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Review

Vitamin D in the aging musculoskeletal system: An authentic strength preserving hormone

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Abstract

Until recently, vitamin D was only considered as one of the calciotrophic hormones without major significance in other metabolic processes in the body. Several recent findings have demonstrated that vitamin D plays also a role as a factor for cell differentiation, function and survival. Two organs, muscle and bone, are significantly affected by the presence, or absence, of vitamin D. In bone, vitamin D stimulates bone turnover while protecting osteoblasts of dying by apoptosis whereas in muscle vitamin D maintains the function of type II fibers preserving muscle strength and preventing falls. Furthermore, two major changes associated to aging: osteoporosis and sarcopenia, have been also linked to the development of frailty in elderly patients. In both cases vitamin D plays an important role since the low levels of this vitamin seen in senior people may be associated to a deficit in bone formation and muscle function. In this review, the interaction between vitamin D and the musculoskeletal components of frailty are considered from the basic mechanisms to the potential therapeutic approach. We expect that these new considerations about the importance of vitamin D in the elderly will stimulate an innovative approach to the problem of falls and fractures which constitutes a significant burden to public health budgets worldwide.
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Contents

1. Introduction

Since its discovery in 1923 the understanding of vitamin D has changed from merely a calciotrophic vitamin to a more complex factor with a role in multiple physiologic systems in the body including cell function and differentiation (Holick, 2002). With the discovery of its receptor in 1969 by Haussler and Norman (1969) much has been advanced in the understanding of vitamin D activity in human tissues. Two different vitamin D receptors (VDR) have been reported, one located at the nucleus acting as a classical nuclear receptor and the other more recently discovered VDR located at the membrane (Norman, 1998). The function of these two receptors is significantly different and may have a role in the ways vitamin D acts in bone and muscle.

Classically, vitamin D acts as a regulator of bone mineral homeostasis by promoting the transport of calcium and phosphate to ensure that the blood levels of these ions are sufficient for the normal mineralization of type I collagen matrix in the skeleton (Haussler et al., 1997). This hormone is produced in the skin after exposure to ultraviolet radiation and must undergo two successive hydroxilations in the liver and the kidney to become biologically active (Holick, 2003). $1,25(OH)_2D_3$ is the active form of vitamin D and has a significantly higher affinity to VDR than its inactive form ($25(OH)_2D_3$) (Holick, 2003).

The presence of VDR almost ubiquitously in the organism may suggest that the physiologic effect of VDR activation may have a significant role in multiple pathways.

Indeed, a role for VDR activation in cell function and tissue development has been demonstrated mainly in bone and muscle (DeLuca et al., 1988) and in lower extent in other tissues such as chondrocytes, liver, and parathyroid cells (Boyan et al., 2004).

As in most of other nuclear receptors, there is a reduction in the number and/or expression of VDR associated with aging (Simpson et al., 1985; Duque et al., 2002). In elderly subjects, serum levels of vitamin D reduce significantly which may have as consequence the reduction in VDR activation and therefore a reduction in their function (Lee et al., 2003).

This reduction in VDR expression with aging has been well documented in bowel (Horst et al., 1990), skin (Lehmann et al., 2004) and more interestingly for this review in bone (Duque et al., 2002) and muscle (Bischoff-Ferrari et al., 2004a,b). The significance of the reduction in VDR expression and activity is seen in two age-related pathologies: osteoporosis and osteomalacic myopathy. These two entities are important in elderly patients because they may be responsible for the occurrence of falls and fractures with appalling consequences in the aged population.

For the purposes if this review we will describe the changes that happen in vitamin D and VDR activity in bone and muscle. Subsequently, the clinical impact of this disorder will be discussed and, finally a potential translational approach from the findings in the bench will be extrapolated to their potential clinical applications and future therapeutic implications.

