 2 | 18 |
| Isaia et al. (2003) | Postmenopausal women referred to an osteoporosis center | 700 | 68 (6) | – | 76 |

minosis D, the women were divided into two subgroups: subjects with hypovitaminosis D (28%) and subjects with normal vitamin D status (72%). Hypovitaminosis D was found in 38.5% of all women during the wintertime, while the prevalence decreased to 12.5% in the period June-November. The prevalence of hypovitaminosis D in northern Italy increases with aging: when all women were divided into four groups according to age, hypovitaminosis D was found most frequent in women > 70 years, particularly in the December-May time period (51%), while 17% had insufficient vitamin D levels in the period from June-November. Passeri et al. observed that serum 25-hydroxyvitamin D was undetectable in 99 of 104 evaluated centenarians (3).

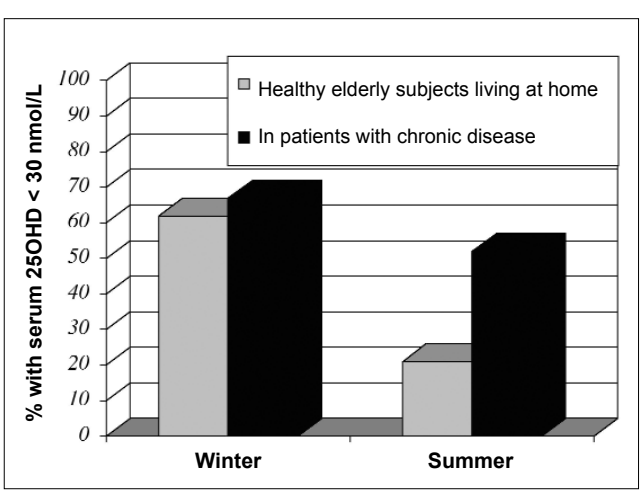


Figure 1 - Seasonal prevalence of hypovitaminosis D in healthy elderly subjects and inpatients with chronic disease (1).

Romagnoli et al. (4) aimed to investigate the prevalence and seasonal variation of hypovitaminosis D among healthy subjects and hospitalised patients living in central Italy. They 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 serum levels of 25OHD were measured by radioimmunoassay. The Authors 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 hospitalisation time. In each group, a significantly higher prevalence of hypovitaminosis D was found in winter compared to 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 incidence of hypovitaminosis, particularly those in group (d) (winter 82.3% and summer 57.8%). The results of the 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 defi-

ciency on skeletal integrity.
A longitudinal evaluation of vitamin D status in healthy subjects from southern Italy was published by Carnevale et al. in 2001 (5). Ninety healthy volunteers were recruited for the study, upon witnessed informed consent. The sample comprised 32 men (mean age 39.4 ± 7.8 years) and 58 pre-menopausal women experiencing regular menses (age 36.9 ± 6.4 years). Each subject was studied twice, in February and in August, since these months represent the nadir and the peak of exposure to ultraviolet (UV) irradiation. No significant difference was found in terms of sun exposure between male and female subjects. The prevalence of hypovitaminosis D, defined by concentrations of 25OHD lower than 30 nmol/L, was 17.8% in winter and 2.2% in summer in the whole sample, while it was 27.8% and 3.4%, respectively, among female subjects; indeed male subjects did not display hypovitaminosis D. These results show a relatively high prevalence of subclinical vitamin D deficiency among young healthy women also from southern Italy, with significant gender-specific differences.
In a study on dietary and nutritional patterns in an elderly population of northern (Province of Pavia) and southern Italy (near Cosenza), vitamin D intake was found generally inadequate with no significant differences (6).
In Italy again recently a high prevalence of hypovitaminosis D was observed during winter in elderly women distributed in the entire national territory (7). The study population included 700 women recruited from 43 osteoporosis centers equally distributed over the territory of Italy. Each center was asked to recruit up to 20 consecutive Caucasian postmenopausal women aged 60-80 years, referred for the first time for an osteoporosis risk assessment. Values of 25OHD lower than 12,5 nmol/L were found in 27% of the women and levels lower than 30 nmol/L were found in 76%. Significant predictors of 25OHD levels were age, sun exposure, number of pregnancies, educational level (years spent at school), days spent on holiday by the sea, and dairy calcium score. In a multivariate model including all these variables, the only one that remained significant was the level of education. The lowest age-adjusted 25OHD levels were also found in smokers. The geographical distribution of the cohort was also relevant. After adjusting 25OHD levels for age, the women at higher risk were those living in central Italy, while women from southern and northern Italy were comparable. These differences disappeared when 25OHD levels were adjusted for level of education, sun exposure, and dairy calcium intake. The women from northern Italy had a relatively higher intake of dairy products and a higher educational level than those of the central region, which may help to explain their lower risk. The relatively low risk of women in southern Italy appears reasonable to attribute to better sun exposure as a result of more sunny days and a lower latitude (comparable to the Mid-Atlantic coastal region in the United States).
High prevalence of hypovitaminosis D was also found in Italian type 2 diabetes patients (8).
25OHD serum levels decline with age earlier in women than in men: Maggio et al. recently observed that in women the age-related decline of 25OHD was already evident shortly after age 50, whereas in men it started only after age 70 and was substantially less steep (9).

