Oral Vitamin D May Avert Lupus Inflammation

Vitamin D supplements lower levels of inflammatory and hemostatic biomarkers.

BY DIANA MAHONEY

The science supporting vitamin D supplementation in lupus patients is catching up to the recommendation that all patients with the autoimmune disease increase their intake of the fat-soluble secosteroids.

Findings from a new study by Dr. Suzan Abou-Raya, professor of geriatric medicine at the University of Alexandria (Egypt), and her associates demonstrate that there is a high prevalence of vitamin D deficiency associated with an increased inflammatory burden and thrombophilic state in patients with systemic lupus erythematosus (SLE). The findings also suggest that oral vitamin D supplementation ameliorates chronic inflammatory and hemostatic markers in this patient group.

The use of supplementary calcium and vitamin D is routinely recommended for SLE patients to help minimize the bone loss and increased risk of developing osteoporosis associated with the disease and its treatment. Beyond supporting bone and mineral hemostasis, "vitamin D is now recognized as having additional pleiotropic roles," according to Dr. Abou-Raya. "We've learned that it has potent immunomodulatory properties that have promoted its potential use in the treatment of autoimmune conditions, including lupus."

The study was designed to evaluate vitamin D status in lupus patients and to assess changes in disease-related inflammatory and hemostatic markers before and after vitamin D supplementation.

To do this, Dr. Abou-Raya and her fellow researchers conducted a randomized, placebo-controlled trial comprising 148 males and premenopausal females who fulfilled the ACR (American College of Rheumatology) classification criteria for SLE. Also enrolled in the study were 75 lupus-free adults who served as controls and who matched the cases in age, sex, ethnicity, and body mass index.

Individuals with other inflammatory disorders and those taking supplemental vitamin D at the time of the study were excluded from participation.

Study patients were randomized in a 1:1 fashion to receive either 2,000 IU per day of oral cholecalciferol (vitamin D_3) or placebo for 6 months together with standard SLE treatment, Dr. Abou-Raya said.

Before and after 6 months of vitamin D supplementation, the investigators evaluated disease activity using the SLE disease activity index (SLEDAI), levels of serum 25-hydroxyvitamin D (25[OH]D) via DiaSorin's Liaison immunoassay, levels of proinflammatory cytokines interleukin-1 (IL-1), IL-6, IL-18, tumor necrosis factor (TNF)–alpha, C-reactive protein (CRP), and the hemostatic markers fibrinogen and von Willebrand factor (vWF).

Individuals with 25(OH)D levels of 10-30 ng/mL were classified as having vitamin D insufficiency and those with levels lower than 10 ng/mL were considered vitamin D deficient, she noted.

With respect to baseline demographics, the mean age of the SLE patients was 38.8 years and the mean disease duration was 5.2 years. The mean baseline vitamin D level in the SLE patients was 19.8 ng/mL, which was significantly lower than the mean 28.7 ng/mL in the control group, Dr. Abou-Raya reported. The baseline levels of the inflammatory and hemostatic markers were significantly higher in the SLE patients. "The overall prevalence of vitamin D insufficiency and deficiency, respectively, was 69% and 39%," she said.

At 6 months, "there was a significant decrease in levels of inflammatory and hemostatic makers in lupus patients who were supplemented with vitamin D" compared with patients who were given placebo together with ongoing therapy, Dr. Abou-Raya reported at the annual European Congress of Rheumatology in London.

After multivariate adjustment, the investigators observed a negative correlation between vitamin D levels and IL-1, IL-6, IL-18, TNF-alpha, CRP, fibrinogen, and vWF, "and lower vitamin D levels were associated with significantly higher SLEDAI scores," she said.

The results suggest that hypovitaminosis D contributes to a chronic inflammatory and thrombophilic state in SLE patients, said Dr. Abou-Raya. "The findings support the routine recommendation for oral vitamin D supplementation in these patients," she said.

Dr. Abou-Raya disclosed having no financial conflicts of interest related to her presentation. ■

MD Encouragement Improves Antiresorptive Tx Adherence

BY SHERRY BOSCHERT

EXPERT ANALYSIS FROM A MEETING ON OSTEOPOROSIS

SAN FRANCISCO – Talking to patients after they start an antiresorptive drug for osteoporosis is better than laboratory testing to convince them to stay on therapy, according to Dr. Douglas C. Bauer.

