

# The use of cholecalciferol in patients with hip fracture

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## Summary

**Introduction.** Major osteoporotic fractures are steadily increasing due to population aging. Programs of secondary prevention against refracture are essential to decrease morbidity and mortality and the cost for individuals and the society. Vitamin D supplementation and optimization of calcium intake are of a pivotal importance to start specific osteoporosis treatment and for its safety and efficacy. Cholecalciferol is the most widely employed drug for vitamin D supplementation,

**Purpose.** Aim of this study was to assess the trends in the use of vitamin D supplements containing cholecalciferol in the population of hip fracture patients older than 65 years, resident in the region of Tuscany (Italy) in the years 2011-2015 and to describe vitamin D status in a subgroup of this individuals directly referred to a bone clinic for further evaluation after hip osteoporotic fracture.

**Methods.** Data were retrieved from the electronic anonymous regional administrative database administered by the Region of Tuscany (Italy) in the years 2011-2015 within the T.A.R.Ge.T. project (Trattamento Appropriato delle Rifratture Geriatriche in Toscana, i.e., "Appropriate treatment of geriatric refractures in Tuscany"), a program endorsed by the region itself. Data pertaining to cholecalciferol prescriptions and hospital discharge codes were retrieved and appropriately crossed to get data on the use of cholecalciferol supplements in patients before and after a hip fracture.

A retrospective analysis was carried out in a subgroup of subjects (n 254) appropriately referred to the local fracture liaison service after the major osteoporotic frac-

ture and vitamin D status in terms of serum 25(OH) vitamin D levels was assessed.

**Results.** The majority of subjects experiencing a hip fracture (98.2% and 88.3% in 2011 and 2015, respectively) did not receive vitamin D supplements at the time of the fracture event. Although a trend in increase in prescriptions for cholecalciferol supplements could be observed in the years of the study, the percentage of treated individuals remained low even after the fracture, since only 30-35% of subjects receives cholecalciferol supplements at one year after the fracture. Cholecalciferol remained the most prescribed drug in this population, while a substantial decrease of cholecalciferol in association with calcium salts was observed. The use of high doses of cholecalciferol has decreased in this population, while diminished the use of the drops has been accompanied by an increase in prescriptions of single monthly dose supplements.

**Conclusions.** The correction of vitamin D inadequacy is preliminary to any treatment for osteoporosis and together with calcium may reduce fracture risk by itself. The prescription of vitamin D supplements is low in patients before and after a hip fracture in a Mediterranean region and despite the overall increase in vitamin use and abuse in the general population. Proper educational programs and active fracture liaison services are needed in order to bridge this gap.

**KEY WORDS:** vitamin D; osteoporosis; aging; prevention; nutrition; calcium intake; frailty.

## Introduction

Optimal vitamin D status is essential for the absorption of calcium and phosphate necessary to preserve mineral homeostasis and bone health and to maintain skeletal muscle performance (1, 2). Cholecalciferol (vitamin D<sub>3</sub>) is the most widely employed supplement to correct vitamin D deficiency and to maintain steadily serum 25(OH) vitamin D [25(OH)D] levels above the thresholds of 20 or 30 ng/ml, which have been set for bone health by international consensus guidelines. Many studies have demonstrated the efficacy, safety and tolerability of cholecalciferol, when employed at physiological, non-toxic doses (3, 4). Further trials are needed to assess the possible non-classic toxic effects of cholecalciferol such as the increase in number of falls observed in some studies employing high, concentrated doses of vitamin D [25(OH)]. For these reason, cholecalciferol supplements are nowadays recommended for the treatment of vitamin D deficiency at common doses in patients with musculoskeletal diseases, while their use in extra-skeletal chronic disorders and the employment of high amounts are debated (5). The characteristics of safety and efficacy, together with the supposed benefits of cholecalciferol in the prevention and treat-

