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REVIEW

Sex differences in magnetic resonance imaging-based biomarkers and in those of joint metabolism

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Abstract

Sex differences in the prevalence, incidence, and severity of osteoarthritis (OA) have long been known. Some differences in the evaluation of this issue across studies may be related to differences in study design, sampling, study size, study populations, targeted joint sites, and definitions of OA. This report highlights recent studies of sex differences in individual joint components imaged by magnetic resonance imaging and in systemic biomarkers of joint metabolism. Particularly important are those studies that examine this issue in young unaffected adults and children before the development of disease. Despite some variation across studies, women appear for the most part to have a thinner and more reduced volume of cartilage in the knee than men, and this may occur from early childhood. It is not clear whether women have a more accelerated rate of cartilage volume loss than men. Few data exist on sex differences in systemic biomarkers of joint metabolism. In these studies, it is critically important to characterize the total body burden of OA and the presence of comorbid conditions likely to influence a given biomarker. Lastly, future research should dovetail studies of sex differences in imaging and biochemical biomarkers with genetics to maximize insight into the mechanisms behind observed sex differences.

Sex differences have been noted in the prevalence, incidence, and severity of osteoarthritis (OA) for many years [1-3]. The incidence of knee, hip, and hand OA is higher in women than men and in women increases dramatically around the time of menopause [3,4], prompting many investigations into the roles of estrogen and other hormones as possible explanatory factors. Results of clinical and epidemiologic studies have been conflicting [5-7], with some showing a protective effect for estrogen or hormone replacement therapy (HRT) on radiographic knee and hip OA [8,9] or progression to joint replacement [10] but no effect on joint symptoms [11]. Differences in study results can be ascribed to differences in (a) study populations and study designs; (b) distribution of, or confounding by, other risk factors such as age, race/ethnicity, body mass index (BMI), and smoking; and (c) joints affected by OA and definitions used to define OA [3] and statistical methodology. A recent systematic review of 17 studies illustrates this point. There was no clear association between sex hormones and hand, knee, or hip OA in women, but study heterogeneity precluded combining them into a single analysis [6]. For example, radiographic OA can be defined by overall radiographic scoring, such as the Kellgren-Lawrence system (grades 0 to 4) [12], or by individual radiographic features, such as osteophytes or joint space narrowing [13]. Other definitions may incorporate joint-specific symptoms with or without accompanying radiographic OA. With these multiple methods of examining sex differences in OA, it is no wonder that the issue is far from settled.

One way to examine the basis of sex differences in OA is to examine sex differences in the individual components of the joint through magnetic resonance imaging (MRI) and joint metabolism biomarkers. Structural features of OA can be examined using overall grading [14] or, more commonly, by individual features, such as cartilage thickness or volume, synovial hypertrophy and effusion, bone marrow lesions, or meniscal pathology. Additionally, rather than studying individuals who already have OA (that is, prevalent disease) as is commonly done, studying unaffected individuals followed prospectively may inform this question better since this approach avoids the question of temporality inherent in cross-sectional studies of prevalent disease, allows an assessment of the predictive value of specific findings for the development of OA, and potentially provides an opportunity for primary prevention and early intervention. This entails the examination of intrinsic characteristics of younger healthy men and women before they develop

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OA or even the examination of normal children. With increasing attention to risk factors for multiple diseases across the life course [15,16], this approach could expose potential mechanisms behind sex differences in OA and identify high-risk people in advance of disease.

Reviews of the epidemiology of sex differences in OA have recently been published [5-7,17]. This review will instead highlight novel study designs or studies of unaffected and younger individuals, including children, to focus on sex differences in (a) structural joint components using MRI and (b) biomarkers of joint metabolism.

Insight into sex differences in structural joint components using magnetic resonance imaging

Cartilage thickness, volume, and defects

Since men and women vary in body size, one might assume that men have greater cartilage volume. Cicuttini and colleagues [18] were among the first teams to test this hypothesis in knee cartilage volume using MRI. In 17 Australian men and 11 women who had normal knee radiographs and who were having knee MRI because of knee pain of less than 3 months in duration, men had larger femoral and patellar cartilage volumes than women, independently of age, height, weight, and bone volume. Sex differences in patellar cartilage volume were magnified with increasing age [18]. In a study of nine healthy German men and nine women in their early 20s without a history of athletic or heavy physical activity, Faber and colleagues [19] confirmed lower cartilage volumes in women than men and showed that this sex difference was related primarily to differences in joint surface area or bone size rather than cartilage thickness, where differences were less pronounced and not statistically significant.

