Vitamin D and its implications for musculoskeletal health in women: An update

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Received 23 October 2006; received in revised form 9 April 2007; accepted 7 May 2007

Abstract

Vitamin D is a hormone that controls phosphorus, calcium, and bone metabolism and neuromuscular function. Vitamin D synthesis is a process in which the skin, liver, and kidney are sequentially involved. The vitamin D pool is completed by the amount taken with food and supplements. Vitamin D deficiency causes osteopenia, precipitates and exacerbates osteoporosis, causes a painful disease, osteomalacia, and increases muscle weakness, which worsens the risk of falls and fractures. A high prevalence of vitamin D insufficiency exists in the apparently healthy population, osteoporotic patients, and patients with prior fractures. Factors contributing to low vitamin D levels include low sunlight exposure, decreased skin synthesis and intestinal absorption, and inadequate diet. The simplest way to correct hypovitaminosis is adequate nutrition and supplements. However, few patients with osteoporosis and/or fractures, receive adequate supplements. Vitamin D insufficiency may alter the regulatory mechanisms of parathyroid hormone and may induce a secondary hyperparathyroidism that increases the risk of osteoporosis and fractures, although the necessary degree of this is not established. Monitoring of serum 25-hydroxyvitamin D levels is the only way to assess vitamin D status. The ideal healthy blood levels of 25-hydroxyvitamin D are controversial, although a range from 30 to 60 ng/mL is widely accepted. The role of vitamin D supplementation is to provide humans with the nutrient in an amount closer to the biological norm for our species. This amount of vitamin D results in optimal function of many aspects of health, including balance and muscle strength, thus reducing the risk of fracture beyond what is possible via the quality and quantity of bone itself.

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Keywords: Vitamin D; Vitamin D insufficiency; Menopause; Osteopenia; Osteoporosis; Osteoarthritis; Neuromuscular function; Fracture; Secondary hyperparathyroidism; Inadequate diet; Aging; Sun exposure; Bisphosphonates; Vitamin D and falls; Postmenopausal women; Musculoskeletal health

Abbreviations: 1,25(OH)2D3, 1α,25-hydroxycholecalciferol; 24,25(OH)2D3, 24,25-hydroxycholecalciferol; 25(OH)D3, 25-hydroxycholecalciferol (1 ng/mL = 2.5 nmol/L); BMD, bone mineral density; BMI, body mass index; FCA, fractional calcium absorption; iPTH, intact parathyroid hormone; MVC, maximum voluntary contraction; OR, odds ratio; CI, confidence interval; PTH, parathyroid hormone; RANKL, receptor activator nuclear factor-κB ligand; RR, relative risk; UVB, ultraviolet B; VDRs, vitamin D receptors

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0378-5122/$ – see front matter © 2007 Published by Elsevier Ireland Ltd.
doi:10.1016/j.maturitas.2007.05.002

Please cite this article in press as: Pérez-López FR, Vitamin D and its implications for musculoskeletal health in women: An update, Maturitas (2007), doi:10.1016/j.maturitas.2007.05.002
1. Introduction

Osteoporosis is a metabolic disorder that is associated to bone mass reduction and changes in bone turnover and bone architectural structure leading to a decreased resistance to low energy trauma. It is often known as a silent illness, because many people do not know they have it until it is too late. Osteoporosis has been estimated to affect 75 million people in Europe, the US, and Japan. In Europe, more than 1.1 million fractures associated to osteoporosis have been estimated to occur every year. The most alarming estimates calculate that in 2050, osteoporosis-related hip fractures could increase 204% in women and 310% in males just because of population aging [1]. Although osteoporosis is thought of as a disease of old age, the most recent research suggests that its roots lie in prior life stages – even in intrauterine life – and lifestyle [2–4]. There have been advances in recent years in the understanding of genes controlling bone metabolism, bone mass, and the rate of loss of bone structure [5].

Osteoporotic fractures are complex phenomena involving not just intrinsic bone strength or fragility, but age-related neuromuscular changes that determine both the frequency and types of falls, as well as other critical factors. Recent studies have demonstrated the significant role of vitamin D in osteoporosis and the risk of associated fractures [6,7], regardless of its importance for prevention of rickets and osteomalacia. Vitamin D insufficiency has been shown to have adverse effects on calcium metabolism, osteoblastic activity, matrix ossification, bone mineral density (BMD), and bone remodeling [8,9]. Vitamin D insufficiency also causes neuromuscular dysfunction and non-specific pain, and chronic vitamin D deficiency has been associated to various conditions related to aging and metabolic cell impairment. Falls due to neuromuscular dysfunction cause many hospital admission, deaths, and health expenditure [10–12]. Vitamin D supplementation reduces the number of fractures and directly improves neuromuscular function, thus helping to prevent falls and subsequent fractures. This review examines the connection between vitamin D levels, bone resorption, and neuromuscular function that may lead to an increased risk of fractures caused by low energy trauma.

2. Vitamin D synthesis

More than 10 substances belong to the group of seco-steroid compounds that exhibit vitamin D activity. The fat-soluble vitamin D mainly occurs in two forms: ergocalciferol (activated ergosterol, vitamin D2), found in plants and irradiated yeast; and cholecalciferol (activated 7-dehydrocholesterol, vitamin D3), formed in human skin after exposure to ultraviolet B (UVB) rays from the sun. After vitamin D is produced in the skin or taken in food, it is converted in the liver and kidneys to form the physiologically active compound of vitamin D, that works as a hormone, sending messages to the intestines to increase calcium and phosphorus absorption to ensure that adequate calcium and phosphorus levels are maintained in blood (Fig. 1) [2]. Despite its consideration as a vitamin, the active ingredient is contained in very small amounts in food usually taken by humans. Vitamin D2 (ergocalciferol) is commonly added to milk and some nutritional supplements.

Most people obtain almost all their vitamin D requirements through short casual sun exposure (as little as 10–15 min of sunshine daily, two to three times per week, on the face and hands). Skin synthesis may generally provide most vitamin D to the body (80–100%) [13], and dietary vitamin D may therefore not be required when there is an adequate exposure to sunlight [14]. Synthesis also has an additional benefit: vitamin D precursors are cholesterol derivatives that decrease during vitamin formation [15]. When sun exposure is reduced, as occurs during winter, cholesterol levels decrease; in summer, by contrast, outdoor activities increase cholesterol use for biosynthesis of vitamin D precursors.

The natural form of vitamin D is cholecalciferol – considered as a prehormone – formed in the skin by the action of light on 7-dehydrocholecalciferol, that is provitamin D3. Sunlight exposure produces thousands of cholecalciferol units that pass into blood. In the circulatory system, vitamin D metabolites bind to a binding protein. In the liver, vitamin D3 is hydroxylated and converted into 25(OH)D3; it passes through the enterohepatic circulation and is reabsorbed. 25(OH)D3 is the circulating compound denoting vitamin status and usually measured for clinical testing. This compound is transformed, mainly in the kidney, into 1,25(OH)2D3, that acts as a hormone on the bowel and bone. Though the best known synthesis of
1,25(OH)_{2}D_{3} occurs in the kidney, the final step in 1,25(OH)_{2}D_{3} synthesis occurs in almost all human tissues [14–16], and the substance exerts local paracrine functions.