ment of extra skeletal diseases, have meant that the prescription of cholecalciferol both by specialists and general practitioners is greatly increased during the last decade (6). The correction and maintenance of vitamin D sufficiency, together with the optimization of calcium intake, are preliminary to any treatment for osteoporosis in both sexes (7, 8). Figures of osteoporotic fractures are steadily increasing worldwide due to the ageing of the population (9). Indeed, the occurrence of major osteoporotic fractures requires the initiation of secondary prevention strategies aimed to increase bone strength and prevent further fractures. Nonetheless, in the absence of effective fracture liaison services between orthopedic departments and bone clinics, the undertaking of such programs is often difficult. Bone antiresorptive and proformative agents are effective in preventing further fractures when prescribed after the occurrence of fragility fractures as agents for secondary prevention (7). The efficacy and safety of osteoporosis therapy is strongly related to vitamin D status and calcium intake. Indeed, the correction of vitamin D deficiency prevents adverse events such as antiresorptive-related hypocalcemia and improves their efficacy in reducing fracture risk. For these reasons is commonly believed that the optimization of both vitamin D status and calcium intake has to precede the start of antifracture therapy. Besides the use of vitamin D supplements is widespread in the population, the assumption of vitamin D is still low in people experiencing osteoporotic fractures, even in some countries of regions in which population-based interventions are directed especially towards elderly people. Recent studies have pointed out that only a small percentage of elderly people experiencing hip fractures receive vitamin D supplementation at the time of the event and the vast majority of them is vitamin D deficient (10-12). Such data are lacking in Italy.

Aim of this study was to evaluate the pattern of prescription of vitamin D supplements and, in particular, cholecalciferol in an Italian region (region of Tuscany), as representative of a Mediterranean country, in the population of hip fracture patients, before and after the event, and vitamin D status in a subgroup of these patients surgically treated and medically managed in a tertiary referral center.

## Methods

Data were extracted from the electronic anonymous regional administrative database administered by the Region of Tuscany (Italy) in the years 2011-2015. This database was built to monitor and control health expenditure of the whole population of Tuscany (whole population: 3,749,813 and 3,752,654 inhabitants in 2011 and 2015, respectively; adults >65 years, 872,766 in 2011 and 929,050 in 2015), including information for statistical and epidemiological analyses. Patients over 65 years of age were included in this analysis, according to the aims of the T.A.R.Ge.T. project (Trattamento Appropriato delle Rifratture Geriatriche in Toscana, i.e., "Appropriate treatment of geriatric refractures in Tuscany"), a program endorsed by the Region of Tuscany (13). Data pertaining to cholecalciferol prescriptions (expressed as number of individuals receiving cholecalciferol) both by hospitals and general practitioners were retrieved as related to the years 2011-2015 in order to estimate the consumption of vitamin D supplements in patients experiencing a hip fracture and after hip fracture. Prescriptions for marketed vitamin

D compounds containing cholecalciferol commonly used in clinical practice (cholecalciferol alone or in combination with calcium carbonate or alendronate) were extracted according to the number of the Anatomical Therapeutic Chemical classification system of drugs, group 5 [ATC5: cholecalciferol (A11CC05), cholecalciferol in combination with calcium (A12AX), and cholecalciferol in combination with alendronate (M05BB03)]. An analysis for the way of cholecalciferol administration was also carried out. For cholecalciferol, an analysis of way of administration (drops 10,000 IU/10ml administered orally, vials, 25,000 or 50,000 IU bottles administered orally, 100,000 IU or 300,000 IU vials administered orally or intramuscularly) was performed.

The flow of data related to prescriptions was properly crossed and longitudinally analyzed with data pertaining to the flow of data containing medical discharge codes and general data flow, in order to restrict the analysis to the population of seniors with hip fracture of both sexes. Hip fractures were defined by the following ICD-9-CM diagnosis codes assigned at discharge as major diagnosis: 820.0-820.1 (femoral neck fractures), 820.2-820.3 (peritrochanteric femoral fractures) and 820.8, 820.9 and 821.1 (other femoral fractures). Patients with diagnosis codes of Paget's disease (ICD-9-CM 731) and neoplasm (ICD-9-CM 140-239) were excluded. Hip fractures caused by road accident or trauma were not included in the analysis. The time of hip fracture was also retrieved in order to establish two separate analyses regarding the period immediately before and after the fracture event.

