MISCELLANEOUS

Indications on the use of vitamin D and vitamin D metabolites in clinical phenotypes

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Background

Many arguments are favouring a renewed interest in vitamin D physiology, with a consequent increase in the number of scientific publications and media reports (1). Not surprisingly, TIME magazine nominated vitamin D as one of the "top medical breakthroughs" in the December issue of 2007. This vigorous increase of interest in vitamin D is powered by the spectacular insights into the pivotal regulatory role of vitamin D with regard to pleiotropic functions, by the data on worldwide trend to nutritional vitamin insufficiency (2) and by new knowledge on intracrine and paracrine actions of vitamin D metabolites (3).
Despite the fact that vitamin D is still called and known as a vitamin, it actually comprises a group of very closely interrelated hormonal compounds also related to the other main calciotropic hormone, the parathyroid hormone. Therefore, vitamin D is now viewed from a controller of calcium homeostasis (calciotropic) to an hormone with pleiotropic actions.
Vitamin D is synthesized in human skin after the photoisomerization of 7-dehydrocolesterol to pre-vitamin D3 under the influence of UV B radiation (wavelength, 280-315 nm) (Fig. 1). The major factors influencing this process are either environmental (latitude, season, time of day, ozone and clouds, reflectivity of the surface) or personal (skin type, age, clothing, use of sunscreen, genetics). From the skin, parental vitamin D3 find its way into the general circulation and it is then metabolized in the liver to 25-hydroxyvitamin D3 [25(OH)D3] (calcifediol) by one of several, high capacity cytochrome P450s (Fig. 1). 25(OH)D3 is an immediate precursor metabolite to the active form of vitamin D3, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], that is the product of the mitochondrial CYP27B1-hydroxylase confined primarily but not entirely to the proximal tubular epithelial cell of the kidney (Fig. 1). 1,25(OH)2D3 synthesis in the kidney is stimulated by parathyroid hormone (PTH) and inhibited by fibroblast growth factor 23 (FGF23) made by osteocytes (4).
As vitamin D has a much shorter half-life than 25(OH)D3 (1-2 days versus 2-3 weeks), 25(OH)D3 was favoured as the best indicator of vitamin D status. Other reasons for 25(OH)D3 be-

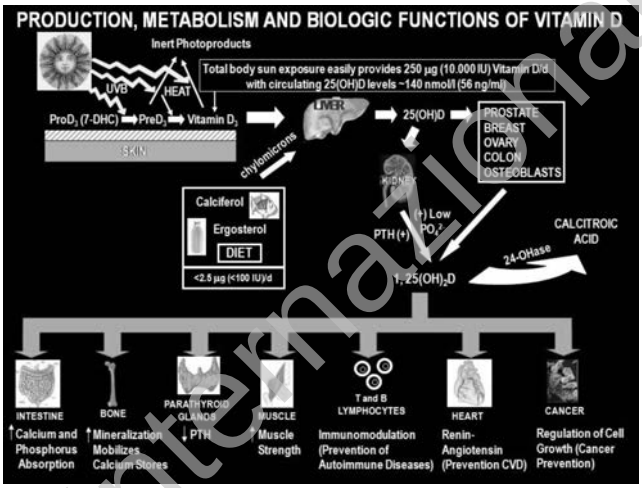

Figure 1

coming the parameter of choice for estimating the vitamin D status include: it enters the host, either by cutaneous synthesis or by ingestion in the diet and it is the most abundant and stable vitamin D metabolite in human serum, as determined by its high affinity to vitamin D binding protein and by other members of the albumin superfamily of circulating proteins. Conversely, 1,25(OH)2D3 circulates in the serum at concentrations that are about 0.1% of those of the prohormone 25(OH)D3 and its synthesis is tightly regulated by the endocrine system. For these reasons 1,25(OH)2D3 levels in the serum are not used to evaluate the vitamin D status in humans (Fig. 2).
Using 25(OH)D3 circulating values and increases in serum PTH levels as markers of inadequacy and deficiency, it was possible to define the different cut-off values for the definition of the vitamin D status (Fig. 2). It is now generally agreed that the serum PTH will start to rise significantly when the serum 25(OH)D3 drops to less than 30 ng/ml; values of 25(OH)D3 between 30 ng/ml and 20 ng/ml are considered to represent vitamin D inadequacy, while those less than 20 ng/ml fall into the vitamin deficiency (Fig. 3). In this latter condition it is likely to observe clinical evidence of osteomalacia.

There is growing evidence about high prevalence of unrecognized vitamin D deficiency worldwide in different age groups (2, 5-7).

Molecular bases of vitamin D metabolism and action

After production of vitamin D3 in the skin, the specific plasma alpha-globulin transport protein vitamin D-binding protein (DBP) is responsible for picking up the vitamin D3 and delivering it, along with the many vitamin D metabolites that it also binds, to all the elements of the vitamin D endocrine system (8). The first stop for vitamin D3 is normally the liver, where it is metabolized into 25(OH)D3, which has a long half-life of about 3-4 weeks. 25(OH)D3 is then transported by DBP to the kidney, which is the endocrine gland that produces the two steroid hormones

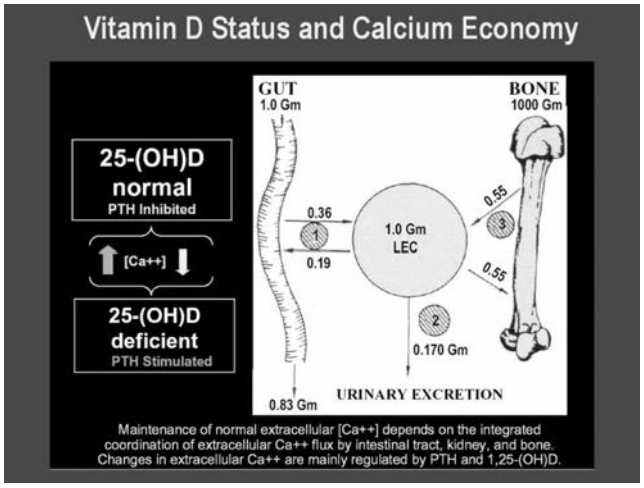

Figure 2

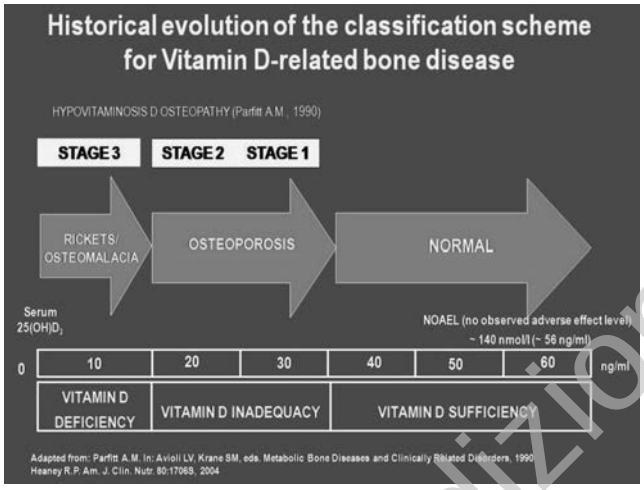

Figure 3

1,25(OH)2D3 (calcitriol) and the candidate hormone 24R,25-dihydroxyvitamin D3 [24,25(OH)2D3] (9). Calcitriol, which is actually the most active form of vitamin D [100-times higher than 25(OH)D3] has a very short half-life, of about a few hours. While calcitriol was first thought to be generated solely in the kidney, it is now recognized in many extrarenal tissues (10-12). The key enzymes in vitamin D metabolism are, therefore, the hepatic vitamin D-25-hydroxylase (CYP27A1,CYP2R1,CYP2A4 and CYP2J3), renal 25-hydroxyvitamin D-1alpha-hydroxylase (CYP27B1), and 25-hydroxyvitamin D-24-hydroxylase (CYP24A1) (13). Also CYP2R1, CYP27B1 and CYP24A1 were observed in tissues other than liver (14). Several liver cytochrome P450 isoforms have also been shown to possess vitamin D sidechain hydroxylation activity, wondering if this activity can be directed at the C26 position as well as the C25 position (13). Moreover cytochrome P450 CYP11A1 converts vitamin D3 to 20-hydroxyvitamin D3 [20(OH)D3] in different tissues (15). DBP then transports both secosteroids to their target tissues where appropriate biological responses are mediated.
The vitamin D metabolizing hydroxylases are regulated by different mechanisms: a rapid response involving protein kinase C and MAP kinase pathways, the binding by calcitriol to the vitamin D receptor (VDR) and the subsequent interaction of the VDR/calcitriol complex with its heterodimer partner retinoid-X-receptor and associated coactivators, and the methylation active on a more intermediate time scale (16-18).

