Climacteric Commentaries

It is essential for the practicing physician to keep up-to-date with knowledge and reading medical journals is an important component in achieving this. As one of the many benefits of membership of the International Menopause Society (IMS), Menopause Live, an e-service for IMS members prepared by IMS members, is issued weekly, bringing a short abstract of a recently published study or review followed by a brief personal commentary. The opinions expressed in these commentaries are those of the commentary authors and are not necessarily supported by the IMS. The articles chosen for Menopause Live are selected by a search of the world literature on issues related to menopause medicine. In order to allow all readers of Climacteric to experience this service, some issues of Menopause Live are included in this section.

Amos Pines, Section Editor

The effect of soy isoflavone on bone mineral density


Tai and colleagues have recently reported that treatment with 300 mg/day of isoflavones (aglycone equivalents) (172.5 mg genistein + 127.5 mg daidzein) for 2 years failed to prevent lumbar spine and total proximal femur bone mineral density (BMD) from declining, as compared with the placebo group. This randomized, double-blind, two-arm-designed study was conducted in a clinical sample of 431 postmenopausal women aged 45–65 years in three centers of Taipei (Taiwan). Each participant also ingested 600 mg of calcium and 125 IU of vitamin D per day. The BMD of the lumbar spine and total proximal femur were measured using dual-energy X-ray absorptiometry at baseline and every half-year thereafter. Serum bone-specific alkaline phosphatase, urinary N-telopeptide of type I collagen/creatinine, and other safety assessments were examined regularly. Serum concentrations of isoflavone metabolites, genistein and daidzein, in the intervention group were remarkably elevated following intake of isoflavones \((p < 0.001)\). However, differences in the mean percentage changes of BMD throughout the treatment period were not statistically significant (lumbar spine, \(p = 0.42\); total femur, \(p = 0.39)\) between the isoflavone and placebo groups. A significant time trend of bone loss was observed at both sites following repeated measurement of BMD \((p < 0.001)\). Differences in bone marker levels were not significant between the two treatment groups. The authors concluded that treatment with 300 mg/day isoflavones (aglycone equivalents) failed to prevent a decline in BMD in the lumbar spine or total femur compared with the placebo group.

Comment

The results of the current randomized, double-blind, placebo-controlled study indicated that a daily intake of 300 mg isoflavones for 2 years generated no difference in the rate of bone loss at the lumbar spine or total femur. Contrasting with these results, several previous studies and meta-analyses\(^{2,3}\) have shown many beneficial effects of soy isoflavones on bone. However, most of the studies included only small sample sizes, there was no control of compliance by assessing isoflavones in blood, and there may have been biases, or short follow-up periods, and therefore long-term effects could not be evaluated. A recent meta-analysis on the effects of supplementation with soy isoflavone extract with an average of 82 mg (47–150 mg) (aglycone equivalents) on BMD\(^{3}\) showed an increase in lumbar spine BMD by 2.4% after 6–12 months. However, no significant change of proximal femur BMD could be found\(^{3}\). It is noteworthy that recent reports have demonstrated the absence of the supposed beneficial effects of isoflavones on bone, supporting the results of this large study by Tai and colleagues\(^{4,5}\). This controversy may be the result of differences in dosage, product forms, length of observations, ethnic dietary habits, or other factors related to the high variability in the soy isoflavone compounds. Interestingly, the results within each center were analyzed separately and did not show any trend of effects.

The main challenge with this study was that the sample size was not sufficient to establish the real effects of isoflavones on fracture incidence. However, the fracture rate reported by Tai and colleagues was higher than the previously reported rate in a large prospective cohort\(^{6}\) and, in view of the 64% increase in bone fracture rate in the isoflavone arm compared with that of the placebo arm, more cautious monitoring in this regard is mandatory.