**European and international studies on prevalence of hypovitaminosis D in Italy**

The definition of vitamin D deficiency is hampered by the fact that large interlaboratory differences exist in assays for serum 25OHD. In a European multicenter study (SENECA study) (10) Van der Wielen et al. measured wintertime serum 25OHD concentrations in 824 elderly people (aged 70-75 years) from 11 countries (12 men and 13 women from Italy). Data was collected between December 1988 and March 1989. In a general structured interview conducted in the participant's home; information was obtained on potential determinants of vitamin D status: use of dietary supplements, use of sunray lamps, presence of chronic disease, activities of daily living, social isolation, and exposure to sunlight. Hours spent outdoors walking, cycling, gardening or other activities were summed to estimate an outdoor leisure time activity score. Questions on sunlight exposure concerned the frequency of going outside during sunny periods and the clothes worn when outdoors during the summer. Town-specific and sex-specific means are reported for the total population under study, along with the proportion of participants with a 25OHD concentration below 30 nmol/L. The results were reported in 1995: 36% of men and 47% of women had 25OHD concentrations below 30 nmol/L. Surprisingly, lowest mean 25OHD concentrations were seen in southern European countries. Lowest mean concentrations of 25OHD were found in the southern European towns of Greece, Spain, and Italy: 42% of Italian men and 92% of women had 25OHD concentrations below 30 nmol/L. People who used sunlamps and/or vitamin D supplements had much higher 25OHD concentrations than those who did not. Two-thirds of people who used vitamin D supplements and/or sun lamps lived in Norway or in Denmark.
The international "Multiple Outcomes of Raloxifene Evaluation" study, a large prospective intervention trial in postmenopausal women with osteoporosis, offered another opportunity to compare vitamin D status and parathyroid function throughout many countries over the world, including Italy. For this study (11), baseline data were available from 7564 (200 from Italy) postmenopausal women (aged 31-80 yr, mean 66.5 yr) 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 had 2 vertebral fractures. The prevalence of serum 25OHD below 25 nmol/L differed widely by country and region, 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. Within Europe there was an unexpected significant positive correlation between serum 25OHD and latitude: in particular, Italy was one of the countries with the lower mean levels of serum 25OHD. This finding might be considered surprising since the Mediterranean countries, in general, experience a greater quantity of sunny days than do northern European countries. This is usually sufficient in young individuals, but not in elderly women who do not like sun exposure during the hours that are effective for vitamin D synthesis. In addition, one should also consider that the latitude of northern Italy is the same as that of southern Canada, and both places have only a few hours daily of UV irradiation effective for skin synthesis of vitamin D. Moreover, the widespread consumption of fatty fish provides an excellent source of dietary vitamin D for residents of northern Europe and may explain the lower prevalence of vitamin D deficiency in this region compared with central and southern Europe. This data suggests 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; in addition, time spent outdoors, clothing habits, skin type and pigmentation may influence differences in vitamin D status between countries. In some countries edible oils and fats are vitamin D enriched, and therefore may become important di-