Several reports have described an hormonal function for the various endogenous metabolites of the vitamin D endocrine complex, none being merely an inactivation product (15, 19). In particular, 25(OH)D3, previously regarded merely as a prohormone, is an agonistic VDR ligand, with gene regulatory and antiproliferative properties synergistic with calcitriol (20).
Vitamin pleiotropy can be summarized by the following numbers: more than 30 cell types express the VDR, more than 10 organs are capable of paracrine 1- -hydroxylation, and more than 200 genes are under the control of calcitriol.
It is certainly plausible that genes that are involved in vitamin D metabolism, transport or activity may be related to risk of several chronic disorders, such as diabetes (21, 22) and osteoporosis (23, 24).
The growing availability of recombinant cytochromes P450 will allow for a search for potential inhibitors or stimulators. Modelling of the vitamin D binding pocket of VDR, DBP, and the vitamin D-related cytochrome P450 will become a major goal now that all three specific proteins have been cloned and overexpressed.

25-Hydroxylation in physiopathology

Vitamin D does not circulate for long in the blood-stream but, instead is immediately taken up by adipose tissue for storage or liver for further metabolism. Vitamin D3 undergoes its first step of activation, namely, 25-hydroxylation, in the liver (25). Even though the liver is the only significant site of 25-hydroxylation *in vivo*, there were occasional reports of other tissues containing this activity (26, 27). Indeed, 25-hydroxylation is carried out by four different cytochrome enzymes.
Dietary studies show regulation, albeit weak, of the liver 25-hydroxylase in animals given normal intakes of vitamin D after a period of vitamin D deficiency (28).
After the seminal work on the key role of the active vitamin D metabolite, calcitriol, in calcium homeostasis and bone mineralization, the precursor 25(OH)D3, calcifediol, was gradually ignored. Today this metabolite has been reconsidered and analyzed for its functions and it is now recognized to play a role in phosphate and calcium absorption, either via a direct effect on VDR or through a local or general increase in calcitriol production.
25(OH)D3 is a common marker of hepatic damage in individuals with chronic hepatitis (29). Patients suffering from chronic hepatitis C present with low levels of 25(OH)D3, with concentrations of vitamin D being associated with severity of inflammation and fibrosis. A relative vitamin D deficiency was associated with reduced expression of cytochrome P450 27A1. Tagher et al. found that circulating 25(OH)D3 was reduced in adults with non-alcoholic fatty liver disease in comparison with controls (30). In the latter patients vitamin D insufficiency favors progression of the liver disease from fatty liver disease to necroinflammation and fibrosis. Hepatic synthesis of calcifediol is also reduced in uremia secondary to a PTH-mediated reduction in liver CYP450 isoforms (31). Interestingly, daily oral 25(OH)D3 supplementation corrects most vitamin deficiencies in haemodialysis patients (32). 25(OH)D3 can be described as a natural non-toxic vitamin D metabolite which is present at high concentrations in serum.

Vitamin D supplementation to prevent osteoporosis

The prevalence of osteoporosis increases with advancing age, and is associated with increased susceptibility to fracture. Osteoporosis affects both sexes, but primarily postmenopausal women, because of the substantial decline in bone mass and changes in bone architecture associated with estrogen deficiency. By the end of the first decade following menopause, half of all White women

have osteopenia or osteoporosis. For all these reasons it has been suggested that early postmenopausal women and patients treated with steroids should receive preventive therapy to preserve their bone mineral density. Indeed, calcium is the prevalent mineral of bone and its absorption from the intestine depends on vitamin D. A positive correlation between bone mass and calcium intake has been demonstrated in children and in adults (33, 34). Although there are many factors which modulate the progression of age-related bone loss syndromes, the pathogenesis of this process has been attributed, at least in part, to decreased calcium absorption by an aging intestine, to an associated elevation in circulating PTH, and to decreased synthesis of 1,25(OH)2D3. Decreased 1,25(OH)2D3 synthesis in the aging kidney results from both age-related progressive loss in the capacity of the renal 1-alpha-hydroxylase to respond to progressive elevation in PTH and an age-related decrease in the circulating 25(OH)D3. Indeed, vitamin D intake as well as solar exposure and cutaneous biosynthetic ability due to atrophic skin changes generally decrease with increasing age (35, 36). For all these reasons it is not surprising the finding that a low vitamin D status is common in adults and in the elderly, regardless of latitude (37, 38). All these changes in vitamin D metabolism render the ageing population at high risk for vitamin D deficiency, leading to severe consequences in terms of fall, osteoporosis, and fragility fractures.

Several studies reported that daily supplementation with vitamin D and calcium reduces fractures (39, 40). The first study that demonstrated that isolated vitamin D supplementation may prevent fractures without adverse effects was carried out in the general community (41). Vitamin D can protect against fractures through concentrations of PTH. Low concentrations of vitamin D are associated with increased concentrations of PTH, increased bone resorption, and lower bone mass. However, intervention in population studies were unable to show an effect in serum PTH levels (41).

The dilemma for the use of parental vitamin D3 for primary prevention in population-wide intervention is that whereas the population attributable risk is large, the absolute individual risk is still low (42). The risk-benefit balance for community based prevention differs from that for intervention in clinically defined groups. Safety, feasibility, and cost effectiveness are crucial.

Fractures associated with falls are a significant cause of morbidity and mortality in elderly people (43). Ninety percent of hip fractures in the elderly are associated with a fall. Given this high prevalence, severity and costs associated with treating osteoporotic fractures and effective methods of reducing or preventing falls and fractures in older people are needed. Although the possible effects of vitamin D and calcium on fracture prevention are generally attributed to increases in BMD, it is accepted that supplementation might increase muscular strength, thereby reducing the risk of falls (44). For this reason, vitamin D supplementation is highly recommended as a standard preventive measure in osteoporosis (38, 45-47). Indeed, vitamin D should be an integral part of effective osteoporosis management.

The most used approach to reducing vitamin D insufficiency or deficiency is supplementation. The daily estimated average of cholecalciferol use in an adult is 3,000-5,000 IU (48). In Europe a common RDA of 400 IU (10 g) daily has been proposed for people aged 65 years or over (49) (Fig. 4). However, according to recent evidences, higher vitamin D intakes than those currently recommended by RDAs should be advised, especially in the elderly population. The majority of the controlled clinical trials and of the intervention studies in populations used parental vitamin D3 (cholecalciferol) administered either daily or intermittently. Fortification of foods with vitamin D provides an alternative approach to direct supplementation.

