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HRT misuse and the osteoporosis epidemic

In a recently published study, Karim and colleagues [1] have evaluated the impact of cessation of hormone replacement therapy (HRT) on the incidence of hip fracture in a large cohort from the Southern California Kaiser Permanente health management organization. This large, longitudinal, observational study included 80,955 postmenopausal women. The women using HRT as of July 2002 were followed up through December 2008, thus giving data from 80,955 postmenopausal women and 532,686 person-years of observation. Bone mineral density (BMD) was assessed in 54,209 women once during the study period using the dual-energy X-ray absorptiometry scan. In this huge cohort of postmenopausal women followed for 6.5 years, HRT discontinuation was associated with a 55% increased risk for hip fracture alone (95% confidence interval (CI) 1.36–1.77). **Hip fracture risk increased as early as 2 years after cessation of HRT (hazard ratio 1.52**; **95% CI 1.26–1.84), and the risk incrementally increased with longer duration of cessation (*p* for trend < 0.0001).** Longer duration of HRT cessation was linearly correlated with lower BMD (β estimate [standard error]) = -0.13 [0.003] *T*-score SD units per year of HRT cessation; $p < 0.0001$). **Compared with HRT users, the women who did not use hormones in the previous year were 58% more likely to have a hip fracture in the following year.**

Overview

This decisive paper [1] clearly demonstrates that women who discontinue HRT significantly increase their risk of hip fracture and lower BMD compared with women who continue taking HRT. This report cannot be ignored or disregarded by health-care providers and, most importantly, by Regulatory Agencies worldwide. Following our forecast on fracture increase in the era after the Women's Health Initiative (WHI) study, the undersigned and colleagues regret to say: we were right [2]. After the drop in the number of hormone users in the USA, we estimated a substantial increase in overall fracture risk in postmenopausal women. Our calculations were based on assumptions: the idea was there but the data were lacking. Now, the data on increased risk after HRT discontinuation also give a realistic insight on osteoporosis risk in women who do not use HRT at all. In fact, the paper by Karim and colleagues [1] analyzes the incidence of fracture after HRT discontinuation: the authors do not compare women using HRT vs. never-users: the number would be even more shocking.

The public health system message for physicians, and particularly for women who have been worried about HRT after a decade of alarming media communications, should be that discontinuation of HRT is associated with an increased fracture risk. Karim and colleagues [1] only evaluated the incidence of hip fractures and did not analyze the effect of HRT discontinuation on other fractures, such as vertebral or wrist fractures. However, we can assume that the burden of HRT withdrawal, particularly on different skeletal sites, such as vertebral bodies where trabecular bone is prevalent, will be far more substantial. Thus, the Karim study results perhaps even underestimated the overall effect of HRT discontinuation on postmenopausal bone health.

The alarming information coming from this study also includes data on the poor use of other bone-protective strategies after HRT discontinuation. While HRT use substantially decreased between July 2002 and December 2008 from 85% to 18%, use of the bisphosphonate drugs increased from 8% to 23% during the study period [2]. The authors

reported no change in hip fracture risk associated with HRT discontinuation after controlling for bisphosphonate use. A complete analysis of fracture risk in women taking bisphosphonates after HRT discontinuation is missing. However, this lack of information is really relevant and highlights the need for a study of the effects of bisphosphonates on fracture risk in the general population rather than in group of high-risk women, as selected in the trials conducted for registration of the different molecules. The paper does not say anything about the use of raloxifene or other bone-protective agents after HRT discontinuation, but the data as reported are really frightening for the future fracture risk of this population.