For the longitudinal study of prescriptions related to the year 2015, only patients fractured within the first 6 months were considered in the analysis in order to have a minimum follow up of 6 months.

A subgroup of 254 consecutive patients referred after hip fracture to the Unit of Bone and Mineral Diseases of the University Hospital of Florence (Florence, Italy) for secondary prevention programs within the local Fracture Liaison Service were retrospectively evaluated in a two-year period (2015-2016) for baseline vitamin D status and records of vitamin D supplementation at the time of the fracture. Baseline serum 25(OH)D levels were referred to the record at pre-surgical screening or at the first medical assessment usually taking place within the first 2-3 months after hip surgery, as part of the baseline assessment for osteoporosis. Data were expressed as percentage of total and as mean  $\pm$  SD. Statistical significances were computed by using the test on proportions.

This study was approved by the Internal Review Board of the University Hospital of Florence.

## Results

Elderly patients (over 65 years of age), resident in the Region of Tuscany and suffering hip fractures in the years 2011-2015 were considered for this analysis.

Within this group, in the 5 years of the study, the number of patients experiencing hip fracture rose from 5818 in 2011 (0.7% of resident elderly population) to 6686 in 2015 (0.7% of resident elderly population) (Table 1), with a female: male ratio of about 3 : 1 (females: 75.9-77.8%, males: 22.2-24.1%) and a mean age at the time of the fracture of 83.3 years.

The proportion of patients under vitamin D<sub>3</sub> supplementation

Table 1 - Patients with hip fractures in the Region of Tuscany in the years 2011-2015 are reported. Within this population, patients on vitamin D supplements before the hip fracture (Fx) and patients receiving vitamin D supplements at one, two, three, six and twelve months after the major osteoporotic fracture are shown; patients are expressed as number and percentage of the total hip fracture patients each year; p refers to values in 2015 as compared to values in 2011; ns=not significant.\*For 2015 only patients fractured in the first 6 months were considered to have a maximum follow up of 6 months to analyze vitamin D prescriptions; therefore data at 12 months are not available.

	2011		2012		2013		2014		2015		p
<b>Patients with hip Fx (n)</b>	5818		5663		6158		6344		6686		
<b>Vitamin D supplements before hip Fx (n and %)</b>	104	1.8%	158	2.8%	374	6.1%	640	10.1%	783	11.7%	0.0376
<b>Vitamin D supplements after hip Fx (n and %)</b>											
- at 1 month	472	8.1%	472	8.3%	751	12.2%	773	12.2%	792	11.8%	ns
- at 2 months	1098	18.9%	1087	19.2%	1489	24.2%	1524	24.0%	1458	21.8%	ns
- at 6 months	1386	23.8%	1374	24.3%	1812	29.4%	1884	29.7%	1686	25.2%	ns
- at 12 months	1646	28.3%	1633	28.8%	2093	34.0%	2174	34.3%	—*	—*	—*

at the time of the fracture was estimated. Only 1.8% (104/5818) of individuals with hip fracture were receiving cholecalciferol before the fracture event in 2011. This percentage has significantly increased over the years, being 11.7% in 2015 (p=0.0376) (Table 1).

As shown in Table 1 and Figure 1, the proportion of patients commencing cholecalciferol after hip fracture significantly rose within the year after the fracture event from 8.1% at 1 month after the fracture event, to 18.9% after 3 months, to 23.8% at 6 months and to 28.1% at one year in 2011 (p<.001). This trend was confirmed within each year of the study. The percentage of patients on vitamin D supplements at 1 month rose significantly along the years of observation (from 8.1% in 2011 to 11.8% in 2015), while the percentage

hip fracture patients on vitamin D supplements at 6 months and one year did not change significantly over time and a decreasing trend was even observed.