Taken all together the results obtained indicate the need for an adequate vitamin D and calcium intakes in the elderly, particularly in individuals living indoors in nursing homes, who exhibit

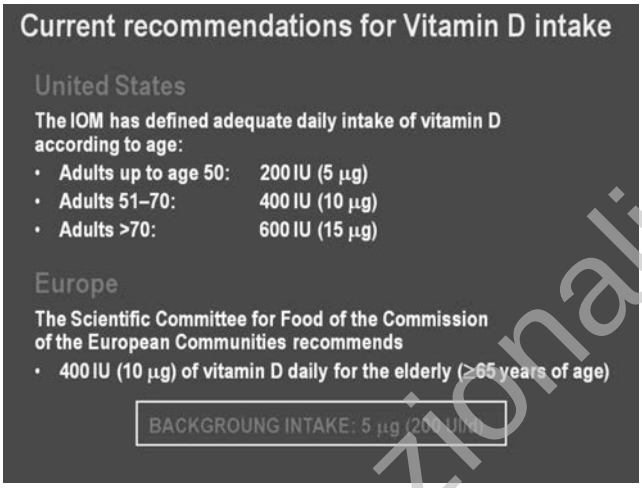

Figure 4

a high prevalence of vitamin D deficiency. Certainly, a more widespread use of vitamin D would be worthwhile to protect the frail elderly. Indeed, parental vitamin D is one of the few treatment modalities where prevention, appropriately targeted, would result in savings to health services (50). There is, therefore, a good case to be made for routine treatment of the frail elderly to reduce the risk of fractures.

Treatment with vitamin D metabolites

The use of isolated parental vitamin D is hampered by limitations of the sources, being unavailable in desirable dose ranges and formulations on the vitamin counters of most pharmacies worldwide. Conversely, the vitamin is easily found in health food suppliers, although some efforts may be required to find them. Also, quality control is a concern when dealing with less regulated sources. Useful alternatives to parental vitamin D3 include prescription of more expensive proprietary vitamin D3 metabolites.

The successful use of the vitamin D metabolites, 1-α-hydroxy vitamin D3 (alfacalcidiol) and 1,25[OH2D3 (calcitriol)] in the correction of calcium malabsorption in postmenopausal osteoporosis and the equally successful use of parental vitamin D3 itself in the prevention of bone loss and fractures in older women have tended to confuse these two treatment modalities in some sections of the medical community. Indeed, the indications for treatment with vitamin D [or 25(OH)D3 (calcifediol)] are quite distinct from the indications for treatment with what are sometimes called the “hormonal” forms of vitamin D, notably calcitriol and alfacalcidiol. Practitioners need to appreciate the important distinction among these different metabolites and vitamin D itself.

Calcitriol

In contrast with primary vitamin D deficiency (i.e. in postmenopausal women) 1,25(OH)2D3 deficiency is caused by insufficient renal production of the active vitamin D hormone. Therefore, disorders associated with calcitriol deficiency could be corrected only increasing the supply of 1-alpha-derivatives. This is certainly true in conditions like hypoparathyroidism and kidney failure, when 1-alpha-hydroxylation does not function respectively for the lack of PTH and for the kidney tubular cell degeneration. However, studies exist on the potential use of calcitriol also in postmenopausal osteoporosis.

Both calcitriol and alfacalcidiol have been proposed as potential therapies for osteoporosis (51, 52). Both compounds strongly stimulate intestinal calcium absorption in a dose-dependent manner, leading to suppression of PTH secretion and to decreased bone turnover. Decreased calcitriol synthesis by the aging kidney results from both an age-related progressive loss in the capacity of the renal 1-alpha-hydroxylase to respond to progressive elevation in circulatory PTH and an age-related decrease in serum calcifediol, the precursor of calcitriol (53).
A number of clinical trials have been conducted over the years with the aim of verifying the efficacy of calcitriol in involutional osteoporosis. The effects reported are heterogeneous both on BMD and on fracture rates, with some showing a significant effect and others no effect on fracture risk (54).The two trials showing the greatest effect of calcitriol on vertebral fracture rates have been those of Tilyard et al. (55) on a large number of patients and that of Gallagher and Riggs (56) on a more modest number. Both studies utilized algorithms for the detection of new fractures similar to the studies reporting lesser effects on vertebral fracture, and may therefore underestimate the benefit. No studies have been undertaken to examine the effects of calcitriol on hip fractures.
It is widely appreciated that the window of efficacy for calcitriol is quite narrow. Whereas 0.4 µg/day may be insufficient for increasing calcium absorption in several patients, a dose of 0.5 µg/day is effective in nearly all patients, with an effect on BMD visible at doses above 0.43 µg/day (57).
Hypercalcemia and impairment of kidney function are rare with doses up to 0.5 µg/day, but more frequent with higher doses (1-2 µg/day). For these reasons, treatment with calcitriol necessitates monitoring of serum and urinary calcium, unlike treatment with parental vitamin D. There is a need to monitor treatment so that hypercalcemia is avoided. Increases in urinary calcium can occur before hypercalcemia and serial estimates can be made to avoid hypercalciuria, and the dose titrated appropriately. The use of calcium supplements is likely to increase the risk of toxicity and to decrease the dose tolerated, but lower doses with higher intakes of calcium might induce similar effects.
Calcitriol is certainly the drug of choice in the treatment of calcitriol deficient conditions by the specialists. General practitioners should better know the conditions that are mandatory for this treatment (i.e. hypoparathyroidism and kidney failure). The osteoporotic patients with overt osteomalacia could certainly benefit of an initial treatment with calcitriol before maintenance to be initiated with parental vitamin D3 administration.

Alfacalcidiol

Alfacalcidiol was initially synthesized in order to treat the bone disease of patients with chronic renal disease more effectively since the renal 1-α-hydroxylation of 25(OH)D3 is compromised in these individuals (58). Alfacalcidiol is a synthetic precursor of calcitriol, being converted into 1,25(OH)2D3 *in vivo* before exerting its biological functions. This activation takes place even with advanced liver disease. Because of this pharmacokinetic profile, alfacalcidiol is considered safer than calcitriol as regard the risk of undesirable events (i.e. hypercalcemia and hypercalciuria). However, as the majority of studies with alfacalcidiol were carried out in Japan, where the daily customary calcium intake is quite lower than in Western countries, the low incidence of hypercalcemia in treated Japanese patients could be explained by the reduced calcium intake.
Although studies designed to pursue the details of the biological response to alfacalcidiol have not been as extensive as those with calcitriol, results of clinical studies designed either to prevent or treat osteoporosis with alfacalcidiol are similar to those obtained with calcitriol (59-61). Other positive actions of alfacalcidiol include increase in muscle strength and neuromuscular coordination, with decrease in the risk of falls (62, 63).
Alfacalcidiol has been largely used in Japan in the last 25 years, but its prescription by general practitioners in Europe is very small and the novel formulations of oral and injectable parental vitamin D will not leave much space for the routine use of this compound either in vitamin D or in 1,25(OH)2D3 deficient conditions.