2. Molecular mechanisms of VDR activation

2.1. Vitamin D–VDR interaction

Genomic effects are initiated by binding $1,25(OH)_2D_3$ to its nuclear receptor which results in changes in the gene transcription of mRNA and subsequent de novo protein synthesis (Freedman, 1999) (Fig. 1). By contrast, non-genomic effects of vitamin D are rapid and mediated through a membrane-bound VDR (Zanello and Norman, 1997) (Fig. 1).

At the nuclear level, the activation of VDR will induce the heterodimerization between the active VDR and an orphan steroid receptor known as retinoic receptor (RXR) (Fig. 1). The formation of this heterodimer will facilitate the interaction between the receptor's zinc finger region with DNA activating the protein transcription process (McCary et al., 1999). By contrast at the membrane level VDR activation will induced the so-called "rapid responses" leading to the formation of a second messenger (cAMP, diacylglycerol, inositol triphosphate, arachidonic acid) or phosphorylation of intracellular proteins (Nemere, 1999) (Fig. 1).

2.2. Vitamin D and muscle

The genomic effect of vitamin D in muscle includes changes in mRNA that will induce de novo protein synthesis that regulate cell proliferation and induction of terminal differentiation (Boland, 1986). The absence of VDR has shown in knock out

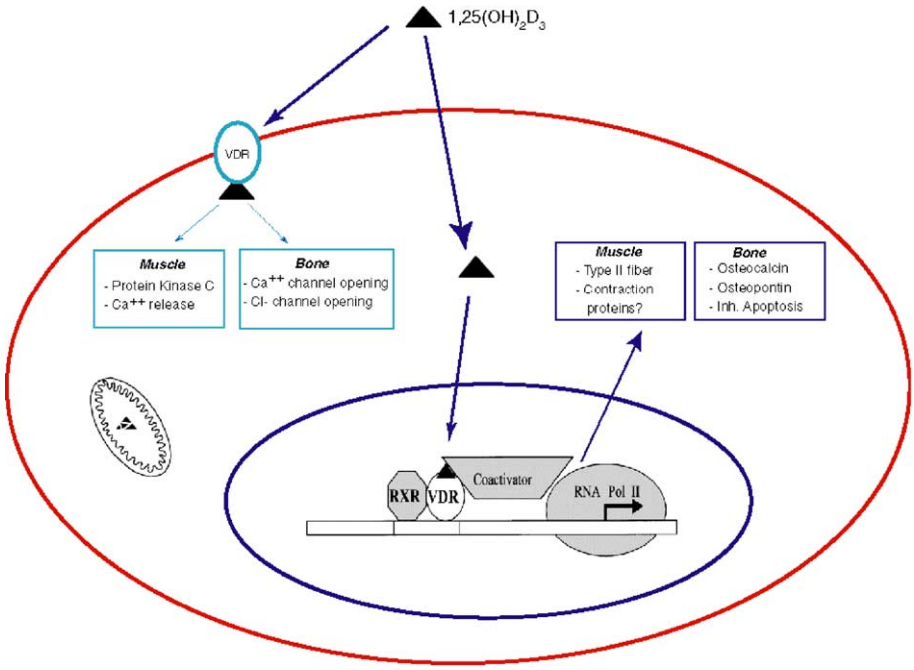

Fig. 1. Physiological process activated after vitamin D–VDR interaction. Genomic effects are initiated by the binding $1,25(OH)_2D_3$ (▲) to its nuclear receptor which results in changes in the gene transcription of mRNA and subsequent de novo protein synthesis. By contrast, non-genomic effects of vitamin D are rapid and mediated through a membrane-bound VDR. The figure shows the genomic and non-genomic effects of this interaction on bone and muscle cell.

mice a lack of muscular development (Kato et al., 1999) which suggests that vitamin D is required for the successful muscle development and growth.