As far as the type of drug is concerned, cholecalciferol alone (A11CC05) was the most prescribed vitamin D supplement already in 2011 and its use further increased in a significant way in the 5 year of observation (p=<.001), while the use of cholecalciferol in combination with calcium salts (A12AX) decreased markedly, almost half half-dying, during the 5 years (p=.001) (Table 2). The association of cholecalciferol and alendronate (M05BB03) was by far the less prescribed form of cholecalciferol and decreased further during the study period, although not significantly (Table 2). No statistical differences were observed between sexes with respect to these parameters.

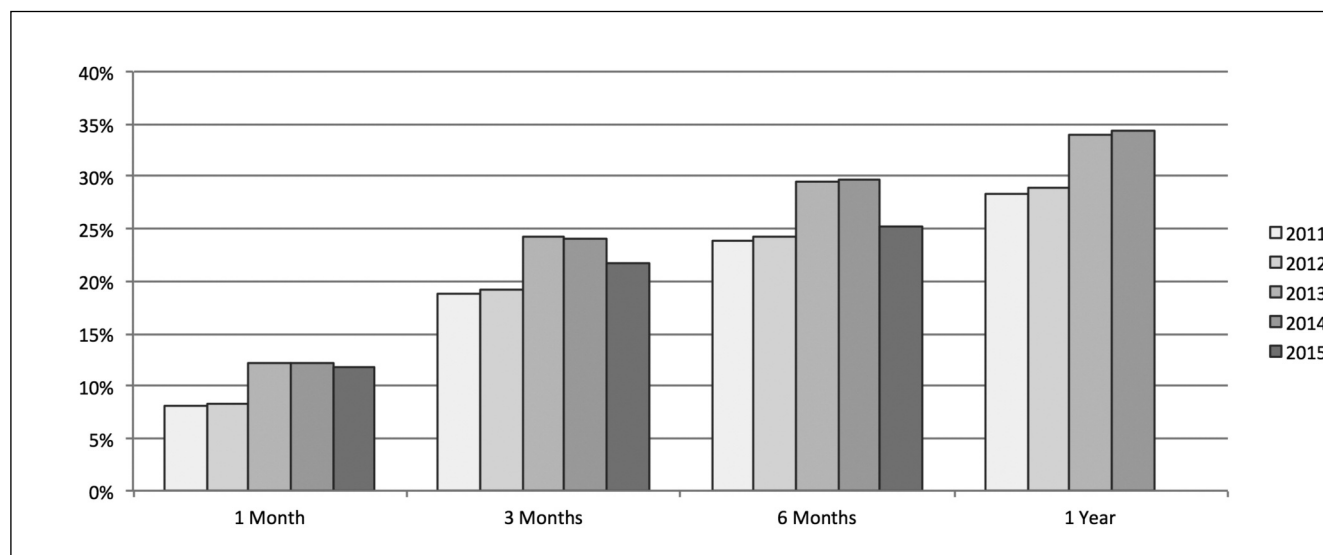


Figure 1 - Patients on vitamin D supplements containing cholecalciferol after 1 month, 3 months, 6 months and one year after hip fracture in the Region of Tuscany in the years 2011-2015.

Table 2 - Percentage of individuals prescribed with different cholecalciferol pharmaceutical specialties identified by specific ATC5 codes in the Region of Tuscany in the years 2011-2015; p refers to values in 2015 as compared to values in 2011.

Drug	ATC5 code	2011	2012	2013	2014	2015	p
Cholecalciferol	A11CC05	46.2%	48.7%	51.8%	58.9%	61.7%	p<.001
Cholecalciferol + calcium salts	A12AX	42.7%	39.6%	36.8%	32.1%	29.2%	p<.001
Cholecalciferol + alendronate	M05BB03	11.0%	11.7%	11.4%	8.9%	9.1%	p=ns
		100.0%	100.0%	100.0%	100.0%	100.0%	