Calcifediol

25(OH)D3 (calcifediol), the predominant circulating form of vitamin D, is for this reason considered to be the most reliable index in a person's vitamin D status. This vitamin D metabolite is another useful alternative in vitamin D supplementation, with lower risk of toxicity when compared to "activated forms" of vitamin D3, such as calcitriol and alfacalcidiol (64).
Beside being the storage form of vitamin D in the human body, calcifediol shows little intrinsic biological activity, at least at physiological concentrations. However, it has been suggested that 25(OH)D3 at very high levels, could mimic calcitriol to act on VDR to exert biological effects (65,66). Accordingly, it is theoretically feasible that calcitriol deficiency/resistance may be treated with needed doses of calcifediol.
Studies carried out in animals showed that calcifediol added to animal feed is absorbed in the intestine better than cholecalciferol and this explains the higher biopotency of 25(OH)D3 versus parental vitamin D3 in protective immunity to infection, in reproductive performance and in bone status markers (67-69). In the supplementation of animal diets calcifediol is today considered more bioavailable than vitamin D3 and, as such, could be considered an equivalent or even more advantageous source of vitamin D.
The extrarenal synthesis of calcitriol has been demonstrated in a number of cell types, including osteoclasts and osteoblasts (10-12,70), suggesting that 25D metabolism is an important intrinsic mechanism for optimizing its biological functions.
An alternate pathway for the metabolism of 25(OH)D3 is the formation of 24,25(OH)2D3, whose physiological role is controversial. Some authors have proposed that 24,25(OH)2D3 production represents a mean to inactivate circulating calcifediol and thus regulate production of calcitriol. In this view, 24,25(OH)2D3 is considered a catabolite of 25(OH)D3 (71).Results from *in vitro* studies and experiments in animal models contradict this conclusion (72). Evidence gathered *in vivo* also supports a physiological role for the natural 24,25(OH)2D3 metabolite during embryogenesis and in processes regulating bone growth, development, and repair (73). What is the mechanism of action of the 24,25(OH)2D3 metabolite in its target cells? Receptor-mediated signalling remains a logical possibility. Alternatively, it should be mentioned that nongenomic effects of 24,25(OH)2D3 have been described. 24,25(OH)2D3 significantly enhance bone mineralization, significantly decreases PTH secretion in humans and when used in combination with calcitriol is superior to either metabolite alone in the healing of experimental dietary rickets (74-76). More importantly 24,25(OH)2D3 supplementation was shown to be able to correct hyperparathyroidism improving skeletal abnormalities in X-linked hypophosphatemic rickets (77).
A number of clinical studies were carried out in humans in order to evaluate the effect of calcifediol in mineral and bone metabolism. In an open randomized study calcifediol, administered at a dosage of 32,000 IU per week, was demonstrated to be the most effective drug in the prevention and treatment of bone loss in patients after cardiac transplantation (78).The reasons for the authors to use calcifediol instead of other vitamin D metabolites were its lower cost, the positive effect previously shown in glucocorticoid-induced osteoporosis (79) and the lower incidence of hypercalcemia and hypercalciuria if compared to calcitriol (64, 80).

In 2000 Sosa et al. showed an increase in femoral neck BMD and a decrease in serum PTH in an open prospective study in osteoporotic postmenopausal women who suffered of proximal femoral fractures treated for one year with 1 gr calcium per day and 10,640 IU 25(OH)D3 per week when compared to a control group treated only with 1 gr calcium daily (81). In this study calcifediol treatment did not produce changes in biochemical markers of bone remodelling or in the BMD of the lumbar spine, and did not reduce the rate of appearance of new fractures. However, the number of patients in this study was small and the follow-up was too short to conclude that this intervention would not be able to reduce fractures in an at risk population. In this as in other studies 25(OH)D3 administration did not influence calcium levels in the serum and in the urines (81, 82).
In 2001 Larrosa et al. demonstrated that calcium and calcifediol supplementation at two different regimens, 16,000 IU per week and 16,000 IU every three weeks, in a cross-sectional study of 100 randomly recruited elderly institutionalized subjects normalized serum 25(OH)D3 levels, improved calcium absorption and compensated secondary hyperparathyroidism, yet higher 25(OH)D3 levels were achieved with the weekly therapeutic scheme (83). The study made possible to conclude that calcium and vitamin D supplementation should be employed routinely in the elderly instituzionalized population. In a paper in 2003 the same group was able to show that treatment with calcifediol is effective in compensating vitamin D deficiency in humans, using an initial weekly dose of 16,000 I.U. for four weeks and then the same maintenance dose every three or four weeks (84).
In two consequent studies Rossini et al. were able to demonstrate a good compliance to weekly treatment with weekly 4,000-6,000 IU calcifediol in postmenopausal and senile osteoporosis, while the daily administration of associated calcium and parental vitamin D was characterized by interruption of the therapy in over 50% of patients within six months (85, 86).
In a recent report our group showed that 20,000 IU calcifediol administered monthly with 500 mg calcium daily for three months to postmenopausal women was capable to correct hyperparathyroidism, without undesirable effects (87).
Certainly calcifediol represents a rational choice in patients who are taking anticonvulsant drugs in those with chronic liver disease, in subjects characterized by malabsorption and also in those with chronic kidney disease.
In children and in adults with cerebral palsy a high incidence of long-bone fractures was related to vitamin D deficiency (88). The use of antipileptic drugs is also associated with bone disease, characterized by low BMD and osteomalacia/rickets (89). Enzyme-inducing antipileptic drugs cause the induction of the hepatic cytocrome P450 enzyme system, lower serum vitamin D levels and decrease BMD (90). The simultaneous supplementation with oral calcium and 25OHD3 is effective in preventing the development of rickets and osteomalacia in patients undergoing antipileptic treatment (91).
As the activation of parental vitamin D3 to the 25-hydroxylated compound is performed in the liver, end-stage liver disease compromizes the production of 25(OH)D3. Moreover, vitamin D is one of the fat-soluble vitamins that require bile acid for absorption. In patients with cholestatic liver disease, absorption of vitamin D is poor because of poor secretion of bile juice (92). Indeed in chronic hepatitis patients had low 25(OH)D3 serum levels, possibly because of reduced CYP27A1 expression (93). Also patients with non-alcoholic fatty liver disease exhibit a marked decrease of circulating 25(OH)D3 levels (94). The role of vitamin D3 deficiency in liver disease progression needs further investigation. Administration of 25(OH)D3 could help to solve these problems.
Finally, calcifediol insufficiency is highly prevalent in chronic kidney disease, for an impairment in liver 25-hydroxylation of vitamin D secondary to a PTH-mediated reduction in liver CYP450 isoforms (95). This opens the avenue to the clinical use of the 25-hydroxylated form also in kidney failure, as originally proposed by DeLuca et al. (96).

Other Metabolites

Vitamin D analogs have been synthesized with similar bioeffects on PTH secretion, but with lower calcemia activity. Two drugs, 19-nor-1,25(OH)2D3 and 1α(OH)D2 are being used for the treatment of secondary hyperparathyroidism in the USA, and two are being used in Japan, 22-oxa-1,25(OH)2D3 and 1,25(OH)2-26,27F6D3 (97). Interestingly, the 22-oxa-derivative of calcitriol exerts an anabolic action on bone reconstruction by allogenic bone transplantation in rats (98). Also bromoacetoxy analogs have been synthesized and tested for improving the pharmacological profile of their parent compounds (99).

Future prospects

Vitamin D is an important calciotropic hormone whose endogenous production greatly overcomes the daily nutritional intake. Its function results in the control of the bone remodelling process with impacts on bone growth, maturation and metabolism. Even if the results of controlled clinical trials do not allow to derive final conclusions and to build guidelines, the administration of parental vitamin D has been shown to be pharmacologically active, safe and cost-effective for the prevention and treatment of osteoporosis.
Importantly, over the past decades several clinical trials have reported the efficacy of vitamin D hormone metabolites, as additional therapies of osteoporosis. However, further studies are needed to evaluate the relative impact of active vitamin D metabolites on fracture prevention. Such strategies should not, however, detract from the identification and treatment of other potentially modifiable causes of osteoporosis. Interestingly, for calcifediol, the first and largest product of the parental compound, evidences exist for a preferential use versus vitamin D in conditions like liver insufficiency, kidney failure, malabsorption and use of compounds influencing the hepatic vitamin D metabolism.

