



## 27th Annual Meeting of the American Society for Bone and Mineral Research

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### Essential Role of Vitamin D in the Management of Osteoporosis

**Nashville** - Often overlooked in the prevention and management of osteoporosis, vitamin D inadequacy in fact plays a major role in the bone-wasting condition and the risk of associated fractures. Because it stimulates calcium absorption, inadequate levels of vitamin D lead to impaired calcium absorption and a compensatory increase in parathyroid hormone, resulting in increased bone resorption and accelerated bone loss (Prince et al. *J Bone Miner Res* 1995;10(6):835-42, Brazier et al. *J Bone Miner Res* 1995;10(11):1753-61). A cross-sectional study of healthy postmenopausal women found that 71% had serum levels of 25-hydroxy-vitamin D [25(OH)D] of <50 nmol/L (Bhattoa et al. *Osteoporosis Int* 2004;15(6):447-51). In a study of elderly patients in Italy, 98% had undetectable levels (<5 nmol/L) of 25(OH)D (Passeri et al. *J Clin Endocrinol Metab* 2003;88(11):5109-15). A recent study of North American postmenopausal women receiving treatment for osteoporosis revealed a 52% prevalence of suboptimal 25(OH)D levels of <75 nmol/L (Holick et al. *J Clin Endocrinol Metab* 2005;90(6):3215-24). Investigators in Italy found a 76% prevalence of vitamin D inadequacy among women with osteoporosis (Isaia et al. *Osteoporosis Int* 2003;14(7):577-82). A study involving patients with a history of fractures or falls showed that 97% had 25(OH)D levels <75 nmol/L and another study showed that 72% of such patients had levels <50 nmol/L (*J Bone Miner Res* 2004;19(suppl 1):S433, Dhesi et al. *Age Aging* 2002;31(4):267-71). New data reported here at the American Society of Bone and Mineral Research annual meeting provided additional insight into the role of vitamin D in bone health and pathology.

Investigators in a multinational study documented vitamin D (Vit D) inadequacy as a worldwide problem. The study involved 2102 postmenopausal women with osteoporosis from 18 countries, representing Europe, Latin America, Asia, the Middle East and the Pacific Rim. The mean age of the group was 67.2 years, with 39% who reported taking Vit D supplements and 79% taking prescription medication for osteoporosis, reported Dr. Paul Lips, Vrije University Medical Centre, Amsterdam, The Netherlands.

The mean serum level of 25(OH)D was 27. Vit D inadequacy was identified as <75 nmol/L, and on the basis of that cut-off, 62% of the women had Vit D inadequacy. Among geographic regions represented in the study, the prevalence of Vit D inadequacy ranged between 53% in Latin America and 54% in Europe to 81% in the Middle East. Parathyroid hormone (PTH) values began to increase at 25(OH)D levels of ≤75 nmol/L, supporting the use of that cut-off as Vit D inadequacy. "We found high rates of Vit D inadequacy in all geographic regions, irrespective of latitude or season," reported Dr. Lips. "The results emphasize the need to make physicians and patients more aware of the problem and the need for Vit D supplementation in postmenopausal women with osteoporosis."

#### Vitamin D Inadequacy

Fracture is a potential consequence of Vit D inadequacy, as demonstrated in a study involving 548 elderly patients (mean age 84 years) presenting with hip fracture, 50 with non-vertebral fragility fracture. The mean 25(OH)D level in the hip fracture patients was 10.3 ng/mL. Review of various cut-off points showed that 97.8% had 25(OH)D levels <75 nmol/L, 91.7% had levels <50 nmol/L and 74.7% had levels <25 nmol/L. Patients with nonvertebral fragility fractures had a mean 25(OH)D level of 46 nmol/L and evaluation of the same cut-off points revealed rates of 82%, 72% and 24%, respectively, for the different definitions of Vit D inadequacy. "The results confirm near-universal Vit D inadequacy in this population of elderly patients with hip fracture, regardless of whether a 50 nmol/L or 70 nmol/L threshold is used to diagnose inadequacy," noted Dr. Stephen Gallacher, Southern General Hospital, Glasgow, UK. "We found no seasonal variation in serum Vit D levels. Given the absence of any clear age, sex or seasonal explanation for differences in Vit D, it is possible that Vit D inadequacy is specifically serving as a marker of hip fracture risk."

Two other studies provided additional evidence of the association between Vit D inadequacy and fracture. One study evaluated the association in 1311 community-dwelling individuals aged 65 years and older. Almost half the population (48%) had 25(OH)D levels <50 nmol/L and 11.3% had levels <25 nmol/L, reported Dr. Natasja Van Schoor, Vrije University Medical Centre. One or more fractures occurred in 132 patients, 115 of whom had osteoporotic fractures. Overall, a 25(OH)D level <30 nmol/L was associated with 1.69 times greater risk of fracture compared to higher levels. An analysis of the risk of osteoporotic fracture associated with a 25(OH)D level <30 nmol/L revealed an odds ratio (OR) of 3.28 for patients aged 65 to 74 years, whereas older patients did not face an increased risk (OR 1.09).

