Hormone therapy’s long-term effect on bone, vertebral fracture

Higher rate of vertebral fracture in group using hormone therapy after 20 years’ follow-up


Summary. This study assessed the incidence of vertebral fracture after 20 years’ follow-up in a group of women who used hormone therapy (HT) in early menopause versus another group who did not use HT. After 20 years, 49 women from a 1990 prospective study of 177 women aged 43 to 57 years that evaluated the effect of different HT regimens on bone were retrieved for this current study. Of the 49 women, 32 used HT (for an average of 5.5 y) and 17 did not—they constituted the control group. There was a higher rate of vertebral fracture in the group receiving HT ($P = 0.03$). Despite the drawback of small sample size, this data suggests that HT in the early years of menopause does not provide long-term protection from vertebral fracture after discontinuance.

Comment. In a utopia, we would prescribe a one-time treatment for those at risk of a chronic disease, and they would never suffer adverse effects. This concept works well for infectious diseases amenable to vaccines. Outside of the short-term use of oral contraceptives (with probable life-long reduction in ovarian cancer risk), there aren’t many noninfectious disease examples. In the bone turnover arena, there is some durable effect of bisphosphonates with prolonged use. In general, a large portion of fracture risk reduction is related to decrease in and duration of net bone loss.

With natural loss of estrogen after menopause, there is a significant increase in bone loss and increased risk of fracture. Delaying this bone loss with estrogen blunts the effect, but for how long? The National Osteoporosis Risk Assessment (NORA) study foreshadowed the answer, showing an increase in fracture risk in women with low bone mass who discontinued estrogen within 5 years, with an odds ratio of 1.65 compared with never users.

Two large observational studies have confirmed the positive effect of estrogen therapy on the risk of hip fracture followed by at least a loss of effect after cessation. In the postintervention follow-up of the Women’s Health Initiative, the original increase of 33% risk reduction turned into a nonsignificant increase after cessation. In the Kaiser Permanente study, not only was the protective effect lost as early as 2 years
after cessation of HT, but a significant increase in fracture risk similar in magnitude to the NORA findings was seen.5

The French E3N study demonstrated some durability in fracture reduction effect (all major osteoporotic fractures, including spine) with HT use greater than 2 years. The duration of the effect was dependent on duration of use (≥5 y) and time since cessation. The fracture risk generally returned to that of a nonuser by year 5, regardless of duration.6

Castello-Branco and colleagues accomplished the difficult task of a truly long-term observation rather than simple extrapolation. Although they pointed out potential confounders, this study group mirrors many of the real-world patients we see. The reality is that the mechanisms by which estrogen most likely reduces fracture risk are neither durable in the hip nor in the vertebrae, as demonstrated in this study. Given the effects by which estrogen likely affects bone metabolism, the lack of a durable effect seems biologically plausible.

The secondary observation of a statistically significant increase in vertebral fracture risk for those who took HT for 5 or more years in early menopause is interesting. Given the very small numbers, particularly in the Genant subgroups and without baseline radiographic studies to determine true prevalence in this small group, it is difficult to make a definitive statement of effect. But if the cessation of estrogen poses a greater risk for hip fracture,3,4,5,6 this study may simply be confirming the same effect in the vertebrae.

When we have sound scientific information to share with our patients, we have advanced. There shouldn’t be any value judgment placed on the outcome—the fact there was no durable effect of HT on vertebral fracture is neither good nor bad. It is simply information the patient and clinician can use to guide appropriate therapy and management.

References

Progression to at-risk obesity in perimenopausal women in SWAN and associated factors

Baseline impaired fasting glucose had the strongest association with risk of progression

Summary. Researchers examined women’s progression from a metabolically benign overweight/obese to an at-risk overweight/obese phenotype and factors associated with that progression over 7 years using discrete-time proportional hazard modeling on data from the Study of Women’s Health Across the Nation (SWAN). Of 866 metabolically benign overweight/obese phenotypes at baseline, 43% progressed to an at-risk phenotype—they had higher baseline body mass index (BMI) and a higher prevalence of cardiometabolic abnormalities, including elevated glucose, triglycerides, and blood pressure and low high-density lipoprotein cholesterol. Baseline impaired fasting glucose showed the strongest association with risk of progression, and physical activity played a protective role in decreasing risk of progression.