etary vitamin D sources, especially in wintertime when sunlight exposure is scarce. Vitamin D addition to margarine is compulsory in Norway, Denmark, the Netherlands, Belgium, and Portugal, prohibited in France, and optional but not done in Hungary, Switzerland, Spain, Italy, Portugal, and Greece. Low 25OHD concentrations could largely be explained by attitudes towards sunlight exposure and factors of physical health status, after exclusion of users of vitamin D supplements or sunlamps. Problems with daily living activities and wearing clothes with long sleeves during periods of sunshine were strong predictors of low wintertime serum 25OHD concentrations. These findings show that free-living elderly Europeans, regardless of geographical location, are at substantial risk of inadequate vitamin D status during winter and that dietary enrichment or supplementation with vitamin D should be seriously considered during this season.

**Possible consequences of hypovitaminosis D observed in Italy**

Vitamin D is essential for maintaining calcium homeostasis and optimising bone health. Low concentrations of vitamin D lead to alterations in calcium and phosphorus homeostasis, secondary hyperparathyroidism, bone loss, osteoporosis, and an increase in fracture risk. More severe degrees of vitamin D deficiency lead to impairment of bone mineralization and osteomalacia.

In 1990 we observed that in the patients with serum levels of 25OHD lower than 10 ng/mL the incidence of hypocalcaemia was significantly raised ($p < 0.03$) (1).

Bettica et al. (2) reported that in subjects with hypovitaminosis D PTH was significantly increased ($p < 0.05$), while mean values of femoral bone mineral density (BMD), 24-h urinary calcium and osteocalcin were significantly lower ($p < 0.05$) than those found in subjects with normal vitamin D status. There was no difference between groups as regards to mean age and mean lumbar BMD. Moreover, in a subgroup of 23 women who were comparable to other subjects for all the parameters considered, the Authors found a significant positive correlation between $1,25(OH)_2D$ and 25OHD serum levels ($r = 0.49$, $p < 0.03$), while no correlations were found between $1,25(OH)_2D$ and age, creatinine clearance and PTH.

Recently Pepe et al. (12) investigated the relative contribution of the major factors regulating calcium homeostasis in determining the circulating levels of PTH in healthy women and men. 25OHD was the main explicative variable almost in every multiple linear regression model, both considering the group as a whole and when considering men and women separately. In subjects with vitamin D insufficiency (25OHD < 30 nmol/L), mean serum levels of parathyroid hormone were significantly higher ($P < 0.001$) than those in subjects of similar age with normal vitamin status. This study demonstrates the central role of 25OHD in regulating PTH secretion in physiological conditions.

Also in the study of Isaia et al. (7) 25OHD and PTH levels were strongly correlated: the best correlation coefficient was obtained after logarithm transformation of both variables ($r = -0.38$). Thirty-eight percent of the women with serum vitamin D below 12,5 nmol/L had PTH levels above 45 pg/mL, a value that corresponds to the 95$^{th}$ percentile of PTH distribution in normal healthy young subjects. Values of PTH above 45 pg/mL were found in only 8% of the women with 25OHD levels above 30 nmol/L. The relationship between vitamin D status and PTH is very similar to that found by others with a ''breaking point'' around 33 ng/mL. A confounder may be 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. In this study dairy calcium intake was reported positively associated with 25OHD levels. This observation indicates that in a large proportion of the patients hypovitaminosis D is associated with low calcium intake, exacerbating the metabolic skeletal consequences.