Otterness and Eckstein [20] hypothesized that smaller joint surfaces in women might explain sex differences in knee OA because of higher articular pressures with smaller surface area. Using healthy men and women, the authors confirmed that men have greater knee subchondral bone area, cartilage thickness, and cartilage volume compared with women, after adjustment for height and weight [20]. Estimated tibial or patellar pressures, using the metric of body weight/joint surface area, however, were equivalent in men and women, suggesting that smaller joint surfaces in women were not a likely explanation for sex differences in knee OA [20].

These authors found that total subchondral bone area and cartilage volume were strongly associated in young healthy men and women. However, while cartilage volume and bone area were strongly related to height in women, their associations with height in men were weak and inconsistent, leading the authors to suggest the possibility that different factors are responsible for bone and cartilage growth in men and women [21].

Longitudinally, Australian women have been shown to have a higher rate of cartilage loss than men [22,23], whereas men may have a higher rate of cartilage loss than women in studies in the US [24,25]. In 135 Australian men and 190 women from 26 to 61 years old (mean age of 45 years), Ding and colleagues [22] reported that, over an average of 2.3 years, women had a higher annual rate of cartilage volume loss than men in all knee compartments, although only tibial cartilage loss was statistically significantly different by sex. These sex differences first appeared at age 40 and increased with age [22]. Importantly, there were no significant sex differences in the crude annual percentage change or in the annual percentage change adjusted for age, BMI, and offspring/control status in cartilage volume in any plates; sex differences were evident only after further adjustment for baseline cartilage volume and bone size, and this could have inflated the difference. The composition of this convenience sample was intriguing; the sample consisted of offspring of people who had undergone knee arthroplasty for knee OA and the rest were from the general population. Interestingly, the magnitude of cartilage loss was higher in offspring than the general population, suggesting a high risk for the development of cartilage loss and presumably, later, for the development of knee OA [22]. Women were also three times more likely than men to have increases in tibial cartilage defects over time [22,23].

A different result was obtained from the Osteoarthritis Initiative (OAI) [24,25], an ongoing multi-center study in which a 3-Tesla MRI of the knee is obtained annually in approximately 4,800 individuals from 45 to 79 years old at baseline either with symptomatic radiographic knee OA (progression cohort) or with risk factors to develop knee OA (incidence cohort) [26]. An early study of the progression subcohort evaluated individuals (79 women and 77 men, mean age of 61 years) with frequent knee symptoms and radiographic knee OA in at least one knee. After 1 year, modest cartilage thickness loss occurred, more in the medial compartment than in the lateral, more in the medial femur than in the medial tibia, and more in the lateral tibia than in the lateral femur. There were no statistically significant differences in the rate of change of cartilage volume or thickness by age, sex, BMI, frequent symptoms, or radiographic Kellgren-Lawrence grade [24]. In the OAI, in contrast to the Australian studies, there was a non-statistically significant trend for men to have a greater rate of change in cartilage volume and thickness than women. The authors conceded that statistical power was limited, the period of observation was short, and only one knee (which may not have been the symptomatic knee) for imaging with Coronal FLASHwe (fast low angle shot with water excitation) was studied [24,25]. When only some

plates demonstrate differences, it is unclear whether this illuminates potential mechanisms, perhaps biomechanical, or represents a chance occurrence. None of these studies accounted for multiple comparisons inherent in the analysis of detailed MRI data, and it remains to be seen whether differences will be replicated in larger samples in which such multiple comparison testing is considered.

Hormonal associations with cartilage metrics by magnetic resonance imaging

Sex hormones and HRT after menopause have received considerable attention in the assessment of radiographic knee and hip OA, symptomatic OA, and joint replacement but with conflicting results [8-11,27-29]. Using MRI outcomes, Wluka and colleagues [30] reported that healthy women who had no knee pain and who were taking HRT had greater knee cartilage volume than women not on HRT, suggesting a chondroprotective role for HRT. Such promising cross-sectional results were not borne out on longitudinal assessment [31]. Serum testosterone levels in such healthy women were not associated with cartilage thickness, cartilage defects, bone surface area, or large bone marrow lesions [32].

