

NEWS Commentary

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Menopause transition affects QOL, CVD, body composition, Melbourne study reports

Guthrie JR, Dennerstein L, Taffe JR, Leher P, Burger HG. The menopausal transition: a 9-year prospective population-based study. The Melbourne Women's Midlife Health Project. *Climacteric* 2004;7:375-89.

Hormonal changes occurring during the menopause transition period are related, either directly or indirectly, to adverse effects on quality of life, body composition, and cardiovascular risk, according to the Melbourne Women's Midlife Health Project, a prospective, longitudinal study conducted in Australia. A total of 438 premenopausal women aged 45 to 55 at baseline were enrolled for 9 years. Follow-up included interviews, physical measurements, and blood samples.

During the study, 51% experienced natural menopause and another 8% were surgically induced. The average age at menopause was 53 years. Late perimenopause was associated with substantial changes in levels of estradiol and follicle-stimulating hormone (FSH), and in the free testosterone index. Levels of total

testosterone and dehydroepiandrosterone sulfate (DHEAS) were unchanged by the menopause transition.

Menopause was found to be directly associated with the following: increases in vasomotor symptoms, vaginal dryness, dyspareunia, and central abdominal fat; decreases in breast tenderness, bone mineral density (BMD) of the spine and femoral neck, and sexual functioning. Cardiovascular disease risk increased in association with decreases in estradiol levels and increases in body mass index and the free testosterone index. Although menopause was significantly associated with a decline in sexual function (based primarily on sexual responsiveness, sexual frequency, and libido) age, previous sexual behavior, and relationship factors also played major roles.

Symptoms related to menopause that affected quality of life included hot flashes, insomnia, vaginal dryness, and breast tenderness. About 75% of the women experienced bothersome hot flashes, which started approximately 2 years before menopause and reached a maximum occurrence approximately 2 years after menopause.

Mood, self-rated health, and life satisfaction were not directly related to the menopause transition. Other health outcomes not found to be associated with menopause included incontinence, impaired fasting glucose levels, memory, and overall weight gain.

Comment. The Melbourne Women's Midlife Health Project is one of the longest-running and most comprehensive of the large, community-based studies started in the late 1980s and early 1990s to better understand the natural epidemiology of menopause. It has yielded a large number of papers on such topics as symptoms, mood, hormonal changes, sexual functioning, cardiovascular health, and bone density.

This article does not present any new findings. Rather, it provides an excellent and useful summary of the many pub-

lished findings from this study, including a more precise definition of the stages of the menopause transition, and extensive data on hormonal changes and sexual functioning, menstrual cycle changes throughout the menopause transition, and positive well-being. This study significantly advances our understanding of what midlife changes can be attributed to the menopause transition and what changes are not directly related.

As with all epidemiologic studies, the Melbourne Study has some limitations (eg, the minimum age of 45 at study entry excluded women who had an earlier menopause, healthy sample bias, primarily Caucasian sample, and only one blood sample per year). However, these limitations do not detract from the significant contributions of this study to our knowledge of the natural menopause transition.

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Comment. The Melbourne study is unique given the breadth of its focus and the length of follow-up (9 years). Despite some caveats, the study has provided us with a distinctive view of the endocrine profiles of a community-based sample of women as they traverse the menopause transition (eg, FSH, estradiol, inhibin A and B, sex hormone-binding globulin, testosterone, and DHEAS). These data were tracked along with careful recording of menstrual changes that preceded the final menstrual period, which have given rise to criteria by which to judge women's progression through the menopause transition. The criteria should help to determine the validity of the Stages of Reproductive Aging Workshop (STRAW) criteria.

Of great importance to understanding the health impact of the menopause transition are the multiple measures tracked, including symptoms, mood, sexuality, life satisfaction, and self-rated health. In addition, risk factors for major diseases associated with aging were tracked, including body composition measures (eg, BMD, weight, central abdominal fat) and cardiovascular disease risk factors (eg, lipid levels, triglycerides, blood pressure). Recent additions to these measures were indicators of memory; physical, sexual, and emotional violence; and attitudes toward aging.

Taken together, the results of this study indicate that the period from the late menopause transition stage through early postmenopause appears to be a time of vulnerability in a woman's lifespan. Like most transitions, this period is time-limited and one that clinicians can view as an opportunity for health-promotion opportunities, linking clinical efforts to observed changes (eg, weight gain). Given the evidence, it appears that the menopause transition is a period of re-regulation that follows dysregulation in hypothalamic-pituitary-ovarian function, and it need not precede serious morbidity.

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Bone benefits persist longer after alendronate than after EPT

Wasnich RD, Bagger YA, Hosking DJ, et al, for the Early Postmenopausal Intervention Cohort study group. Changes in bone density and turnover after alendronate or estrogen withdrawal. *Menopause* 2004;11:622-30.