Camil Castelo-Branco
Hospital Clinic Barcelona and University of Barcelona, Spain

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Postmenopausal hormone therapy and coronary artery atherosclerosis


A recent study raised once again the issue of potential effects of postmenopausal hormone therapy (HT) on the development of coronary artery atherosclerosis. The study group of postmenopausal hormone therapy (HT) on the development of coronary artery atherosclerosis. A recent study raised once again the issue of potential effects of postmenopausal hormone therapy (HT) on the development of coronary artery atherosclerosis. The study group of postmenopausal hormone therapy (HT) on the development of coronary artery atherosclerosis. Interestingly, the most prestigious journals in

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of hormone use. Women with natural menopause initiating HT before age 55 years had lower CAD severity compared with never-users. Interestingly, the same results were obtained from the WHI estrogen-alone arm (10-year follow-up period), where less coronary calcifications were detected by fast coronary CT scans in hormone users aged 50–59 at baseline who were compared to women in the placebo arm.

Thus, the cardioprotective effects of HT in the early post-menopause seem realistic and well substantiated by good-quality clinical data.

References


Vasomotor symptoms and negative affect

Gibson CJ, Thurston RC, Bromberger JT, Kamarck T, Matthews KA. Negative affect and vasomotor symptoms in the Study of Women’s Health Across the Nation Daily Hormone Study. Menopause 2011; Sept 1. Epub ahead of print

Vasomotor symptoms (VMS) during the preceding day have been positively associated in a recent study with next-day negative affect expressed as: mood swings, feelings easily hurt, irritable, difficulty concentrating, forgetful, anxious and blue/down in a sample of 625 women aged 42–52 years, of five racial/ethnic groups who reported at least one menstrual period in the last 3 months, were not using sex steroid hormones, had an intact uterus and at least one ovary. Subjects were drawn from a subsyudy of the Study of Women’s Health across the Nation (SWAN), known as the Daily Hormone Study (DHS). Women were asked to keep a diary during an entire menstrual cycle until bleeding or 30 days, whichever occurred first, of 14 mood and physical states, rating how strongly they were felt using a Likert scale ranging from 1 = ‘not at all’ to 4 = ‘a lot’. They were also asked to register whether or not they had experienced abdominal pain/cramps, trouble sleeping and hot flushes/night sweats during the previous 24 h. Covariates previously related to both VMS and mood such as age, education, site, and ethnic/race group were considered in the analysis. Older age, less education, perimenopause status and poorer health were related to the report of VMS on the previous day, and being Chinese was associated with fewer reports of daily VMS. The most interesting result in this study was the predictive value of reported VMS, adjusted by same-day negative affect as a predictor of next-day negative affect (odds ratio (OR) 1.27; 95% confidence interval (CI) 1.03–1.58; p < 0.01) and negative affect not being predictive of next-day VMS (OR 1.11; 95% CI 0.85–1.35; p = 0.55), thus indicating a consequential effect of VMS over negative affect.

Comment

The predictive value of reported VMS on negative affect in an antecedent–consequent direction in this study seems to support the long-held domino hypothesis which places VMS in general and night sweats in particular as predictors of both sleep problems and mood symptoms during the menopause transition, using subjective reported VMS as measurements to evaluate such a relationship. In this study, the predictive power of previous-day VMS over next-day negative mood is meaningful but, in a secondary analysis that added trouble sleeping to the model, the predictive power of VMS for next-day negative mood was reduced (OR 1.24; 95% CI 0.99–1.56; p = 0.06), while reported trouble sleeping per se was a stronger predictor of negative affect (OR 1.97; 95% CI 1.64–2.38; p < 0.001). Whether trouble sleeping was influenced by VMS and/or other somatic symptoms, such as urinary urgency, muscular pains or by mood symptoms such as anxiety, was not reported. A prior study by Burlenson had already found sleep problems as a more robust predictor of both next-day positive (b = −0.08; p < 0.01) and negative (b = 0.10, p < 0.001) mood than VMS in general. Thus, a distinction between daytime hot flushes and night sweats in diary reports would be very useful to determine whether previous-day VMS in general or night sweats in particular are predictors of next-day negative mood. The inclusion of other menopause-related symptoms that may influence sleep length and quality in multivariate models would also help to further clarify the VMS–sleep–mood relation.

Another subanalysis of the SWAN series has further studied the relationship between VMS, sleep problems and mood,
using EEG sleep measures, with the surprising result of reported VMS and mood symptoms not being related to either rapid eye movement (REM) latency (the time span between the start of sleeping and the start of REM sleep) or the delta sleep ratio (ratio of slow-wave activity in the first to that in the second non-REM sleep episode).