In healthy men without knee pain, on the other hand, cartilage volume was directly related to serum testosterone levels, but testosterone was not associated with change in cartilage volume [33]. The authors of these studies acknowledged that serum measures of androgens may not accurately reflect levels and activity at the site of interest, and so the implication of these findings is unclear [32,33].

Leptin, a 16-kDa non-glycosylated hormone encoded by the obese gene and secreted by adipocytes, osteoblasts, and chondrocytes, has received some attention in OA and may be related to sex differences in OA [34]. Leptin is elevated in OA cartilage and osteophytes [35,36], and higher concentrations have been found in synovial fluid in OA [37]. Women and those with higher BMI have higher leptin levels as well [38]. Ding and colleagues [39] evaluated cross-sectional associations between serum leptin levels and cartilage volume and cartilage defects in a subsample (n = 190, 48% were women, and mean age was 63 years) of the Tasmanian Older Adult Cohort, a population-based cohort of incidence and progression of OA and osteoporosis. In multi-variable analyses controlling for sex, age, BMI, smoking, radiographic knee OA, bone size, and other diseases (rheumatoid arthritis, cardiovascular disease, asthma, and diabetes), log-transformed leptin levels were significantly associated with knee cartilage volume but not with cartilage defects. Importantly, for the purposes of this review on sex differences in cartilage volume, leptin levels partially mediated the relationship between sex and cartilage volume, with a decrease in the R^2 of the multi-variable model from 51% to 30% with additional adjustment for leptin levels [39]. Leptin did not mediate sex associations with cartilage defects. These studies suggest that leptin may mediate some sex differences in OA.

Imaging of cartilage in children

In keeping with the premise that sex differences in cartilage may be intrinsic or present many years in advance of OA onset, Jones and colleagues [40] performed a cross-sectional study of knee cartilage thickness and volume and bone surface area in 49 boys and 43 girls from 9 to 18 years old. One might expect boys to have larger cartilage volume than girls, and the authors controlled for multiple factors – such as age, BMI, bone area, number and type of sports participated in, vigorous physical activity, and lower limb muscle strength – that could influence these relationships. After adjustment, boys had greater cartilage thickness and volume than girls in all Tanner stages, with sex accounting for 20% of patellar volume, 26% of medial tibial volume, and 8% of lateral tibial cartilage volume. There was no difference in cartilage volume between pre- and post-menarchical girls.

Although many factors are related to the sex difference in cartilage parameters, these results imply that sex differences exist from early stages in the life course and that OA is likely determined or at least influenced by events in early life, even in the absence of joint injury. This principle is consistent with murine mesenchymal stem cell studies in which cells from male animals produced a 'richer extra-cellular matrix' [41] and larger culture pellet than cells from female animals. Furthermore, the regenerative potential of male cells was superior to that of female cells, with male cells providing better cartilage repair in nude mice than female cells did [41]. Koelling and Miosge [42] recently described sex differences in chondrogenic progenitor cells in cartilage from men and women undergoing knee joint replacement for OA. The authors observed that gene expression patterns differed by sex for ESR-1 and -2 genes, the transcription factor Sox9, and types I and II collagen [42]. There were also sex differences in the effect of sex hormones upon collagen II gene expression and in regulatory effects independently of Sox9 and Runx2. These studies showed that sex differences in cartilage occur from early development and persist through end-stage OA, suggesting that therapies might need to be tailored to men and women.

Meniscus and ligaments

Girls and women have different biomechanics, gait, and structural and morphometric properties of tendons and ligaments than boys and men [43-47]. It is likely that these intrinsic differences contribute to the increased frequency of ligamentous injury in young female athletes

[43-47]. Whether these issues potentially contribute to the sex disparity in OA in later life is unclear, and surprisingly little attention has been devoted to sex differences in these structures using MRI in adults [48]. Fayad and colleagues [48] described differences in anterior cruciate ligament bundle volumes in 33 men and 30 women (mean age of 43, range of 15 to 70 years) referred for clinical MRI. Although there was a sex difference in anterior cruciate ligament volume, this was explained entirely by differences in height [48].