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The TARGET project in Tuscany: the first disease management model of a regional project for the prevention of hip re-fractures in the elderly

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Summary

Background: **The official inquiry on osteoporosis in Italy, promoted by the Italian Senate in 2002 concluded that proper preventive strategies should be adopted at regional level in order to prevent osteoporotic fractures. Tuscany is the first Italian region who has promoted an official program (the TARGET project) aimed to reduce osteoporotic fractures by ensuring adequate treatment to all people aged ≥65 years old who experience a hip fragility fracture.** ***Objective:*** **this paper provides information concerning the implementation of TARGET project in Tuscany, assuming that it may represent an useful model for similar experiences to be promoted in other Italian Regions and across Europe.** ***Methods:*** **we have examined the model proposed for the regional program, and we have particularly analyzed the in-hospital and post-hospitalization path of hip fractured patients aged >65 years old in Tuscany after the adoption of TARGET project by Tuscany healthcare system and during its ongoing start-up phase.** ***Results:*** **orthopaedic surgeons have been gradually involved in the project and are increasingly fulfilling all the clinical prescriptions and recommendations provided in the project protocol. Different forms of cooperation between orthopaedic surgeons and other clinical specialists have been adopted at each hospital for the treatment of hip fractured elderly patients. GPs involvement needs to be fostered both at regional and local level.** ***Conclusions:*** **The effort of Tuscany region to cope with hip fractures suffered from elderly people must be acknowledged as an interesting way of addressing this critical health problem. Specific preventive strategies modelled on the Tuscany TARGET project should be implemented in other Italian regions.**

KEY WORDS: disease management; osteoporosis; hip fractures; treatment.

Introduction

The "disease management" approach is a medical perspective aimed to cope with high prevalent and expensive diseases directly from the prevention to the treatment and rehabilitation, in order to improve patients' outcomes and to lower general costs sustained by healthcare authorities. Osteoporosis and related fractures in the Italian population meet the criteria of being highly prevalent and expensive: actually the World Health Organization (WHO) considers this disease to be second only to cardiovascular diseases as a critical health problem worldwide (1). Specifically in Italy, the incidence and costs of hip fractures are already comparable to those of acute myocardial infarctions as a consequence of the ageing of Italian population (2). Actually, more than 75,000 Italian elderly people are hospitalized each year following a hip fracture, with women aged >75 years old accounting for 80% of total events (3). The main Epidemiological Study on the Prevalence of Osteoporosis in Italy (ESOPO) reported a high prevalence of osteoporosis: 23% among all women, with age-specific rates ranging from 9% (40 to 49 year olds) to 45% (70 to 79 year olds), but also 15% of men aged ≥60 years old are osteoporotic (4,5). Therefore, about 4 million of Italian women and 800 thousand men are thought to be affected by osteoporosis (3), a condition that enhances the risk of fracture, including hip fractures (6). Furthermore, it must be always kept in mind that hip fractures have a 5% acute mortality rate and a 15–25% 1 year-mortality (7, 8). Despite that, only a minority of fractured patients starts any treatment, and a relevant size of subjects stop their therapy within 2-3 months (9). The official inquiry promoted by the Italian Senate in 2002 - specifically addressing the topic of the burden of osteoporosis in Italy - had investigated all these issues and concluded that proper preventive strategies should have been adopted at regional level all over the country (10). These official recommendations actually foster regional healthcare authorities to develop appropriate "disease management" models to address the issue of osteoporotic fractures. Nevertheless, until now very few interventions have been promoted by Italian regions in order to reduce the number of osteoporotic fractures and especially the burden of hip fractures both in terms of financial expenditures sustained by the National Healthcare System and in terms of population health. Tuscany has been the first Region to design and implement a specific project - known as TARGET project (Appropriate Treatment of GEriatric Refractures in Tuscany) - with the aim of reducing osteoporotic fractures by ensuring adequate treatment to all people aged ≥65 years old who experience a hip fragility fracture. The TARGET project represents the first Italian program officially involving regional healthcare authorities, with the aim of reducing the incidence of hip fragility fractures. This paper provides information concerning the implementation of TARGET project in Tuscany, which may represent an useful model for similar experiences to be promoted in other Italian Regions and across Europe.

Methods

First of all, we have examined the institutional documents produced by the Regional Authority about the project, and the Tuscany regional data concerning hip fractures in the elderly and pharmacological treatments prescribed to these patients. It must be pointed out that the model proposed for the TARGET project is based on the need of ensuring proper antifracture treatments to elderly hip fractured patients and stopping short treatment courses due to unacceptably low compliance rates which represent a waste of public money. Actually, the number of patients treated with antifracture drugs declined from 13.1% to 12.0% between 2005 and 2007 (3,9), and the Average Medication Possession Rate (MPR) of hip fractured patients was found to be 27%. Moreover, 77.9% of hip fractured patients have a MPR <50% vs. 55% of that of the general population on treatment because of osteoporosis (3,9). Only 2.0% of hip fractured patients had MPR >90% (MPR value which is required to maximize risk fracture reduction) vs. 18.6% of treated patients in the general population (namely all people assuming antiresorptive agents), thus meaning that patients who most need to be properly treated (i.e. elderly hip fractured people) are currently mistreated. On the other hand, the analyses of regional databases have shown an increase in the number of hip fractured patients between 2000 and 2005. This finding strongly confirms the need for ensuring proper pharmacological treatments to this population, which has the highest risk of subsequent fragility fractures.

For this purpose, Tuscany Region, University of Florence and University of Siena have developed a specific protocol for the TARGET project, which is aimed to reduce the number of hip re-fractures in elderly patients by enrolling all people aged ≥65 years old who experience a hip fracture in Tuscany. The goal of the project is to provide these patients with a long term antifracture treatment within 60 days from the fracture event. Orthopaedic surgeons are now requested to cooperate with other specialists and GPs in order to get a complete clinical evaluation of the patient, and define the most appropriate treatment course for each individual patient. The project defines a structured path where hip fractured patients aged ≥65 automatically enter just because they are hospitalized. Fracture events of each individual patient are registered in the regional databases almost in real time because in Tuscany all hospital records are sent to the Regional Healthcare Authority within 10-15 days after the hospital discharge. The availability of these loaded institutional database make possible to know if the hip fractured patient has started any antifracture therapy, thus meaning that the analysis of regional databases allows an early identification of fractured patients with low adherence to therapies. Actually, hip fractured patients have access to medications reimbursed from the Regional Healthcare Authority, who is also able to follow patients compliance to the treatment on individual basis. In the databases are also recorded all the other fractures (both hip and non hip fractures) occurring in the same patient during the years following the first hip fracture. The project has a 4-years prospective phase from 2010 to 2013 and a retrospective control period (from 2006 to 2009). Since the project is expected to decrease the number of hip re-fractures, reductions of fractures incidence and costs sustained from the healthcare system will be compared and discussed.

After having examined all these issues included in the protocol proposed for the regional program, we have analyzed how it is proceeding the in-hospital and post-hospitalization path of hip fractured patients aged >65 years old in Tuscany after the adoption of TARGET project and during its ongoing start-up phase from January 2010 to September 2010. The start-up of the project has been preceded by several meetings ruled by the regional health authority at central level with the key players of the program (namely orthopaedic surgeons and the other specialist treating osteoporosis). During these meetings, the protocol of the project has been presented and optimized. Subsequently, we have started our inquiry concerning how the TARGET project is going to be implemented at hospital level. This inquiry included: (1) visits to the hospital departments, (2) meetings with the orthopaedic surgeons, other specialists and GPs during CME (Continuous Medical Education) workshops addressing the issue of "treatment of severe osteoporosis in Tuscany", (3) phone interviews with orthopaedic surgeons and other specialists. Our questions were aimed to investigate the practical organization of a structured path for hip fractured patients, resulting in a full clinical evaluation and a final prescription of a proper antifracture drug. In this perspective, it was important to evaluate the degree of cooperation between orthopaedics and other specialists (i.e. endocrinologists, rheumatologists, geriatrists or specialists in internal medicine) within the same hospital or with ambulatorial specialists outside the hospital concerning the clinical evaluation of the patient and the choice of the ideal antifracture therapy for each subject. Other points of interests we focused on were the administration of vitamin D, and communication between hospital specialists and GPs.