Carnevale et al. (5), by subdividing samples according to serum 25OHD levels (either lower or higher than 30 nmol/L), observed higher PTH ($p < 0.02$) in subjects with lower values of 25OHD. In both sexes summer 25OHD levels were higher, while PTH values were significantly lower. Male subjects did not display hypovitaminosis D, having throughout the year significantly higher calcium and 25OHD levels together with lower PTH values, than women. In the whole sample, serum 25OHD correlated positively with serum calcium and inversely with PTH. Moreover, the seasonal percentage variations in PTH were inversely correlated with those of urinary calcium excretion. Only in women, during winter when serum levels of 25OHD are lower, bone remodelling markers (serum alkaline phosphatase, urinary pyridinoline and deoxypyridinoline) were described higher while urinary calcium levels were lower than in summer. Higher PTH and urinary deoxypyridinoline levels were observed in subjects with lower values of 25OHD. This data shows significant gender-specific differences in both calcium homeostasis and skeletal remodelling indexes; the seasonal fluctuations in the vitamin D-PTH axis are accompanied by cyclical variations of bone turnover rate, which were more pronounced in women.

Passeri et al. (3) in centenarians affected by severe hypovitaminosis D observed that PTH and serum C-terminal fragment of collagen type I were elevated in 64 and 90% of subjects, respectively, with a trend toward hypocalcaemia; bone alkaline phosphatase levels were close to the upper limit. In these patients ultrasonographic bone parameters were correlated with resorption markers. Authors conclude that the extreme decades of life are characterized by a sequence of events linking vitamin D deficiency, low serum calcium, and secondary hyperparathyroidism with an increase in bone resorption and severe osteopenia. Higher levels of 25OHD are required in older compared to younger persons to avoid the age-associated compensatory hyperparathyroidism (9).

As expected by pathophysiology, numerous authors have found a relationship between vitamin D status and BMD. A recent study on this topic has been carried out on 156 Italian postmenopausal women. Malavolta et al. (13) found a positive statistically significant correlation between BMD, both at the spine and hip, and 25OHD, and a negative statistically significant correlation between BMD and PTH. No statistically significant correlation was found between BMD and $1,25(OH)_2D$. Crude logistic regression showed age, 25OHD and PTH were significant predictors of low BMD, while $1,25(OH)_2D$ was not. Backward logistic regression showed 25OHD was the best predictive model for spine osteoporosis together with age, and alone it was the best predictive model for femoral neck osteoporosis.

Del Puente et al. (14) investigated the predictive value of serum 25OHD levels and other clinical variables for BMD changes in healthy women participating in a population-based longitudinal study carried out in Napoli. 139 women (45 to 79 years of age) were examined at study entry and then again after two years (24 ± 2 months) following the same protocol. They underwent medical examination, questionnaire, anthropometric measurements, blood sampling and urine collection; BMD was measured by dual energy X-ray absorptiometry at the lumbar spine and femoral neck. The results indicated that the serum 25OHD level was the only independent determinant of BMD variations at the femoral site.

Isaia et al. (7) observed that the mean age-adjusted 25OHD values were significantly (P < 0.05) lower in the 25 women who sustained a hip fracture (17.7 ± 5,5 nmol/L) than in all the others (27,5 ± 24,7 nmol/L). Such a difference was not found for any other fracture. The prevalence of hip fracture was 5.8% in subjects with 25OHD levels lower that 12,5 nmol/L, and 3.9% in women with 25OHD levels ranging from 12,5 to 30 nmol/L; none of the subjects with 25OHD levels greater that 30 nmol/L had a history of hip fracture. Moreover women with low 25OHD levels (< 30 nmol/L) had worse scores for daily living activities (ADL) and mobility ADL (move outdoors, use stairs, walk at least 400 m, carry a heavy object). However, given the cross-sectional nature of this study, we cannot rule out the opposite causal relationship, i.e. that patients with a poorer ADL score or prior fracture are at greater risk of hypovitaminosis. In any event, these results indicate that prior hip fracture represents a paradoxical risk factor for hypovitaminosis D!

