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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. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Peter F. Schnatz, DO, Chair-Elect, 2008-2009 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Schnatz. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Does hormone therapy decrease colorectal cancer risk?

Johnson JR, Lacey JV Jr, Lazovich D, et al. Menopausal hormone therapy and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2009;18:196-203.

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We evaluated colorectal cancer risk associated with the duration and recency of specific menopausal hormone therapy formulations (ie, unopposed estrogen versus estrogen plus progestin) and regimens (ie, sequential versus continuous estrogen plus progestin use) among 56,733 postmenopausal women participating in the Breast Cancer Detection Demonstration Project follow-up study. Hormone therapy use and other risk factors were ascertained through telephone interviews and mailed questionnaires from 1979 to 1998. The final cancer group included 960 women who were identified from self-report, medical records, state registry data, and the National Death Index. Poisson regression was used to generate multivariable rate ratios (RR) and 95% confidence intervals (95% CI). We observed a decreased risk of colorectal cancer among ever users of unopposed estrogen therapy (RR, 0.83; 95% CI, 0.70-0.99). Among estrogen users, the largest reduced risk was observed for current users (RR, 0.75; 95% CI,

0.54-1.05) and users of \geq ten years duration (RR, 0.74; 95% CI, 0.56-0.96). We found a reduced risk among users of estrogen plus progestin therapy (RR, 0.78; 95% CI, 0.60-1.02), with sequential regimen users (progestin <15 days per cycle) having the largest risk reduction (RR, 0.64; 95% CI, 0.43-0.95). Past users of \geq 5 years ago (RR, 0.55; 95% CI, 0.32-0.98) had the largest risk reduction. In this study, estrogen plus progestin use, especially sequential regimen use, was associated with the largest overall reduction of colorectal cancer risk.

Comment. This is a retrospective study, the stated purpose of which was to identify separate risk estimates for colon cancer according to menopausal hormone formulations. A paper published 9 years earlier¹ from the same database found a suggested inverse relationship between the use of HT and colon cancer. The current paper analyzed postmenopausal women divided into groups of never users, those who had ever used estrogen, and those who had ever used estrogen plus progestin (EPT), and then further divided them by sequential hormone use and length of time exposed to HT. What the current authors found was that those who had ever used unopposed estrogen had a decreased risk of colon cancer. Those who had used sequential EPT had the largest risk reduction. What does

this information add to our knowledge of this topic?

Estrogen receptors have been detected on colonic cells, with estrogen-receptor β being over-expressed in healthy colon cells and reduced in colon cancer cells. This overexpression, coupled with negligible expression of estrogen-receptor α , is thought to provide protection by HT against colon cancer. What is also known is that prescribing patterns for HT vary among race, with African-American, Asian, and Latina women receiving less treatment than Caucasian women. An evaluation of how many women were represented in each group rather than a designation of “nonwhite” and a designation of “person-years” only would have been informative. It would also have been beneficial if the groups had been matched by age, ethnicity, and HT use (perhaps this is a paper that will be published later).

African-American women have the highest risk for colon cancer, higher even than white males; and colon cancer in these women is often detected at a more advanced stage. If HT really does reduce the risk of colon cancer, all women should have a discussion with their healthcare provider about the potential benefits of HT for them. A prospective study of matched groups of women would be very informative regarding risk reduction across ethnic groups in which there is a dearth of comparative information available. Women who use HT are more likely to have mammograms, as well as Pap smears and colonoscopies. Colonoscopy, however, is still at the bottom of the list even for women who regularly undergo other types of health screening. It would be helpful if healthcare providers encouraged women to have a colonoscopy. It has been shown that if a healthcare provider strongly recommends a test, a patient will often agree.

As March is National Colon Cancer Awareness Month, this might be a good time to consider a large-scale prospective randomized trial of HT use with timed colon cancer screening across ethnic groups by those in this field.

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Reference:

1. Troisi R, Schairer C, Chow WH, et al. A prospective study of menopausal hormones and risk of colorectal cancer (United States). *Cancer Causes Control* 1997; 8:130-138.

Long-term alendronate use and osteoclast increase

Weinstein RS, Roberson PK, Manolagas SC. Giant osteoclast formation and long-term oral bisphosphonate therapy. *N Engl J Med* 2009;360:53-62.