Results

Medical personnel from all departments of orthopaedics and/or traumatology of public hospitals in Tuscany have been contacted through direct visits, meetings at CME workshops or phone interview. Direct visits were made to 7 large hospitals: the Trauma Center of Florence University Hospital (CTO), Torregalli/S. Giovanni Hospital, SS. Annunziata/P.Nicheri Hospital, Pisa University Hospital, Siena University Hospital, Empoli and Massa/Carrara Hospital. To be noticed that Florence and Siena are actually the coordinating institutions and therefore have been constantly monitored, while Pisa University Hospital was visited five times. A specific meeting with all medical personnel working at orthopedic divisions (where hip fractured patients are hospitalized) has been accomplished at Trauma Center of Florence University Hospital (CTO). A specific meeting with orthopedic surgeons and other specialists working within Pisa district (*"Area Vasta Pisana"*) has been carried out in Pisa. Table 1 summarizes the number of hospitalizations and surgical interventions due to hip fractures at each public hospital in Tuscany (note: USL stands for local health authority) and gives the measure of how important it is to ensure a substantial involvement of all Tuscany hospitals in the TARGET project.

Table 1 - Number of hospitalizations and surgical interventions due to hip fractures at Tuscany hospitals in 2008.

Hospitals	Hospitalizations	Interventions
USL 1 – Massa/Carrara	**428**	**395**
USL 2 - Lucca	**447**	**381**
USL 3 - Pistoia	**629**	**569**
USL 4 - Prato	**485**	**442**
USL 5 - Pisa	**303**	**249**
USL 6 - Livorno	**898**	**718**
USL 7 - Siena	**371**	**315**
USL 8 - Arezzo	**684**	**572**
USL 9 - Grosseto	**540**	**469**
USL 10 - Firenze	**1.151**	**900**
USL 11 - Empoli	**468**	**416**
USL 12 - Viareggio	**377**	**352**
A. O. Pisa University Hospital	**439**	**408**
A. O. Siena University Hospital	**300**	**199**
A. O. Careggi University Hospital	**828**	**744**
TOTAL	***8.348***	***7.129***

Orthopaedic surgeons have been gradually involved in the project and are increasingly fulfilling the clinical prescriptions and recommendations fostered in the protocol. Different forms of cooperation between orthopaedic surgeons and other clinical specialists have been adopted at each hospital for the treatment of hip fractured elderly patients. At the Trauma Center of Florence University Hospital (CTO), orthopaedic surgeons have directly involved other specialists (i.e. endocrinologists and specialists in internal medicine) from the ambulatorial service dedicated to the diagnosis and treatment of osteoporosis (belonging to the Department of Internal Medicine). These latter specialists systematically cooperate with orthopaedics as consultants inside the hospital, in order to fully evaluate the demineralization status (and possible causes) of elderly patients hospitalized because of hip fractures. First level and eventual second level biochemical analyses are performed while the patients are still hospitalized. The choice of the ideal antifracture therapy is individually tailored on the basis of patient's characteristics and needs, taking into account the potential compliance to the therapy. Before the discharge from the hospital, patients are provided with an informative letter for their general practitioner (where it is highlighted the involvement in the TARGET project), and are requested to book a visit at the ambulatorial service dedicated to the diagnosis and treatment of osteoporosis located at CTO. To the date, once a week there is an ambulatorial session completely devoted to the patients involved in TARGET project at CTO. The visit is performed within 30-60 days and it is possibly accomplished when the fractured patient comes back for the orthopaedic control. During the ambulatorial visit – which includes the prescription of antifracture therapies and calcium/vitamin D supplementations – it is possible to evaluate patients' bone mineral density through a DEXA (Dual Energy X-rays Absorbiometry) examination and to administer intravenous antifracture treatments. Patients who receive an intravenous therapy are provided with a reminder form because they have to book a second infusion in the subsequent year. The same cooperative scheme has been adopted at Siena University Hospital between orthopaedic surgeons and specialists belonging to the Department of Internal Medicine. Patients discharged from the orthopaedic divisions are requested to book a visit at ambulatorial services dedicated to diagnosis and treatment of osteoporosis, for a clinical evaluation and proper therapeutical prescriptions. In addition to the informative letter for their general practitioners concerning the hospitalization, all patients discharged from Siena University hospital are provided with a second letter containing only information about the TARGET project. In this letter, it is also indicated if the first vitamin D supplementation has been administered while the patient was still hospitalized at Siena University Hospital or it must be provided directly by the general practitioner. Similar cooperative schemes between othopaedics and other specialists with specific expertise in diagnosis and treatment of osteoporosis have been adopted in other smaller hospitals. At Torregalli/S. Giovanni hospital (Florence), orthopaedics can be helped in the clinical evaluation of hip fractured patients by the specialists working at the contiguous department of rheumatology (which is also provided with an ambulatorial service). Orthopaedic surgeons working at Empoli (Florence), Pistoia, Pescia, Prato and Grosseto hospitals have started collaborating with the reumathologists working at adjacent departments of internal medicine (or at ambulatorial services located in the same hospitals), in order to evaluate the demineralization status of the patient and to choose the ideal antifracture therapy. A special case is that of Ss. Annunziata/P. Nicheri hospital (Florence), where it has been built up an interdivisional unit of orthogeriatrics, which is hold together by orthopaedics and geriatrists, thus representing a pre-existing model of cooperation where fractured patients are operated by the surgeons but they are subsequently followed by geriatrists. In this particular case, it has been much more simple to introduce the TARGET project and to have the different specialists working together. Within the area belonging to Pisa district (*Area Vasta Pisana*), orthopaedics working at hospitals of Pontedera (Pisa), Viareggio, Lucca, Livorno, and Piombino have the opportunity of cooperating with specialists in rheumatology or internal medicine working at the same hospital in order to fulfill the objectives of the project in terms of clinical evaluation and therapeutical prescriptions. However, in case of fractured patients requiring evaluations or treatments (i.e. intravenous antifracture therapies) which could not be administered outside University hospitals, there is the opportunity of referring to the ambulatories ruled by the Division of Rheumatology at Pisa University. There are also some cases of cooperation between surgeons working in a hospital (orthopaedics located in Massa, Carrara, Lunigiana and Arezzo) and rheumatologists working at public ambulatorial services outside the hospital (Massa and Arezzo). In these cases, all patients who need an additional clinical evaluation and/or requiring an antifracture therapy which is difficult to provide inside the hospital are requested to book a visit at ambulatorial services located in Massa (for Lunigiana, Massa and Carrara hospitals) or those located in Arezzo (for patients discharged from Arezzo hospital). A different case is that of the orthopaedics/traumatology division of Pisa University Hospital, which is actually provided with an ambulatorial service devoted to diagnosis and treatment of osteoporosis completely ruled by the same orthopaedics. In this case, the surgeons have decided to accomplish by themselves the clinical evaluation of hip fractured patients concerning demineralization status and therapeutical prescriptions. However, patients candidate to intravenous therapies are asked to book a visit at ambulatories of the Division of Rheumatology at the same Pisa University hospital.

