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PERSPECTIVES

Menopause as a potential cause for higher prevalence of low back pain in women than in age-matched men

Yi Xiang J. Wang*

Department of Imaging and Interventional Radiology, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, New Territories, Hong Kong Special Administrative Region

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Summary Female sex hormones play an important role in the aetiology and pathophysiology of a variety of musculoskeletal degenerative diseases. Postmenopausal women show accelerated disc degeneration due to relative oestrogen deficiency, resulting in narrower intervertebral disc space in women than age-matched men, increased prevalence of spondylolisthesis, and increased prevalence of facet joint osteoarthritis. Postmenopausal women also show higher osteoporosis related spine fracture rate, particularly at the thoracic—lumbar junction site. I propose the concept that low back pain (LBP) is more prevalent in postmenopausal women than age-matched men and is associated with the physiological changes caused by the relatively lower level of sex hormones after menopause in women. Considering hormone replacement treatment (HRT)'s consistent efficacy reported with menopause-associated osteoarthritis, an in-depth understanding of the role of the gonadal hormones in LBP modulation warrants further study. HRT initiated at early postmenopausal phase may be protective for recurring LBP. If this is the case, further cost—benefit analysis should be performed for optimal HRT regimen in cases of women with high risk of recurring severe LBP.

Oestrogens participate in a variety of biological processes through different molecular mechanisms. Oestrogen has favourable effects on the lipid profile, antioxidant activity, and enhanced fibrinolysis [1]. Female sex hormones also play an important role in the aetiology and pathophysiology of a variety of musculoskeletal degenerative diseases. The

* Corresponding author. Department of Imaging and Interventional Radiology, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, New Territories, Hong Kong Special Administrative Region.
E-mail address: yixiang_wang@cuhk.edu.hk.

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prevalence of osteoarthritis (OA) is higher among women than among men, and this prevalence increases considerably after menopause [2,3]. Moreover, with the same degree of radiographic damage, OA is also more symptomatic in women [2,3]. Young men are more susceptible to disc degeneration than young women, probably due to increased mechanical stress and physical injury [4–6]. However, recent evidence suggests that disc degeneration is common or more severe in elderly women than in elderly men [7,8]. Postmenopausal women show accelerated disc degeneration due to relative oestrogen deficiency [9,10]. Postmenopausal women also show narrower intervertebral disc space than age-matched men [8,11], increased prevalence of spondylolisthesis [12–14], and increased prevalence of facet joint arthritis [15].

In the literature, the reported population-based low back pain (LBP) prevalence varies as it depends on the definitions of LBP as well as the survey method. A number of reports suggest that women have higher prevalence of LBP than men [16–19], despite the fact that young and middle-aged men have higher prevalence and more severe intervertebral disc degeneration [4–6]. The higher LBP prevalence in women is probably due to many factors, including heightened pain sensitivity among women [20,21], menstrual cycle fluctuations, biologic response and stress to pregnancy and childbearing, and perimenopausal abdominal weight gain [19]. Recently, it has been show that genetics also plays a role in the development of LBP [1,22,23]. A very recent systematic review, which was limited to population based studies with the same LBP criteria applied to both men and women in the same community, demonstrates, compared with middle-aged individuals, a further increased LBP prevalence in women than in men was noted after menopause age [24]. By contrast, in an evaluation of pain characteristics of adults aged $\geq$ 65 years referred to a tertiary pain care clinic, the older patients had relatively more physical problems concordant with their complaints, but fewer psychological factors contributing to disability than the younger patients [25,26].

In some studies, LBP is strikingly more prevalent in postmenopausal women than age-matched men. In 1969, Lawrence [27] surveyed 713 men and 809 women aged $\geq$ 35 years with lumbar radiography in Manchester, UK. Back–hip–sciatic pain was present at the time of the survey in 79 (11%) of the men and in 153 (19%) of the women. In those with pain at the time of the survey, the incidence had risen up to age 40 years in men and then remained constant, but in women it continued to rise sharply up to and over the age of 65 years (Figure S1A). In 1995, Papageorgiou et al [28] reported the South Manchester Back Pain Survey with a study population of 4501 (age 18–75 years). The 1-month period prevalence of LBP was 31.2%, 33.1%, 38.5%, and 34.9% for the age ranges of 18–29 years, 30–44 years, 45–59 years, and $\geq$ 60 years, respectively, for men; 32.2%, 41.5%, 49.2%, and 43.7% for the age ranges of 18–29 years, 30–44 years, 45–59 years, and $\geq$ 60 years, respectively, for women. In 2010, Cho et al [29] published LBP data collected for 4181 individuals from a rural farming community in Korea. The participants had a mean age of 56.6 years and 55.5% were women. Six-month prevalence of LBP was 38.5 % for men and 55.6 for women. The prevalence of LBP increased significantly with age in women (Figure S1B). Data from the Osteoporotic Fractures in Men (Hong Kong) and Osteoporotic Fractures in Women (Hong Kong) Studies were published in 2013 [8]; 2000 Chinese men and 2000 Chinese women, aged $\geq$ 65 years, were prospectively recruited from local communities for a prospective cohort study from August 2001 to March 2003. The LBP prevalence was 30.6% for men and 53.3% for women ($p < 0.001$). While postmenopausal women also show higher osteoporosis-related spine fracture rate compared with age-matched men, and vertebral fracture is a known cause of back pain and related disability [30], the accelerated spine degeneration caused by the relatively lower level of sex hormones after menopause in women [9,10], including narrower intervertebral disc space, higher lumbar spondylolisthesis prevalence, and increased prevalence of facet joint osteoarthritis, may be an additional source of LBP in elderly women.