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BACKGROUND: Bisphosphonates decrease bone resorption and are commonly used to treat or prevent osteoporosis. However, the effect of bisphosphonates on their target cells remains enigmatic, since in patients benefiting from therapy, little change, if any, has been observed in the number of osteoclasts, which are the cells responsible for bone resorption. **METHODS:** We examined 51 bone-biopsy specimens obtained after a 3-year, double-blind, randomized, placebo-controlled, dose-ranging trial of oral alendronate to prevent bone resorption among healthy postmenopausal women 40 through 59 years of age. The patients were assigned to one of five groups: those receiving placebo for 3 years; alendronate at a dose of 1, 5, or 10 mg per day for 3 years; or alendronate at a dose of 20 mg per day for 2 years, followed by placebo for 1 year. Formalin-fixed, undecalcified planar sections were assessed by bone histomorphometric methods. **RESULTS:** The number of osteoclasts was increased by a factor of 2.6 in patients receiving 10 mg of alendronate per day for 3 years as compared with the placebo group ($P < 0.01$). Moreover, the number of osteoclasts increased as the cumulative dose of the drug increased ($r = 0.50$, $P < 0.001$). Twenty-seven percent of these osteoclasts were giant cells with pyknotic nuclei that were adjacent to

superficial resorption cavities. Furthermore, giant, hypernucleated, detached osteoclasts with 20 to 40 nuclei were found after alendronate treatment had been discontinued for 1 year. Of these large cells, 20 to 37% were apoptotic, according to both their morphologic features and positive findings from in situ end labeling. **CONCLUSIONS:** Long-term alendronate treatment is associated with an increase in the number of osteoclasts, which include distinctive giant, hypernucleated, detached osteoclasts that are undergoing protracted apoptosis.

Comment. Bisphosphonates (BPs) affect bone remodeling by inhibition of osteoclast function and resultant inhibition of osteoblast function. BPs are apparently deposited in mineralized bone and are removed during the process of osteoclast-mediated bone resorption. During this process, the BP is “taken up” by the osteoclast and promotes apoptosis of the cells in which they are taken up. It would seem from the article by Weinstein et al, and the accompanying editorial,¹ that the process is far more complicated than my simple explanation and that the apoptosis is not straightforward, somehow resulting in formation of giant osteoclasts that may be nonfunctional or dysfunctional. From the two articles it remains unclear to me what, if any, impact this observation has on skeletal health.

It is now more than 10 years since the first BP was available for clinical use in the United States, and there are increasing reports of adverse events seemingly related to this therapy. This could be the result of an increasing number of patients being treated, with a very small percentage developing important side effects for as yet unexplained reasons. Alternatively (and not mutually exclusively), the longer duration of BP therapy in an increasing number of patients may result in adverse effects of BP on the bone remodeling system itself. The most common side effect, gastrointestinal intolerance, has been known from the earliest days of BP use, but the link between BPs and femoral shaft fractures, for example, is much more uncommon and has been seen or recognized only in recent years.

There is no generally accepted way to document possible oversuppression of bone remodeling, nor the presence of giant osteoclasts, other than by invasive bone biopsy—a clinical option that would only be undertaken as a research project or as a more definitive study in a patient who has already sustained a skeletal side effect. Monitoring one of the serum markers of bone resorption, which should be suppressed by BP therapy, may well be a suitable noninvasive effective to predict the likelihood of oversuppression of remodeling, but I am unaware of any studies supporting this approach. However, in my practice I do monitor markers in patients in whom serial dual energy x-ray absorptiometry studies, properly performed, demonstrate a stable bone mineral density over a 2-year period. Most of the time, the result is in the bottom half of the reference interval and I feel comfortable temporarily discontinuing therapy and monitoring the serum marker—restarting therapy as the values begin to rise to the top half of the reference interval. This is an unproven clinical practice, and I let my patients and their referring physicians know that when making this recommendation.

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Reference:

1. Glowacki J. The deceiving appearances of osteoclasts. *N Engl J Med* 2009;360:80-82.

Treating urinary incontinence with weight loss

Subak LL, Wing R, West DS, et al, for the PRIDE Investigators. Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med* 2009; 360:481-490.