Bone mineral density testing determines the need for antiresorptive medication, but it's less helpful in monitoring the effects of treatment or adherence to therapy than is talking to patients. A test showing bone loss in the first year of treatment can confuse patients and does not necessarily mean they are not responding to treatment, said Dr. Bauer, professor of medicine and of epidemiology and biostatistics at the University of California, San Francisco.

Besides, most of the patients who stop osteoporosis therapy within 3 years do so within the first few months of treatment, so annual bone density testing is unlikely to improve adherence, he added.

Biochemical markers of bone turnover eventually may become the standard for monitoring treatment, "but we're not there yet," he said at the meeting, sponsored by the university.

Studies have shown that follow-up discussions after a patient starts antiresorptive medication is the factor that improves adherence, not measuring bone density or bone turnover markers.

Dr. Bauer said he tells patients not to expect routine follow-up bone density testing and asks about and encourages adherence at every patient visit. If a patient develops a fracture while on therapy or is considering a drug holiday after 5 years on alendronate, then he said he considers ordering follow-up bone mineral density testing. "There's a caveat: This may not be the right algorithm for tertiary care centers with severe or complex patients," said Dr. Bauer.

Although bone mineral density measurements are very precise, small differences in position or "noise" in the measures can produce apparent changes that are not clinically meaningful. To assess whether a change in bone density is "real," he recommended a useful equation called the "least significant change" equation: Multiply the coefficient of variations by three; if the sum is less than 4.5%, then the change may be due to chance.

For example, if the coefficient of variations in hip bone density is 1.5%, the least significant change is 4.5%. If a patient lost 3% in bone density, there is approximately a 10% chance that there was no change in bone density, he said.

"A somewhat more fundamental question is not just whether the measurements [are] real, but are they meaningful?" Dr. Bauer said.

Analyses of data from the Fracture Intervention Trial (FIT) show that patients on alendronate who lost up to 4% in total hip bone density in the 1-2 years of treatment still had 53% fewer vertebral fractures compared with their counterparts on placebo who lost similar amounts of bone density. Patients who lost up to 4% in spine density had 60% fewer vertebral fractures compared with their counterparts on placebo (Osteoporos. Int. 2005;16:842-8).

Then there's the "regression to the mean" argument that patients with an unusual response in the first year of antiresorptive therapy will develop a more typical response if treatment is continued, he said. A separate analysis of FIT data showed that 92% of patients who lost up to 4% of hip bone density in the first year of therapy gained a mean of nearly 5% in bone density in the second year of treatment (JAMA 2000;283:1318-21).

A more recent analysis of annual bone mineral density data in FIT showed that variation in the change in bone density over a 3-year period was mainly measurement-related, within-person variation.

Treatment-related, between-person variation played a much smaller role (BMJ 2009;338:b2266).

That helps explain how patients can "lose" bone density but still have fewer fractures, Dr. Bauer said. "It's reassuring that 98% on alendronate gained more than 0.02 g/cm^2" in FIT.

Antiresorptive therapy decreases biochemical markers of bone turnover, but there is a lot of biologic variability and no clear threshold for efficacy. Biochemical marker measurements could be used to identify nonadherence to treatment, but "it's cheaper just to ask," he said.

Biochemical marker measurements could identify nonadherence, but 'it's cheaper just to ask.'

DR. BAUER

In a study of 2,382 osteoporotic women starting a year of risedronate therapy, the women were randomized to get bone turnover markers measured at weeks 13 and 25 or to routine visits without marker measurements. The results showed no difference in adherence rates between the groups (J. Clin. Endocrinol. Metab. 2007;92:1296-304). In the marker measurement group, the adherence rate was 225% worse than in the control group if the marker results suggested a "bad" response to therapy (less than a 30% decrease in marker levels).

"That was unexpected," Dr. Bauer said. "Bone turnover markers by themselves are not helpful for increasing adherence" to therapy.

A separate randomized study of 75 women starting raloxifene treatment for low bone density randomized them to no monitoring; nurse visits at months 3, 6, and 9; or nurse visits plus bone turnover marker measurements. The nurse visits improved adherence to therapy compared with no monitoring, but biomarker measurements did not add anything to the nurse visits (J. Clin. Endocrinol. Metab. 2004;89:1117-1123). In general, approximately 30%-40% of patients stop taking antiresorptive drugs within 1 year, he said.

Dr. Bauer said he has received research funding from Amgen, Novartis, and Procter & Gamble. ■