In a study that was mostly of asymptomatic individuals in Australia, women were over four times more likely than men to have meniscal tears by 1.5-Tesla MRI [49]. In contrast, 32% of the men and 19% of the women in the Framingham cohort (n = 991, 57% were women, and mean age was 62.3 years) had meniscal tears or destruction by 1.5-Tesla MRI, with the prevalence in both sexes increasing with age [50]. In a study of women who were older than 40 years of age, had knee OA, and had been screened into a clinical trial for OA, meniscal tears were present in 73%, and not surprisingly, these were associated with significant impairment in walking endurance and balance after OA duration, symptoms, disability, body composition, and relevant clinical characteristics were controlled for [51].

Finally, Stehling and colleagues [52] recently reported associations between various knee lesions on 3-Tesla MRI and physical activity in 236 individuals from 45 to 55 years old in the asymptomatic incidence subcohort of the OAI. Although assessment of sex differences in MRI features was not the purpose of the paper, ligamentous abnormalities were more likely in men than women (23% versus 12.5%) and meniscal lesions were more common and more likely to be severe in men (54% versus 42%). In contrast, cartilage abnormalities were slightly more common in women (76.5% versus 72%) but full-thickness cartilage defects were more common in men (24% versus 14.7%). The prevalence of some features was higher than in previous studies, especially since these were asymptomatic individuals, and this is likely related to increased sensitivity from the stronger magnetic field used in this study.

These few studies show widely disparate results, likely because of different study designs, statistical power, MRI protocols, and study populations varying by geographic location, age distribution, clinical characteristics, and source of participants. These factors make interpretation impossible and mandate further research to determine whether sex differences exist in these parameters and to understand the mechanisms behind such differences.

Bone marrow lesions and bone cysts

In OA, bone marrow lesions are common and are associated with knee OA progression and pain [53-55]. In the first description of these in healthy men and women free of knee pain, Davies-Tuck and colleagues [56] reported that sex was not associated with the presence, development, or persistence of bone marrow lesions on knee 1.5-Tesla MRI over 2 years in the Melbourne Collaborative Cohort Study. Studies evaluating the coexistence of these lesions with cartilage loss, meniscal abnormalities, and bone cysts have for the most part not focused on sex differences in these relationships [54]. Tanamas and colleagues [57] reported that bone cysts were more common in men than women in a study of the relationship between bone cysts and subsequent knee replacement 4 years later, but further investigation into the role of sex differences in these lesions was not conducted.

Sex differences in biomarkers of joint metabolism

Another way to understand the etiopathogenesis of sex differences in OA is to examine factors representative of joint metabolism. In order for synovial and systemically measured biomarkers to be used to identify high-risk individuals before OA occurs or before it becomes clinically manifest, normative data in various populations, including subgroups by sex, are required. For some markers, such as type I collagen N-telopeptide (NTX-I) and osteocalcin (which are markers of bone resorption and synthesis, respectively), much is known about sex differences and (within women) the effects of menopause and HRT, but for other markers, much less is known. Reports using markers for OA frequently control for sex but do not describe sex differences specifically [58,59]. Critically important is knowing what other factors – such as the body burden of OA, BMI, hormonal status, or other medical conditions – might confound a sex difference in a specific marker, especially when considering a biomarker that is ubiquitous in connective tissue, such as hyaluronan (HA) [60]. This report will examine sex differences in several of the more frequently used markers in OA, targeting presumably different processes.

Type II collagen degradation

Mouritzen and colleagues [61] described a marker of type II collagen turnover, cartilage-derived urinary collagen type II C-telopeptide degradation products (CTX-II), in 615 healthy men and women from 20 to 87 years old. Levels were similar in men and women from 30 to 45 years old and then increased in both men and women, with the levels of women being slightly higher than those of men (Figure 1 from [61]). Levels were also higher in post-menopausal women compared with pre-menopausal women; and in post-menopausal women, those taking HRT had lower levels than those not taking HRT. Furthermore, those taking HRT for a longer time had lower levels than those taking HRT for a shorter duration [61].

