

NEWS Commentary

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Suboptimal vitamin D levels common among women using osteoporosis therapy

Holick MF, Siris ES, Binkley N, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 2005;90:3215-3224.

More than half of North American women receiving osteoporosis therapy have low serum levels of vitamin D, according to this cohort study. Serum levels were obtained from 1,536 postmenopausal women older than age 55 years (mean age, 71) who had been receiving osteoporosis therapy for at least 3 months. Participants were evenly distributed across geographic regions based on latitude.

The mean serum level of 25-hydroxyvitamin D was 30.4 ng/mL. Approximately 52% of the women had suboptimal vitamin D levels, defined as below 30 ng/mL; 36% were below 25 ng/mL, and 18% were below 20 ng/mL. A multivariate analysis found eight variables associated with low vitamin D levels: older than age 80, nonwhite race, body mass index greater than 30 kg/m², use of ther-

apeutic agents known to decrease vitamin D levels, lack of exercise, physician not discussing the importance of vitamin D supplements with the patient, low education level (did not finish high school), and taking a daily vitamin D supplement with less than 400 IU.

Comment. Holick and colleagues provide important evidence that the public health message on the benefits of vitamin D has not been delivered successfully to physicians or patients. More than 50% of women already receiving therapy for the treatment or prevention of osteoporosis did not reach adequate serum 25-hydroxyvitamin D levels of 30 ng/mL (75 nmol/L). This is not surprising when 40% of women reported that they consumed less than 400 IU of vitamin D per day. In fact, despite being treated for osteoporosis, about one-third never discussed the importance of vitamin D to bone health with their physicians.

Based on recent evidence from two meta-analyses of well-designed randomized, controlled trials, consumption of at least 700 to 800 IU/day of vitamin D is needed for optimal prevention of both fracture [Bischoff-Ferrari *JAMA* 2005] and falls [Bischoff-Ferrari *JAMA* 2004]. A recent pragmatic trial suggests that even more vitamin D may be needed for individuals starting at 25-hydroxyvitamin D levels below 16 ng/mL (40 nmol/L) [Grant *Lancet* 2005] to reach the target serum 25-hydroxyvitamin D level of 30 ng/mL (75 nmol/L) [Dawson-Hughes *Osteoporos Int* 2005]. Every strategy for the prevention or treatment of osteoporosis should include vitamin D in a dose of at least 700 to 800 IU/day. This is especially attractive as vitamin D is well-tolerated and inexpensive.

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Recurrent vasomotor symptoms common for EPT users in WHI after study was discontinued

Ockene JK, Barad DH, Cochrane BB, et al. Symptom experience after discontinuing use of estrogen plus progestin. *JAMA* 2005;294:183-193.

Postmenopausal women who discontinue estrogen-progestogen therapy (EPT) are significantly more likely to experience recurrent vasomotor symptoms than placebo recipients, especially women who had symptoms before starting EPT, according to a cross-sectional survey of participants in the Women's Health Initiative (WHI). Approximately 8 to 12 weeks after the WHI trial was stopped, investigators mailed a questionnaire to postmenopausal women who were still taking the study pills, either placebo or EPT (0.625 mg/day conjugated equine estrogens plus 2.5 mg/day medroxyprogesterone acetate), when the trial was stopped. A total of 8,405 women completed the survey, a response rate of 89.9%. Their mean age at study discontinuation was 69.1 years. The primary end points were vasomotor symptoms and pain or stiffness.

After discontinuing the study pills, 21.2% of all EPT users experienced moderate or severe vasomotor symptoms compared with 4.8% of placebo users. Conversely, 36.7% of the EPT-withdrawal group and 59.5% of placebo recipients had no vasomotor symptoms. Among women who were experiencing these symptoms at baseline (n = 950), the rates for symptoms after therapy withdrawal were 55.5% and 21.3%, respectively. Among women with no vasomotor symptoms at baseline, 6.4% had symptoms after stopping EPT versus 1.2% of placebo recipients.

The adjusted odds ratio (OR) showed that the presence of symptoms at baseline was the most important factor influencing symptom occurrence after treatment withdrawal. Overall, 91.1% of the

EPT-withdrawal group who reported vasomotor symptoms had experienced them in the past. Among women who had these symptoms at baseline, the adjusted ORs were 5.36 (95% CI, 4.51-6.38) and 3.21 (95% CI, 2.90-3.56) for recurrence of vasomotor and pain or stiffness symptoms, respectively, for the EPT group compared with the placebo group. Women whose symptoms had been relieved by EPT also were likely to suffer symptoms after EPT withdrawal: OR, 5.82 (95% CI, 4.92-6.89) for vasomotor symptoms, and OR, 2.16 (95% CI, 1.90-2.40) for pain or stiffness.

Nearly half of the women with symptoms after treatment withdrawal reported use of at least one management strategy. Lifestyle management strategies included drinking more fluids, exercising, using fans, changing diet, using layered or cotton clothing, and drinking less caffeine or alcohol. Medical management strategies included talking to their clinicians, taking vitamin E, using vaginal lubricants, or taking other medications.

Comment. This is a very interesting paper, despite limitations described by the authors. In this study, women discontinuing EPT or placebo in the WHI trial were followed up 8 to 12 months later to determine their symptom profile and actions they had or had not taken.