Skin synthesis is photoregulated, so that inactive metabolites (tachysterol and lumisterol) are produced when there is an excess of UVB rays. In addition, vitamin D3 is sensitive to irradiation and is inactivated by it. Vitamin production also depends on skin pigmentation, and there is a negative feedback mechanism. Skin also has an essential role in the photoendocrine system of vitamin D, regardless of its importance in the early steps of vitamin synthesis. Epidermal keratinocytes have all the components of the vitamin D endocrine system: vitamin D receptors, they may locally produce 1,25(OH)_{2}D_{3} and have 24-hydroxylase, all of which suggests potential local paracrine and autocrine effects [16]. 1,25(OH)_{2}D_{3} may protect keratinocytes from incorrect DNA repairs caused by UVB rays. Local formation of active hormone in the skin opens up new perspectives for prevention of cancer and other diseases [17].

1,25(OH)_{2}D_{3} regulates gene expression in more than 30 tissues. The CYP24 or 24-hydroxylase enzyme gene, responsible for vitamin D degradation, is the most affected of all regulated genes [18]. The active hormone 1,25(OH)_{2}D_{3} enter the cell and binds to the specific vitamin D receptor – a transcription factor – that triggers a great variety of genes expressing its biological activity. The receptor belongs to the superfamily of steroid hormonal receptors. It is closely related to retinoic acid and thyroid hormone receptors [19].

Vitamin D has a universal action of turning on an intracellular transport mechanism, and the particular type of cell then uses this mechanism to achieve whatever function is wanted by the tissue (e.g., intestinal calcium transport, cell differentiation, induction of apoptosis in cancer cells, etc.). All cells have a calcium-sensing receptor that modulates cell functions in response to extracellular calcium. The calcium entry structure functions as both transporter and a vitamin-D responsive channel [20].

3. Intestinal vitamin D absorption

Vitamin D taken with certain types of food is added to the synthesized vitamin pool. Vitamin D in diet
is absorbed from the small bowel through the lymphatic system in the presence of bile acids. In order to be assimilated, vitamin D should be dissolved in oil, because it is soluble in fat. When an attempt is being made at reducing fat contents in diet, vitamin D absorption is reduced. Certain diseases that decrease fat absorption, such as pancreatic enzyme deficit, Crohn’s disease, cystic fibrosis, sprue, and some liver diseases may also lead to vitamin D deficit due to malabsorption.

Although the list of vitamin D-rich foods is limited, it is acquired from foods such as egg yolks, butter, cod liver oil, and cold-water fish such as salmon, herring and mackerel. The prevailing type of diet influences 25(OH)D3 levels. Depending on diet, decreasing levels are found in the following order: meat-eaters, fish-eaters, vegetarians, and vegans [21]. The amount of fish eaten per week is a factor influencing 25(OH)D3 levels in the population, and the type of food eaten may partly account for differences in vitamin D levels between countries with different cooking cultures. Milk and margarine with added vitamin D still appear to be the most common source of this important vitamin in some countries. Other foods may also be fortified with vitamin D. In the United States and Canada there are rules governing food fortification with vitamin D. However, no common regulations exist in European countries. The amount of vitamin D contained in foods of an animal origin depends on animal diets, while vitamin D levels in fortified foods depend on the legal regulations in each country and manufacturers’ interests. Thus, milk may be fortified, but milk derivatives – such as yoghurt and cheese – may not have an adequate amount of vitamin D.

For many people, a daily supplement containing vitamin D may be the best way to ensure an adequate vitamin D status when there is no adequate skin exposure to the sun. Vitamin D supplements are available in two forms, vitamins D2 and D3. Vitamin D3 is believed to have the most potent properties and is the preferred form of the vitamin. Adolescents, women of childbearing age, and postmenopausal women should ensure that they are getting adequate vitamin D. Breastfed babies are a population particularly sensitive to vitamin D deficiency. Human breast milk has a low vitamin D content which, together with the trend to a longer breastfeeding period, has raised concerns. If the vitamin D status of the mother is low, this only magnifies the poor nutrition of the breastfeeding baby. Adequate daily intake is 200 international units (IU) of vitamin D from infancy to 50 years of age. For adults aged 51–70 years 400 IU are required, while 600 IU are recommended for individuals over 70 years of age. Too much vitamin D can occur from taking excess vitamin D supplements and may cause serious problems, such as nausea, vomiting, and weakness, or even confusion and heart rhythm abnormalities. However, these are the symptoms of hypercalcaemia per se, irrespective of the cause and not due directly to excess vitamin D. Both vitamin D and vitamin A are fat-soluble substances and may be in the same foods or vitamin supplements. Recent studies have shown that excess intake of vitamin A as retinol present in animal and fortified foods may be harmful for vitamin D metabolism and bone [22,23]. By contrast, a different form of vitamin A, beta-carotene, occurring in some fruits and vegetables does not interfere with vitamin D absorption and is poorly converted in retinol. Foods and vitamin supplements with low retinol levels should therefore be selected to ensure vitamin D absorption.

4. Calcium homeostasis and prevalence of vitamin D insufficiency

Vitamin D is essential for intestinal calcium absorption, calcium and phosphorus regulation in blood, and skeletal and dental health. 1,25(OH)2D3 works in concert with PTH and calcitonin to regulate serum calcium and phosphorus levels. PTH is released in response to low serum calcium levels and induces the production of 1,25(OH)2D3. By contrast, reduced PTH levels stimulate synthesis of the inactive metabolite 24,25(OH)2D3. In intestinal epithelium, 1,25(OH)2D3 functions as a steroid hormone inducing expression of calbindin D28K, a protein involved in intestinal calcium absorption. Increased absorption of calcium ions requires concomitant absorption of a negatively charged counter ion to maintain electrical neutrality. When plasma calcium levels fall, the major action sites of 1,25(OH)2D3 and PTH are bone, where they stimulate bone resorption, and the kidneys, where they inhibit calcium excretion by enhancing resorption by distal tubules. The role of calcitonin in calcium homeostasis is to decrease elevated serum calcium levels by inhibiting bone resorption.
Calcium concentration is kept at constant, supersaturated levels as compared to bone mineral content. When calcium and phosphorus plasma levels are less than saturated, bone mineralization is impaired, which causes rickets in children and osteomalacia in adults. Vitamin D represents the hormone system that maintains calcium levels in blood. It is the only hormone known to induce the proteins involved in intestinal absorption. Vitamin D also stimulates phosphate absorption in the bowel. When dietary calcium is not available or not absorbed, vitamin D hormone absorption in the bowel. When dietary calcium is not available or not absorbed, vitamin D hormone stimulates osteoblasts to produce receptor activator nuclear factor-κB ligand (RANKL). RANKL subsequently stimulates osteoclastogenesis and activates resting osteoclasts for bone resorption [24,25]. For mobilization of calcium present in bones to occur, combined action of vitamin D and PTH is required [26]. The renal distal tubule is responsible for resorption of at least 1% of calcium filtered under the effects of these two hormones [27]. Calcium loss from the skeleton during this whole readjustment process eventually promotes osteoporosis. However, not all cases of hypovitaminosis D develop secondary hyperparathyroidism. In women with postmenopausal osteoporosis and low vitamin D levels (25(OH)D3 < 30 nmol/L), PTH increase occurs in one third of cases, in which calcium homeostasis is maintained by increasing bone turnover as compared to people who have normal vitamin D levels. By contrast, subjects with hypovitaminosis D in whom PTH secretion is not increased have low calcium levels, bone turnover is reduced, and bone is protected from bone mass loss as compared to cases of hypovitaminosis with secondary hyperparathyroidism [28]. We do not know yet the mechanisms leading to two different situations occurring in the body: maintenance of calcium homeostasis or bone protection from bone mass loss. On the other hand, the combination of hypovitaminosis D and PTH increase is associated with loss of muscle strength and muscle mass in both women and men over 65 years of age [29]. Inadequate vitamin D levels have been widely studied in recent years, particularly in postmenopausal women.