Furthermore, the non-genomic effect of vitamin D in muscle includes the activation of protein kinase C (PKC) and the release of Ca into the cytosol (de Boland and Boland, 1993; Morelli et al., 1993) (Fig. 1). This effect is thus responsible for the active transportation of Ca into sarcoplasmatic reticulum by Ca-ATPase increasing the calcium pool which is essential for muscle contraction. In addition, the activation of PKC has an effect on protein synthesis in the muscle cell (Selles and Boland, 1991).

In summary vitamin D is required for several important functions that will maintain the integrity and function of the muscle cell. Indeed, to reach a normal level of function in the muscle cells the levels of vitamin D and VDR should be normal such is not the case in aging individuals.

2.3. Vitamin D and bone

The action of $1,25(OH)_2D_3$ in bone includes also a genomic and a non-genomic mechanism. The genomic activation of VDR will induce the expression of several

proteins in the osteoblasts being the most important the transcription of nuclear factor-kappaB ligand (RANK-L). This protein is responsible for the activation and differentiation of the osteoclasts which will then become bone resorption cells (Goltzman, 2002). A recently discovered and most probably genomically regulated, effect of vitamin D on bone is the inhibition of osteoblast apoptosis (Duque et al., 2002, 2004a,b). This effect has a particular significance in aging bone as it will be mentioned further in this review.

Additionally to the genomic action of vitamin D in bone, the non-genomic effect includes the opening of Ca and chloride channels (Fig. 1) which are essential to increase the levels of calcium stored in the endoplasmic reticulum as well as to enhance the mobility and changes in conformation that are required for the normal osteoblast function (Caffrey and Farach-Carson, 1989).

2.4. Aging and VDR

There are not many studies assessing the changes induced by aging in VDR expression. A decrease in VDR expression with aging has been reported in intestine and bone in rats (Horst et al., 1990), duodenum (Liang et al., 1994), kidney (Sandgren and DeLuca, 1990) and human muscle (Bischoff-Ferrari et al., 2004a,b). Furthermore, our group has reported a reduction in VDR expressing osteoblasts in aging C57BL6 mice (Duque et al., 2002).

Overall, the significance in VDR expression with aging in the intestine and kidney may connote a reduction in calcium metabolism due to refractoriness to vitamin D. Additionally, a more significant effect on cell differentiation, function and survival is seen after the reduction of VDR activity in muscle and bone. In muscle it may reduce the functional response of the myocites to $1,25(OH)_2D_3$ as well as a diminution in type II fibers (Bischoff-Ferrari et al., 2004a,b). Furthermore, the reduction in VDR in bone has an effect on the increasing levels of apoptosis seen in aging osteoblasts (Duque et al., 2002) as well as a reduction in the expression of proteins responsible for bone mineralization such as osteocalcin and osteopontin (Gerstenfeld et al., 1996).

In conclusion, although a significant reduction in VDR associated with aging has been described in multiple systems in mammals, the mechanism by which age is associated with this reduction remains unknown and is currently matter of active research.

3. Significance of vitamin D deficiency in the aging muscle and bone

3.1. Osteomalacic myopathy

The term osteomalacic myopathy describes the effect that the deficit in vitamin D has on muscular function and strength (Yoshikawa et al., 1979). Several case reports of both young and elderly adults have been described in which prolonged vitamin D deficiency was associated with severe muscle weakness, often leading to marked disability which improved within several weeks of vitamin D supplementation