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BACKGROUND: Obesity is an established and modifiable risk factor for urinary incontinence, but conclusive evidence for a beneficial effect

of weight loss on urinary incontinence is lacking. **METHODS:** We randomly assigned 338 overweight and obese women with at least 10 urinary-incontinence episodes per week to an intensive 6-month weight-loss program that included diet, exercise, and behavior modification (226 patients) or to a structured education program (112 patients). **RESULTS:** The mean (\pm SD) age of the participants was 53 ± 11 years. The body-mass index (BMI) (the weight in kilograms divided by the square of the height in meters) and the weekly number of incontinence episodes as recorded in a 7-day diary of voiding were similar in the intervention group and the control group at baseline (BMI, 36 ± 6 and 36 ± 5 , respectively; incontinence episodes, 24 ± 18 and 24 ± 16 , respectively). The women in the intervention group had a mean weight loss of 8.0% (7.8 kg), as compared with 1.6% (1.5 kg) in the control group ($P<0.001$). After 6 months, the mean weekly number of incontinence episodes decreased by 47% in the intervention group, as compared with 28% in the control group ($P=0.01$). As compared with the control group, the intervention group had a greater decrease in the frequency of stress-incontinence episodes ($P=0.02$), but not of urge-incontinence episodes ($P=0.14$). A higher proportion of the intervention group than of the control group had a clinically relevant reduction of 70% or more in the frequency of all incontinence episodes ($P<0.001$), stress-incontinence episodes ($P=0.009$), and urge-incontinence episodes ($P=0.04$). **CONCLUSIONS:** A 6-month behavioral intervention targeting weight loss reduced the frequency of self-reported urinary-incontinence episodes among overweight and obese women as compared with a control group. A decrease in urinary incontinence may be another benefit among the extensive health improvements associated with moderate weight reduction.

Comment. The epidemic of obesity as a major health problem has grown all over the world. Recent estimates show that about two thirds of the US adult population is overweight and more than one third (over 72 million people) is obese. The highest prevalence of obesity is among

women aged 40 to 59 years (41%), an age where urinary incontinence prevalence increases (up to about 45% for monthly or more incontinence episodes). Observational studies have almost universally shown that a high BMI is associated with incontinence. Obesity is considered an “established” risk factor for both stress and urge incontinence, though the risk appears to be greatest for stress incontinence. From these observational studies, there also emerges a dose-response effect: the higher the BMI, the greater the odds of incontinence. In longitudinal studies, weight gain has been associated with both the development and worsening of incontinence. Therefore, based on good epidemiological evidence, incontinence can clearly be added to the long list of symptoms associated with being overweight or obese.

While the mechanism of obesity on incontinence is not fully known and may be multifactorial, evidence does suggest that the increased intra-abdominal pressures associated with added body fat transmit higher pressures in the bladder. The increased intra-abdominal pressure puts excess stretch and strain on the tissues, nerves, and muscles of the pelvic floor such that the main continence mechanisms, urethral support, the urethral sphincter, and the pelvic floor muscles cannot compensate.

A few studies have evaluated weight loss as a treatment for incontinence. Most of these assessed the effects of bariatric surgery on incontinence symptoms in morbidly obese women. All found an improvement in or resolution of incontinence of greater than 50% after significant surgical weight loss; and the greater the percentage of weight lost, the greater the improvement in incontinence. Small-scale randomized clinical trials of medical and behavioral weight loss in both overweight and obese women have also shown a 50% or more reduction in incontinence episodes in the weight-loss arms.

This current Program to Reduce Incontinence by Diet and Exercise (PRIDE) study by Subak

et al is unique in that it was specifically designed and powered to evaluate a medical and behavioral weight reduction program as a treatment for incontinence. Consistent with the previous literature, this well-designed study confirmed a nearly 50% reduction in any incontinence episodes and a nearly 60% reduction in stress incontinence episodes in the treatment group where the mean weight loss was 8% (17.2 lb) over 6 months. Additionally, the percentage of women in this study who were “moderately” to “very” satisfied with the diet and exercise weight-loss program to treat their incontinence (75%) is consistent with reported satisfaction rates for other nonsurgical incontinence treatments.

The results of the PRIDE study add significantly to the body of evidence informing clinicians to recommend weight reduction programs as primary treatment for incontinence, especially stress incontinence, in overweight or obese women.

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References:

1. Ogden CL, Carroll MD, McDowell MA, Flegal KM, for the Division of Health and Nutrition Examination Surveys. Obesity among adults in the United States—no statistically significant change since 2003-2004. NCHS Data Brief Number 1. Hyattsville, MD: National Center for Health Statistics. 2007.
2. Hunskaar S. A systematic review of overweight and obesity as risk factors and targets for clinical intervention for urinary incontinence in women. *Neurourol Urodyn* 2008;27:749-757.

