

Clinicians' FORUM

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, experts in a range of fields related to midlife women's health tell readers how they handle these situations.

The viewpoints expressed in "Clinicians' Forum" are those of the contributors, and not necessarily those of *Menopause Management* or The North American Menopause Society (NAMS).

Question: What practice pearl from the recent Annual Meeting of The North American Menopause Society (NAMS) in San Diego would you like to see clinicians incorporate into their practices?

Answers:

I attended a session by Karen Matthews, PhD, entitled "Are Changes in Cardiovascular Risk Factors in Midlife Women due to Chronological Aging or to the Menopausal Transition?"¹ The authors measured cardiovascular disease (CVD) risk factors—including lipids and lipoproteins, glucose, insulin, blood pressure, fibrinogen, Lp(a) and hs-Crp—over 10 years in 1,054 women from the Study of Women's Health Across the Nation (SWAN). These women, who had had a final menstrual period (FMP) not due to surgery and without hormone therapy (HT) use before the FMP, were compared with women who had not had their FMPs, with two models for each risk factor: 1) a linear model that assumed a constant slope across the 24-month period (before and after the FMP), consistent with chronological aging, and 2) a piecewise linear model that allowed the slope to differ in accordance with the follicle-stimulating

hormone changes tightly linked to the menopausal transition, a model consistent with ovarian aging.

Of the risk factors studied, only total cholesterol (TC), low-density lipoprotein cholesterol-C (LDL-C) and apolipoprotein B (apoB, a direct count of the number of atherogenic lipoprotein particles) demonstrated substantial increases over the 24-month period before and after the FMP, which is consistent with the nonlinear model of ovarian-induced change related to the menopausal transition. The other risk factors were consistent with a linear model, indicative of chronological aging. These changes were independent of age as well as ethnicity, weight, weight gain and medications. This was the first analysis to document the effects of the natural menopausal transition with significant follow-up, assessment of risk factors, accurate and detailed timing of

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menopause and extensive covariant adjustment.

How can clinicians incorporate these findings into their practices? Those clinicians caring for midlife women are ideally positioned to focus on screening for and affecting change in modifiable

cardiovascular risk factors at a critical time of change. Consider how often we hear patients say, “My cholesterol has *always* been *normal!*” Given the fact that many women have “normal” lipid values and most have no or nonspecific warning signs before their first CVD event, aggressive prevention is the key. Early menopause

would be an ideal time to screen women for cardiovascular risk, using the usual Framingham major risk factors, easily remembered as “FLASH:”

- Family history of premature CVD (< 55 years in a male relative and < 65 in a female relative)
- Low high-density lipoprotein-C (HDL-C) (<50 mg/dL)
- Age >55
- Smoking
- Hypertension.

Framingham risk scoring, however, underestimates lifetime risk. This was addressed by the 2007 Women’s American Heart Association guidelines, which describe women as “at increased lifetime risk” if they are over age 50 and have one other risk factor:

- FLASH risk factors (family history, low HDL-C, smoking, hypertension)
- Physical inactivity
- Obesity, especially central adiposity
- Dyslipidemia (triglycerides > 150 mg/dL, HDL-C < 50 mg/dL)
- Subclinical vascular disease (eg, coronary calcification or abnormal carotid intimal medial thickness, both adjusted for age)
- Metabolic syndrome
- Poor exercise capacity or abnormal heart rate recovery after stopping exercise.

Women have “high lifetime risk” if they have

established CVD or equivalents (such as diabetes, abdominal aortic aneurysm, chronic renal failure, Framingham 10-year risk score >20%).

Because of the increased potential for visceral adiposity, weight gain and insulin resistance in menopause, this is an ideal time to focus on a calorie-restricted, low-glycemic-index diet and a systematic approach to regular aerobic *and* resistance-training exercise. Motivating midlife women to exercise is, of course, difficult, and a previous award-winning poster (2008 NAMS Annual Meeting) by Dr. Michelle Segar² has shown us that the most successful way to moti-



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vate women to exercise is to focus on the immediate short-term favorable benefits on stress level and mood, putting the weight-loss goal on hold until after 6-9 months of fitting exercise into a healthy lifestyle.

Given existing data, and augmented by the findings of Dr. Matthews and colleagues from SWAN, lipoprotein risk assessment should focus on directly counting atherogenic particles, rather than on traditional lipid values, as per new guidelines from the American Diabetes Association/American College of Cardiology and the American Association of Clinical Chemistry (and, hopefully, the upcoming National Cholesterol Education Panel-Adult Treatment Panel IV). The majority of women in the current study transitioned to above-optimal LDL-C values (> 100 mg/dL), and it appears that most women started and ended with apoB values above optimal (> 80 mg/dL). Healthcare providers for women can easily assess atherogenic lipoprotein status with non-HDL-C (TC minus HDL-C;

optimal < 120 mg/dL) or they can directly count atherogenic particles by apoB or by nuclear magnetic resonance (NMR)-derived LDL-particle count (optimal < 1,000 nmol/L). These methodologies are superior to LDL-C assessment as a means to evaluate and manage lipoprotein-associated risk. All midlife women at “increased lifetime risk” should at least be encouraged to adopt therapeutic lifestyle changes to optimize these lipoprotein parameters, and consideration should be given to pharmacologic treatment. All patients deemed to have “high lifetime risk” should be treated pharmacologically to achieve lipoprotein goals, usually with an appropriately dosed statin medication.