In the analysis carried out on the treatment modality for cholecalciferol alone (A11CC05), cholecalciferol drops were the most prescribed in 2011, but their use significantly decreased during the years of observation (p< .001), in parallel to the increase of prescription of 25,000 IU single-dose cholecalciferol, which was the most prescribed form in 2015 (p< .001) (Figure 2). The use of high concentrated doses of vitamin D (i.e. 300,000 IU vials) decreased substantially in the study period (p< .001), while the prescription of 100,000 IU vials slightly rose from 2011 to 2015 (< .001) (Figure 2). In the retrospective analysis on the 254 consecutive patients (73.2% women, 26.8% men, mean age 82.9±9.1 years) evaluated after surgical treatment for hip fracture, baseline (i.e. recorded at first medical evaluation after within 2-3 months after the fracture event) serum 25(OH)D levels were recorded and analyzed. Mean serum levels of 25(OH)D were 13.7±9.8 ng/ml, with no statistical differences between men and women. Only 20.9% had serum 25(OH)D levels above 20 ng/ml and just 7.1% of hip fracture patients had serum 25(OH)D levels above 30 ng/ml (Figure 3). The majority of individuals (42.9%) was severely vitamin D deficient [i.e. serum 25(OH)D levels below 10 ng/ml] at the time of the hip fracture (Figure 3). In this group of hip fracture patients, 15.0% was receiving vitamin D supplements at baseline.

**Discussion**

Figures of hip fracture are constantly growing in the population due to population aging (9).

Despite the widespread and steadily increasing use of vitamin D supplements in the population, often dispensed for a variety of diseases (5, 6), this study shows that the intake of vitamin D supplements by subjects either experiencing or having experienced a major osteoporotic fracture, such as a hip fracture, remains low at the time of the event and even after.

The analysis on the data retrieved by a regional prescription database in a Mediterranean country and the subgroup retrospective survey in patients addressed to medical management of osteoporosis in an Italian tertiary referral center, confirmed previous data showing that only a small percentage of individuals was taking vitamin D supplements at the time of the major osteoporotic fracture (10-12). Just 1.8% of the total patients experiencing a hip fracture in Tuscany in 2011 (104 on vitamin D supplementation/5818 hip fracture patients) was under cholecalciferol treatment at baseline. This percentage increased during the years, to reach 11.7% in 2015 (783 on vitamin D supplementation/6686 hip fracture patients). Thus, the use of cholecalciferol has steadily increased during the last years. While only 1:50 patients with hip fracture was on vitamin D supplementation in 2011, 1:10 individuals experiencing hip fracture was receiving cholecalciferol supplementation at the time of the fracture in 2015. This might reflect the vitamin D supplementation strategies in the elderly populations applied in some regions by the local health system, but it may be due also to increased awareness of the need of vitamin D supplementation in people at high risk for fracture.

