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This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause and healthy aging. Each review has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Chrisandra L. Shufelt, MD, MS, NCMP, Chair-elect of the 2012-2013 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Shufelt.

## BMD screening to predict fracture

### *Repeat screening may not be necessary in adults untreated for osteoporosis*

Berry SD, Samelson EJ, Pencina MJ, et al. Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture. *JAMA*. 2013;310(12):1256-1262.

**Level of evidence: II-3.**

**Summary.** Do changes in bone mineral density (BMD) after 4 years help improve prediction of fracture risk beyond baseline BMD? To answer this question, this population-based cohort study of 310 men and 492 women (median age, 74.8 y) from the Framingham Osteoporosis Study used two measures of femoral neck BMD taken from 1987 to 1999.

Mean BMD change was  $-0.6\%$  per year; 76 participants had an incident hip fracture and 113 participants experienced a major osteoporotic fracture. A second BMD measure after 4 years, however, did not meaningfully improve hip or major osteoporotic fracture risk. Only 3.9% were reclassified as high risk, and the number reclassified as low risk declined by 2.2%. Thus, a repeat measure within 4 years may not be necessary in adults of this age untreated for osteoporosis.

**Comment.** This study adds to the growing body of literature questioning the usefulness of repetitive BMD screening tests. Patients at high

risk on the first screening were similarly high risk on the second screening, and those at low risk remained so. The results of another recent study<sup>1</sup> suggest that FRAX and BMD screening may miss as many as 10% of women with silent vertebral fractures who would benefit from treatment. Another study suggested that among women with T-scores better than  $-1.5$ , less than 10% would transition to osteoporosis within 15 years.<sup>2</sup> Results of studies such as this, along with the current report, suggest that short-interval BMD screening in women with normal bone mass or mild osteopenia ( $BMD > -1.5$ ) is unlikely to modify clinical practice.<sup>2</sup> Repeated and short-interval screening, therefore, may not be as useful as initially presumed.

Unfortunately, BMD screening and the FRAX assessment do not identify all patients with osteoporosis. Certainly, a routine patient screening with BMD should not occur more often than every 2 to 5 years; indeed, this article suggests that a single BMD measure in an older population may be sufficiently predictive on its own.

Currently, an ideal screening algorithm for osteoporosis is lacking. It is critically important, therefore, that clinicians use care in screening for and treating osteoporosis, using the current guidelines. In the meantime, further studies are needed to help identify which individuals are more likely to transition in a short time interval

to being high risk and hence may benefit from a shorter-interval screening test.

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#### References

1. Greenspan SL, Perera S, Nace D, et al. FRAX or fiction: determining optimal strategies for treatment of osteoporosis in residents in long-term care facilities. *J Am Geriatric Soc.* 2012;60(4):684-690.
2. Gourlay ML, Fine JP, Preisser JS, et al; Study of Osteoporotic Fractures Research Group. Bone-density testing interval and transition to osteoporosis in older women. *N Engl J Med.* 2012;366(3):225-233.

## Exercise may lessen CVD risk in postmenopausal women

### *Exercise improves antioxidant capacity and decreases body iron burden*

Bartfay W, Bartfay E. A case-control study examining the effects of active versus sedentary lifestyles on measures of body iron burden and oxidative stress in postmenopausal women. *Biol Res Nurs.* September 19, 2013. [Epub ahead of print]. **Level of evidence: II-2.**

**Summary.** This age-matched, case-control study examined the effects of active (n=25) versus sedentary (n=25) lifestyles in women aged 55 to 65 years. Outcomes were measures of body iron burden (total serum iron, transferrin saturation, and serum ferritin levels; glutathione peroxidase activity; and oxidative stress as quantified by 4-hydroxynonenal, malondialdehyde, and hexanal). In sedentary women, measures of body iron burden and oxidative stress were significantly higher, while red cell glutathione peroxidase activity was higher in active women. Exercise may lessen the

risk of developing CVD in postmenopausal women by improving antioxidant capacity and decreasing body iron burden.

**Comment.** The relationship of aerobic exercise to reduction in serum iron and ferritin has interested exercise physiologists for decades. Most studies have been performed in younger participants and revealed lower serum iron and ferritin in exercise-trained participants. Decrease in oxidative load and increase in reductive capacity and glutathione have been shown to be concomitant exercise derivatives.