(Schott and Will, 1976). In addition, muscular weakness and hypotonia have been described as characteristic symptoms of rickets. Moreover, this weakness may be present as a proximal myopathy either as diffuse skeletal pain or as muscular weakness in the absence of a specific pattern (Skaria et al., 1975). Clinical findings in osteomalacic myopathy include proximal muscle weakness, diffuse muscle pain or gait impairments such as a waddling gait (Schott and Will, 1976). Skaria and coworkers reported that 25 out of 30 patients with proven osteomalacia showed an abnormal electromyogram with signs of both myopathy and reduced nerve conduction velocity (Skaria et al., 1975). Although the involvement of peripheral nerves in the disease is reported by some investigators (Ronin et al., 1991), another report describes a normal nerve conduction velocity (Mallette et al., 1975). From the cellular perspective muscle biopsies obtained in osteomalacic patients reveal an atrophy of type II muscle fibers with enlarged interfibrillar spaces and infiltration of fat, fibrosis and glycogen granules (Yoshikawa et al., 1979). Interestingly, other conditions that could affect the muscle anatomy and function in elderly people such as a neuropathic myopathy affects typically both type I and type II fibers whereas in atrophy secondary to immobilization only type I fibers are reduced (Jones, 1992).

Since the fast and strong type II fibers are the first to be recruited to avoid falling and due to the fact that primarily type II fibers are affected by vitamin D deficiency, it is tempting to hypothesize that vitamin D deficiency may increase the risk of falls in senior people. Indeed, the histopathological changes of osteomalacic myopathy are quite similar to the changes seen in the age-related muscle loss (Table 1). This process, recently given the name sarcopenia, is attributed to the reduction of the numbers of both type I and type II fibers with marked type II fiber atrophy (Vandervoort, 2002). Age-related muscle loss or sarcopenia begins around the age of 50 becoming more dramatic beyond the seventh decade of life (Morley, 2003). Loss of muscle mass among the aged directly results in diminished muscle function. Since

Table 1
Muscular changes in normal and abnormal processes associated to aging

Process	Clinical Findings	Fat infiltration	Muscle Fiber I	Muscle Fiber II
Osteomalacic myopathy	Proximal weakness Pain Lower limbs more affected Gait disorders	Described with glycogen granules and fibrosis	atrophic	Reduced number and atrophic
Sarcopenia	Generalized and proximal weakness Lower limbs more affected	Described	Reduced number	Reduced number and atrophic
Neuropathyc myopathy	General weakness Four limbs affected	No described	Reduced number	Reduced number
Immobilization	General weakness Four limbs affected	No described	Reduced number	No change

From Mallette et al. (1975), Yoshikawa et al. (1979), Gandevia et al. (1995), McComas (1996), Jones (1992) and Vandervoort (2002).

the last decade, it has been recognized that sarcopenia is a key factor in the pathophysiology of the development of frailty and mobility decline. In fact, loss of muscle mass has been associated with falls, cognitive decline, depression and mortality in elderly people (Morley, 2003).

Although several physiological mechanisms have been implicated in the development of sarcopenia, the role of vitamin D metabolism is still not well clarified (Sorensen et al., 1979). In summary, as sarcopenia has been postulated as a key marker of the frailty process, we can hypothesized that a vitamin D deficit or VDR dysfunction may be associated with this entity as well as with the syndrome of frailty.

3.1.1. Gait and balance in elderly population

Many older adults walk with significant mobility impairment with a prevalence range from 20% to 50% according to different series (Alexander, 1996; Bloem et al., 2000). Among those older adults who do have a gait disturbance the cause could be often easily identifiable (e.g., Parkinson's disease or previous stroke with hemiparesis). However, there are many older adults with an impaired gait that does not appear to be a result of any well defined disease. Sudarsky and coworkers found that, in patients attending a neurology clinic, the cause of the gait disturbance was ''unknown'', even after neuro-imaging, in about 10–20% of older adults with a disturbed gait (Sudarsky, 1990; Sudarsky and Ronthal, 1983). In a study of the ''oldest old'' which age ranged from 87 to 97 years, Bloem and coworkers observed that about 20% of those studied had a normal gait, 69% had a gait disorder due to known disease, and about 11% of the subjects had an idiopathic ''senile gait disorder'', i.e., a gait disorder of unknown origin (Bloem et al., 2000).