Kojima and colleagues [62] described serum levels of C2C, a marker of intra-helical type II collagen cleavage, in 69 Japanese men (mean age of 43 years) and 71 Japanese women (mean age of 44 years; 34% of the women were post-menopausal) who did not have joint or spinal pain or major medical conditions and who were not taking medications affecting bone metabolism. In individuals younger than 50 years, C2C was higher in women than men, and the reverse was the case in those older than 50 years. C2C levels were unrelated to menopausal status. Since CTX-II and C2C are both markers of type II collagen cleavage, why would results be different for each marker? The authors propose that differences might be because the markers are the product of different areas in the type II collagen molecule that get degraded, and the markers' different locations in the joint [62].

Matrix protein degradation

Cartilage oligomeric matrix protein (COMP) is a 64-kDa pentameric matrix protein found in most joint tissues, including cartilage, bone, tendon, ligament, synovium, and vascular smooth muscle. It is elevated in OA [63-67], predicts incidence of radiographic hip OA [65,66], and is higher with increasing body burden of OA-affected large joints [63,64,67]. Clark and colleagues [63] described the first and largest population-based assessment of serum COMP using competitive enzyme-linked immunosorbent assay (ELISA) with monoclonal antibody 17-C10 in Caucasians in the Johnston County Osteoarthritis Project (JoCo OA). COMP increased with age and was higher in OA than controls but did not significantly vary by sex. Later, in the same study population, Jordan and colleagues [64] used a sandwich ELISA with monoclonal antibodies 16-F12 and 17-C10 and reported that serum COMP levels among Caucasians but not African-Americans were higher in men than women (Figure 1, page 679 from [64]). Serum COMP levels were associated with a 30% increased risk of hip OA development in older Caucasian women in the Study of Osteoporotic Fractures [65]; those in the highest three quartiles of change in this marker had a fivefold increase in the risk of incident hip OA compared with those in the lowest quartile of change [66]. No direct comparison of these results to men was possible in this study. No further specific evaluations of sex differences in COMP in relation to OA have been conducted.

Synovial inflammation

HA is a ubiquitous glycosaminoglycan formed from alternating units of glucosamine and glucuronic acid. It is a constituent of synovium and cartilage and is indicative of synovial inflammation and has been shown to be an important marker of systemic burden of OA in women [60]. Elliott and colleagues [60] reported that men had higher serum HA levels than women did in the JoCo OA; importantly, this effect was independent of differences in age, race/ethnicity, OA burden in knees or hips, BMI, or comorbidities. This was confirmed in a recent study of mitochondrial DNA haplogroups and their effect upon serum levels of multiple biomarkers in Spanish patients with knee and hip OA [68].

Systemic and synovial cytokines

Pagura and colleagues [69] examined systemic and synovial measures of cytokines (interleukin [IL]-1-alpha/beta, tumor necrosis factor-alpha, and IL-6) and growth factors (insulin-like growth factor-1 [IGF-1], transforming growth factor-beta [TGF-β], and interleukin 1 receptor antagonist [IRAP]) in a small study of 9 Canadian men and 8 women awaiting knee replacement and compared them with 21 age- and sex-matched controls recruited from the local community. Men had higher levels of serum and synovial IGF-1, but there were no sex differences in any of the other markers. However, the very small sample size and undetectable levels of cytokines, except for IL-6, render the impact of this study questionable [69].

Growth factor

Lastly, in the largest study of serum TGF-β to date, Nelson and colleagues [70] reported that this marker was higher in women than men in the JoCo OA and that the associations between this marker and prevalent radiographic knee and hip OA, osteophytes, and joint space narrowing were similar in men and women. A single measure of this marker was unable to predict incidence or progression of radiographic knee or hip OA, osteophytes, or joint space narrowing in either men or women [71].

Summary and suggestions for future research

Sex differences in prevalence, incidence, and severity of radiographic and clinical OA have been described, but specific examination of sex differences in MRI biomarkers and in biomarkers of joint metabolism are few, and results vary considerably. Despite some variation across study designs and study populations, women appear to have a thinner and more reduced volume of cartilage in the knee than men, and this may occur from early childhood. The relationship between cartilage volume and bone area cannot be ignored in analyses of these issues. Whether women have a more accelerated rate of cartilage volume loss than men remains unsettled. Few data exist on sex differences in other tissues of the knee by MRI and in systemic biomarkers of joint metabolism, and those that do exist frequently vary in the assessment of potential mediators of sex differences.