In the second study, Japanese investigators measured 25(OH)D in 70 elderly (mean age 84 years) hip fracture patients, in most cases within an hour of presentation. The mean 25(OH)D level was 33.25 nmol/L. The “extremely low” 25(OH)D levels were accompanied by elevated PTH levels (62.8 pg/mL), suggesting that severe Vit D inadequacy is a common finding in patients with hip fracture, concluded the research team, representing institutions in Kumamoto, Kyoto, Osaka and Kobe.

### Maintaining Calcium Homeostasis

Although calcium and Vit D are important to bone health, adequate Vit D may contribute more to calcium homeostasis than does calcium intake, according to a study of 2300 adult residents of Iceland. Evaluation of calcium intake, 25(OH)D levels and serum PTH showed that the lowest PTH levels were found in patients who had 25(OH)D levels >45 nmol/L, irrespective of calcium intake. Among individuals with 25(OH)D levels of 25 to 45 nmol/L, serum PTH was increased compared to 25(OH)D levels >45 nmol/L only in people who had calcium intake <1200 mg/day. In people with 25(OH)D levels <25 nmol/L, serum PTH was increased compared to >45 nmol/L across the entire spectrum of calcium intake. “Our results suggest that Vit D adequacy may be more important than abundant calcium intake in maintaining desired values of PTH,” concluded Dr. Gunnar Sigurdsson, University of Iceland, Reykjavik. “Vit D seems to have a considerable calcium-sparing effect and as long as Vit D adequacy is ensured, calcium intake >800 mg/day may be unnecessary for maintaining calcium homeostasis.”

A small Japanese study provided evidence that Vit D inadequacy interferes with bisphosphonate therapy for osteoporosis and may account for at least some bisphosphonate treatment failures. The findings came from assessment of 24 postmenopausal women with osteoporosis, followed for 12 months during bisphosphonate treatment. Patients with serum 25(OH)D levels >37.5 nmol/L had suppression of the bone turnover marker urinary NTX, but women with lower 25(OH)D levels did not. Patients with the higher serum 25(OH)D levels also had significantly greater increases in lumbar spine bone mineral density ( $P<0.01$ ).

“These results suggest that Vit D inadequacy could be one cause for nonresponse to treatment of osteoporosis,” observed Dr. Muneaki Ishijima, Juntendo University School of Medicine, Tokyo, Japan. “We have to pay more attention to the Vit D status of postmenopausal women in the treatment of osteoporosis. The effort is needed to obtain a more adequate effect of treatment of osteoporosis.”

Good rationale exists for inclusion of Vit D with a weekly bisphosphonate dose, according to Dr. Sol Epstein, Mount Sinai School of Medicine, New York, New York, who conducted a literature review of the current status of osteoporosis treatment. It demonstrated general consensus that a serum 25(OH)D level of 75 nmol/L is needed to minimize PTH levels. Recent studies have suggested a 50% to 60% prevalence of Vit D inadequacy in osteoporosis patients, including many patients receiving treatment for the condition. Including Vit D with a weekly bisphosphonate dose would help ensure minimum recommended levels of 25(OH)D without compromising the therapeutic effect of the bisphosphonate, Dr. Epstein concluded.

### Combination Therapy

The rationale cited by Dr. Epstein was evaluated in a multinational clinical trial involving 708 postmenopausal women with osteoporosis. The patients were randomized to once-weekly bisphosphonate therapy or to a combination once-weekly tablet containing a bisphosphonate and Vit D 2800 IU for 15 weeks.

The amount of Vit D in the combination therapy is consistent with the National Osteoporosis Foundation recommendation of 400 to 800 IU/day and well below the 2000 IU/day established as the tolerable upper intake level for adults by the US National Academy of Sciences Institute of Medicine. A recent review of Vit D in health and disease states found no evidence that Vit D toxicity occurs with daily intake up to 10,000 IU (Heaney RP. *J Steroid Biochem Mol Biol* 2005 Jul 15;[Epub].

The mean serum 25(OH)D level was 55 nmol/L at baseline and declined to 46 nmol/L in the bisphosphonate-only group but increased to 57.75 nmol/L in patients who received the combination therapy, a 26% difference ( $P<0.001$ ), Dr. Epstein and colleagues reported. The combination reduced the rate of Vit D inadequacy (<22.5 nmol/L) by 91% and the proportion of patients with 25(OH)D levels <37.5 nmol/L by 64% compared to bisphosphonate alone ( $P<0.001$ ). Urinary NTX was suppressed to a similar degree in the two treatment groups. Antiresorptive efficacy, safety and tolerability also were similar in the two groups.

Collectively, the data reported at the ASBMR meeting underscored the role of Vit D in bone health. The studies corroborated previous investigations that documented high rates of Vit D inadequacy in patients at risk for osteoporosis and in those who already have the condition, increasing the risk of fracture. Including Vit D with weekly bisphosphonate therapy may help ensure adequate levels of 25(OH)D with no adverse effects on treatment efficacy. □

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