Interestingly, those subjects with a gait disorder of unknown origin had a higher risk of falls, fractures, hospitalizations and mortality after a three year follow up period, compared to the group of age-matched subjects who had a normal gait (Montero-Odasso et al., 2003; Woo et al., 1999). Nutt and Alexander have coined the term ''lower-level'' gait disorders to refer to an altered gait that is a result of either lower extremity muscular problem or peripheral neural dysfunction (Nutt et al., 1993; Alexander, 1996). Supporting this approach, Hough and coworkers found that at least 50 % of ambulatory elders consulting for gait impairment have a joint or muscle problem in the lower limbs to explain it (Hough et al., 1987). Moreover, a recent systematic review showed that lower limb muscle weakness is significantly associated to falls and subsequent disability in older adults (Moreland et al., 2004).

Few studies have been conducted to answer the question about the effects of vitamin D on balance and gait performance. Specifically, vitamin D plus calcium compared with calcium alone improved body sway by 9% within two months in elderly ambulatory women and similarly, vitamin D plus calcium compared with calcium alone increased musculoskeletal function by 4–11% in institutionalized elderly women (Pfeifer et al., 2000) The cellular effect on muscle after vitamin D supplementation was demonstrated in one study where treatment with vitamin D increased the relative number and size of type II muscle fibers of elderly women within three months of treatment (Sorensen et al., 1979).

In summary, idiopathic gait disorders and balance problems in elderly are prevalent problems with elderly people and reflect several conditions affecting the lower limbs performance in which the muscle function plays a key role. There is evidence that vitamin D could improve the muscle strength, mass and function; however and due to the shortage of studies, is still an area for further clinical research.

3.1.2. Falls, fractures and mobility problems in elderly population

Since the trials conducted by Tinetti and coworkers, it is known that the reported incidence of falls is about 30% per year for those aged 65 and older and 40–50% for those aged 80 and older (Tinetti et al., 1988). Falls constitute the largest single cause of injury mortality in elderly individuals; moreover, they are an independent determinant of functional decline, leading to 40% of all nursing home admissions and substantial societal costs (Tinetti, 1987). Poor balance is one of the principal causes of falls in elderly people. Although several mechanisms are implicated in the balance control, the muscle tissue is a principal component of the balance system. The loss of muscular strength and muscular mass associated with the aging process lead to poor balance as well to gait disorders.

Previously, the moderate protective effect of vitamin D on fracture risk has been attributed primarily to bone mineral density changes. However, vitamin D may also directly improve muscle strength, thereby reducing fracture risk through fall prevention. Two randomized controlled trials from Dawson-Hughes and Chapuy have found that vitamin D reduced fractures within 8–12 weeks, a finding more consistent with muscle strength benefits than improvement in the bone density in which a greater period of time is needed to be achieved (Dawson-Hughes et al., 1997; Chapuy et al., 1992).

However, the potential effect of vitamin D on falls is not well established. Several randomized controlled trials have addressed this matter with mixed results including several trials that reported no significant results (Table 2). The available evidence will be discussed in detail in the next section.

3.2. Senile osteoporosis

Senile osteoporosis is the term used to describe a reduction in bone mineral density associated to age which predisposes to fragility fractures. As human population ages, the incidence of senile osteoporosis and fractures has risen dramatically in recent years. The mechanisms of senile osteoporosis differ markedly of other osteoporosis since it is the consequence of a deficit in osteoblastic activity in bone with the subsequent deficit in bone formation (Goltzman, 2002).