Discussion

The start-up phase of the TARGET project was supposed to go faster than it actually has happened. However, the first analysis of Regional Healthcare System databases which will be finished by the end of the year 2010 will allow us to map hospitals which are fulfilling the objectives of the project and hospitals which are not following the protocol approved at regional level. Furthermore, thanks to these analyses it will be possible to track the patient from the hospital admission following hip fracture to the discharge from orthopaedic division, and be sure that fractured elderly people do receive a proper therapy after leaving the hospital. Regional databases would help for early identification of fractured patients showing low adherence to therapies, or identification of patients withdrawing their therapy before completing one year of treatment. As there is a need for specific codification of osteoporotic fragility fractures at hospital admissions, and Tuscany has been involved as pilot Region by the Italian Ministry of Health, the TARGET patients database will also be integrated in the proposed National registry of fragility fractures. However, fractures treated within the TARGET project should be regarded as fragility fractures since they occurred most frequently in women aged >75 years old, the age group where the prevalence of osteoporosis is known to be higher. This means that one out 5 patient will suffer a new hip fracture during the following 4 years after the first event, resulting also in a higher disability and mortality risk. A point of optimization is represented by the involvement of general practitioners (GPs). Although GPs belonging to the medical cooperatives of the three districts (*Aree Vaste*) of Florence, Siena, and Pisa have been involved in educational meetings concerning the treatment of severe osteoporosis in Tuscany, a strong effort to foster the GPs' awareness concerning the TARGET project should be made both at regional and local level. However, the insertion of the TARGET objectives into the goals that local health authorities and hospital managers must fulfill every year will foster both orthopaedics and GPs in accomplishing the protocol approved by the regional health authority. The achievement of the objectives of the project

is important both in terms of population health and financial expenditures, as the over 7,000 hip fractures occurring each year in people aged >65 in Tuscany result in costs exceeding 95 million Euros (costs entirely sustained by the Regional Healthcare System). In addition to that, it must be pointed out that ¼ of the costs sustained to provide antifracture therapies (approx. 55 millions € /year all over Italy) are wasted in providing very short treatment courses that are unlikely to reduce fracture risk (3, 9). In this perspective, preventive strategies based on disease management models should be carried out through specific regional programs, such as the Tuscany TARGET project, as stated in 2002 by the Italian Senate Commission during the official inquiry on osteoporosis.

Conclusion

The effort of Tuscany Region to cope with hip fractures suffered from elderly people must be acknowledged as an interesting way of addressing this critical health problem. Specific preventive strategies modelled on the Tuscany TARGET project should be implemented in other Italian regions.

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E-mail: admin@ectsoc.org

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WEB SITES OF INTEREST

Clinical Cases in Mineral and Bone Metabolism: www.gruppocic.it
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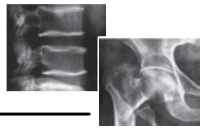
OSSEOR®

