Native vitamin D optimizes anti-osteoporotic medication effects

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INTRODUCTION

Current treatments for osteoporosis use extremely effective drugs to reduce fracture risk [1]. It is well known, however, that in common clinical practice the expected therapeutic effect might not correspond to the one actually obtained. In fact, some patients have a suboptimal response to treatment in terms of fracture reduction and risk.

Such clinical picture is also known as inadequate response to anti-fracture therapy [2]. The possibility of an inadequate response to treatment seems to be correlated to multiple factors, including the advanced age of the patient, a non-optimal treatment compliance, a very high fracture risk at the beginning of treatment, and many others [2]. Nevertheless, for many years it has been known that untreated hypovitaminosis D is able to reduce the effects of osteoporotic medication in a clinically significant way.

THE ROLE OF HYPOVITAMINOSIS D AND OF ITS CORRECTION WITHIN OSTEOPOROTIC TREATMENT

The first evidence for the prevalence of hypovitaminosis D in patients treated for osteoporosis dates back several years [3]. A study on 1500 American women with postmenopausal osteoporosis, undergoing treatment to prevent fragility fractures, indeed showed that approximately 50% of these subjects had serum levels of 25(OH)VitD < 30 ng/mL and that about 10% had levels of 25(OH)VitD < 15 ng/mL. It is known that such low levels may be responsible for a skeletal clinical picture in which osteomalacia overlaps with osteoporosis [4]. It is not surprising, then, that hypovitaminosis D, if not corrected, might represent a risk factor for possible inadequate response to treatment.

Over the years, this hypothesis has been carefully explored in several studies, most of them conducted in Italy. Adami et al. showed that of the 900 subjects participating in the ICARO study treated with anti-osteoporotic medication, 25% had an inadequate response to treatment, which was defined as the occurrence of a new vertebral or non-vertebral fracture within 6 months from the beginning of the treatment [5]. This suboptimal response can be explained, in part, by the lack of a concomitant administration of calcium and vitamin D, an absence which could double fracture risk in these patients [5].

Another study by the same author provided even more interesting results [6]: in a population of about 1,500 women with postmenopausal osteoporosis undergoing treatment with anti-osteoporotic agents (with an adherence > 75%) for 13.1 months, the impact of vitamin D repletion was evaluated compared to its deficiency [serum 25(OH)VitD < 50 nmol/L] in terms of variations in bone density and risk of incident fractures. Less than 30% of the participating subjects in the multicentric Italian study were taking > 600 IU/day of vitamin D. Bone density increase was significantly higher in subjects with normal vitamin D serum levels and substantially absent in those with vitamin D depletion. Vitamin D depleted subjects had nearly double the risk of experiencing a new fracture compared to those with vitamin D repletion, even after adjusting for all available confounding factors [6].

Similar results were reported in a subsequent study in Spain on women with postmenopausal osteoporosis undergoing treatment with oral bisphosphonates and examined for about 12 months [7]. Even though there were no differences in the risk for new fragility fractures, patients with serum levels of 25(OH)VitD > 30 ng/mL showed an improvement in bone density, which was three times higher compared to patients with lower 25(OH)VitD levels dur-

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ing treatment. Almost identical results were reported in an American study conducted in the same period on 200 women with postmenopausal osteoporosis undergoing treatment with oral and intravenous bisphosphonates; in this case, the definition of inadequate response to treatment was based on bone density loss and on the occurrence of new fractures during treatment [8]. Patients with a mean 25(OH)VitD ≥ 33 ng/mL had approximately 4.5-fold greater odds of a favorable response to therapy compared to those with lower levels. More consistent results were seen in two subsequent studies by Spanish authors. These trials examined very large samples of subjects and included only those with high compliance to anti-osteoporosis treatment. In these cases, the definition of inadequate response to treatment was only based on the occurrence of new fractures during treatment [9, 10]. In the first study, subjects with inadequate response to treatment had lower levels of vitamin D with respect to the population that had not experienced incident fractures, and double the proportion of subjects with levels of 25(OH) VitD < 20 ng/mL (49.2% *vs* 26.0 %, respectively) [9]. The second study screened about 7,500 subjects undergoing treatment with oral bisphosphonates [10]. Even with a compliance > 80%, fracture risk while in treatment was 2.69 times higher in subjects with vitamin D deficiency.