In addition to the cellular changes found in senile osteoporosis which include a deficit in osteoblastogenesis, increased adipogenesis and osteoblast apoptosis (Chan and Duque, 2002) with aging there is a significant reduction in vitamin D levels due predominantly to low levels of sun exposure in addition to poor intake and alterations in vitamin D absorption (Lips, 2001). This reduction in vitamin D levels will induce a compensatory increase in the levels of parathyroid hormone which will induce bone resorption escalating the deterioration in bone quality. Furthermore, as

Table 2
Clinical trials of treatment with vitamin D and effect in mobility, falls and fractures

Trial/design	Intervention	Participants	Muscle outcomes	Falls outcomes	Fractures outcomes
Pfeifer et al. (2000) RCT Double blind	800 IU/day and 1200 mg calcium for 8 weeks 1 year follow up	$N = 148$; Healthy women Baseline levels: 25(OH)D: 10 μg/L	↓ sway in 2/3 measures on balance platform at 8 weeks	Intervention group had ↓ number of falls (30 vs 17) and ↓ number of people who fell (19 vs 11)	Not evaluated
Bischoff et al. (2001) RCT Double blind	800 IU/day and 1200 calcium for 12 weeks	$N = 122$. Older women in long-term stay geriatric institutions Baseline levels: Not reported	Improved muscle performance ($P = .0094$)	Intervention group had ↓ number of falls (250 vs 55), 49% reduction in falls (95% CI = 14–71%)	Not evaluated
Dawson-Hughes et al. (1997) RCT Double blind	700 IU/day and 500 mg calcium for 3 years	$N = 445$ Healthy, ambulatory men and women Baseline 25(OH)D: Men = 33.0 ± 16 μg/L Women = 28.7 ± 13.3 μg/L	Not evaluated	No difference in percentage of people who fell, number of falls per person slightly higher in intervention group	Reduced non-vertebral fractures (26 vs 11)
Graafmans et al. (1996) RCT Double blind	400 IU/day for mean 2 years; falls monitored for 28 weeks	$N = 354$ Men and women living residences Baseline 25(OH)D: Median 10.8	Not evaluated	No difference between groups in the odds of having a fall, OR = 1.0 (95% CI = 0.6–1.5)	Not evaluated
Latham et al. (2002) RCT Double blind	300,000 IU/single dose	$N = 243$ Frail older people Baseline 25(OH)D: Median 16 μg/L	Manual muscle strength; Balance test and timed walk: No difference between groups	Falls over 6 months: No difference between groups	Not evaluated

Table 2 (*continued*)

Trial/design	Intervention	Participants	Muscle outcomes	Falls outcomes	Fractures outcomes
Chapuy et al. (2002) RCT Double blind	Vitamin D 800 IU/day and: 1,200 mg of calcium for 2 years	*N* = 610 women residents of apartments for the elderly Baseline levels 25(OH)D: 8.5 ± 5.3 μg/L	Not evaluated	No significant difference in falls (63.9% in active versus 62.1% in placebo)	relative risk of hip fracture in placebo group RR = 1.69, 95% CI = 0.96–3.0)
Trivedi et al. (2003) RCT Double blind	100,000 IU/single dose every 4 month	*N* = 2686 community elderly Baseline levels not reported	Not evaluated	Not evaluated	relative risk of hip fracture in placebo group RR = 1.69, 95% CI = 0.96–3.0)
Dukas et al. (2004) RCT Double blind	(1-OH)Vitamin D3 + calcium intake of 512 mg	*N* = 378 community dwelling elderly men and women	Not evaluated	Significant reduction of number of falls in the intervention group. (OR = 0.6 95%CI = 0.41–1.16)	Not evaluated

Abbreviations: RCT: randomized controlled trial; 25(OH)D = 25 hydroxyvitamin D; IU = international units; RR = relative risk; OR = odds ratio; CI = confidence interval.

mentioned above, the absence of vitamin D activity in the osteoblasts will determine low levels of osteoblastic activity and survival with a subsequent deficit in the number of osteoblasts available to build new bone (Priestwood and Duque, 2003).

3.2.1. Bone turnover and vitamin D

The process of bone turnover involves the coordinated activity of the osteoclasts, or bone resorbing cells, and the osteoblasts which are responsible for bone formation (Goltzman, 2002). After the third decade of life when the peak of bone mass is reached there is a continuous decline in bone density associated to a predominant osteoclastic activity (Priestwood and Duque, 2003). Furthermore, a more accelerated bone loss is then seen after the seventh decade of life when the osteoblastic activity is markedly reduced (Chan and Duque, 2002).