The definition of vitamin D adequate and inadequate levels, indirectly expressed by serum levels of 25(OH)D3, is controversial. Initially, vitamin D was considered to be deficient when 25(OH)D3 levels were less than 8–10 ng/mL (20–25 nmol/L) and were associated with biochemical and histological findings consistent with osteomalacia. However, several epidemiologic and mechanistic studies suggest that 25(OH)D3 levels should be maintained above 30 ng/mL (equivalent to 75 nmol/L) for a maximum calcium absorption and to maintain an optimal health [30–35]. 25(OH)D3 levels below 31 ng/mL are associated with a reverse relationship with intact PTH (iPTH), and when 25(OH)D3 levels are 4.6 ng/mL or lower, maximum iPTH levels are reached (55 pg/mL) [30]. Maluche et al. [36] think that bone turnover is related to the ratio of 84-amino acid iPTH and amino-terminally truncated C-PTH fragments. When iPTH predominates bone turnover is activated, while certain fragments (particularly PTH7–84) act as iPTH antagonists. These effects are probably exerted through the PTH receptor. Specific PTH receptors have been shown in osteoblasts and, to a lesser extent, in osteoclasts.

While no consensus exists about optimum vitamin D levels, they may be considered adequate when PTH levels are not elevated and vitamin D supplementation does not decrease PTH levels. Levels of 25(OH)D3 under 20 ng/mL have been associated with increased bone turnover, decreased bone mineral density, a reduction in femoral neck cortical, decreased intestinal absorption of calcium, occurrence of osteoporosis and fractures, and decreased neuromuscular function [37–42]. This is a worldwide public health problem that does not respect frontiers and causes serious complications, and it is expected to become even more important in the coming years because of bad dietary habits and aging of the population. Zadshir et al. [43] evaluated 25(OH)D3 levels in more than 15,000 adults aged over 18 years from the US population studied in the third National Health and Nutrition Examination Survey (NHANES III). Lower levels were seen in women as compared to men and among elderly (65 years or more) as compared to young individuals (40–59 and 18–39). White men and women had significantly higher mean levels of vitamin D than Hispanic men and women and than Black men and women. Authors concluded that there is a higher prevalence of both mild to moderate and severe vitamin D deficiency among women and minority populations. Bouillon [44] estimated that there are in Europe 225 million people with inadequate vitamin D levels. In Spain, a country with quite a lot of hours of sun and where social life outdoors is a cultural habit – though little physical...
activity is done in the sun – the prevalence of suboptimal vitamin D levels is quite high [9,45–47]. Among postmenopausal women (osteoporotic and nonosteoporotic, according to WHO criteria) living in Madrid, 64% are considered to have vitamin D insufficiency when the cut-off value of 25(OH)D3 serum levels used is 37 nmol/L. In addition, BMD in the hip is directly related to 25(OH)D3 in women having levels below such limit, while BMD in the hip and lumbar spine have a negative relationship to PTH serum levels in the total group of women [46].

Vitamin D insufficiency has been related to different conditions, including inadequate sun exposure, type of diet, low intake of foods fortified with vitamin D, age-related decrease in the capacity for skin synthesis, body mass index, exercise, use of drugs (e.g. anti-epileptic drugs and anti-tuberculous drugs) or diseases that accelerate vitamin D metabolism (e.g. reticulo-endothelial malignancies, sarcoidosis, tuberculosis), malabsorption syndromes, and chronic liver disease. Furthermore, osteoporosis is more common in people who are unwell for whatever reason. This may in part be due to relative immobilisation or be a part of the disease process, e.g. malignancies or chronic neuromuscular diseases, but such people will have less UV exposure and indeed may have poorer appetites. Thus they are more likely to be vitamin D deficient. This does not imply that vitamin D deficiency was the original cause of their osteoporosis.

4.1. Vitamin D circannual rhythm and seasonal variations

Biological cycles extending over 1 year ± 2 months are called circannual rhythms. Cross-sectionally, 25(OH)D3, PTH, and osteocalcin levels in a healthy population aged 18–69 years show the presence of circannual rhythms, and a moderate negative correlation exists between 25(OH)D3 and PTH in both sexes [48,49]. A monthly longitudinal study conducted over 1 year on 10 healthy subjects showed, using the cosine curve method, the existence of a circannual rhythm in 25(OH)D3 levels, with fluctuations from 5.0 to 16.5 ng/mL, on which seasonal variations where added [50]. This 25(OH)D3 rhythm is associated with complex interactions with PTH and biological markers of skeletal homeostasis. Studies performed in the Northern hemisphere and in areas distant from the equator have shown a significant seasonal variation in 25(OH)D3 levels. During the winter, the circulating amount of vitamin D decreases, and PTH secretion and bone resorption increase. These changes are associated with an increase in falls resulting in wrist and hip fractures.

A retrospective 18-month study on 41 healthy subjects (aged 21–80 years) conducted in Germany allowed for an improved understanding of circannual metabolic changes, showing the existence of an annual rhythm in bone turnover. Parameters with a circannual periodicity include 25(OH)D3, 1,25(OH)2D3, PTH, and bone-specific alkaline phosphatase in serum, and urinary total pyridoline, deoxypyridoline, and amino terminal telopeptide of collagen type I. Peak 25(OH)D3 levels were recorded in August, while bone turnover parameters and PTH reached peak values in the winter months. The results were more marked in premenopausal women, subjects under 50 years of age, and subjects who showed an individual 25(OH)D3 rhythm [51]. Seasonal and/or circannual changes in calsciotropic hormones and bone turnover increase during winter may be neutralized by oral administration of vitamin D3 and calcium. A prospective, randomized, controlled 2-year study conducted in Germany analyzed spontaneous changes during the first year, and over the second year compared oral treatment with cholecalciferol (500 IU/day) and calcium (500 mg/day) during the winter months (October–April) versus no treatment, showing that the supplement administered was able to neutralize the hormonal and metabolic changes occurring during the winter. By contrast, the above described circannual rhythm persisted in the control group during the second year. In addition, the treated group gained bone mass in the lumbar spine and femoral neck as compared to the control group [52].

Seasonal changes in 25(OH)D3 are also detected in subtropical countries, and low vitamin D levels are even detected during summer. Pasco et al. [53] studied a population of Australian women aged 55 years or over who did not usually receive vitamin D supplements. Seasonal 25(OH)D3 variations cycled with a 1-month lag as compared to ultraviolet light, with the maximum peaks in summer and the lowest peaks in winter. PTH periodicity was the reverse to 25(OH)D3 with a 1-month lag, and serum C-telopeptide levels lagged peak serum PTH by 1–2 months. During end
winter, a greater number of falls were associated with fractures. Hip and wrist fractures showed a harmonic seasonal cycle, with a maximum peak at about 1.5–3 months after low 25(OH)D$_3$ levels.