The major strength of Karim and colleagues' study [1] is that the large group of women can be considered as representative of the general population, rather than selected for low BMD or previous fractures. Therefore, these results have general relevance to all postmenopausal women and should be taken into account in the calculation of the HRT benefits and risk ratio. The current attitude on HRT, which is based on biased interpretations of the WHI, has undermined confidence in the use of HRT, leading to hormone avoidance or discontinuation in many women. In addition, in the last decade, guidelines have been modified, with recommendations against HRT for chronic disease prevention including osteoporosis. At that time, we wrote that these recommendations were contrary to all the available evidence [3]. Being the most effective treatment in the management of climacteric symptoms, HRT has also an important role in reducing bone turnover, preserving bone density and quality, leading to the prevention of postmenopausal osteoporosis and related fractures. In the early postmenopausal years, HRT is thus the most effective, reliable, safe and cheap pharmacological intervention for the prevention and treatment of osteoporosis [4]. **The use of HRT for osteoporosis prevention is based on biology, epidemiology, animal and preclinical data, observational studies and randomized, clinical trials, and thus bone protection has been included among the benefits of HRT in recent recommendations issued by both the International Menopause Society and the Endocrine Society [5,6]. In fact, osteoporosis prevention can actually be considered as a major additional effect in perimenopausal women who use HRT for treatment of climacteric symptoms.**

The paper by Karim and colleagues [1] provides important information and underlines the need to identify new approaches for long-term osteoporosis prevention. These strategies can include lower HRT doses and selective estrogen receptor modulators (SERMs), or a mixture of the two combined to form a new class of menopausal therapy called 'tissue selective estrogen complex' or TSEC, based on the blended profiles of tissue selective activity of the components [7-10]. Unfortunately, data on fracture incidence using lower HRT doses or TSEC are lacking at the moment. Nevertheless, and in the meantime, the current view and recommendations from Regulatory Agencies about HRT need to be revisited and revised without delay.

- HRT protects women against postmenopausal osteoporosis and related fractures.
- HRT withdrawal leads to an increased risk of fracture in postmenopausal women.
- The current view and recommendations from Regulatory Agencies about HRT need to be revisited and revised without delay.
- New strategies for long-term osteoporosis prevention should be sought.

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References

1. Karim R, Dell RM, Greene DF, Mack WJ, Gallagher JC, Hodis HN. Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization. Menopause 2011 Jul 19. Epub ahead of print
http://www.ncbi.nlm.nih.gov/pubmed/21775911
2. Gambacciani M, Ciaponi M, Genazzani AR. The HRT misuse and osteoporosis epidemic: a possible future scenario. Climacteric 2007;10:273–5.
http://www.ncbi.nlm.nih.gov/pubmed/17653953
3. Gambacciani M, Genazzani AR. The Xmas present for women's health: a strike to osteoporosis prevention. Maturitas 2004;48:9–11.
http://www.ncbi.nlm.nih.gov/pubmed/15223102
4. Genazzani AR, Gambacciani M, Schneider HP, Christiansen C; International Menopause Society Expert Workshop. Postmenopausal osteoporosis: therapeutic options. Climacteric 2005;8:99–109.
http://www.ncbi.nlm.nih.gov/pubmed/16096166
5. Sturdee DW, Pines A, on behalf of the International Menopause Society Writing Group. Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. Climacteric 2011;14:302–20.
http://www.ncbi.nlm.nih.gov/pubmed/21563996
6. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: An Endocrine Society Scientific Statement. J Clin Endocrinol Metab 2010;95(Suppl 1):S1–66.
http://www.ncbi.nlm.nih.gov/pubmed/20566620
7. Lees B, Stevenson JC. The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17β and dydrogesterone. Osteoporosis Int 2001;12:251–8.
http://www.ncbi.nlm.nih.gov/pubmed/11420773
8. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA 2002;287:2668–76.
http://www.ncbi.nlm.nih.gov/pubmed/12020302
9. Ettinger B, Ensrud KE, Wallace R, et al. Effects of ultralow-dose transdermal estradiol on bone mineral density: a randomized clinical trial. Obstet Gynecol 2004;104:443–51.
http://www.ncbi.nlm.nih.gov/pubmed/15339752
10. Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. Fertil Steril 2009;92:1045–52.
http://www.ncbi.nlm.nih.gov/pubmed/19635616