The prescription of vitamin D, which has to be strongly ad-

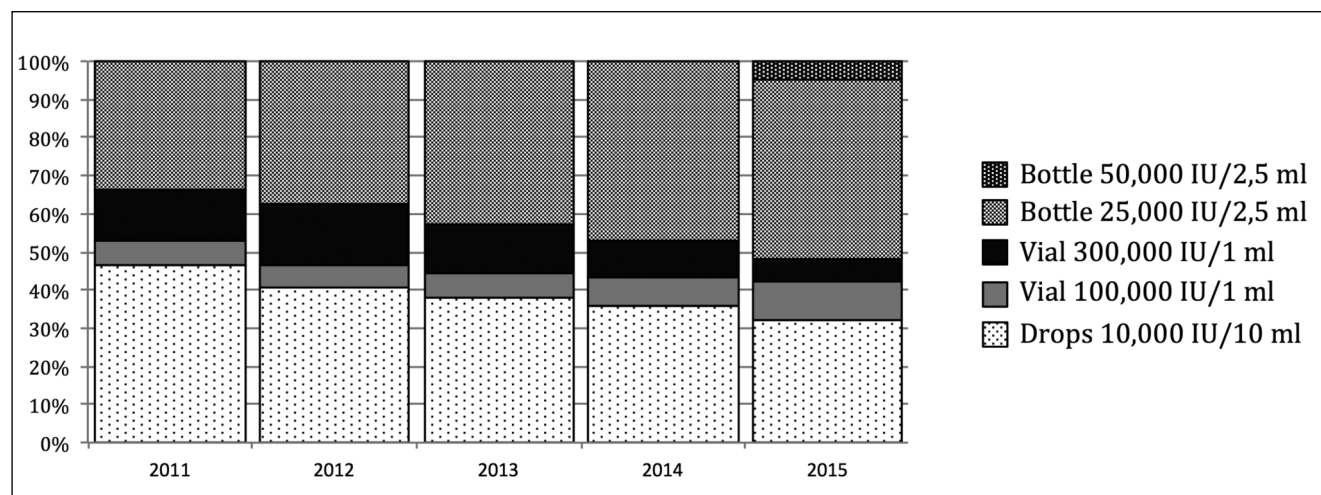


Figure 2 - Treatment modality with cholecalciferol supplements in the years in Region of Tuscany in the years 2011-2015 in the total population of hip fracture patients receiving vitamin D supplements. Data referring to the 50,000 IU cholecalciferol bottle were obtained just for 2015, since its introduction on the market.

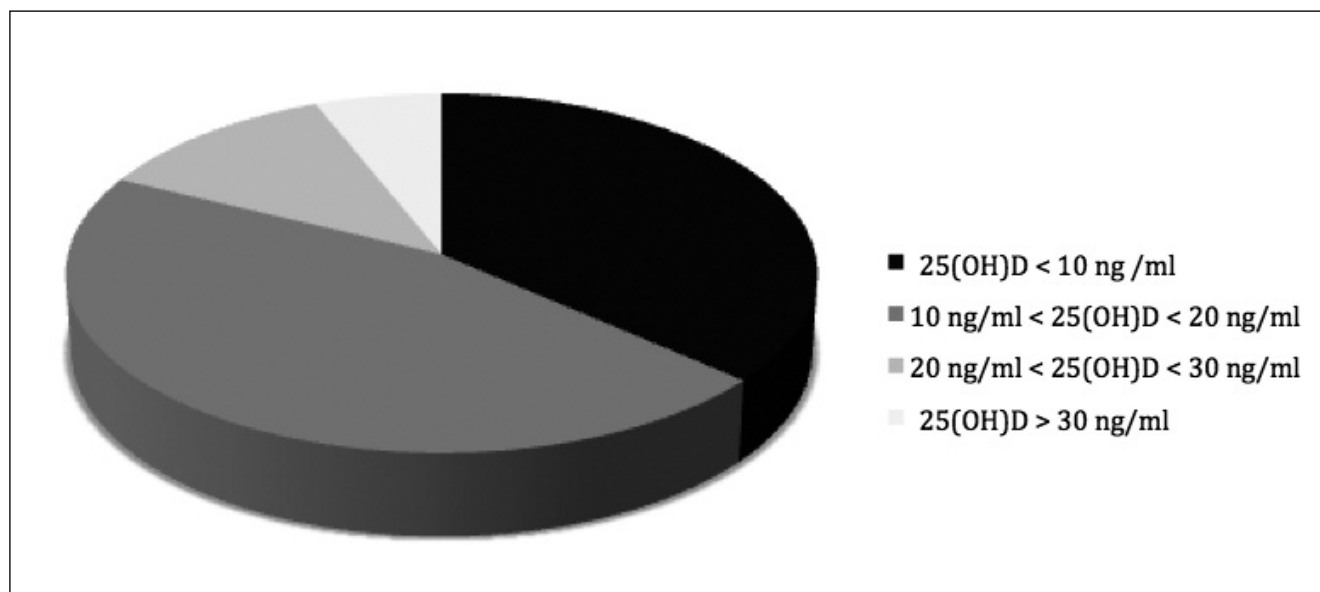


Figure 3 - Vitamin D status in a population hip fracture patients (n 254) evaluated soon after the fracture event (up to 3 months after hip fracture), at the first evaluation in a tertiary referral center with a fracture liaison service (University Hospital of Florence): proportion of patients with serum 25(OH) vitamin D [(25(OH)D] levels above 30 ng/ml (vitamin D sufficient), between 20 and 30 ng/ml (vitamin D insufficient), between 10 and 20 ng/ml (vitamin D deficient) and below 10 ng/ml (severely vitamin D deficient).