ranelato di stronzio



RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO. 1. DENOMINAZIONE DEL MEDICINALE. OSSEOR 2 g granulato per sospensione orale. **2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA**. Ogni bustina contiene 2 g di ranelato di stronzio. Eccipiente: ogni bustina contiene inoltre 20 mg di aspartame (E 951). Per l'elenco completo degli eccipienti, vedere paragrafo 6.1. **3. FORMA FARMACEUTICA**. Granulato per sospensione orale. Granulato giallo. **4. INFORMAZIONI CLINICHE**. **4.1. Indicazioni terapeutiche**. Trattamento dell'osteoporosi nelle donne in postmenopausa per ridurre il rischio di fratture vertebrali e dell'anca (vedere paragrafo 5.1). **4.2 Posologia e modo di somministrazione**. ***Posologia.*** La dose raccomandata è di una bustina da 2 g una volta al giorno per somministrazione orale. A causa della natura della patologia curata, il ranelato di stronzio è destinato per un impiego a lungo termine. L'assorbimento del ranelato di stronzio è ridotto dal cibo, dal latte e dai suoi derivati e, pertanto, OSSEOR deve essere somministrato nell'intervallo tra i pasti. Dato il suo lento assorbimento, OSSEOR deve essere assunto al momento di andare a letto, preferibilmente almeno due ore dopo il pasto (vedere paragrafi 4.5 e 5.2). Le pazienti in trattamento con ranelato di stronzio devono assumere supplementi di vitamina D e di calcio, se il loro apporto con la dieta è insufficiente. *Pazienti anziani*. L'efficacia e la sicurezza del ranelato di stronzio sono state dimostrate in un vasto campione di donne in postmenopausa di tutte le età (fino a 100 anni all'inclusione) affette da osteoporosi. Non è richiesto alcun adattamento posologico in relazione all'età. *Insufficienza renale*. Il ranelato di stronzio non è consigliato nelle pazienti con insufficienza renale grave (clearance della creatinina inferiore a 30 ml/min) (vedere paragrafi 4.4 e 5.2). Non è richiesto alcun adattamento posologico nelle pazienti con insufficienza renale da lieve a moderata (clearance della creatinina 30-70 ml/min) (vedere paragrafo 5.2). *Insufficienza epatica*. Poiché il ranelato di stronzio non viene metabolizzato, non è richiesto alcun adattamento posologico nelle pazienti con insufficienza epatica. *Popolazione pediatrica*. La sicurezza e l'efficacia di OSSEOR nei bambini di età inferiore ai 18 anni non sono state stabilite. Non ci sono dati disponibili. ***Modo di somministrazione***. Per uso orale. Il granulato delle bustine deve essere assunto dopo sospensione in un bicchiere contenente un minimo di 30 ml di acqua (approssimativamente un terzo di un normale bicchiere). Anche se gli studi relativi all'utilizzo hanno dimostrato che il ranelato di stronzio rimane stabile in sospensione nelle 24 ore successive alla preparazione, la sospensione deve essere bevuta immediatamente dopo la sua preparazione. **4.3 Controindicazioni**. Ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti. **4.4 Avvertenze speciali e precauzioni di impiego**. *Impiego nei pazienti con insufficienza renale.* In assenza di dati relativi alla sicurezza ossea in pazienti con insufficienza renale grave in trattamento con il ranelato di stronzio, OSSEOR non è consigliato nelle pazienti con clearance della creatinina inferiore a 30 ml/min. (vedere paragrafo 5.2). Nel rispetto di una buona pratica clinica, si raccomanda un controllo periodico della funzionalità renale nelle pazienti con insufficienza renale cronica. Il proseguimento della terapia con OSSEOR nelle pazienti che sviluppano una grave insufficienza renale deve essere valutato su base individuale. *Tromboembolismo venoso.* Negli studi di fase III controllati verso placebo, il trattamento con il ranelato di stronzio è stato associato ad un incremento dell'incidenza annuale di tromboembolia venosa (TEV), inclusa l'embolia polmonare (vedere paragrafo 4.8). La causa di tale incremento è sconosciuta. OSSEOR deve essere utilizzato con cautela nelle pazienti con aumentato rischio di TEV, incluse quelle pazienti con una pregressa TEV. Durante il trattamento di pazienti a rischio, o che possono sviluppare un rischio di TEV, deve essere prestata particolare attenzione ai possibili segni e sintomi di TEV e devono essere adottate adeguate misure preventive. *Reazioni cutanee.* Casi di sindromi da ipersensibilità severa, incluso in particolare rash farmacologico con eosinofilia e sintomi sistemici (DRESS), talvolta fatali, sono stati riportati in corso di trattamento con OSSEOR (vedere paragrafo 4.8). La sindrome di DRESS è caratterizzata da rash, febbre, eosinofilia e coinvolgimento sistemico (ad es. adenopatia, epatite, nefropatia e pneumopatia interstiziali). Il tempo di insorgenza è stato generalmente di circa 3-6 settimane e nella maggior parte dei casi il quadro clinico si è risolto con l'interruzione del trattamento con OSSEOR e con l'inizio di una terapia corticosteroidea. La guarigione può essere lenta e in alcuni casi sono state riportate ricadute della sindrome dopo interruzione della terapia con corticosteroidi. Il paziente deve essere informato di interrompere il trattamento con OSSEOR immediatamente e in maniera definitiva quando insorge un rash e di consultare un medico. I pazienti che hanno interrotto il trattamento con OSSEOR a seguito di reazioni da ipersensibilità o a seguito di altre gravi reazioni allergiche non devono riprendere la terapia. *Interazioni con i test di laboratorio.* Lo stronzio interferisce con i metodi colorimetrici per la determinazione delle concentrazioni ematiche ed urinarie del calcio. Perciò, nella pratica clinica, devono essere usati metodi di spettrometria ad emissione atomica con plasma ad accoppiamento induttivo o di spettrometria ad assorbimento atomico per assicurare un'accurata valutazione delle concentrazioni ematiche ed urinarie di calcio. *Eccipiente.* OSSEOR contiene una fonte di fenilalanina, che può essere pericolosa per le pazienti affette da fenilchetonuria. **4.5 Interazioni con altri medicinali ed altre forme di interazione.** Il cibo, il latte ed i suoi derivati, e le specialità medicinali contenenti calcio possono ridurre la biodisponibilità del ranelato di stronzio approssimativamente del 60-70%. Pertanto, la somministrazione di OSSEOR e di tali prodotti deve essere distanziata di almeno due ore (vedere paragrafo 5.2). Poiché a livello gastrointestinale i cationi bivalenti possono formare un complesso scarsamente assorbibile con le tetracicline orali e con gli antibiotici chinolonici, è sconsigliata la somministrazione contemporanea di ranelato di stronzio con questi farmaci. Come misura precauzionale, l'assunzione di OSSEOR deve essere sospesa durante il trattamento con tetracicline orali o con antibiotici chinolonici. Uno studio clinico *in vivo* sulle interazioni farmacologiche ha dimostrato che l'assunzione di idrossidi di alluminio e magnesio, nelle due ore antecedenti o contemporaneamente al ranelato di stronzio, causava una lieve diminuzione nell'assorbimento del ranelato di stronzio (diminuzione del 20-25% dell'AUC), mentre l'assorbimento rimaneva praticamente inalterato quando l'antiacido veniva somministrato due ore dopo il ranelato di stronzio. È pertanto preferibile assumere gli antiacidi almeno due ore dopo l'assunzione di OSSEOR. Tuttavia, poiché l'assunzione di OSSEOR è consigliata al momento di coricarsi, quando questo schema posologico non è applicabile, l'assunzione contemporanea rimane accettabile. Non è stata osservata alcuna interazione con la supplementazione orale di vitamina D. Nel corso degli studi clinici, non è stata dimostrata alcuna interazione clinica, né un significativo aumento dei livelli ematici di stronzio, con i farmaci che, nella pratica corrente, sono comunemente prescritti in concomitanza con OSSEOR, tra i quali: farmaci antinfiammatori non steroidei (compreso l'acido acetilsalicilico), anilidi (come il paracetamolo), H_2 bloccanti ed inibitori della pompa protonica, diuretici, digossina e glicosidi cardiaci, nitrati organici ed altri vasodilatatori per patologie cardiache, calcio-antagonisti, beta-bloccanti, ACE-inibitori, antagonisti dell'angiotensina II, agonisti selettivi dei recettori beta-2-adrenergici, anticoagulanti orali, inibitori dell'aggregazione piastrinica, statine, fibrati e derivati delle benzodiazepine. **4.6 Fertilità, gravidanza e allattamento**. ***Gravidanza.*** OSSEOR è destinato esclusivamente alle donne in postmenopausa. I dati relativi all'uso di ranelato di stronzio in donne in gravidanza non sono disponibili. Studi su animali hanno mostrato, ad alte dosi, effetti ossei reversibili nella prole di ratti e di conigli trattati durante la gravidanza (vedere paragrafo 5.3). Se OSSEOR è assunto inavvertitamente in gravidanza, il trattamento deve essere interrotto. ***Allattamento.*** Dati chimico-fisici suggeriscono l'escrezione di ranelato di stronzio nel latte materno. OSSEOR non deve essere utilizzato durante l'allattamento. ***Fertilità.*** Non sono stati osservati effetti sulla fertilità di maschi e femmine in studi su animali. **4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari**. Il ranelato di stronzio non altera o altera in modo trascurabile la capacità di guidare veicoli o di usare macchinari. **4.8 Effetti indesiderati**. OSSEOR è stato studiato in sperimentazioni cliniche che hanno coinvolto circa 8.000 persone. La sicurezza a lungo termine è stata valutata con studi di fase III, in donne in postmenopausa con osteoporosi, trattate fino a 60 mesi con 2 g/die di ranelato di stronzio (n=3.352) o con placebo (n=3.317). L'età media, al momento dell'inclusione, era di 75 anni e il 23% delle pazienti arruolate aveva un'età compresa tra 80 e 100 anni. Non sono state riscontrate differenze nella natura delle reazioni avverse tra i gruppi di trattamento, a prescindere dal fatto che l'età dei pazienti fosse inferiore o superiore a 80 anni al momento dell'inclusione. Il tasso di incidenza globale delle reazioni avverse con il ranelato di stronzio non differisce da quello del placebo e le reazioni avverse sono state di solito lievi e transitorie. Le più comuni reazioni avverse sono state nausea e diarrea, generalmente riferite all'inizio del trattamento, senza differenza apprezzabile tra i gruppi nelle fasi successive. L'interruzione della terapia è dovuta principalmente alla nausea (1,3% e 2,2%, rispettivamente, nei gruppi placebo e ranelato di stronzio). Negli studi di fase III, l'incidenza annuale di eventi di tromboembolia venosa (TEV) osservata in 5 anni è stata approssimativamente dello 0,7% con un rischio relativo di 1,4 (95% CI = [1,0; 2,0]) nelle pazienti trattate con ranelato di stronzio rispetto al placebo (vedere paragrafo 4.4). Le seguenti reazioni avverse sono state riportate durante gli studi clinici e/o durante l'utilizzo post-marketing del ranelato di stronzio. Le reazioni avverse, definite come effetti indesiderati almeno possibilmente attribuibili al trattamento con il ranelato di stronzio, durante gli studi di fase III, sono elencate qui di seguito, usando la seguente convenzione (frequenza versus placebo): molto comune (>1/10); comune (>1/100, <1/10); non comune (>1/1.000, <1/100); raro (>1/10.000, <1/1.000); molto raro (<1/10.000), non nota (la frequenza non può essere definita sulla base dei dati disponibili).

Classificazione sistemica organica (CSO)	Percentuale di pazienti che hanno riportato la reazione avversa al farmaco.	
Categoria di frequenza	Trattamento	
Reazione avversa	Ranelato di stronzio (n=3352)	Placebo (n=3317)
Disturbi psichiatrici		
Frequenza non nota[a]:		
stato confusionale	–	–
Patologie del sistema nervoso		
Comune:		
cefalea	3,3%	2,7%
disturbi della coscienza	2,6%	2,1%
perdita della memoria	2,5%	2,0%
Non comune:		
crisi convulsive	0,4%	0,1%
Patologie vascolari		
Comune:		
Tromboembolismo venoso (TEV)	2,7%	1,9%
Patologie respiratorie, toraciche e mediastiniche		
Frequenza non nota[a]:		
iperreattività bronchiale	–	–
Patologie gastrointestinali		
Comune:		
nausea	7,1%	4,6%
diarrea	7,0%	5,0%
feci molli	1,0%	0,2%
Frequenza non nota[a]:		
vomito	–	–
dolore addominale	–	–
irritazione della mucosa orale (stomatiti e/o ulcerazioni della bocca)	–	–
Patologie epatobiliari		
Frequenza non nota[a]:		
aumento delle transaminasi sieriche (in associazione con reazioni cutanee di ipersensibilità)	–	–
Patologie della cute e del tessuto sottocutaneo		
Comune:		
dermatite	2,3%	2,0%
eczema	1,8%	1,4%
Frequenza non nota[a]:		
reazioni cutanee di ipersensibilità (rash, prurito, orticaria, angioedema)	–	–
sindromi di ipersensibilità severa inclusa sindrome di Stevens-Johnson, necrolisi epidermica tossica e DRESS (vedere paragrafo 4.4).	–	–
alopecia	–	–