Recently Di Monaco et al. (15) evaluated the association between serum levels of 25OHD and functional recovery after hip fracture in a cross-sectional study. A total of 350 hip-fracture patients consecutively admitted to a rehabilitation hospital were investigated; thirty-five patients were excluded because their hip fracture was caused by major trauma or cancer affecting the bone or they could not complete rehabilitation. Patients underwent 25OHD assessment at a mean of 21.3 ± 8.1 days after the hip fracture; functional recovery was evaluated by using Barthel Index scores. Low levels of 25OHD were generally found (median, 17 nmol/L). By using the Spearman rank correlation test, a significant positive correlation was observed between serum 25OHD and Barthel Index score assessed on admission (rho = .218, P < .001) and discharge (rho = .198, P < .001), but not with the change in Barthel Index score attributable to rehabilitation. Linear multiple regression showed that the association between 25OHD and Barthel Index score was independent of 11 confounding variables: age, sex, hip-fracture type, pressure ulcers, cognitive impairment, neurological impairment, infections, time between fracture occurrence and 25OHD evaluation, co-morbidity, surgical procedure type, and previous hip fractures.

The relationships between vitamin D, functional status, and disability in a sample of elderly, community-dwelling subjects was investigated in Italy by Zamboni et al. (16). Serum values of 25OHD and albumin were determined in all participants. Anthropometric measures were obtained, and body composition was assessed using dual-energy X-ray absorptiometry. Arm and leg isometric strength was tested. Reported disability was evaluated using a modified version of the Activities of Daily Living Scale and physical performance with the 6-minute walking test and two items of the Short Form 36 Health Survey Questionnaire (SF-36). A significantly higher prevalence of hypovitaminosis D, defined as level of 25OHD < 37.5 nmol/L, was observed in women than in men (55.4% and 35.1%, respectively; p < .001). In women, 25OHD was significantly associated with muscular strength and levels of physical function as assessed by SF-36. After adjusting for body mass index, albumin, appendicular fat-free mass, and season, muscle strength was still significantly lower in women with hypovitaminosis D than in those without. Women with reported disability showed significantly lower 25OHD values than those without. No relationship between muscular strength, physical function, or reported disability and 25OHD was found in men. Therefore in community-dwelling elderly women, 25OHD is related to muscular function and reported disability; because of the high prevalence of hypovitaminosis D in the elderly population, this association seems to be clinically relevant.

**New strategies of prevention of hypovitaminosis D in Italy**

The frequent finding of a high prevalence of vitamin D deficiency, in spite of the large amount of scientific data regarding the important role in the pathogenesis of skeletal and non-skeletal disease, indicates that the treatments used up to now are insufficient or inadequate.

*A) Yearly bolus*

Vitamin D deficiency is a well recognized risk for hip fracture and vitamin D insufficiency is so frequent in the elderly that a population-wide preventive intervention might be desirable, especially in winter. Recently we have reported the results from the first community intervention on hip fracture using a single yearly bolus of vitamin D in women aged 65 years or more, carried out in a health district of the Veneto region in Italy (17). A vial containing 400,000 IU vitamin D2 was offered for oral administration to all women aged  65 years at several outpatient clinics together with the influenza vaccination which is administered to > 70% of the elderly. The intervention took place during the winters of 2000-2001 and 2001-2002. The only exclusion criteria for treatment were age and gender, and the control group included women who did not participate in the Health District initiative. Analysis of hip fracture incidence was carried out for 4 years, from 1999 to 2002. Patients with incident hip fracture were identified as soon as they were admitted to one of the 3 hospitals of the Health District and interviewed regarding their participation in the vitamin D preventive intervention program. In 120 of the women (age range 68-90 years), serum concentrations of 25OHD were measured from October to June, both before and 1 and 4 months after vitamin D administration.