Additional evidence of equal significance then led to a more refined definition of the importance of correcting hypovitaminosis D in subjects undergoing anti-osteoporosis treatment. Nurmi-Luthje et al. investigated which factors could predict mortality following hip fracture in the elderly [11]. They highlighted that osteoporosis treatment associated with calcium and vitamin D intake could reduce mortality after hip fracture in both genders. At 36 months, they observed a 43% reduction in mortality in females who used calcium and vitamin D in concomitance with anti-osteoporotic drugs. Among 23,615 patients with a mean age of roughly 78 years who had suffered hip fracture, mortality within five years after the fracture was about 25% lower in subjects treated with calcium and vitamin D (or only with vitamin D) and in subjects who underwent therapy for the prevention of osteoporotic fractures, compared to untreated patients. The reduction was roughly 28% in subjects who combined anti-osteoporotic medication with vitamin D, compared to untreated ones [12].

THE MOST RECENT DATA FROM ITALY

Given the great interest in the data discussed here, we performed a study in order to verify whether calcium and/or vitamin D intake had an effect on anti-osteoporotic treatment in terms of the occurrence of new fractures and all-cause deaths [13]. Our investigation involved a sample of elderly persons from different Italian regions and with a prior fragility fracture.

Data were obtained from administrative databases (hospital discharge forms, medical exemption certificates and use of medicines prescribed through the National Health Service) of five Italian Local Health Boards (ASLs): Naples 3 South, Pescara, Udine, Verona and Frosinone. Data analyzed involved 3.3 million patients, representing about 5% of Italy's population. The study also included 3,475 patients, age ≥ 50 years, with both hip or vertebral fracture and concomitant osteoporosis, who were examined between January 2011 and December 2015.

On the basis of these same databanks, patients were characterized according to whether they were undergoing any type of pharmacological treatment as well as to the presence and degree of comorbidity during the year prior to the fracture. The same patients were followed for at least one year after the occurrence of their first fracture (the reference date), with the aim of assessing the incidence of new fractures or of death by any cause.

Participants in this study were elderly; after the occurrence of their first fracture, almost half (41.5%) were still untreated for osteoporosis. Patients who were untreated after their first fracture were older than treated ones (83.6 ± 8.7 *vs* 78.2 ± 8.7 years, p < 0.001). Among treated patients, 83.6% were taking those medications recommended by AIFA (the Italian state drug agency) in note 79, together with vitamin D and calcium supplementation, while only 16.4% were taking note 79 AIFA medications only. Patients following the combined therapy had a higher rate of adherence than those taking only the medications (Fig. 1).

Patients treated for osteoporosis after their first fracture had a lower likelihood of new fracture occurrence than untreated subjects (Fig. 2A). Cox analysis, adjusted for all possible confounding factors, demonstrated that treated patients had a 44.4% lower risk of new fracture compared to untreated subjects (HR = 0.556, 95% CI = 0.420-0.735, p < 0,001). Even more interesting is that subjects following the combined treatment (AIFA note 79 medications together with vitamin D and calcium supplementation) had a significantly lower risk of new fracture occurrence compared to those patients taking only the AIFA medications (Fig. 2B). The combined therapy was associated with a risk reduction of 64.4% for new fractures with respect to those patients who only used drugs for osteoporosis (HR = 0.356, 95% CI = 0.237-0.533, p < 0.001).