In New Zealand, vitamin D insufficiency (25(OH)D$_3$ < 50 nmol/L) was also common. During the summer, 28–58% of healthy postmenopausal women had a suboptimal vitamin D status, while in winter the proportion increased to 56–74% [54]. The change in monthly ultraviolet dose from summer to winter was followed 6–8 weeks later by a corresponding change in 25(OH)D$_3$. In addition, 25(OH)D$_3$ showed a slight negative correlation with age (r = -0.15), weight (r = -0.11), body mass index (r = -0.13), fat mass (r = -0.14), and percent body fat (r = -0.16). Together, these variables account for approximately 20% of seasonal changes in 25(OH)D$_3$. It therefore appears that winter and ultraviolet light cause a reduction in skin synthesis of vitamin D precursors and increase PTH secretion, bone resorption, falls leading to fractures, and hip and wrist fracture rate. It seems plausible to abolish the negative changes occurring during winter and to prevent bone impairment with adequate vitamin D and calcium supplements. It remains to be shown whether prolongation of this intervention for years places women in better conditions to face hormonal change due to menopause and decreases the prevalence of osteoporosis in subsequent years.

4.2. Aging

In young postmenopausal women, estradiol levels predict lumbar BMD and PTH predicts BMD in the femoral neck [55]. PTH increase has been suggested to contribute to bone loss in postmenopausal women. This increase has been attributed to a decreased kidney function, decreased calcium absorption efficiency, and decreased 25(OH)D$_3$ levels. The effect of vitamin D deficiency upon PTH secretion is clearly age-dependent [56,57]. When the 25(OH)D$_3$ results are stratified in three age groups (up to 50 years, 51–70 years, and over 70 years), it is seen that, assuming equal vitamin D levels in cases with vitamin D deficiency, a higher PTH secretion response is seen in older people. These differences have been attributed to a decreased capacity by elderly people to secrete vitamin D in the skin despite sun exposure. However, kidney clearance is also decreased in advanced age, and both effects would tend to compensate each other. The situation suggests that a “resistance” of the parathyroid gland to vitamin D occurs with age, and higher vitamin D levels would be required to maintain normal PTH levels [57].

In an analysis of more than 900 postmenopausal women showed, using simple linear regression, that serum PTH was a positive function of age and weight and an inverse function of serum 25(OH)D$_3$ and serum ionized calcium. When stepwise regression was performed, serum 25(OH)D$_3$ was the most significant (negative) determinant of serum PTH, followed in decreasing order of significance by serum ionized calcium (negative) and body weight and age (positive) [58]. PTH may also increase with age due to a number of variables that condition its secretion and renal clearance. Renal function may be decreased with aging, diuretic use, and estrogen deficiency, thus influencing the increase in circulating PTH [57]. Gastrointestinal absorption of vitamin D supplements is not impaired with age, but transformation into the active hormone in the liver may be decreased [59]. This closes a cycle of negative synergies due to aging that are associated to the direct effects of PTH on bone turnover [38]. Study of fasting fractional calcium absorption (FCA) and the relationship between FCA and free 1,25(OH)$_2$D$_3$ (representing intestinal sensitivity to) in young and elderly women shows the latter to have a greater resistance than the former to the intestinal action of 1,25(OH)$_2$D$_3$, which may contribute to a negative calcium balance, secondary hyperparathyroidism, and bone loss [60].

4.3. Inefficiency of sun exposure for vitamin D synthesis

Skin characteristics modify the amount of vitamin D formed, with Black people having the greatest difficulties for vitamin synthesis after similar exposure times. 25(OH)D$_3$ insufficiency is highly prevalent among black people, and more common than in people from any other race, because pigmentation decreases vitamin D production and a diet with an inadequate vitamin content is very often an additional factor. Despite low vitamin D levels, black people have lower osteoporotic fracture rates than other ethnic groups, possibly because of their special characteristics in intestinal absorption of vitamin D and calcium, skeletal resis-
tance to PTH action and/or other unknown mechanisms [61–64].

The prevalence of hypovitaminosis D, secondary hyperparathyroidism, musculoskeletal pain, and osteoporosis is also high among women wearing clothes that prevent sunlight exposure. Among Muslim women who follow the traditional habits, a negative correlation exists between 25(OH)D₃ and PTH blood levels and urinary deoxypyridoline levels denoting an increased bone turnover [65]. Turkish women living in an urban environment, both in Germany and Turkey, have a high prevalence of vitamin D insufficiency, quite higher than men of the same origin, particularly veiled women [66]. The factors best predicting low 25(OH)D₃ levels included sex, body mass index, lack of sun exposure, and living at a higher latitude. In addition, wearing a scarf and number of children were found to be an independent risk factor for vitamin D deficiency in Turkish women living in Turkey and Germany. Moreover, osteoporosis prevalence is increased in postmenopausal women who wear the traditional clothes (concealing clothing) that cover the arms, head and legs [67].

Compliance with ultra-orthodox Jewish habits (low sun exposure, diet, clothing), particularly in urban areas, also has a negative impact upon vitamin D levels and bone metabolism [68].

4.4. Obesity

Obesity is associated with reduced 25(OH)D₃ and increased PTH circulating levels [69–72]. Limited mobility and increased storage of vitamin D in fat tissue have been postulated as potential causes, but obesity is actually a consequence of low vitamin D levels. Snijder et al. [73] examined the relationship between adiposity, anthropometric parameters, and 25(OH)D₃ and PTH levels and found that the total amount of body fat – as measured by dual energy X-ray absorptiometry – is inversely related to circulating 25(OH)D₃ levels and positively related to PTH levels. Weaker associations were seen with anthropometric parameters, suggesting a specific role for fat tissue. In obesity, vitamin D production in the skin is not impaired, but after sun exposure obese individuals only produce half the amount of vitamin D produced by non-obese individuals. By contrast, circulating 25(OH)D₃ levels following oral administration of vitamin D supplements are similar in obese and non-obese individuals [71]. These results suggest a decreased passage of vitamin D formed in the skin into the general circulation due to its subcutaneous accumulation in obese people.

Obesity (body mass index, BMI ≥ 30 kg/m²) and black race are risk factors for vitamin D deficiency and secondary hyperparathyroidism. Yanoff et al. [74] have shown that white obese adults have higher 25(OH)D₃ levels than black obese adults, and that the prevalence of hypovitaminosis D increases as BMI increases. In addition, PTH levels are negatively and significantly correlated to 25(OH)D₃ levels, and a higher prevalence of secondary hyperparathyroidism is found among black people as compared to white people.

4.5. Diseases and treatments that alter vitamin D levels

Conditions interfering with vitamin D absorption (Crohn’s disease, intestinal resection, etc.), Down’s syndrome, use of glucocorticoids, heparin, warfarin, methotrexate, some anti-epileptic and anti-tuberculous drugs promote a decreased bone mass and cause vitamin D insufficiency [75–79].

Type 2 diabetes mellitus is associated with a significant bone turnover decrease even in patients with very low vitamin D levels, very old patients, and institutionalized populations. Dobnig et al. [80] prospectively studied 583 elderly people (70 years or older) with type 2 diabetes mellitus in nursing homes from four countries. The control group consisted of 1081 people, 88% of whom had 25(OH)D₃ levels less than 15 ng/mL. Patients with diabetes had significantly higher age-, weight- and mobility-score-adjusted calcaneal stiffness, radial speed of sound and phalangeal speed of sound bone ultrasound measurements compared to controls. Diabetic patients treated with oral antidiabetic drugs or insulin had PTH and osteocalcin levels 20.7% and 22.3% lower than control group subjects, respectively. Bone turnover is a significant factor, independent from BMD measurement by ultrasound. Decreased PTH levels and increased glucose levels separately contribute to a decreased turnover in elderly female patients with type 2 diabetes mellitus. Though a theoretical bone protection effect occurs, the fracture rate is similar in both groups.
5. Vitamin D in osteoporosis and fracture risk

Bone health has been related to adequate vitamin D levels in men and women throughout their lives [81–83]. When serum levels of 25(OH)D3 are less than 10 ng/mL, they are associated with biochemical and histological findings consistent with osteomalacia, that causes muscle and bone pain [88,89]. In a study on 150 patients with non-specific and persistent musculoskeletal pain refractory to conventional treatment, 140 patients were found to have vitamin D deficiency (mean 25(OH)D3 levels = 12.1 ng/mL) [84]. In this study, 16% of Asians, 24% of Anglo-Americans, 40% of Hispanics, and 50% of Afro-Americans had very low 25(OH)D3 levels (less than 8 ng/mL). 25(OH)D3 levels lower than 30 ng/mL cause increases in PTH circulating levels, increase turnover, promote bone resorption, and increase the prevalence of osteoporosis.