These results encourage a more precise measurement of sleep quality and objective physiologic VMS versus subjective recall and report that may be misleading, as was found in the Hilo study of Japanese American women. Finally, mechanisms related to estrogen and other sex steroid variations that affect directly, and not through the occurrence of VMS, sleep quality and length as well as mood during the menopause transition, through their impact on the serotonergic, adrenergic and noradrenergic systems, have been previously analyzed but still need to be explored in order to understand the constant but complex correlation between these menopausal symptoms, especially in severely symptomatic women.

Deborah Legorreta
Mexico City, Mexico

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Effects of weight changes on the bone


Villalon and colleagues report a study of the effect of weight loss and weight regain on bone mineral density (BMD) in postmenopausal overweight or obese women. They measured BMD and body composition by dual-energy X-ray absorptiometry, biochemical markers of bone formation and resorption, and aerobic power by spirometry (VO₂ peak). They found that weight loss over a 6-month period results in significant loss of bone from the lumbar spine and hip. Subsequent weight regain over a 12-month period did not produce any increase in BMD. They conclude that weight maintenance and fitness may be a better strategy than weight reduction for bone and metabolic health.

Comment
This study has many limitations and drawbacks. First, the authors are using data drawn solely from the placebo arm of a prospective, randomized trial, which was presumably not a pre-planned part of their original study design. Thus, the study is uncontrolled with regard to weight loss and weight regain in this placebo group, as there are no matched weight-steady women for comparison. Second, the numbers involved are extremely small, 23 women. They then split them into subgroups according to being above or below the median weight loss over the 6-month period, resulting in even smaller numbers. Third, two different densitometers were used and the results between them may not be strictly comparable, even though each individual was measured only on one system. The weight reduction was achieved by a supervised endurance exercise program. No mention is made of their diet and whether this changed during the study. Furthermore, no mention is made whether or not the participants continued with any unsupervised exercise during the 12-month follow-up. The median weight loss achieved was 3.9 kg, but there was quite a wide range of values. Body composition measurements showed that this weight loss was due to a significant decrease in fat mass with no change in fat-free mass. This was associated with significant loss of BMD, but these changes were small in the lumbar spine (−1.7%) and negligible in the hip (−0.04%). The authors state that this was accompanied by an increase in a marker of bone resorption (CTX), but this was not statistically significant. There was a significant decrease in a bone formation marker (bone ALP) but this decrease of −0.7% would appear biologically meaningless. During the 12-month follow-up there was a significant increase in fat mass, with again no change in fat-free mass. There were no significant changes in the BMD or bone biochemical markers during the follow-up.

It is impossible to draw any meaningful conclusions from this study. The association between lean body mass and bone has long been known, but the association between fat mass and bone is more controversial. However, it seems likely
that increased fat mass has a positive effect on the skeleton, not only through load bearing but also through production of factors that influence bone such as estrogens and adipokines. Whether weight loss has a meaningful adverse effect on bone mass and fracture risk remains to be determined. Of much more importance is the association between obesity and increased risk for cardiovascular disease and for breast cancer. Thus, weight normalization should always be encouraged, irrespective of any minor deleterious effect on the skeleton.

John Stevenson
National Heart & Lung Institute, Imperial College
London, Royal Brompton Hospital, London, UK

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Stopping HRT: were women ill advised?

Cumming GP, Currie HD, Panay N, Moncur R, Lee AJ. Stopping hormone replacement therapy: were women ill advised? *Menopause Int* 2011;17:82–7

The aim of a recently published study by Cummings and colleagues was to survey the views of women who stopped hormone replacement therapy (HRT) after 2002, including those who later restarted1. A questionnaire survey was carried out on the UK-based menopause website www.menopause-matters.co.uk, evaluating how women were influenced by HRT advice. The main outcome measures were the answers to questions regarding stopping/restarting HRT in response to the advice in the early 2000s and advice given today. A total of 1100 responses were obtained. Of those who made the decision to stop HRT themselves, 56.4% (*n* = 425/754) said that they were influenced by the media. In those who would potentially most benefit from HRT, 72.8% (*n* = 220/302) stopped without medical advice. Overall, women aged under 50 years were significantly more likely to stop HRT themselves than women over 50 years (*p* < 0.001). In women in whom symptoms returned, 37.5% (*n* = 362/966) said these affected their ability to work, 45.1% (*n* = 436) had problems with decision making, 53.6% (*n* = 518) admitted to relationships being negatively affected and 29.2% (*n* = 286) said that symptoms affected their social relationships. Overall, 46.5% of women (*n* = 485/1044) would not have stopped HRT given the current understanding of risk. Compared with women over 50, significantly more women under the age of 50 said that they would not have previously stopped their HRT based on their current understanding of risk (*p* < 0.001).