Surprisingly, although the monthly blood and iron loss ceases with menopause, the effect of increased iron reserves in menopause has had little investigation. This study illuminates some of the metabolic effects of increasing iron and ferritin and the potential increase in oxidative stress with menopause. The findings indicate increased iron and oxidative stress with menopause, with mitigation of that effect by exercise. Blood analysis contributes to but cannot answer all our questions about this important menopausal issue.

A recent SWAN study by Kim and colleagues<sup>1</sup> presented a 5-year longitudinal analysis of premenopause through the menopause transition. Women showed a similar iron and oxidative load increase with menopause, which researchers correlated with increased insulin resistance. They postulated that the iron rise and oxidative stress resulted in insulin resistance. An alternative hypothesis might be that with estrogen decline, skeletal muscle atrophies.

If we recall that muscle is the largest reservoir of estrogen receptors in a woman's body, the loss of estrogen stimulation is associated with decline in muscle volume and function. Because lean body weight determines the daily caloric need for steady-state body weight, the menopausal muscle loss makes weight gain easier. With the increase in testosterone-to-estrogen ratio of menopause, the weight gain is more likely to be central obesity. The hourglass

shape of the menstruating woman becomes the apple shape of menopause. Central obesity is associated with increased products of inflammation such as interleukin-1, interleukin-6, tumor necrosis factor, and hepatic steatosis. Fatty liver is associated with increase in circulating iron and ferritin.

The findings reported by Bartfay and colleagues support the alternative hypothesis and lend credence to the potential of exercise to prevent the adverse changes of a sedentary menopausal lifestyle.

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#### Reference

1. Kim C, Nan B, Kong S, Harlow S. Changes in iron measures over menopause and association with insulin resistance. *J Womens Health (Larchmt)*. 2012;21(8):872-877.

## Diabetes and mortality in WHI women

*Mortality outcomes did not differ by racial subgroup when stratified by diabetes status*

Ma Y, Hebert JR, Balasubramanian R, et al. All-cause, cardiovascular, and cancer mortality rates in postmenopausal white, black, Hispanic, and Asian women with and without diabetes in the United States; the Women's Health Initiative, 1993-2009. *Am J Epidemiol*. September 17, 2013. [Epub ahead of print]. **Level of evidence: II-3.**

**Summary.** Using data from the Women's Health Initiative (WHI), researchers compared all-cause, cardiovascular, and cancer mortality rates in white, black, Hispanic, and Asian postmenopausal women with and without diabetes. Of 158,833 participants, 84.1% were white, 9.2% were black, 4.1% were Hispanic, and 2.6% were Asian. Within racial subgroups, women with diabetes had about a 2 to 3 times higher risk of all-cause, cardiovascular, and cancer mortality than did those without diabetes,

yet the hazard ratios for mortality outcomes were not significantly different among racial groups.

**Comment.** The diabetes epidemic is upon us, bringing the metabolic abnormalities associated with increased all-cause mortality and any number of morbidities, including cardiovascular disease, dementia, and several cancers. Underlying this disease state in most patients are the metabolomics associated with insulin resistance. For the last decade, diabetes has been classified as a coronary heart disease-risk equivalent, which puts all afflicted persons into a high-risk classification, qualifying them for aggressive therapies to attain stricter goals of therapy. Existing data indicate that diabetes-associated risk for women is greater than that for men and that racial and ethnic differences are at play, with higher risks in blacks and Hispanics than in whites and Asians. This new WHI data shed light for the first time on the mortality issue in postmenopausal women.

Although all postmenopausal women with diabetes must be advised of their high morbidity and mortality rate, the authors correctly conclude that clinicians should devote therapeutic energies to prevention of type 2 diabetes much earlier in life. Fortunately, it is now much easier for providers to predict which women are at increased risk of developing diabetes. The warning list includes features of the metabolic syndrome (increased waist size, hypertension, dyslipidemia, and dysglycemia, especially hypertriglyceridemia), a family history of diabetes, and a personal history of polycystic ovarian syndrome or a multitude of gestational issues (including hypertension, albuminuria, dysglycemia, diabetes, preeclampsia, eclampsia, small- or large-for-gestational-age babies, and preterm delivery). A very simple biomarker is an abnormal triglyceride and high-density lipoprotein cholesterol ratio (>3.5), with the caveat that insulin-resistant African Americans (including adolescents) may not have high ratios. Much data now even suggest that women and men

born of mothers who had pregnancy-related issues are also at increased risk of diabetes and its consequences.