Comment. This analysis is quite timely and raises a number of important issues. First, there is little surprise that those women who progressed to the at-risk group had higher baseline BMI and more cardiometabolic abnormalities. Further, an increase in BMI was only modestly associated with a progression to the at-risk group, flying in the face of conventional wisdom that simply carrying excess fat confers an increased risk for cardiovascular morbidity and mortality. This leads to a question: why didn’t all the metabolically benign women become at-risk women?

Could these women comprise a new subset of overweight/obese categorized as “metabolically healthy”? Emerging evidence is indicating that this may well be the case as it relates to heart disease. Khan and associate’s SWAN analysis found that the greatest association with progression to the at-risk group was noted in women with baseline impaired fasting glucose, predisposing them to type 2 diabetes and increased risk for heart disease. Those who remained metabolically benign lacked this insulin resistance. Animal studies provide a possible explanation for this in the increased expression of vaspin, an enzyme that has been shown to increase insulin sensitivity and reduce food intake, in the insulin-sensitive group. In a novel study of bear hibernation, Nelson and colleagues detailed the metabolic and hormonal pathways in adipose tissue that allow a bear to be metabolically healthy during the overweight hibernation state. Indeed, there are also persons with a genetic abnormality who can maintain normal insulin sensitivity in the obese state. It appears, therefore, that being insulin sensitive confers some protection from cardiometabolic disease in those who are overweight/obese.

Outside of genetic endowment, what else can augment insulin sensitivity? Curiously, it is regular physical activity, the very element that the SWAN analysis pegged as the only protective lifestyle factor. Women who did not progress to being at-risk were more physically active. It is now clear that physical activity, independent of its effect on reducing adiposity, provides other beneficial effects such as optimizing blood sugar control and insulin sensitivity.

From this analysis, the practitioner can glean valuable insights to apply to the prevention and treatment of cardiovascular risk in women, especially those in perimenopause. First, women of all ages should be encouraged to maintain an active lifestyle. This means scheduled exercise as well as an increase in activities of daily living. Second, the practitioner should be able to provide appropriate referrals to licensed registered dietitians so that all women can learn basic nutrition education and nourish themselves with whole foods throughout their lifespan. Third, overweight/obese women need to be screened for glucose dysregulation as they enter the perimenopause. Identifying those with insulin resistance and other metabolic abnormalities should prompt a serious discussion about the need to incorporate nutrition and physical activity. Fourth, rather than depend on scale weight alone, women’s waist circumference should be measured because visceral adiposity is most highly
correlated with cardiovascular risk. Finally, an overweight/obese woman and her practitioner may become complacent if she demonstrates no insulin resistance and has less than two metabolic syndrome abnormalities. It is imperative to note that she is still at increased risk of other diseases and physical disability. Therefore, the practitioner should encourage at the very least no further weight gain, regular physical activity, healthy nutrition, and a gradual, sustainable reduction in excess body fat.

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References

**Sexual function with venlafaxine versus estradiol for hot flashes**

**Overall sexual function did not change in women on these medications for hot flashes**


**Summary.** This 8-week randomized, controlled trial of women aged 40 to 62 years compared sexual function between women taking 0.5 mg oral estradiol per day and 75 mg venlafaxine per day compared with placebo. Women were aged an average of 54.6 years (standard deviation, 3.8 y), 59% white, with an average of 8.1 daily hot flashes. Overall sexual function in women with hot flashes did not change over the 8 weeks with low-dose oral estradiol or venlafaxine. There was a subtle increase in desire with estradiol and decreases in orgasm and pain with venlafaxine.

**Comment.** The request to write a piece on the article by Reed and colleagues came at about the same time as the text *Health Humanities Reader*, edited by Jones, Wear, and Friedman, arrived at my office. As I browsed the chapter dealing with sex and gender education, it was striking how limited sex education was for many clinicians a little more than 45 years ago. In contrast, as I read the paper by Reed and colleagues, it was clear that we as clinicians today are better informed in the areas of human sexual wellness and dysfunction and expect a comprehensive degree of sexual function endpoints in clinical trials, such as this one comparing pharmacologic interventions and their effect on sexual function. Look back to 1968, the first year that a sex education course was formally offered at a US medical school. This offering was an elective course series of evening lectures that included topics such as sexual problems in the female, homosexuality, and marital counseling. Of interest, this elective, given at the Indiana University School of Medicine, did not come from a curriculum committee proposal but at the request of the second-year medical student class to the Dean of their school. Today, sexual health and dysfunction are topics not only addressed in medical school but also by professional societies and continuing professional educational activities.