A systematic review of 30 reports analyzed the prevalence of inadequate vitamin D levels in postmenopausal women with osteoporosis, measuring 25(OH)D3 in serum and using different cut-off values [85]. The prevalence of 25(OH)D3 levels less than 12 ng/mL ranges from 12.5% to 76% in osteoporotic populations, while the prevalence reaches 50–70% of patients with a history of fracture when a cut-off value of 15 ng/mL is used. Factors associated to inadequate vitamin D levels include low sunlight exposure, low vitamin D diet, nursing home environment, winter, and age over 70 years.

A 64% prevalence of inadequate vitamin D levels was found in more than 2500 osteoporotic women from 18 countries (North, Central and Southern Europe, Middle East, Latin America, Asia and Pacific Rim). Mean 25(OH)D3 levels were 26.8 ng/mL (SE 0.3), and PTH achieved a nadir at 25(OH)D3 serum levels higher than 35 ng/mL [86]. In these osteoporotic women, 25(OH)D3 levels were slightly lower among women from non-equatorial versus equatorial countries. A weakly significant relationship (r = 0.2) was also found between 25(OH)D3 and latitude, even after adjustment for other factors such as BMI, travel to sunny areas, race, general health, vitamin D supplementation, and education. However, the results did not support a clear influence of the location in relation to the equator on 25(OH)D3 levels. Other environmental and cultural factors (environmental conditions, diet, supplements, sunlight exposure, clothing) would have a greater influence upon vitamin D metabolism [87]. The multinational European study sponsored by the World Health Organization recently reported the circulating levels of 25(OH)D3 in 8532 European osteoporotic women. Values lower than 80 nmol/L were seen in almost 80% of women, and approximately one third had levels under 50 nmol/mL, suggesting a high risk of sustaining osteoporotic fractures [88]. Low 25(OH)D3 levels were found in the population from both sunny and poorly insolated countries regardless of latitude, and not only in women over 70 years of age, but also at lower ages. Authors concluded that hypovitaminosis D is a worldwide problem, and women should receive vitamin D supplements, including young postmenopausal women.

Despite recommendations that women should ensure adequate calcium plus vitamin D intake for postmenopausal bone health [89,90], the role of these supplements on reducing fractures has been conflicting. There are recent randomized clinical trials of calcium and vitamin D supplementation that failed to show any benefit for osteoporotic hip fracture reduction in people aged 70 years or older with special characteristics [91–93] and in postmenopausal women, 50–79 years, who were already enrolled in a Women’s Health Initiative (WHI) clinical trial [94,95], However, they deserve a detailed analysis. The randomized placebo-controlled trial by Porthouse et al. [91] studied the effect of oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people. In an open controlled trial, a daily oral supplementation with calcium and vitamin D does not seem to reduce the risk of hip fracture, as compared to placebo, in women aged 70 and over with one or more risk factors for fracture of the hip with a median follow-up of 25 months [92]. However, the study’s power was only able to detect a difference of 30% in the rate of hip fractures between the two groups; so a difference of anything less than this would be a negative finding in this particular study. Furthermore, there was no mention of spinal fractures which is also another important outcome of those at risk of fractures. This type of fractures may not have been reported in the questionnaires provided to the patients since only 20–30% are symptomatic. Other methodological bias are included in the rapid responses to the paper [92].

Grant et al. [93] randomized people aged 70 years and older (85% of whom were women) who were...
mobile to receive vitamin D and calcium versus placebo who were followed up for between 24 and 62 months. They concluded that their findings do not support routine oral supplementation with calcium and vitamin D3, either alone or in combination, for the prevention of further fractures in the population studied. The mean baseline concentrations of 25(OH)D for a sample of 60 people were 15.2 ng/mL, rising to 24.9 ng/mL after 1 year of supplementation; therefore, the subjects were vitamin D deficient at the start of the trial, and the vitamin daily dose of 800 IU failed to rise 25(OH)D3 levels sufficiently to maximize calcium absorption. These results contrast with those from the Decalyos Study [89,96] that compares the effect of 1200 mg/day calcium and 800 IU/day vitamin D3 supplementation versus placebo in institutionalized elderly women in seven European countries and demonstrates that the supplementation is effective in decreasing the incidence of both hip and non-vertebral fractures. In a group of institutionalized patients Chapuy et al. [97] reported very low serum 25(OH)D3 – lower than those reported by Grant et al. [93] – at baseline and rose significantly under treatment to normal values – higher than those reported by Grant et al. [93]. Furthermore, based on a recent expert panel and supportive evidence, serum concentrations of at least 30 ng/mL 25(OH)D should be referred to as desirable [98].

In cases of established vitamin D deficiency, higher oral vitamin D3 doses (8–12,000 IU daily for 3 months or more) are sometimes required to reach optimal vitamin D status. As I already discussed, the elderly need a higher dose D vitamin to overcome the hyperparathyroidism associated with the decreasing renal function in older adults. On the other hand, calcium carbonate may be poorly absorbed in the absence of adequate gastric acid, a frequent condition since the elderly are especially prone to hypochlorhydria; a more appropriate choice would be calcium citrate, as absorption of this does not seem to be affected by low gastric acid. It is well known that hip fractures – the endpoints in both British studies – are inversely related to the level of physical activity [99] and those who suffer fractures of the femoral neck may have had the same bone density as controls [100]. It should be considered that maintaining an adequate vitamin D level into old age not only prevent osteoporosis and hip fractures, more important preserves muscle coordination and balance which are important to prevent falls and fractures.

The recently published WHI involving calcium and vitamin D3 supplementation concluded that the intervention resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones [93]. The study involved nearly 36,000 postmenopausal women who were randomly assigned to receive either 1000 mg of calcium and 400 IU of vitamin D3 or placebo, with an average follow up of 7 years. In the WHI trial not all women adhered completely to the supplement regimen (at the end of the study only 59% were taking the intended dose) and women in the placebo group used vitamin D and calcium; among those who took 80% or more of the recommended dosage, there was a 29% decrease in the hip fractures. In another analyses of subgroups of participants, women 60 and older had a significant 21% reduction in broken hips. Since higher vitamin D supplements have been administered experimentally without any hypercalcemia [101], it seems unlikely that the vitamin D treatment contributed to the excess risk of renal stones. Finally, the lead author indicates that “All this means any supplementation of this kind is potentially beneficial, particularly in women over 60 years old” [102]. Authors also suggested a number of factors that could account for the limited benefits provided by the supplementation in the trial, including: (1) higher doses of vitamin D might be required to produce a statistically benefit to bone health, (2) the benefit may have existed only for those women who took the supplement exactly as prescribed in the trial, (3) fewer hip fractures occurred among the population studied than researchers anticipated (lowering the power of the study to show a significant finding) that could be attributed to a higher-than-expected average body mass index of 29 among participants since larger women have stronger bones and the fact that many women were already using supplements or were on hormone therapy.