Comment

Since publication of the results of the Women’s Health Initiative (WHI) trial in 20022 and the Million Women Study in 20033, there has been much confusion around the use of HRT, with media reporting frequently emphasizing the risks and ignoring the benefits of HRT. As a result, many women world-wide either chose to, or were advised to stop using their HRT. Although for some there may have been no recurrence of symptoms from stopping, it is unclear how many women have suffered from recurrence of menopausal symptoms, which may have adversely affected their quality of life or indeed have had a detrimental effect on bone mass or cardiovascular health4. A post-WHI European survey indicated that two-thirds of menopausal women were suffering from at least one severe symptom and, although most felt that menopause should be treated, only 22% were using a recognised preparation5. The aftermath of the publication of the Million Women Study and the re-evaluation of the data emerging from the WHI studies have shown that the messages that emerged from them were confusing and flawed.

The findings of this study suggest that the negative impact of published research and its reporting from the early 2000s are being mitigated by current press coverage. Media reports appear to have influenced younger women more than older women. This is worrying, as it is particularly important that young women with early menopause continue HRT at least until the average age of the menopause, to preserve quality of
life and to prevent long-term complications such as osteoporosis, cardiovascular disease and cognitive impairment. The study highlights the responsibility of the shoulders of researchers and the media with regards to the potential impact their publications can have on vulnerable people. 

The limitations of the study are that this was a relatively small questionnaire survey. The data could potentially have been biased by the type of women using the Menopause Matters website and by the type of women choosing to answer the survey, i.e. those with greater concerns would have been more likely to have taken the time to respond to the survey. Nevertheless, bias was eliminated as much as possible by not petitioning women to respond to the survey and by not offering incentives. Also, each questionnaire could only be completed once per computer. Internet provider addresses were checked for duplicates and none were found6.

An attempt was made by Menopause Matters to expand the survey by inviting participants through Our Menopause World, a global electronic menopause news service of the International Menopause Society, to fill in a questionnaire on the Menopause Matters website. The response to this was surprisingly low compared to previous UK national surveys by Menopause Matters which had had an excellent response7. It suggests that international surveys are better conducted by the regional or national affiliates themselves as they are likely to be sensitive to local issues, with the IMS providing a central coordinating role. Clearly, more data are desirable, not only on HRT usage, but also on the incidence of clinical outcomes, to determine precisely how much damage has been done by the often unnecessary discontinuation of HRT by many women following WHI and the Million Women Study.

Nick Panay
Queen Charlotte’s & Chelsea and Chelsea & Westminster Hospitals, London, UK

References

Adherence to osteoporosis medications


Li and associates have recently reported a study aimed at estimating persistence with osteoporosis therapies and assessing persistence by different users (stable and switching), type of osteoporosis drug, and calendar year of initiation among postmenopausal women, 50 or more years old included in UK General Practice Research Database (GPRD) between January 1995 and March 20081. Persistence with osteoporosis medications was estimated as the proportion of women who continued therapy at 6 months and at 1, 3, and 5 years. During the study period, there were 66,116 women who had a first-ever prescription for an oral bisphosphonate, oral raloxifene, or oral strontium ranelate. Diagnosis of osteoporosis was not an inclusion criterion and the most frequent female co-morbidities were heart disease, chronic pulmonary disease, rheumatoid arthritis, diabetes mellitus, hyperthyroidism, inflammatory bowel disease and chronic liver disease. Overall, women were continuing with osteoporosis therapy at 6 months after the index date in the full study population in 44% of episodes and in 32%, 16%, and 9% of episodes at 1, 3, and 5 years later, respectively. At 6 months from initiation, monthly ibandronate treatment and weekly alendronate and risedronate treatment had the highest persistence rates, 56.8%, 52.8, and 53.1%, respectively. Daily alendronate and strontium ranelate had the lowest persistence rates (27.0% and 30.0%, respectively). The authors concluded that persistence with osteoporosis therapies had improved over the study period, but persistence in the first 6 months remained below 50%, leaving a large unmet need to improve the management of postmenopausal women through novel adherence programs and therapies.