Most studies of OA have been limited to Caucasians. Future studies should examine these relationships in

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other race/ethnic groups and, perhaps more importantly, delve into aspects that are likely to shed light upon mechanisms behind sex differences. In particular, studies of imaging and biochemical biomarkers, rather than merely control for sex, should specifically examine whether sex differences exist in that biomarker. Additionally, studies should establish whether risk factors act similarly or differently in men and women, with an eye to determining whether sex-specific therapies make sense. Studies of mesenchymal stem cells, outlined above [41], suggest that this may not be such a far-fetched idea.

Another question deserving attention is whether height, weight, and bone area can adequately serve as proxies for body size, a crucial issue in understanding sex differences in imaging biomarkers. Future studies might evaluate other potential proxies, such as height × weight and others [19], in relation to sex differences in joint structures by MRI. Finally, sex differences in the genetics of OA have been noted for multiple genes and joint sites [72-74], and studies of sex differences in these genetic effects should dovetail with those using advanced imaging and biochemical biomarkers for maximal mechanistic insight.

Abbreviations

BMI, body mass index; COMP, cartilage oligomeric matrix protein; CTX-II, C-terminal telopeptides of type II collagen; ELISA, enzyme-linked immunosorbent assay; HA, hyaluronan; HRT, hormone replacement therapy; IGF-1, insulin-like growth factor-1; IL, interleukin; JoCo OA, Johnston County Osteoarthritis Project; MRI, magnetic resonance imaging; OA, osteoarthritis; OAI, Osteoarthritis Initiative; TGF-β, transforming growth factor-beta.

Competing interests

The authors declare that they have no competing interests.