After therapy withdrawal, residual skeletal effects are greater with alendronate than with estrogen plus progestin (EPT), according to this report from the Early Postmenopausal Intervention Cohort (EPIC) study, a randomized, placebo-

controlled, multinational trial. A total of 1,609 postmenopausal women aged 45 to 59 years were enrolled in the EPIC study.

This article reports 6-year data (4-year results were previously published) on women assigned to these five groups: placebo; 5 mg alendronate for 2, 4, or 6 years followed by placebo; or 4 years of open-label EPT (either continuous-combined 0.625 mg conjugated equine estrogens plus 5 mg medroxyprogesterone acetate or a cyclic regimen of 2 mg 17 β -estradiol plus 1 mg norethisterone acetate, then 1 mg estradiol alone). Women in whom EPT was contraindicated or who declined EPT were randomized to either alendronate or placebo. End points were bone mineral density (BMD) at the lumbar spine and hip as well as bone turnover markers, measured by urine N-telopeptides (NTx) of type I collagen.

Compared with baseline, significant increases in spine and hip BMD were observed during active-treatment phases for the 5-mg alendronate groups and the EPT groups, while placebo recipients had significant decreases in BMD.

After discontinuation of therapy, BMD decreased at all skeletal sites. In comparing the 4-year treatment groups, the mean BMD changes 2 years after therapy withdrawal were -7.7% at the spine and -5.2% at the hip for EPT recipients versus -2.4% at the spine and -1.1% at the hip for alendronate recipients. Mean changes from baseline to year 6 were gains of 2.2% and 2.7% at the spine and hip, respectively, for the 4-year alendronate group, losses of 0.8% at both the spine and hip for the EPT groups, and losses of 3.3% (spine) and 2.5% (hip) for placebo. The between-group differences were statistically significant.

Bone turnover markers showed similar trends. Among alendronate recipients, levels of NTx dropped significantly from baseline during the treatment phase, then gradually increased after therapy withdrawal. EPT recipients had similar NTx decreases during treatment, but therapy withdrawal led to much greater increases

than with alendronate, rising to levels higher than the placebo group after 6 years. The mean changes in NTx from baseline to study end were -53.3% for alendronate (the 4-year group), -29.7% for EPT, and -35.8% for placebo.

Comment. This article is interesting in that it is the first randomized, controlled trial in early postmenopausal women to compare BMD gains with alendronate against gains with two different EPT regimens, and to compare BMD losses once treatment is stopped. Interestingly, BMD gains during the treatment phases were highest in the EPT users. Not unexpectedly, BMD losses after therapy cessation were much slower with alendronate than with either EPT regimen.

As clinicians, we must remember that factors other than BMD, such as microarchitecture, contribute to bone strength. Furthermore, factors independent of BMD affect the risk of falls and subsequent fractures. Although BMD is very important for risk assessment, direct comparisons between agents and their effects on BMD cannot be linearly equated to fracture risk reduction.

This study was not powered to look at fracture risk reduction. Whether the more sustained BMD gains after discontinuation of alendronate actually relate to fracture reduction is expected but not proven. Based on the large number of participants needed to power fracture outcome studies, and the expense of conducting such large randomized controlled trials, we are not likely to get direct fracture outcome comparison trials any time soon.

The important take-home message for clinicians is that women who stop EPT lose BMD rapidly. Therefore, they should be assessed sooner rather than later for their bone status with both central dual energy x-ray absorptiometry and bone turnover markers. With women who stop therapy with a long-acting bisphosphonate such as alendronate, one might anticipate additional BMD benefits beyond the treatment regimen time frame, and one

could potentially wait longer to assess BMD and bone turnover markers.

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Comment. This study compared the impact of discontinuation of alendronate versus EPT on bone density and bone turnover markers in postmenopausal women. The lack of blinding in EPT users (alendronate users were blinded) is likely a contributing factor to the dramatically higher reporting of side effects in the EPT groups (88% vs 11% for alendronate and 13% for placebo) and the substantially greater rate of loss to follow-up (75% for EPT vs no more than 48% for the alendronate and placebo arms). The potential

bias introduced by the significant loss to follow-up in the EPT arm is substantial.

There are several important findings from this study: that different EPT regimens had different effects on bone density; that the slower decline in bone density for those on alendronate compared with those on EPT is true for women without osteoporosis, as has been shown for women with osteoporosis; [Greenspan *Ann Intern Med* 2002] and that the effects of medication withdrawal on NTx markers are the inverse of the effects on bone density, as expected. This study also highlights the very different biologic effects of these classes of drugs on bone metabolism.

What this study does not answer is the critical question of whether the effects of these medications on bone biology translate into changes in fracture rates. Although the obvious assumption is that higher bone density and lower bone turnover should be

associated with lower fracture risk, some argue that the persistent suppression of bone turnover markers might actually have a negative effect on bone quality. Given the relatively young age of the study participants and the long retention of alendronate effects, bone density and bone turnover marker data may not be adequate to support the use of bisphosphonates in early postmenopausal women without osteoporosis until we better understand the fracture implications of these findings.

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Diagnosis and Management of Hypothyroidism in Women

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