—Gregory Pokrywka MD, FACP, FNLA, NCMP

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“Does Vitamin D Prevent Cancer and Cardiovascular Disease?” by Dr. Edward Giovannacci, MD, ScD, was particularly interesting and provided some great clinical pearls on nutritional

support. Recently, there has been considerable interest in the potential protective role of vitamin D in many disease states, such as CVD and cancer (including colon, prostate and breast).

Studies have suggested that low or deficient levels of vitamin D are associated with an increased risk of CVD and cancers. Many

women, particularly African-Americans, are vitamin D deficient, and this may be placing them at increased risk for these diseases. Serum vitamin D levels ≥ 32 ng/mL are considered normal. The standard recommendation of 400-800 IU/day is probably inadequate, as 400 IU raises the serum level by only about 4 ng/mL. To achieve levels >30 ng/mL, supplementation with

1,000-2,000 IU may be required. There is no credible evidence of any significant risk associated with this level of supplementation.

Dr. Giovannacci's presentation was a great overview of evidence on CVD and cancer studies. Vitamin D was classically considered a regulator of calcium homeostasis. It is now clear that the hormonal form of dihydroxy 1,25 vitamin D3 (also known as calcitriol) plays a larger role in the regulation of cellular growth and differentiation.

- CVD is the leading cause of mortality in women; any reduction in incidence or mortality would have a tremendous impact. Several studies evaluating CVD and vitamin D levels—Ludwigshafen Risk and Cardiovascular Health (LURIC) and the National Health and Nutrition Examination Survey

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—Gloria Richard-Davis, MD, FACOG



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(NHANES)—revealed a decreased risk of CVD and mortality when vitamin D levels were >30 ng/mL, and an increased risk if levels were <15 mg/mL. LURIC all-cause mortality seems to be higher in vitamin D-deficient groups. In NHANES, all-cause mortality was increased when vitamin D levels were <30 ng/mL.

- There is strong evidence that vitamin D plays a protective role in colorectal cancer, and less compelling evidence for such a role in breast or prostate cancer. Animal in vitro work suggests a vitamin D effect on cell proliferation. Garland, in 1980, first published an association with vitamin D and colon cancer levels. Lower UV exposure is, of course, associated with lower vitamin D levels—and with higher rates

of cancer. The Nurse's Health Study showed a decrease in colon cancer.

Findings on the benefit of vitamin D for breast cancer are less clear. The Nurse's Health Study showed an increased risk of breast cancer when vitamin D levels were low in women over age 60, but not in the younger women. Goodwin's study of 600 women with breast cancer revealed better survival rates with vitamin D levels >30 ng/mL. The Women's Health Initiative (WHI) vitamin D and calcium study, with 7 years of follow-up, showed no significant effect on CVD or cancer; this may be due to the low dose (400 IU), although there was some trending toward a positive effect.

Over half of all Americans take some type of supplement, spending more than \$12 billion per year. Yet we know very little about the benefits of those supplements. While research on vitamin D shows some promising protective effects on CVD and cancer (particularly colorectal), more research is needed. The Vitamin D and Omega 3 Trial (VITAL) will enroll 20,000 subjects to evaluate CVD and cancer with vitamin D supplements of 1,000-2,000 IU, utilizing a number of primary and secondary outcomes. This study will be powered to answer some of the deficits noted in studies mentioned above. Basic studies on various ranges and dose-response are lacking. Intermediary endpoints, such as inflammatory markers and parathyroid hormone, would be helpful in evaluating treatment effects, and more studies on endpoints related to CVD and cancer incidence and mortality are needed.

—*Gloria Richard-Davis, MD, FACOG*

Growing up in California I spent most of my days playing outside in the sun, taking the importance of vitamin D for granted. In college I was taught that vitamin D was a nutrient I make in my skin, so I shouldn't worry about it.

People now wear sunscreen, avoid the sun, stay inside more and live where sun is a luxu-

ry. At the NAMS meeting we heard how vitamin D deficiencies are now implicated in diseases of the bone, mood and heart, and in cancer risk. Asking patients about vitamin D exposure (natural or supplemented) and/or checking plasma vitamin D levels may help prevent or make us aware of risks our patients may face.

We can help our patients understand nutrition, healthy living and aging. Teach them how to get more vitamin D. It's easy, cheap, and may make them feel better! Thanks, NAMS!