vised in these patients at high risk for further fractures, increased significantly within the year after the fracture, but it plateaued at around 30-35%. Still, 7:10 patients did not receive any vitamin D supplement at one year after the fracture and, likely, did not take any osteoporotic drug. This trend was maintained for all the 5 years of observation. The slight increase in the number of patients prescribed with vitamin D supplements in the first months after hip fracture might refer to the group of subjects appropriately referred to fracture liaison services activated within the hospitals where the orthopedic treatment for hip fracture was first performed. Indeed, group of patients can be appropriately referred to these services for the commencement of programs of secondary prevention of re-fracture (14). These procedures have to be encouraged and reinforced in order to address these patients towards effective programs of secondary prevention against refracture. The retrospective analysis on a subgroup of patients referred to such a service within the hospital soon after the fracture, demonstrate that even in a Mediterranean country such as Italy almost a half of patients experiencing a hip fracture is severely vitamin D deficient and only less than 10% have serum 25(OH)D levels above 30 ng/ml, which is considered the threshold to be achieved in subjects at high risk for fracture (15). Since vitamin D sufficiency is required to begin osteoporotic therapy, given the high prevalence of vitamin D deficiency in elderly people throughout the year even in Mediterranean countries such as Italy, elders experiencing a major osteoporotic fracture such a hip fracture or at high risk for fracture should receive vitamin D supplementation straight away, despite waiting for the determination of serum 25(OH)D levels (7, 15-17). In the retrospective survey, only 15.0% of patients received cholecalciferol at the time of the fracture event. Since these patients were addressed to the secondary prevention programs within the fracture liaison service in tertiary referral centers, they were then prescribed or reinforced with vitamin D supplements in order to later support osteoporotic therapy. In a lon-

gitudinal analysis (data not shown), almost all patients were assuming vitamin D preparations one year after hip fracture, demonstrating the high adherence to this supplement.

Cholecalciferol alone was by far the most employed vitamin D supplement in patients with hip fracture, and its use further increased in the 5 years of the study, reflecting the trend in the general population (6). In parallel, the use of cholecalciferol in association with calcium salts has significantly decreased over time, reflecting the substantial reduction of the use of calcium supplements in the last years because of side effects and/or the fear for possible increased risk for vascular calcifications. Also cholecalciferol in association with alendronate has decreased, although not significantly, and this may be a sign of the constant reduction of the usage of anti-osteoporosis drugs, even in patients at high risk for fracture (18).

Interesting results were observed regarding the way of administration of cholecalciferol alone. While in 2011 the use of drops of cholecalciferol was the preferred way of vitamin D supplementation, an increase in the use of 25,000 IU single-dose cholecalciferol, usually administered monthly, was documented, so that it has progressively become the supplement of choice in the whole population of patients with hip fracture during the years of the survey. Remarkably, the use of high concentrated cholecalciferol supplements (300,000 IU vials) has gradually decreased. This may be due to the increased awareness of the possible side-effects (i.e. falls) of high doses of vitamin D<sub>3</sub> (19). At the same time, a rise in prescriptions of 100,000 IU cholecalciferol vials has been recorded. All in all, the use of high concentrated forms of cholecalciferol remains low.

## Conclusion

Vitamin D inadequacy is highly prevalent in patients experiencing a major osteoporotic fracture such a hip fracture. The

use of vitamin D supplements is low in patients admitted to surgical departments for the treatment of hip fractures and remains low after the event. The results of this study performed in a Mediterranean region confirm previous results obtained in other countries.

There is therefore the need to reinforce the use of vitamin D, along with proper nutritional advice for sufficient calcium intake, for optimal musculoskeletal health and prevention programs. Fracture liaison services activated in the hospital taking care of the hip fracture patients, along with specific educational interventions for the patients themselves and general practitioners, can be the turning point to ameliorate vitamin D and nutrition status in this category of subjects. These interventions are a good start for commencing efficacious programs against re-fracture to decrease further disability and decreasing costs for the individuals and the community.

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