It seems that it is too early to discard the possibility that a cheap supplementation with an adequate amount of vitamin D may have a protective effect on bone health. Vitamin D supplementation remains a necessity in those unwilling or unable to benefit from UV light exposure, particularly as the paucity and low supplementation levels of fortified foods makes it impossible to achieve a suitable intake from diet alone.
5.1. Vitamin D and antiosteoporotic treatments

Osteoporotic fractures cause a high morbidity and mortality, particularly hip fractures, and their prevalence increases with age. Falls and fractures in elderly people represent a public health concern because they induce prolonged painful conditions, functional limitation, disability, and even death. The risk of osteoporotic fracture is related to several factors including bone mineral density and quality, use of certain drugs, decreased sensorial capacity, muscle weakness, and neuromuscular control of swaying [103,104]. Different programs and methods have been proposed to prevent the risk of fall, including regular exercise, vitamin D and calcium supplements, withdrawal of psychotropic treatments, correction of visual defects, changes in environments where a risk of falls exist, use of hip protectors, and multifactorial programs to reduce conditions predisposing to falls [105,106].

It has been known for a long time that women with a femoral neck fracture have calcium metabolism changes, significantly elevated serum PTH levels, and significantly decreased levels of 25(OH)D3 and 1,25(OH)2D3 inducing an increased risk of osteoporosis and osteomalacia [107]. Increased fracture risk among elderly people is not only due to a decreased bone quantity and quality, but also to the increased risk of sustaining a fall as a result of the muscle weakness caused by decreased muscle mass and strength. The cause of this muscular condition should be sought in general malnutrition and a deficient intake of proteins, amino acids, calcium, and vitamin D [108–110].

More than one decade ago, Finnish researchers postulated that long-term treatment with vitamin D in the aged decreased fracture incidence by improving both the quality of bone formed and nerve and muscular control of movements, thus reducing the trend to sustain falls [111].

Nurmi et al. [112] conducted a prospective study in two Finnish hospitals including consecutive patients with a fresh hip fracture in whom 25(OH)D3 levels were measured. Results were rated as mild hypovitaminosis D when levels were under 37.5 nmol/L, and as severe hypovitaminosis D when values were under 20 nmol/L. Mild and severe hypovitaminosis D was found in 53% and 9% of patients, respectively. In patients receiving treatment with both vitamin D and calcium supplements, 25(OH)D3 levels ranged from 37.5 to 74 nmol/L, and exceeded 74 nmol/L more frequently than in patients not receiving supplements. A worse hypovitaminosis status was found among patients admitted to institutional and residential care centers, despite the availability of staff to take care of vitamin D supplementation.

Vitamin D levels were suboptimal in elderly people who had sustained a fragility hip fracture and had greater possibilities to show lower levels than people of the same age and sex not sustaining such fractures. Gallacher et al. [113] retrospectively studied a population in the Glasgow area (UK) with hip fracture who had not received vitamin D or calcium, and found mean vitamin D levels of 24.7 nmol/L (9.9 ng/mL); 91.6% of patients had 25(OH)D3 levels under 50 nmol/L, with no differences between the patients by sex, age, or season. This study confirmed the almost universal vitamin D insufficiency in patients who sustain hip fractures. Very similar results were found in another study conducted in London, but the prevalence of vitamin D insufficiency was slightly lower as compared to Glasgow. In addition, seasonal differences were seen in mean levels [114]. Dixon et al. [115] studied the prevalence of inadequate 25(OH)D3 levels in 954 elderly patients with or without fragility fractures in different regions of the United Kingdom. Mean age – by geographic region – ranged from 60 and 67 years, and 49% of patients had sustained a previous fragility fracture. Patients with a previous fracture had lower 25(OH)D3 levels than patients sustaining no fractures. In patients who had sustained a hip fracture, mean 25(OH)D3 ranged from 24.7 and 36.1 nmol/L, and the levels measured were <80 nmol/L in 90–99% of these patients and <50 nmol/L in approximately 80%. Measurable inadequate vitamin D levels are therefore very common in the elderly, particularly among those who have already sustained fractures. On the other hand, the levels in the different British cities were similar to those reported for other European countries.

Adequate vitamin D levels, supplements of calcium and other minerals, and exercise help decrease the risk of falls and fractures [31,40,116,117]. An additional benefit is tooth loss reduction [118].

In women with postmenopausal osteoporosis, a combination of an antiresorptive drug with vitamin D and calcium is recommended. Osteoporosis management guidelines recommend using calcium and vitamin D supplementation unless patients are calcium replete.
and vitamin D replete. Since almost all people over 65 years of age have inadequate vitamin D levels, the significance of supplemental treatment should be emphasized. However, Bayly et al. [119] found in an audit that prescription of supplements was suboptimal despite all recommendations. Vitamin D and calcium co-prescription widely ranged from 74% and 12%. In the United States, 25(OH)D₃ levels were tested in osteoporotic women on antiresorptive treatment and were found to be lower than 30 ng/mL in 52% of women, and less than 20 ng/mL in 18% [120]. Suboptimal levels (15–30 ng/mL) may increase fracture risk through a secondary PTH increase. When vitamin D insufficiency is not corrected, the success of antiresorptive treatment is reduced. There is also evidence of the presence of associated osteomalacia. Other causes of osteoporosis include hyperparathyroidism, vitamin D deficiency, idiopathic hypercalciuria, hyperparathyroidism secondary to renal failure, malabsorption syndromes, hyperthyroidism, and Cushing syndrome. Vitamin D deficiency is the most common secondary cause of low bone mineral density [121].

In 5–15% of cases treated with bisphosphonates, BMD may continue to fall despite treatment. However, addition of a daily dose of vitamin D 1000 IU is associated with BMD gains of 1.45% in the lumbar spine and 1.15% in the femoral neck in cases previously receiving bisphosphonates alone [122]. This suggests a poor patient compliance with treatment as regards diet and lifestyle. Response to vitamin D occurs irrespective of its baseline levels and indicates an improved nutritional status [123]. Bone mass gain occurs at different rates in different sites and indicates the different response to vitamin D already reported in other studies [124,125].

An attempt has been made in recent times to improve treatment compliance by incorporating vitamin D into a bisphosphonate. Recent data from a multicenter, randomized study in women with osteoporosis comparing a weekly dose of alendronate incorporating vitamin D₃ 2800 IU versus placebo suggested that after 4 weeks, treatment was associated with approximately a 23% relative increase in fractional calcium absorption (FCA). The absolute 7.0% FCA increase is likely to be clinically significant and would support the increase in BMD seen during the first year of alendronate treatment [126]. On the other hand, a prospective, randomized, observer-blind, controlled, 2-year study in 197 osteoporotic postmenopausal women showed alendronate with added vitamin D to be superior in significantly increasing lumbar and femoral BMD as compared to alendronate or vitamin D monotherapy or the control group that received calcium alone. In addition, the combination therapy may decrease the low risk of vitamin D-induced hypercalcemia and hypercalcemia, and alendronate-induced hypocalcemia [127]. However, there are no fracture data demonstrating superiority of this combination to the bisphosphonate alone.