—*Kristi Saunders, MS, MD, NCMP*



Kristi M. Saunders, MS, MD, NCMP

One of the topics I found most interesting at the recent NAMS meeting was related to vitamin D and the clinical implications on health and disease prevention. While our knowledge about vitamin D is expanding rapidly, this information is likely to have tremendous implications regarding our approach to patient care and vitamin supplementation.

We have known for years that vitamin D is essential for the promotion of calcium absorption and related effects in promoting bone health while preventing rickets and osteoporosis. Newer data, however, have raised the issue of the potential benefits of vitamin D related to overall health and chronic disease prevention. Among these data, observational and case-controlled studies have suggested that vitamin D concentrations >25-30 ng/mL may be associated with a lower risk of coronary artery disease (CAD) and certain cancers, including colon and breast cancer. Aside from data showing a higher risk of colon cancer in the areas of the country with lower sun exposure, there are studies show-



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ing an inverse relationship between vitamin D and other conditions.

Interestingly, the WHI looked at calcium and vitamin D supplementation in chronic disease (including CAD and cancer), cerebral vascular accidents and total mortality.¹ While there was no significant effect, it should be noted that these patients were taking only 400 IU of vitamin D, resulting in serum 25-OH concentrations of approximately 20 ng/mL, well below the range considered necessary for disease prevention. Despite this low dose of oral vitamin D and subsequent moderate elevations in serum vitamin D concentrations, it is interesting that the overall relative risk of total mortality was 0.91 (confidence interval, 0.83 to 1.01). While this is not statistically significant, it is an interesting trend that warrants further investigation.

With this information we need to promote further vitamin D research looking at specific endpoints like cancer, CAD, heart failure, diabetes mellitus and insulin resistance. Various ranges of vitamin D should be considered along with the potential differences between oral supplementation and vitamin D through sun exposure. In the meantime, many practitioners have begun routinely checking plasma vitamin D concentrations and starting patients with values < 20 ng/mL on supplementation. One proposed protocol would be to start 1,000 IU of vitamin D per day, recheck plasma concentrations in a few months and, if not above 35 ng/mL, increase to 2,000 IU per day.

—Peter F. Schnatz, DO, FACOG, FACP, NCMP

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After attending the pre-meeting symposium in San Diego, I would like to see clinicians incorporate screening for depression in the midlife woman. Although most women do not experience depression during the menopause transition, it is important to know which patients have had a past history of depression, as they are five times more likely to experience depression during this

time. Depression is more likely to be associated with vasomotor symptoms due to the hormonal fluctuations believed to be a cause. Of particular importance is the role of depression as a risk factor for coronary heart disease, the leading cause of death among women in the US. Depression plays a role in the pathogenesis of subclinical coronary atherosclerosis, which has been clearly demonstrated in cynomolgus monkeys. In addition, clinical meta-analyses have also found that depression can predict heart disease in healthy individuals.

—Chrisandra Shufelt, MD, MS, NCMP



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My involvement in the “Meet the Expert” session was very enjoyable. While leading a table discussion about hypertension and menopause I felt that the back-and-forth conversation generated was just as important and also just as informative as the “expert opinion” itself. The general topics of conversation centered on the changes that take place during menopause that impact blood pressure and the treatment of hypertension. We reviewed the role of the AT1 receptor, the use of angiotensin II receptor blockers, diuretics and the impact of anti-hypertensive therapy on other menopausal symptoms. The impact of other cardiovascular comorbidities was also brought up. Diabetes and dyslipidemia therapy and the impact on hypertension proved to be an important discussion.

Finally, what was most interesting to me was the number of different specialties represented at the table. The number of different practitioners treating and considering the impact of hypertension on their patients was greater than I originally expected.



James A. Underberg, MD, MS, FACPM, FACP, FNLA

The Meet the Expert sessions were enjoyable and were a great source of practical pearls for all who attended, as well as for those leading the sessions. I would encourage anyone invited to give a session to do so, and would also encourage those attending future meetings to take part in this wonderful session.

—James A. Underberg, MD, MS, FACPM,
FACP, FNLA

Recently, the safety and efficacy of long-term bisphosphonate use has been questioned. Patient fears about long-term safety can further compound an already poor adherence rate to pharmacologic osteoporosis therapy. The practice pearl I would like to see clinicians incorporate into their practices is to reassure patients about the long-term safety of bisphosphonates.

In “Update on Current and Future Osteoporosis Treatments,” Dr Steven Harris talked about the lack of clear safety issues and loss of ef-

ficacy related to long-term use of bisphosphonates. The risk of bisphosphonate-induced osteonecrosis of the jaw is extremely low with oral bisphosphonates (rate of 1/10,000 to <1/100,000), while most cases have occurred with intravenous formulations in malignancy. Although an association has not been clearly identified, the risk of atypical fractures with long-term use of bisphosphonates may be a rare, idiosyncratic response. Dr Harris recommended that “high-risk” patients on bisphosphonates be continued on treatment long-term. If therapy is stopped after 2 to 5 years, a persistent effect on biomarkers and bone mineral density is maintained (best characterized with alendronate).

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