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## For cardiovascular risk, not all oral menopausal estrogen formulations are alike

*Oral estradiol was safer than conjugated equine estrogens*

Smith NL, Blondon M, Wiggins KL, et al. Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. *JAMA Intern Med.* September 30, 2013. [Epub ahead of print].

**Summary.** Although many studies have compared cardiovascular risks in menopausal hormone therapy users versus nonusers, few data address the comparative safety of different oral estrogen formulations. Investigators conducted a case-control study of menopausal women taking oral estradiol (E2) or conjugated equine estrogens (CEE) from 2003 through 2009. Cases had incident venous thromboembolism (VTE), myocardial infarction (MI), or ischemic stroke; controls had no history of these cardiovascular events. Endogenous thrombin potential-based normalized activated protein C sensitivity ratio (nAPCsr), a measure that predicts VTE risk in the setting of estrogen use, was assessed in a subset of controls.

A total of 68, 67, and 49 cases of incident VTE, MI, and stroke were identified during the study period. More than 90% of participants were white; mean age varied from 63 to 68. In analyses adjusted for confounders such as body-mass index and smoking status, CEE use was associated with higher risk for VTE (odds ratio, 2.1;  $P=0.045$ ) and MI (OR, 1.9; not statistically

significant) but not ischemic stroke. Among controls, nAPCsr was higher in CEE users ( $P<0.001$ ), suggesting a greater tendency to clot.

**Comment.** Although oral estrogen may carry higher risk for venous thromboembolism than does transdermal estrogen,<sup>1</sup> many users of menopausal hormone therapy prefer oral formulations for their convenience (and because of concerns about patch adherence). Estradiol and conjugated equine estrogens may seem comparable with respect to efficacy for menopausal symptoms, but a 1-month supply of 1-mg E2 tablets costs US\$4.00 at some chain pharmacies whereas 0.625-mg CEE tablets cost \$84.92 (<http://www.goodrx.com/>). Accordingly, for menopausal women who opt to use oral estrogen formulations, E2 is a wise choice from the perspective of both cost and cardiovascular safety.

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### Reference

1. Committee on Gynecological Practice. Postmenopausal estrogen therapy: Route of administration and risk of venous thromboembolism. *Obstet Gynecol.* 2013; 121(4):887-890.

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## Menopause Editor's picks from October 2013

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

**Relationship between objectively recorded hot flashes and sleep disturbances among breast cancer patients: investigating hot flash characteristics other than frequency.**

Marie-Hélène Savard, PhD, Josee Savard, PhD, Aude Caplette-Gingras, PhD, Hans Ivers, PhD, and Celyne Bastien, PhD.



**More vasomotor symptoms in menopause among women with a history of hypertensive pregnancy diseases compared with women with normotensive pregnancies.**

Jose T. Drost, MD, Yvonne T. van der Schouw, PhD, Gerrie-Cor M. Herber-Gast, PhD, and Angela H.E.M. Maas, MD, PhD.



**High-intensity aquatic exercises (HydrOS) improve physical function and reduce falls among postmenopausal women.**

Linda Denise Fernandes Moreira, PhD, Fernanda Cerveira Abuana Osorio Fronza, MS, Rodrigo Nolasco dos Santos, MS, Luzimar Raimundo Teixeira, PhD, Luis Fernando Martins Krueel, PhD, and Marise Lazaretti-Castro, PhD.

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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.

### **2014 Call for Abstracts**

Don't miss the opportunity to submit your research abstracts to NAMS for presentation at the 25th Annual Meeting (October 15-18, 2014) in Washington, DC.

- Submit your abstracts through the NAMS website:  
[www.menopause.org](http://www.menopause.org)
- Information submitted for consideration must not be identical to that presented at any meeting prior to the NAMS meeting, and the study must have been published as of April 30, 2014
- The abstract submission deadline is April 30, 2014
- Top abstracts will be accepted for oral presentation and up to four poster prizes will be awarded (top prize: \$1,000)
- All accepted abstracts will be published in the NAMS journal, *Menopause*, after the meeting