Analysis of all-cause deaths also produced interesting results. Patients treated for osteoporosis after their first fracture had a significantly lower all-cause mortality risk than those who were untreated (Fig. 3A). Cox analysis, again adjusted for all possible confounding factors, demonstrated that treated patients had a 64% lower mortality risk compared to untreated subjects (HR = 0.360, 95% CI =

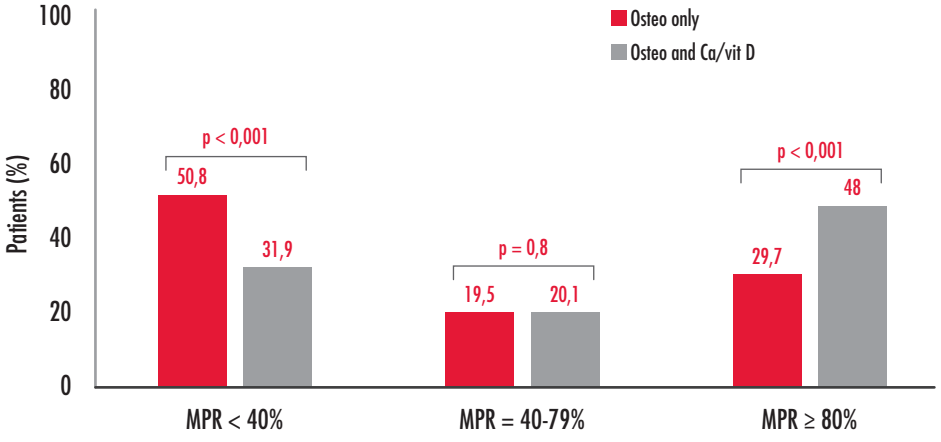

FIGURE 1.
Adherence to treatment during follow-up.

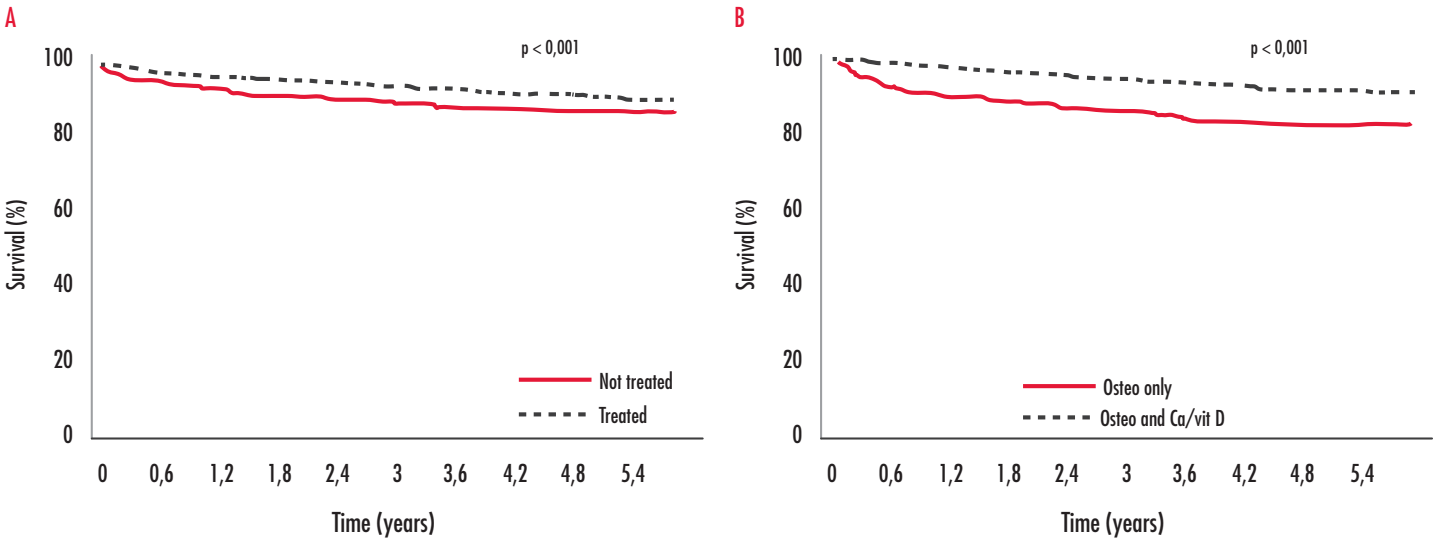

FIGURE 2.
Survival curves (Kaplan-Meier) without subsequent fracture in patients with previous fracture. **A)** Patients treated with osteoporosis medications *vs* not treated patients. **B)** Patients treated with AIFA note 79 medications only (osteo only) *vs* patients treated with AIFA note 79 medications and calcium/vitamin D (osteo and Ca/vit D).