5.2. Vitamin D and neuromuscular function

Vitamin D insufficiency is not only important for bone metabolism, but has an impact also on muscular and neuronal function. Laboratory, epidemiologic, and clinical studies demonstrate a direct effect of vitamin D on muscle strength. Indeed, 1,25(OH)₂D₃ receptors have been identified in human muscle tissue [128], and patients with osteomalacia have a reversible myopathy associated to low vitamin D levels [129]. Other studies also relate vitamin D insufficiency to muscle weakness [130], muscle pain [84], increased body sway [131], increased risk of fall [81,116,131–134] and an increased in fall-related fractures [131]. The effect of vitamin D on muscle tissue is thought to occur through specific vitamin D receptors (VDRs). A biopsy of the gluteus medius muscle was taken during total hip replacement surgery in a group of patients, and biopsy specimens of the transversospinalis muscle were taken from another group of women during spinal surgery to study the concentration of muscular intracellular VDRs. Serum levels of 25(OH)D₃ and 1,25(OH)₂D₃ on admission for surgery were also tested. VDRs were found in all muscle tissue samples, with no differences depending on the muscle biopsy site. In an univariate analysis, increased age was associated with a decreased VDR expression, while significant correlations were found between VDR expression and 25(OH)D₃ and 1,25(OH)₂D₃ serum levels. In the multivariate analysis, older age was a significant predictor of decreased VDR expression, independent from biopsy site and serum levels of 25(OH)D₃ [133].

Glerup et al. [13] conducted a cross-sectional study in veiled Arab women with hypovitaminosis D and in a control group of Danish women. Muscle strength of the quadriceps was assessed using a dynamometer to measure maximum voluntary contraction (MVC)
and electrically stimulated values, and maximal relaxation rate (MRR). Tests were repeated 3 and 6 months after administration of a high dose of vitamin D. Before treatment, all muscle function parameters were lower in Arab women as compared to Danish women, regardless of whether or not bone involvement was found, as measured by elevated alkaline phosphatase levels. All muscle parameters significantly improved after 3 months of treatment, and after 6 months only MVC values were lower as compared to the Danish control group. Hypovitaminosis D myopathy is a significant symptom of muscle involvement, occurring even before bone metabolism parameters are impaired. When hypovitaminosis D myopathy is suspected, alkaline phosphatase values may be normal if there is no bone involvement. Myopathy should be diagnosed by measuring 25(OH)D₃ levels.

Cross-sectional studies show that elderly people with higher 25(OH)D₃ serum levels have an increased muscle strength and a lower number of falls. Elderly people have muscle weakness – particularly in proximal muscles – associated to deficient vitamin D levels that decreases motion ability and capabilities, which promotes or causes falls and – in people at risk – increases the number of falls [134,135]. Dhesi et al. [134] conducted a comprehensive cross-sectional study of neuromuscular and psychomotor function as related to 25(OH)D₃ and PTH levels in elderly subjects sustaining falls and healthy volunteers of a similar age. People who fell usually showed impairments in aggregate functional performance time, isometric quadriceps strength, postural sway, and choice reaction time, particularly in cases with 25(OH)D₃ levels lower than 12 ng/mL. At the same time, PTH was an independent variable for muscle strength. In a subsequent randomized study, the same authors measured the effects of vitamin D supplementation on neuromuscular function in subjects aged over 65 years with a history of falls and 25(OH)D₃ levels of 12 ng/mL or less, who were administered a single intramuscular dose of ergocalciferol 600,000 IU or placebo. A complete study of neuromuscular function was performed 6 months after the intervention. The group treated with vitamin D showed significant increases in 25(OH)D₃ levels and improvements in functional performance, reaction time and balance, but no changes in muscle strength. The authors concluded that the benefits of vitamin D supplementation – in people with deficiency who had sustained falls – would be neuroprotective or neuromuscular in nature [103,134].

Similarly, the prospective, population-based study by Visser et al. [29] showed that low 25(OH)D₃ levels and high PTH levels increased the risk of sarcopenia in subjects aged 65 years or over controlled for 5 years. Sarcopenia was defined as the lowest sex-specific 15th percentile of the cohort, translating into a loss of grip strength greater than 40% or a loss of muscle mass greater than 3%. Risk If sarcopenia was higher in subjects with baseline 25(OH)D₃ levels less than 25 nmol/L as compared to those with levels higher than 50 nmol/L, with odds ratio (OR) of e.57 (95% confidence interval 1.40–4.70, based on grip strength) and 2.14 (0.73–6.33, based on muscle mass). PTH levels of 4 pmol/L or higher, as compared to levels under 3 pmol/L, were associated to an increased risk of sarcopenia, with OR of 1.71 (1.07–2.73) based on grip strength and 2.35 (1.05–5.28) based on muscle mass.

Bischoff et al. [81] performed a randomized, double-blind study to assess the effects of daily supplementation with cholecalciferol (800 IU) plus calcium 1200 mg or calcium 1200 mg alone for 12 weeks on musculoskeletal function, number of falls, and vitamin D levels in subjects with a mean age of 85 years admitted to a geriatric center. Patients receiving vitamin D + calcium showed increases in 25(OH)D₃ (71%) and 1,25(OH)₂D₃ (8%), and a 49% decrease in the number of falls as compared to the group administered calcium alone. Bischoff-Ferrari et al. [116] conducted a meta-analysis of randomized, double-blind, controlled studies of the effects of vitamin D on falls in subjects with a mean age of 60 years published until February 2004. An analysis of 5 of the 38 randomized, controlled studies available, including 1237 patients, suggested that vitamin D decreased the corrected OR of falls by 22% (corrected OR, 0.78; 95% confidence interval [CI], 0.64–0.92) as compared to patients given placebo or calcium alone. The number needed to treat (NNT) was 15 (95% CI, 8–53), i.e. 15 patients would need to be treated with vitamin D to prevent one person from falling. Five studies, including a total of 10,001 patients, were added to perform a sensitivity analysis that continued to show a significant, but less marked, benefit of vitamin D. The meta-analysis also included a subgroup study that showed the effect of vitamin D to be independent from calcium supplementation, type
of vitamin D administered, treatment duration, and sex of patients.

Vitamin D may improve muscle strength through muscle receptors for the vitamin. Vitamin D levels under 20 ng/mL cause an increased body sway, and levels under 12 ng/mL decrease muscle strength [108]. Levels of 25(OH)D₃ have been related to musculoskeletal function in the lower limbs in people aged 60 years or over [136]. Subjects showed better results in the tests when vitamin levels were at least 30 ng/mL. When the 8-foot walk test of subjects in the lowest and highest quintiles of 25(OH)D₃ levels was compared, the latter group was able to decrease the mean result by 0.27 s. When the same quintile comparison was applied to the sit-to-stand test, a 0.67 s reduction was seen in people with high 25(OH)D₃ levels. Authors concluded that in ambulatory active and inactive subjects, levels ranging from 40 to 94 nmol/L are associated to a better musculoskeletal function in the limbs as compared to values under 40 nmol/L.

A prospective cohort study including more than 1200 subjects participating in the Longitudinal Aging Study Amsterdam was very recently published. This study measured baseline 25(OH)D₃ levels and fractures prospectively occurring over 1 year. 25(OH)D₃ levels (<10 ng/mL) were associated to an increased risk of consecutive falls, and vitamin D represented an independent risk factor for sustaining a fall. An adjusted OR of 1.78 (CI 1.06–2.99) was reported for subjects who had sustained two or more falls as compared to those with no or a single fall. The OR reported for subjects sustaining three or more falls as compared to those with two falls or less was 2.23 (1.17–4.25) [137]. On the other hand, in a group of 389 women from the prospective multicenter study of 9526 community-dwelling women enrolled in the Study of Osteoporotic Fractures, Faulkner et al. [138] found that high levels of 1,25(OH)₂D₃, i.e. the active hormone, were associated to a low fracture rate. There is thus an increasing evidence that vitamin D insufficiency increases the risk of fall, particularly in people aged 65–75 years.

