Editorial
Future Rheumatology

Vitamin D and response to treatment in postmenopausal osteoporosis

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"The impact of vitamin D deficiency on the response to treatment in postmenopausal osteoporosis has been occasionally underestimated."

During the last two decades, a number of drugs have been registered for the treatment of both postmenopausal and glucocorticoid-induced osteoporosis, and this has been based on many randomized clinical trials (RCTs) demonstrating their ability to reduce fracture risk [1]. The registration of other formulations of the same drugs were achieved by the so-called 'bridging' clinical trials, with bone mineral density (BMD) changes as the primary end point.

In all of these clinical trials, the patients were recruited only if 25-hydroxyvitamin D levels (25OHD) were within the normal range, and vitamin D supplements were provided throughout the clinical trial, with a careful monitoring of treatment compliance.

Such clinical settings, characterized by levels of 25OHD well above the lower normal range, are rare in routine clinical practice for a number of reasons. According to several studies, 40–100% of elderly women and men have a vitamin D deficiency [2]. These proportions are likely to be considerably higher, and vitamin D deficiency more severe, among people living in nursing homes. The proportion of individuals with vitamin D deficiency rises with aging, and the level of 25OHD is directly related to bone mass, fracture incidence and frailty [3]. The patients receiving treatment for osteoporosis in a routine setting are not only osteoporotic, but also often older and more frail than those recruited in clinical trials. Thus, people placed on pharmacological treatment for osteoporosis are likely to be at the highest risk of vitamin D deficiency.

More than 50% of postmenopausal women taking medications for osteoporosis were found to have suboptimal levels of 25OHD below 30 ng/ml (75 nmol/l) in the USA [4]. In Italy, 35% of the patients receiving pharmacological treatment for severe osteoporosis and followed by qualified osteoporosis centers had vitamin D deficiency [5]. These high proportions of patients on pharmacological treatment for osteoporosis with vitamin D deficiency may sound somewhat surprising, since all guidelines recommend that any pharmacological intervention should include calcium and vitamin D supplements. However, the implementation of these guidelines are hampered by a number of factors.

The definition of vitamin D deficiency has been changed only recently [6], and many laboratories still report normal levels of 25OHD to be those greater than 10 ng/ml (25 nmol/l), which are totally inadequate for bone health. The messages coming from the literature are somewhat confusing (see below for an example), and the acquaintance of guidelines is rather poor. Formulations combining calcium salts with vitamin D are typically used in osteoporosis. The treatment adherence to these formulations is modest as a result of the poor tolerability to calcium [7]. The consequence of this is that many patients receive neither calcium nor vitamin D. Providing adequate calcium intake is a puzzling problem for the many patients who are intolerant to both dairy products and calcium supplements. We have recently shown that an inadequate calcium intake can be compensated by higher doses of vitamin D supplements [8]. Thus, in patients in whom it is extremely difficult to bring calcium intake to the recommended amounts, a possible partial solution may be to increase vitamin D intake to achieve 25OHD levels of above 50 ng/ml (125 nmol/l), rather than the recommended 30 ng/ml (75 nmol/l).

The impact of vitamin D deficiency on the response to treatment in postmenopausal osteoporosis has been occasionally underestimated. For example, from a recent *post-hoc* analysis of the Multiple Outcome of Raloxifene Evaluation (MORE) trial, it was concluded that vitamin D

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insufficiency does not affect the BMD response to raloxifene [9]. The BMD changes were analyzed according to individual 25OHD levels as measured at the time of randomization, and they were found to be somewhat greater among vitamin D insufficient patients. The most obvious interpretation of this finding is opposite to that anticipated by the title of that paper – patients with vitamin D insufficiency are expected to exhibit greater changes in BMD from the vitamin D supplementation provided during clinical trials than people with normal 25OHD levels. In the Incidence and ChAracterization of inadequate clinical Responders in Osteoporosis (ICARO) study [10], we assessed the rate of inadequate clinical response to treatment in patients receiving treatment with antiresorptive agents (alendronate, risedronate and raloxifene) for severe osteoporosis. In patients not taking or noncompliant to supplements of calcium and vitamin D, the rate of clinical fracture was 98% higher than that observed in patients correctly taking vitamin D supplements. More recently, we evaluated treatment outcomes after at least 1 year therapy with antiresorptive agents [5]. A third of these patients were found to be vitamin D deficient. In these patients, BMD slightly decreased during the first year of observation, while it rose by approximately 2% in vitamin-D-replete women. It was also observed that the proportion of patients with incident clinical fracture was almost double in vitamin-D-deficient as compared to vitamin-D-replete women. Similar results on BMD changes have also been reported by Deane *et al.* [11].

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In conclusion, undiagnosed vitamin D deficiency is frequent even among patients receiving pharmacological treatment for osteoporosis. Vitamin D deficiency is associated with the complete abolition of the benefits expected from osteoporosis therapy, and is also likely to be associated with an increased risk for a number of severe conditions such as cancer and cardiovascular diseases [2]. Educational intervention that aims to increase awareness of the epidemiology and clinical consequences of vitamin D deficiency in osteoporotic patients is highly warranted.

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