This article by Reed and associates offers clinicians useful information regarding the sexual effects of two treatments for vasomotor...
symptoms, with the bottom line that there were no adverse sexual consequences reported with either 0.5 mg of oral estradiol daily or 75 mg venlafaxine daily. The domains of desire, arousal, lubrication, orgasm, satisfaction, and pain were examined in this trial, and these results can be used by clinicians to individually counsel patients when addressing their options for relief of vasomotor symptoms. However, although it is the expectation that most patients today will be informed about sexual health and function, it is important to note that some patients may still need basic sex education and counseling. Clearly, sex education, counseling, and research remain important topics of education and research in the healthcare field.

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Exogenous testosterone's effects in menopausal women: a matter of dosage?

In a short-term trial, only markedly supraphysiologic testosterone levels enhanced sexuality, lean body mass, and muscle strength


Summary. Although androgen administration can augment sexuality as well as musculoskeletal parameters in menopausal women, data are insufficient to address the dosages and serum levels of testosterone needed to achieve these benefits. Investigators randomized post hysterectomy menopausal women (mean total and free testosterone levels, 13.0 ng/dL and 2.2 pg/mL, respectively [below the range for healthy premenopausal women]) to 12 weeks of transdermal estradiol (0.05 mg daily) followed by 24 weekly intramuscular injections of placebo or testosterone enanthate at doses of 3.0 mg, 6.0 mg, 12.5 mg, or 25.0 mg while continuing transdermal estrogen.

In 62 evaluable women who received testosterone, total and free serum testosterone levels increased in a dose-dependent fashion. Among women randomized to the 25-mg (highest) dose, mean total testosterone serum level at 24 weeks was 210 ng/dL (5-6 times higher than values in healthy premenopausal women). Compared with women who received placebo, those who received the highest testosterone dose had better measures of sexual desire, arousal, frequency of sexual activity, lean body mass, and physical strength. Frequency of adverse effects was generally similar among groups; however, excess hair growth was significantly more common in women who received the two highest doses of testosterone.

Comment. This well-executed study confirms that, while testosterone can enhance sexuality and musculoskeletal parameters in menopausal women receiving estrogen, the levels needed to achieve these benefits are markedly supraphysiologic. The authors note that they did not recruit participants with low sexual desire; thus, it remains unknown whether lower doses of testosterone might provide benefits in women with baseline sexual dysfunction. In addition, this short-duration trial did not permit determination of cardiovascular risks or benefits associated with prolonged testosterone supplementation, underscoring the need for long-term randomized trials addressing safety concerns.

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Menopause Editor’s picks from August 2014

NAMS spotlights selections from the most recent issue of the Society’s official journal, Menopause, chosen by its editor in chief, Isaac Schiff, MD.

Epidemiology and spectrum of positive bacteriological culture in intrauterine fluid collected from women with postmenopausal bleeding.
Sik Wing Yeung, MBChB, MRCOG, Chun Wai Cheung, MBChB, MRCOG, Alyssa S.W. Wong, MBBS, MRCOG, Hiu Lan Fan, MBChB, MRCOG, Joyce H.Y. Chan, MSc, Daljit S. Sahota, PhD, and Terence T.H. Lao, MBBS, FRCOG, MD.

Post hoc analysis of the efficacy and safety of desvenlafaxine 50 mg/day in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder.
Susan G. Kornstein, MD, Anita Clayton, MD, Weihang Bao, PhD, and Christine J. Guico-Pabia, MD, MBA, MPH.

Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women.
David R. Walega, MD, Leah H. Rubin, PhD, Suzanne Banuvar, MPA, Lee P. Shulman, MD, and Pauline M. Maki, PhD.

New Member Forum on www.menopause.org

What are your clinical challenges with vertebral fracture? Post on our Member Forum to discuss August’s First to Know papers:
www.menopause.org/member-login?ReturnUrl=%2fforum

The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I Properly randomized, controlled trial.
Level II-1 Well-designed controlled trial but without randomization.
Level II-2 Well-designed cohort or case-control analytic study.
Level II-3 Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III Meta-analyses; reports from expert committees; descriptive studies and case reports.