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References

1. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, Fang F, Schwartz TA, Abbate LM, Callahan LF, Kalsbeek WD, Hochberg MC: **Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: The Johnston County Osteoarthritis Project.** *J Rheumatol* 2007, **34:**172-180.
2. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, Fang F, Schwartz TA, Nelson AE, Abbate LM, Callahan LF, Kalsbeek WD, Hochberg MC: **Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: The Johnston County Osteoarthritis Project.** *J Rheumatol* 2009, **36:**809-815.
3. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G: **A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis.** *Osteoarthritis Cartilage* 2005, **13:**769-781.
4. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM: **Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization.** *Arthritis Rheum* 1995, **38:**1134-1141.
5. Belo JN, Berger MY, Reijman M, Koes BW, Bierma-Zeinstra SM: **Prognostic factors of progression of osteoarthritis of the knee: a systematic review of observational studies.** *Arthritis Rheum* 2007, **57:**13-26.
6. de Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, Bierma-Zeinstra SM: **No clear association between female hormonal aspects and osteoarthritis of the hand, hip and knee: a systematic review.** *Rheumatology (Oxford)* 2009, **48:**1160-1165.
7. de Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, Bierma-Zeinstra SM: **Limited evidence for a protective effect of unopposed oestrogen therapy for osteoarthritis of the hip: a systematic review.** *Rheumatology (Oxford)* 2009, **48:**104-112.
8. Nevitt MC, Cummings SR, Lane NE, Hochberg MC, Scott JC, Pressman AR, Genant HK, Cauley JA: **Association of estrogen replacement therapy with the risk of osteoarthritis of the hip in elderly white women. Study of Osteoporotic Fractures Research Group.** *Arch Intern Med* 1996, **156:**2073-2080.
9. Spector TD, Nandra D, Hart DJ, Doyle DV: **Is hormone replacement therapy protective for hand and knee osteoarthritis in women? The Chingford Study.** *Ann Rheum Dis* 1997, **56:**432-434.
10. Cirillo DJ, Wallace RB, Wu L, Yood RA: **Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative.** *Arthritis Rheum* 2006, **54:**3194-3204.
11. Nevitt MC, Felson DT, Williams EN, Grady D: **The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: The Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial.** *Arthritis Rheum* 2001, **44:**811-818.
12. Kellgren JH, Lawrence JS (Eds): *The Epidemiology of Chronic Rheumatism, Atlas of Standard Radiographs*. Oxford: Blackwell Scientific; 1963.
13. Burnett SJ, Hart DJ, Cooper C, Spector TD: *A Radiographic Atlas of Osteoarthritis*. London: Springer-Verlag; 1994.
14. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, Kothari M, Lu Y, Fye K, Zhao S, Genant HK: **Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis.** *Osteoarthritis Cartilage* 2004, **12:**177-190.
15. Jeffreys M, Lawlor DA, Galobardes B, McCarron P, Kinra S, Ebrahim S, Smith GD: **Lifecourse weight patterns and adult-onset diabetes: the Glasgow Alumni and British Women's Heart and Health studies.** *Int J Obes (Lond)* 2006, **30:**507-512.
16. Everson SA, Maty SC, Lynch JW, Kaplan GA: **Epidemiologic evidence for the relation between socioeconomic status and depression, obesity, and diabetes.** *J Psychosom Res* 2002, **53:**891-895.
17. Richette P, Corvol M, Bardin T: **Estrogens, cartilage, and osteoarthritis.** *Joint Bone Spine* 2003, **70:**257-262.
18. Cicuttini F, Forbes A, Morris K, Darling S, Bailey M, Stuckey S: **Gender differences in knee cartilage volume as measured by magnetic resonance imaging.** *Osteoarthritis Cartilage* 1999, **7:**265-271.
19. Faber SC, Eckstein F, Lukasz S, Mühlbauer R, Hohe J, Englmeier KH, Reiser M: **Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging.** *Skeletal Radiol* 2001, **30:**144-150.
20. Otterness IG, Eckstein F: **Women have thinner cartilage and smaller joint surfaces than men after adjustment for body height and weight.** *Osteoarthritis Cartilage* 2007, **15:**666-672.
21. Otterness IG, Le Graverand MP, Eckstein F: **Allometric relationships between knee cartilage volume, thickness, surface area and body dimensions.** *Osteoarthritis Cartilage* 2008, **16:**34-40.
22. Ding C, Cicuttini F, Blizzard L, Scott F, Jones G: **A longitudinal study of the effect of sex and age on rate of change in knee cartilage volume in adults.** *Rheumatology (Oxford)* 2007, **46:**273-279.
23. Hanna FS, Teichtahl AJ, Wluka AE, Wang Y, Urquhart DM, English DR, Giles GG, Cicuttini FM: **Women have increased rates of cartilage loss and progression of cartilage defects at the knee than men: a gender study of adults without clinical knee osteoarthritis.** *Menopause* 2009, **16:**666-670.
24. Eckstein F, Maschek S, Wirth W, Hudelmaier M, Hitzl W, Wyman B, Nevitt M, Le Graverand MP; OAI Investigator Group: **One year change of knee cartilage morphology in the first release of participants from the Osteoarthritis Initiative progression subcohort: association with sex, body mass index, symptoms and radiographic osteoarthritis status.** *Ann Rheum Dis* 2009, **68:**674-679.
25. Eckstein F, Wirth W, Hunter DJ, Guermazi A, Kwoh CK, Nelson DR, Benichou O; OAI Investigators: **Magnitude and regional distribution of cartilage loss associated with grades of joint space narrowing in radiographic**