Results: 23,325 and 24,747 women received the vitamin D bolus during winters 2000-2001 and 2001-2002 respectively, i.e. 45-47% of eligible women. The number of women who accepted the bolus declined with advancing age, from 50-55% in women aged 60-70 years to 22-26% in those aged > 90 years. The two-year intervention on the community decreased the incidence of fracture by 10% (p = 0.050) in comparison with the previous two years. The age-adjusted risk reduction (RR) of hip fracture during 2001 and 2002 in women who had received vitamin D, with respect to women who had not, decreased by 17% (p = 0.056) and 25% (p = 0.005) respectively. The RR was considerably greater and statistically significant over both 2001 and 2002 in the cohort aged > 75 years (Figure 2). 25OHD concentrations, in the subset of women in whom it was measured, rose significantly (p < 0.0001) by 9 ng/mL over the 4 months after administration.

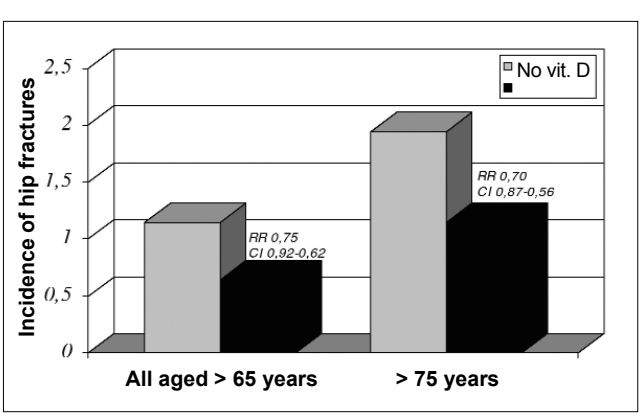


Figure 2 - Effect of vitamin D yearly bolus in winter on age-adjusted hip fracture risk in elderly women: a community primary prevention study (17).

Despite several obvious limitations due to its nature, this study sufficiently documents that yearly vitamin D bolus supplements, given as primary prevention to elderly Caucasian women, may decrease the incidence of hip fracture. For its safety and excellent feasibility and cost-effectiveness, this primary intervention has a great potential for community distribution. Safety, feasibility and cost-effectiveness are crucial for a successful primary pharmacological prevention program. Although we did not thoroughly investigate the incidence of side-effects, no reports of drug-related side-effects were reported to the Health District. The risk of vitamin D intoxication is negligible for the increases in 25OHD that follow treatment, even in patients already taking daily vitamin D supplements (400-800 IU). The feasibility of this primary pharmacological prevention is very good and comparable to that of a vaccination program. The cost-effectiveness is also quite obvious. The cost of one vial of 400,000 IU vitamin D2 is e 2.12. Thus, for an estimated Number Needed to Treat (NNT) of 200 women, a hip fracture can be prevented for only e 424. As expected, vitamin D was more effective in women aged > 75 years, in whom the risk of both vitamin D insufficiency and hip fracture is higher. By concentrating efforts to increase participation in the prevention program among these women, cost-effectiveness is expected to be even more rewarding. We must also take into account the additional benefits expected for the risk of other fractures and other conditions associated with vitamin D insufficiency.