Vitamin D plays an important role in the process of bone turnover. It is responsible for the stimulation of osteoclastic activity through a complex mechanism of osteoblast/osteoclast communication. Osteoblasts are stimulated by vitamin D to release RANK-ligand a member of the tumor necrosis factor receptors which interacts with the membrane located RANK in the osteoclasts inducing osteoclast recruitment and activation (Goltzman, 2002). Finally, in addition to the stimulation of osteoclastic activity, vitamin D may also play a role in bone formation either through the protection of osteoblasts against apoptosis (Duque et al., 2004a,b) or stimulating the trans-differentiation of adipocytes into osteoblasts within the bone marrow (Duque et al., 2004a,b).

3.2.2. The fragility fracture

This concept is associated to those fractures which are not related to a significant trauma and are associated to a lack of bone strength (Johansen et al., 2000). The presence of fragility fracture in a patient is the strongest known risk factor of future fractures (Ross et al., 1991; Wasnich et al., 1994). For the purposes of this review there are several arguments to suggest that the lack of vitamin D action is an important predisposing factor for fragility fractures. In fact, bone strength is the consequence of a coordinated and well regulated bone turnover with a certain level of coordination among bone cells. The absence of vitamin D will determine an initial reduction in bone turnover due to the lack of osteoclastic activity followed afterward by a compensatory osteoclastic response induced by PTH.

In addition, the reduction in osteoblastic activity due to osteoblast apoptosis will also induce a reduction not only in bone formation but also in the differentiation of new osteoclasts since osteoblasts are responsible for their differentiation as previously described. Indeed, the typical feature of senile osteoporosis is a marked deficit in bone turnover which could be explained for a reduction in the activity of vitamin D as one of the main factors.

In summary, vitamin D is required for an appropriate bone turnover. Although the cellular actions of vitamin D in bone are clearly affected by its decreasing levels associated to aging the recovery after vitamin D supplementation has been partially documented. More research is needed to clarify the effect of vitamin D supplementation in elderly subjects at the cellular level in the bone.

4. Giving vitamin D: does it work?

As stated, we may suggest that there is a biological and clinical explanation for using vitamin D in order to improve both the muscle function and bone strength in elderly people. During the last 10 years several trials have included among their primary or secondary outcomes clinical variables addressing the question if supplementation with vitamin D improves muscle function and prevents mobility decline, falls and fractures (Table 2).

For example, Pfeifer and coworkers compared the effect of eight weeks of treatment with a daily dose of vitamin D (800 IU) and calcium (1200 mg) versus calcium 1200 mg alone in 148 healthy elderly women (Pfeifer et al., 2000). After one year of follow up they found a reduced rate of number of total falls and fallers. This study also demonstrated an improvement in the balance measured as body sway in the vitamin D group, suggesting that vitamin D may improve postural stability in people who received the combined treatment. Bischoff and coworkers studied 122 elderly women in a long-stay geriatric center and compared the rate of falls before and after the intervention. The subjects were randomized to either 1200 mg calcium and 800 IU vitamin D or 1200 mg calcium alone. Women treated with vitamin D and calcium experienced a 49% of relative reduction of falls in comparison to the calcium alone group, (Bischoff et al., 2003). As in both of these studies the participants had a severe vitamin D deficiency, it was postulated that the correction of muscle weakness due to vitamin D deficiency decreased the fall incidence. By contrast, a well designed study of 445 healthy participants aged 65 years and older who had high serum levels of 25(OH) D did not find differences in the rate of falls after supplementation with vitamin D and calcium. The participants were randomized for taking a daily dose of 700 IU of vitamin D and 500 mg of calcium or placebo for more than three years. The main outcome evaluated was the number of non-vertebral fractures, which was significantly lower in the treatment group, and falls were a secondary outcome (Dawson-Hughes et al., 1997). Furthermore, Lips and coworkers investigated the effect of vitamin D on falls as a sub study of a large trial. This well designed trial involved participants living in apartments for elderly persons who were given 400 IU of vitamin D3 or placebo for an average of two years, calcium supplementation was not considered (Lips et al., 1996). After prospective monitoring of falls over a 28-week period, no difference was found in the risk of falls between the intervention and control groups.