Editor’s picks from March-April *Menopause*

NAMS spotlights the most recent issue of the Society’s official journal, *Menopause*, selected by its Editor-in-Chief, Dr. Isaac Schiff. The complete contents can be found on the NAMS Web site (www.menopause.org).

Gast GC, Grobbee DE, Pop VJ, et al. Vasomotor symptoms are associated with a lower bone mineral density. *Menopause* 2009;16:231-238.

In this study, vasomotor symptoms were associated with a reduced bone density. It could be hypothesized that women with vasomotor symptoms might be more susceptible to the beneficial effects of estrogens, possibly by neutralizing the effect of estrogen fluctuations.

◆
Crandall CJ, Zheng Y, Crawford, SL, et al. Presence of vasomotor symptoms is associated with lower bone mineral density: a longitudinal analysis. *Menopause* 2009;16:239-246.

To determine the association between vasomotor symptoms and bone mineral density, data were analyzed from 2,213 participants of the Study of Women’s Health Across the Nation. Even in the earliest menopause transition stages, women with vasomotor symptoms had lower bone mineral density on average compared to women without vasomotor symptoms.

◆
Gast MJ, Freedman MA, Vieweg AJ, De Melo NR, Girao MJ, Zinaman MJ, for the Dyspareunia Study Group. A randomized study of low-dose conjugated estrogens on sexual function and quality of life in postmenopausal women. *Menopause* 2009;16:247-256.

Painful sexual intercourse is among the most troubling of the symptoms of menopause. This study demonstrates the value of a regimen of vaginal conjugated estrogens and low-dose oral hormone therapy to relieve dyspareunia in a large, prospective, randomized, multinational study.

◆
Torrens JI, Sutton-Tyrrell K, Zhao X, et al. Relative androgen excess during the menopausal transition predicts incident metabolic syndrome in midlife women: Study of Women's Health Across the Nation. *Menopause* 2009;16:257-264.

With the onset of menopause, ovarian estradiol production declines dramatically, but the concomitant drop in sex hormone-binding globulin and more modest drop in androgen production leads to an increase in the ratio of bioavailable testosterone to estradiol. In the Study of Women’s Health Across the Nation,

the magnitude of this ratio—called Relative Androgen Excess—is shown to be associated with incident cases of metabolic syndrome.



Elavsky S. Physical activity, menopause, and quality of life: the role of affect and self-worth across time. *Menopause* 2009;16:265-271.

A two-year follow-up survey was conducted with middle-aged women previously enrolled in a

randomized controlled exercise trial to examine the relationship between physical activity and menopause-related quality of life (QOL). The results indicated that increasing physical activity over time may enhance QOL, albeit indirectly via its effects on physical self-worth and positive affect.

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.

Continued

NAMS/Medscape Educational Collaborations

NAMS is pleased to acknowledge the tens of thousands of healthcare professionals who have visited MedscapeCME.com to participate in novel educational programs on menopause-related topics with content developed by NAMS. Many offer an opportunity to receive CME. Take a look at the NAMS Web site (<http://www.menopause.org/MS.aspx>)

- *Spotlight Program*: “Postmenopausal Systemic Hormone Therapy: Putting Risks Into Perspective”
- *Expert Viewpoint*: “The Beneficial Effect of Hormone Therapy on Mortality and Coronary Heart Disease in Younger Versus Older Postmenopausal Women”
- *Expert Interview*: “Hormone Therapy and Breast Cancer: An Expert Interview With JoAnn E. Manson, MD, DrPH
- *Town Hall Webcast*: “Postmenopausal Systemic Hormone Therapy: Reaching Consensus at Last on Benefit and Risk”
- *Clinical Update*: “The Practical Clinical Application of the NAMS 2008 Position Statement on Estrogen and Progestogen Use in Postmenopausal Women”
- *Test & Teach*: “Managing Vasomotor Symptoms in Women With Cardiovascular Risk”
- *Test & Teach*: “Selecting Menopausal Estrogen Therapy: Oral or Transdermal?”
- *Symposium Highlights*: “Comprehensive Breast Care: An Update for the Menopause Practitioner”
- *Spotlight Program*: “Dialogues in Menopause Management: Facilitating Counseling About Hormone Therapy”
- *Test & Teach*: “Dialogues in Menopause Management: Case-Based Approach to Counseling Patients About Hormone Therapy”

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