The combination of vitamin D and calcium has long been recommended to reduce the risk of bone fracture in older people, particularly those at risk of or suffering from osteoporosis. Several studies have reported that vitamin D and calcium supplements decrease the rate of fall by up to 50% in elderly women, but not men. A recent double-blind, randomized, placebo-controlled study analyzed the effects of supplementation with cholecalciferol 700 IU plus calcium 500 mg or placebo for 3 years in a population of 199 men and 246 women aged 65 years or over living at home. Fifty-five percent of women and 45% of males reported at least one fracture in the three subsequent years. After 3 years of supplementation, the results suggested that treatment decreased the risk of fall in ambulatory (mobile) older women by 46%, and the benefit was most marked in non-active women (a 65% reduction) [139]. It should be noted that the same supplement had no effect in men, regardless of how active they were. Sex differences in effects have been explained on the grounds that women have less muscle strength and mass and therefore sustain falls more easily. Differences in number of falls between less active and active women would not be due to the effect of supplementation, but to the fact that active women place themselves in situations with a risk of falling just because they are more active. It should be finally noted that no significant differences were shown in 25(OH)D₃ levels between the placebo and treated groups neither in women nor in men.

A secondary analysis of a double-blind, randomized, controlled trial studied 64 institutionalized elderly women (age range: 65–97; mean 25(OH)D₃ levels: 16.4 ng/mL (S.D. ± 9.9) who received daily for 3 months calcium 1200 mg plus cholecalciferol 800 IU or the same dose of calcium alone. A complete balance assessment was performed in these women using an electronic device [140]. Treatment with vitamin D plus calcium decreased the fall rate by 60% as compared to calcium alone. Postural and dynamic balance were added to the regression analysis, and they both attenuated the effect of vitamin D plus calcium on the rate of falls.

6. Vitamin D and osteoarthritis

Osteoarthritis (OA) is one of the leading causes of disability in all elderly populations that results in enormous societal burden, including the need for joint replacement at an annual cost to the community of billions of euros. Toxicity from long duration of exposure to pharmaceuticals and the desirability of a treatment with the potential to reduce the rate of disease progression favor approaches that avoid or minimize chronic pharmaceutical use in favor of safer
interventions. It is a disorder of the whole synovial joint organ. However, information has been accumulated in recent times that suggests the importance of bone turnover in OA, and that subchondral bone is metabolically active [141,142]. Radin and Rose [143] postulated that changes in subchondral bone play an essential role in the onset and progression of cartilage lesion, and that OA is a bone disease, rather than a synovial disease. Different epidemiologic studies have demonstrated a lower prevalence of osteoporotic hip fractures and a greater prevalence of elevated BMD in patients with OA, and a potential reverse relationship between osteoporosis and osteoarthritis [144,145]. However, subjects with radiologically documented osteoarthritis lose bone mass in a different way from those who have normal X-rays. This relationship changes depending on the OA site and the site where BMD is measured [146]. It is also suspected that even when bone mineral content is increased, BMD is not increased in some skeletal sites [147].

Hunter et al. [148] showed in a twin population radiological evidence of knee osteophytes, increased bone turnover, increased PTH levels, and decreased vitamin D levels in patients with OA. The authors concluded that bone resorption was increased in women with OA of the knee consistent with subchondral metabolic activity. However, these results should be taken with caution because of the high prevalence in the general population of low vitamin D levels that could explain the coexistence of OA and osteoporosis [145].

A population-based survey of the Framingham Study studied 228 subjects with primary radiographic knee OA and BMD who were classified by 25(OH)D₃ serum levels as vitamin D deficient if levels were ≤15 ng/mL, with hypovitaminosis D if levels ranged from 16 to 32 ng/mL, and vitamin D replete if levels were higher than 32 ng/mL. Mean age was 74.4 years, and 36% were males. Subjects with hypovitaminosis D had a 7.3% higher BMD than vitamin D deficient subjects. A positive association was also found between 25(OH)D₃ serum levels and BMD in patients with primary OA of the knee. Because of the high prevalence of low 25(OH)D₃ levels in patients with OA of the knee and the positive association between 25(OH)D₃ and BMD, administration of vitamin D supplements may increase BMD in patients with OA [149]. However, there is not any study concerning the effect of vitamin D supplementation in patients with OA. Treatment with either estrogen, raloxifene, alendronate, ibandronate, strontium ranelate, or salmon calcitonin have shown to inhibit cartilage degradation in postmenopausal women [150–153]. Further studies are needed on the effect of antosteoporotic treatments and the influence of the vitamin D endocrine system on the subchondral and sinovial unit.

7. Final remarks

Skeletal development is programmed by the sequential activation of specific genetic pathways leading to the formation of an adult skeleton that is both light and strong. Systemic hormones, including PTH, vitamin D metabolites, calcitonin, and gonadal and adrenal steroids regulate blood calcium levels and contribute to the overall calcium economy of the body. Many other hormones have subtle but important effects on skeletal behavior and its modeling and remodeling activity. Vitamin D is a seco-steroid hormone sequentially produced in skin, liver, and kidney that controls phosphorus, calcium, and bone metabolism and neuromuscular function. The theoretically healthy population, postmenopausal and elderly women, osteoporotic women, and women with previous fractures have a high prevalence of inadequate vitamin D levels. It is likely that a vitamin D insufficiency status sustained over time leads to bone and muscle metabolic impairment, particularly from the years subsequent to menopause. Prospective evidence filling the multiple gaps in knowledge is required to support or reject the possibility that prolonged hypovitaminosis – together with estrogen drop due to menopause – represents the link between musculoskeletal health, osteoporosis, increased falls, and risk of low energy fractures. If hypovitaminosis is so widespread, effective measures to correct it will have to be taken from the early stages, even during intrauterine development. If not corrected, hypovitaminosis could lead to an unprecedented evolutionary change in the strength and resistance of human skeleton as a result of change in lifestyle, diet, exercise, increased life expectancy, and sun exposure avoidance.

Treatment of osteoporosis and fractures related to hypovitaminosis D, postmenopause, and aging represents an enormous burden of suffering, quality of life impairment, and health costs, particularly affecting postmenopausal women. The good news is that
a wide variety of antiosteoporotic treatments have been available for some years now, while the bad news is that drug adherence and compliance are poor, and healthcare professionals should therefore make an effort to educate patients and relatives, particularly during the first visit, at which the following therapeutic objectives should be established: improve lifestyle, perform exercise appropriate to personal conditions, follow an adequate diet, and use drugs and vitamin D supplements ensuring musculoskeletal health in the long-term. Vitamin D intake is an integral part of management of patients with low BMD and fracture risk to strengthen bone and improve neuromuscular coordination, as discussed in this review. The widespread vitamin D supplementation would be useful in people with deplete reserves, associated to antiresorptive treatments, and in patients fragile fractures. The acquisition of vitamin D may be reached by adequate limited sun exposure, an appropriate diet, food fortification, and with pharmacologic supplements. These possibilities are influenced by cultural, geographic, economic, and gastronomic factors [2,21,52,116,120,121].

Conflict of interest
None.

References


Please cite this article in press as: Pérez-López FR, Vitamin D and its implications for musculoskeletal health in women: An update, Maturitas (2007), doi:10.1016/j.maturitas.2007.05.002

Please cite this article in press as: Pérez-López FR, Vitamin D and its implications for musculoskeletal health in women: An update, Maturitas (2007), doi:10.1016/j.maturitas.2007.05.002