In addition, the Frailty Intervention Trial in Elderly Subjects investigated the effect of a single dose of 300,000 IU vitamin D supplementation or placebo on muscle strength, walking velocity and new falls in 243 hospitalized frail older patients (Latham et al., 2003). The outcomes were evaluated for a period of six months. Despite a significant increase in 25(OH) D levels in the treatment group, no differences were found between the vitamin D and control group across any of the outcomes.

The effect of vitamin D on the prevention of fractures shows variable results. A large study conducted by Chapuy and coworkers showed a reduction in fractures in women with a severe vitamin D deficit (serum 25OHD 14 ng/ml) after a supple-

mentation with vitamin D (Chapuy et al., 1992). The same author in a study conducted in older women in France found significant increases in 25(OH)D levels and a decreased risk of hip fracture, but no difference in the number of fallers between the active and control groups over two years of follow up (Chapuy et al., 2002). The study from Dawson-Hughes and coworkers, which fails in detect a reduction in the number and rate of falls, showed a significant decrease in non-vertebral fractures (Dawson-Hughes et al., 1997). In addition, the recent study from Trivedi, which involved 2686 subjects receiving 100,000 IU of vitamin D3 every four months, showed a reduced rate of fractures by 22% (Trivedi et al., 2003).

The variability of the results assessing the effect of vitamin D on fractures and falls prevention has aimed the researchers to postulate several different hypothesis. First, as both muscle and brain contain VDR, it has been postulated that calcitriol improves both muscle and central nervous system function affecting balance (Gallagher, 2004). Second, a direct effect on muscle without a significant effect on bone has also been found. In a recent meta-analysis combining five randomized controlled trials found a 13% reduction of falls after treatment with vitamin D without documented changes on bone mass (Bischoff-Ferrari et al., 2004a,b). In the other hand, a systematic review of controlled trials which was undertaken to assess the effectiveness of vitamin D supplementation on muscle strength, physical function, and falls in older people did not find enough evidence to establish the role of vitamin D (Kenny et al., 2003).

In summary, all the positive findings come from studies which utilized a vitamin D supplementation of at least 800 IU per day or equivalent together with calcium, suggesting a rationality of this approach for preventing falls and improving the balance in elderly population.

5. Conclusion

In this review we have considered the importance of vitamin D as a real hormone responsible for both muscle and bone strength. With aging there is a significant reduction in the genomic and non-genomic effect of vitamin D which has been associated with increasing incidence of falls and fractures. Several research groups have focused their efforts to find a feasible and single intervention for reducing falls and fractures. This evidence has supported the notion that supplementation with vitamin D plus calcium could reduce the rate of fractures in senior people, not only by increasing bone mass, but also by decreasing the risk and the prevalence of falls. As this effect seems to be independent of the bone actions of vitamin D, researchers began to call it as an ''extra bone effect'' (Latham et al., 2003).

These extra bone effects are achieved at a muscular level trough a strengthening of the muscle mass which improves the balance in senior people. These data have biological and clinical plausibility since the improvement of balance and muscular strength are important components for reducing the rate of falls in elderly people.

We can conclude that there is rationality for the supplementation of vitamin D in the elderly population in order to reduce the number of falls and the subsequent rate

of fractures. These findings portray important clinical implications since vitamin D supplementation is a costliness, secure, and easy to implement intervention.

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