It is certainly not surprising that more than half of the women with vasomotor symptoms at randomization to active EPT also reported these symptoms after discontinuing use of EPT. This has always been a dilemma of clinical practice — we advise women to take EPT for “the shortest duration,” etc, but if symptoms recur they may need to go back on treatment, and despite the best intentions, short-term therapy inevitably becomes long-term therapy. The problem remains as to how to deal with the situation.

To me, one of the most interesting findings is the withdrawal placebo effect. Women on placebo reported a 21.3% increase in symptoms after placebo was discontinued. We all know that studies of

postmenopausal therapies for vasomotor symptoms show a significant placebo response, with 30% to 50% of participants reporting reduced symptoms. What has not been reported before is the recurrence of symptoms with discontinuation of placebo, an area ripe for further research.

The 30% to 50% response with placebo is about the same level of response as reported in studies of soy, isoflavones, and other herbal products. It is, therefore, not surprising that the authors state, “The use of herbal or natural hormones by respondents in the current study was reported as one of the least effective strategies.” This supports recommending against expensive but largely ineffective over-the-counter remedies.

The overall lesson from this article appears to be a suggestion that part of the counseling of women considering ET/EPT is to note that symptoms may only be delayed, and they have at least a 50-50 chance of recurring when such therapy is discontinued.

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Studies find no substantial link between low androgen levels and sexual function, or androgen levels and natural menopause

Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. *JAMA* 2005;294:91-96.

Low serum androgen levels are not associated with low levels of female sexual function, according to this cross-sectional,

community-based study from Australia. Serum levels of total and free testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) were obtained from 1,423 randomly selected women aged 18 to 75 years, 85% of whom were older than 35. Women were excluded if they were pregnant, taking psychiatric medications or oral contraceptives, had abnormal thyroid function, or had diagnosed polycystic ovarian syndrome. Self-reports on the Profile of Female Sexual Function were used to assess sexual function.

A comparative analysis found no clinically significant relationship between low levels of total or free testosterone or androstenedione and sexual function scores. A low score for sexual responsiveness in women aged 45 years and older was significantly associated with the lowest DHEAS levels (odds ratio [OR], 3.90; 95% CI, 1.54-9.81). For women aged 18 to 44 years, the lowest DHEAS levels were significantly associated with low sexual desire (OR, 3.89; 95% CI, 1.27-11.67), sexual arousal (OR, 6.39; 95% CI, 2.30-17.73), and sexual responsiveness (OR, 6.59; 95% CI, 2.37-18.34).

Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab* 2005;90:3847-3853.

An analysis of data from the same study indicates that although serum androgen levels decline sharply in the early postmenopausal years, the decline is not a result of natural menopause, and the postmenopausal ovary appears to continue to produce testosterone. For this analysis, serum levels of total testosterone (T), calculated free T, DHEAS, and androstenedione were compared from both the study population and a reference population of 595 women free of factors known to affect androgen levels.

Serum levels of all four androgen measures declined with age ($P < 0.001$), with the decline being greater in the earlier decades than in later decades. In women aged 45 to 54 years, androgen lev-

els were similar in both premenopausal women and postmenopausal women of the same age, indicating that natural menopause does not have a significant effect on androgen levels. In postmenopausal women older than 55 years, those who had undergone bilateral oophorectomy had significantly lower levels of total T and free T (but not DHEAS or androstenedione) than those who had experienced natural menopause, suggesting ongoing ovarian production, the authors note.

Comment. While *endogenous* serum androgen concentrations (ie, testosterone or androstenedione) are highly correlated with erectile function in men, and some small studies demonstrate an association with female sexual function, other studies have suggested that endogenous estrogens are paramount in this regard. The improbability that any hormonal relationship determines sexual function might best be explained by the poor correlation between serum androgen levels and intracellular concentrations. Further, sexual function in human females is highly dependent on external, nonhormonal factors including prior sexual history, availability of a partner, emotional intimacy, privacy, mood, etc.

These two articles from an experienced group of Australian investigators describe the changes in endogenous androgens that accompany aging and the menopause transition, and whether these hormonal changes were associated with changes in sexual function. They did not find “clinically important” associations between these hormonal changes and sexual function, except in specific subgroups of women. Women aged 18 to 44 years with the lowest DHEAS levels had lower sexual desire, sexual arousal, and sexual responsiveness; women aged 45 years and older with the lowest DHEAS levels had lower sexual function.

While the “holy grail” of the psychoneuroendocrinologist would be to prove that a hormone (ie, an androgen)

could direct a behavior, the likelihood of making such a finding in this study seems extremely remote. Given the provisos listed above (eg, biological, psychological, social, situational) and the extremely complex nature of sexual function combined with the primitive nature of our instruments for assessing sexual function (ie, The Profile of Female Sexual Function), it is more surprising that these investigators found any correlations between the hormones and behaviors they assessed.

The absence of strong associations of hormones with aging or menopause should not be confused with the results of treatment studies of women with low sexual desire or other sexual dysfunctions. Several published, randomized, controlled trials indicate that *exogenous* testosterone in both oral and nonoral formulations have a positive effect on sexual function, primarily desire, arousal, and orgasmic response, in women after spontaneous or surgically induced menopause.

The studies under review here should also give the clinician great pause when considering whether to measure androgens in a clinical setting as an index or a marker of sexual dysfunction. Laboratory testing of testosterone levels, for example, should be used only to monitor for supraphysiologic testosterone concentrations before and/or during therapy, not to diagnose testosterone insufficiency or sexual dysfunction.

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The Role of Testosterone in the Treatment of Hypoactive Sexual Desire Disorder in Postmenopausal Women

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