Oestrogen with or without a progestogen prevents early postmenopausal bone loss and augments bone mass in late postmenopause as effectively as the bisphosphonates [29]. Hormone replacement treatment (HRT) has consistently been shown to be protective against menopause-associated OA [31–35].

However, to date the clinical data on HRT's effects on LBP remain contradictory. For example, Baron et al [36] found that women on HRT maintained intervertebral disc height compared with untreated postmenopausal women. They suggested that the oestrogenic milieu may be relevant because of the significant impact it has on the hydrophilic glycosaminoglycans, the water content, collagen, and elastin of the intervertebral discs. The maintenance of adequate disc height may allow the intervertebral discs to retain their discoid shape and viscoelastic function, containing vertical forces which may threaten spinal architecture leading to vertebral body compression fractures [36]. Kyllönen et al's [37] longitudinal clinical study supports that oestrogen–progestin replacement therapy was beneficial for lumbar spine mobility. In an experimental study, Li et al [38] reported that resveratrol, a phytoestrogen, is a potent anabolic mediator of bovine intervertebral disc cartilage homeostasis to slow the progression of disc degeneration. However, in one study Musgrave et al [39] reported that women taking HRT had more back pain and back pain-related disability than did those not taking HRT. In another study Symmons et al [40] also reported that oestrogen use was more common in the group reporting back pain than in the group without back pain. Considering that HRT is known to decrease vertebral fracture rate [31], and protect intervertebral disc [36], and maybe also facet joint [12], Musgrave et al's [39] and Symmons et al's [40] findings look counterintuitive. In one systemic review, Bressler et al [25] noted that there is an under-representation of the older population in the LBP pain literature. They stressed the need for future studies to improve the reporting of age information to make prevalence studies more informative and applicable.

The expert views of HRT have evolved during the past 10 years since the publication of Women's Health Initiative trials [41,42]. Since the initial publication of the Women's Health Initiative hormone trial results, multiple secondary analyses have yielded interesting data that suggested that

the risk of coronary heart disease was dependent upon both the timing of initiating hormone exposure as well as the age of the woman at the time of HRT initiation [43,44]. Specifically, in the oestrogen-alone trial, a nonstatistically significant reduction in coronary heart disease risk was noted in participants aged 50—59 years [44]. Dose regimen, combination of oestrogen with progestins versus oestrogen alone, the administration route, and duration of treatment such as the choice of repetitive or periodic administration simulating the menstrual cycle are some of the factors that may be involved in benefit discrepancies. The Estrogen and Thromboembolism Risk study confirmed that oral oestrogens increased venous thromboembolism risk, whereas transdermal oestrogens had little or no impact on the development of thrombosis [45]. Recent Korean data do not support HRT history for the risk of breast cancer in women [46]. The presence of gene polymorphisms may also be implicated. HRT may benefit a large number of postmenopausal women, but a subset of women may have higher risk of cardiovascular and thrombotic complications [47]. Oestrogen receptor modulators and phytoestrogens may retain the desired effects but avoid undesirable effects [48]. Considering HRT's efficacy reported with menopause-associated OA in many studies, an in-depth understanding of the role of the gonadal hormones in LBP modulation warrants further study. HRT initiated at early postmenopausal phase may be protective for recurring LBP, as LBP tends to be a recurring phenomenon in nature. HRT protects both bone [31] and disc tissue [12,36]. If this is the case, further cost—benefit analysis should be performed for optimal HRT regimen in cases of women with high risk of recurring severe LBP.

Conflicts of interest

The author has no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jot.2016.05.012.

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