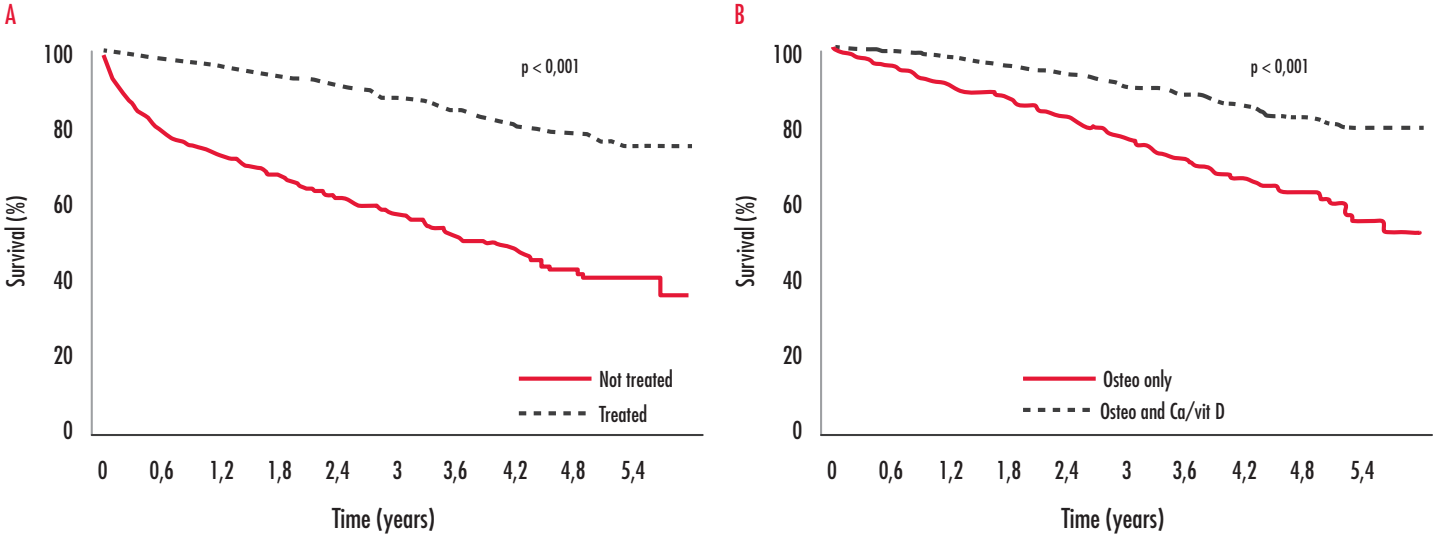

FIGURE 3.
Survival curves (Kaplan-Meier) for all-cause mortality in patients with previous fracture. **A)** Patients treated with osteoporosis medications *vs* not treated patients. **B)** Patients treated with AIFA note 79 medications only (osteo only) *vs* patients treated with AIFA note 79 medications and calcium/vitamin D (osteo and Ca/vit D).

0.310-0.418, p < 0.001). In addition, subjects following the combined therapy had a lower all-cause mortality risk than those patients taking only the AIFA note 79 medications (Fig. 3B). The combined treatment was associated with a 53% reduction of mortality risk with respect to those subjects who used only drugs for osteoporosis (HR = 0.471, 95% CI = 0.356-0.623,p < 0.001).

CONCLUSIONS

Osteoporosis treatment is without doubt associated with a significant reduction of the risk for new fractures, especially when used in high-risk individuals, such as those with previous fractures. An important additional datum in this regard, which has forcefully emerged from real-world evidence studies, shows that death after fracture also appears to be reduced if osteoporosis therapy is used. A more recent but equally clear and important datum coming from the literature is the fact that vitamin D has a significant beneficial effect in enhancing the anti-frac-

ture effect of anti-osteoporotic drugs and contributes to further reducing mortality due to hip fracture.
Although further investigations are needed to clarify the possible effects of vitamin D on patient survival, these data consolidate and reinforce the importance of correcting hypovitaminosis D in subjects with a high risk of fragility fracture.

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