*B) Weekly administration*

The yearly administration of vitamin D is insufficient to guarantee high and constant levels of serum 25OHD, particularly in patients affected by osteopenia or osteoporosis. 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. This has led to the conclusion that serum 25OHD should be higher (at least 70-80 nmol/L) than estimated previously, and that the vitamin D requirement in the elderly for anti-fracture efficacy may be 800 IU/day or even more. Nevertheless, in clinical practice the daily administration of vitamin D might be burdened by a reduced adherence, in particular if in combination with calcium supplements as commonly used, and therefore does not guarantee the correction of vitamin D deficiency in the long term.
In a recent study (18) we wanted to examine the compliance and the effects on 25OHD and PTH serum levels of the common preparations of vitamin D in combination with calcium used daily, and of a weekly approach with vitamin D. 271 women affected by postmenopausal osteopenia or osteoporosis complicated by hypovitaminosis D were randomised to assume either oral 4000 IU weekly or 800-880 IU daily in combination with calcium. After 1 year the compliance to treatment and the 25OHD and PTH serum levels were evaluated. Approximately 50% of the patients that would have had to assume the combination of vitamin D and 1 g calcium daily interrupted the treatment within 6 months because of intolerance to the calcium supplement, and another

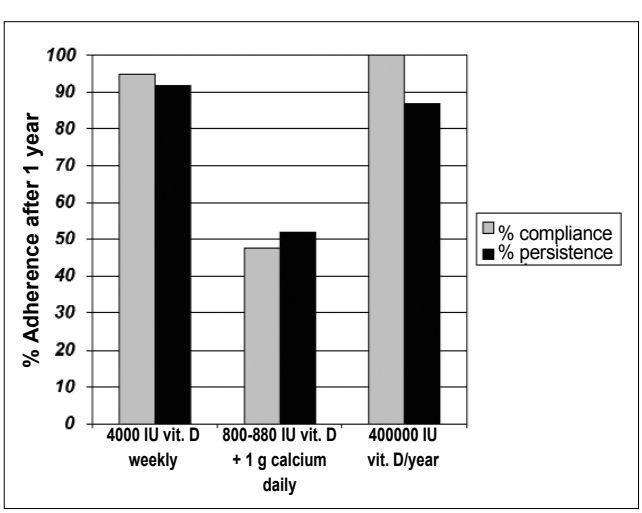


Figure 3 - Adherence (compliance and persistence) to different vitamin D treatment methods (18).

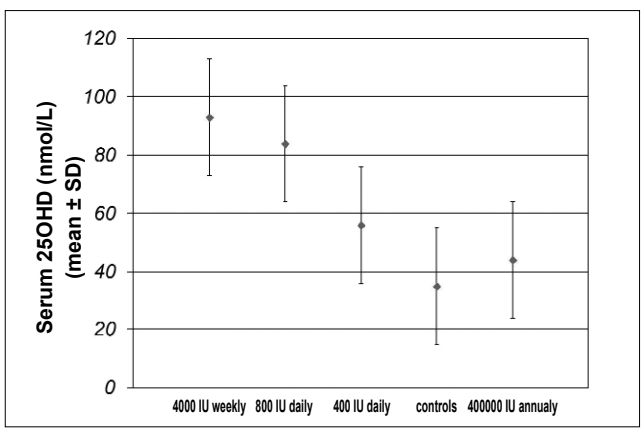


Figure 4 - Serum levels of 25OHD observed during different vitamin D treatment methods (18).

30% assumed half of the prescribed dose (Figure 3). In contrast, after 1 year the adherence to the weekly vitamin D supplement was over 90% and guaranteed serum levels of 25OHD similar to those obtained with 800-880 IU of cholecalciferol a day (Figure 4), reducing the risk of secondary hyperparathyroidism.
Therefore in clinical practice the daily administration of vitamin D combined with calcium is burdened by a reduced compliance and therefore does not guarantee the correction of vitamin D deficiency in the long term. The weekly administration of vitamin D could represent a valid alternative.

## Conclusions

Vitamin D deficiency is extremely common in the entire national territory of Italy, particularly in elderly women. Unfortunately, in spite of the vast evidence on consequent secondary hyperparathyroidism and hip fractures, the problem of hypovitaminosis D is still clearly ignored in Italy or the treatments used up to now are insufficient or inadequate. A population-based strategy to correct this condition and new treatment methods with vitamin D that guarantee a better and long term compliance appear urgent. Preliminary experiences are heartening.

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