Comment

During the last 20 years, diagnosis of osteopenia and osteoporosis has improved remarkably, allowing the early detection
of women at risk of suffering low-intensity or fragility fractures. As a result of increased life expectancy, currently women spend more than one-third of their lives in a state of estrogen deprivation, which in turn leads to a number of significant long-term changes. Hence, osteoporosis is highly prevalent among postmenopausal women.

Treatment of osteoporosis involves lifestyle changes (i.e. diet and exercising) and also pharmacological therapy, both aimed at increasing bone mass and resilience. In order to prevent fractures, osteoporosis medications are prescribed for prolonged periods of time. Many fragility microfractures are not recognized or are devoid of clinical symptoms, and thus patients may not perceive treatment benefits. This situation may, in fact, decrease long-term compliance. Advanced osteoporosis (very low bone mineral density) may lead to multiple fractures, stooped posture, loss of height, chronic pain and reduced mobility. In addition, there are some diseases and treatments that increase osteoporosis risk, such as those described in the studied GPRD population. Therefore, after providing a detailed pathophysiological explanation for the spontaneous clinical course of the disease and the risk of fractures, osteoporosis treatment (healthy lifestyle and pharmacological agents) requires a high degree of adherence and persistence.

Reports indicate that osteoporosis treatment with any of compounds analyzed in the study by Li and colleagues reduces the incidence of low-intensity fractures in a wide variety of populations at risk. Data supporting treatment efficacy have been drawn from controlled clinical trials. Despite this, in ‘day-to-day clinical practice’ (outside clinical trials), patient adherence and persistence to therapy are, in fact, not as high as those found in controlled trials.

Primary non-adherence among patients may vary in relation to disease or health conditions, personality and type of therapy. In the US, reports indicate that only 50% of patients adhere to treatments for chronic illnesses or improvement of lifestyle habits. One-third of patients do not take properly or appropriately adhere to their medication, exposing themselves to additional risks and increasing mortality rate twofold. Factors involved in treatment adherence may vary among patients. Moreover, each patient has an individual perception regarding whether she or he is being persistent or not to one medication or another. Thus, higher perception of treatment need, disease severity, satisfaction with physician consultation, fewer side-effect concerns, and knowledge about disease and medication may increase adherence. Interventions aimed at increasing adherence should be tailored according to the patient’s beliefs and medication characteristics. Communication has a relevant role in health literacy regardless of the patient’s level of education. Clinicians should provide comprehensive educational materials that may strengthen compliance with osteoporosis medication. On the other hand, new educational programs directed at patients should be developed to increase awareness of osteoporosis and fractures, treatment benefits and cautions and lifestyle changes. Internet-based information may also be an easy way to develop and obtain comprehensive, good-quality educational material without commercial bias. Pharmacists may also have an important role in improving medication adherence, although their role in long-term treatments is not well known. Physicians and other health-care professionals for women should improve their knowledge of the importance of compliance with osteoporosis medication. In the American population, low satisfaction with osteoporosis treatment is associated with 22–67% increased risk of stopping or changing medication during the first year of prescription. In Europe, poor persistence with osteoporosis treatment has resulted in a failure to significantly reduce fracture risk.

A better approach to the woman with bone loss and risk of fractures would contribute to increasing the therapeutic effects of osteoporosis medications, reducing morbidity and mortality, and lower health-care costs linked to the management of osteoporosis and its complications. New treatments are available with longer administration intervals: given monthly, quarterly, every semester or even annually. It remains, however, to be determined whether these therapeutic options will succeed in increasing adherence and decreasing adverse events. There is a need for future amelioration management in women with bone mass loss who are at risk for fractures.

Faustino R. Pérez-López
Department of Obstetrics and Gynecology, University of Zaragoza, Zaragoza, Spain
and
Peter Chedraui
Institute of Biomedicine, Facultad de Ciencias Médicas, Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador

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