osteoarthritis - data from the Osteoarthritis Initiative (OAI). *Osteoarthritis Cartilage* 2010, **18:**760-768.
26. Osteoarthritis Initiative, Study Overview and Objectives [http://www.oai.ucsf.edu/datarelease/StudyOverview.asp].
27. Gao W, Cai D, Zeng C, Liu B, Li Y, Wen X, Chen Y: **Serum concentrations of selected endogenous estrogen and estrogen metabolites in pre and post-menopausal Chinese women with osteoarthritis.** *J Endocrinol Invest* 2010 Mar 25. [Epub ahead of print].
28. Hannan MT, Felson DT, Anderson JJ, Naimark A, Kannel WB: **Estrogen use and radiographic osteoarthritis of the knee in women. The Framingham Osteoarthritis Study.** *Arthritis Rheum* 1990, **33:**525-532.
29. Sowers MR, McConnell D, Jannausch M, Buyuktur AG, Hochberg M, Jamadar DA: **Estradiol and its metabolites and their association with knee osteoarthritis.** *Arthritis Rheum* 2006, **54:**2481-2487.
30. Wluka AE, Davis SR, Bailey M, Stuckey SL, Cicuttini FM: **Users of oestrogen replacement therapy have more knee cartilage than non-users.** *Ann Rheum Dis* 2001, **60:**332-336.
31. Wluka AE, Wolfe R, Davis SR, Stuckey S, Cicuttini FM: **Tibial cartilage volume change in healthy postmenopausal women: a longitudinal study.** *Ann Rheum Dis* 2004, **63:**444-449.
32. Hanna FS, Bell RJ, Cicuttini FM, Davison SL, Wluka AE, Davis SR: **The relationship between endogenous testosterone, preandrogens, and sex hormone binding globulin and knee joint structure in women at midlife.** *Semin Arthritis Rheum* 2007, **37:**56-62.
33. Hanna F, Ebeling PR, Wang Y, O'Sullivan R, Davis S, Wluka AE, Cicuttini FM: **Factors influencing longitudinal change in knee cartilage volume measured from magnetic resonance imaging in healthy men.** *Ann Rheum Dis* 2005, **64:**1038-1042.
34. Mutabaruka MS, Aoulad AM, Delalandre A, Lavigne M, Lajeunesse D: **Local leptin production in osteoarthritis subchondral osteoblasts may be responsible for their abnormal phenotypic expression.** *Arthritis Res Ther* 2010, **12:**R20.
35. Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, Pottie P: **Evidence for a key role of leptin in osteoarthritis.** *Arthritis Rheum* 2003, **48:**3118-3129.
36. Simopoulou T, Malizos KN, Iliopoulos D, Stefanou N, Papatheodorou L, Ioannou M, Tsezou A: **Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism.** *Osteoarthritis Cartilage* 2007, **15:**872-883.
37. Ku JH, Lee CK, Joo BS, An BM, Choi SH, Wang TH, Cho HL: **Correlation of synovial fluid leptin concentrations with the severity of osteoarthritis.** *Clin Rheumatol* 2009, **28:**1431-1435.
38. Teichtahl AJ, Wluka AE, Proietto J, Cicuttini FM: **Obesity and the female sex, risk factors for knee osteoarthritis that may be attributable to systemic or local leptin biosynthesis and its cellular effects.** *Med Hypotheses* 2005, **65:**312-315.
39. Ding C, Parameswaran V, Cicuttini F, Burgess J, Zhai G, Quinn S, Jones G: **Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study.** *Ann Rheum Dis* 2008, **67:**1256-1261.
40. Jones G, Glisson M, Hynes K, Cicuttini F: **Sex and site differences in cartilage development: a possible explanation for variations in knee osteoarthritis in later life.** *Arthritis Rheum* 2000, **43:**2543-2549.
41. Matsumoto T, Kubo S, Meszaros LB, Corsi KA, Cooper GM, Li G, Usas A, Osawa A, Fu FH, Huard J: **The influence of sex on the chondrogenic potential of muscle-derived stem cells: implications for cartilage regeneration and repair.** *Arthritis Rheum* 2008, **58:**3809-3819.
42. Koelling S, Miosge N: **Sex differences of chondrogenic progenitor cells in late stages of osteoarthritis.** *Arthritis Rheum* 2010, **62:**1077-1087.
43. Hashemi J, Chandrashekar N, Mansouri H, Slauterbeck JR, Hardy DM: **The human anterior cruciate ligament: sex differences in ultrastructure and correlation with biomechanical properties.** *J Orthop Res* 2008, **26:**945-950.
44. Onambele GN, Burgess K, Pearson SJ: **Gender-specific *in vivo* measurement of the structural and mechanical properties of the human patellar tendon.** *J Orthop Res* 2007, **25:**1635-1634.
45. Shultz SJ, Beynnon BD, Schmitz RJ: **Sex differences in coupled knee motions during the transition from non-weight bearing to weight bearing.** *J Orthop Res* 2009, **27:**717-723.
46. Stijak L, Radonjic V, Nikolic V, Blagojevic Z, Aksic M, Filipovic B: **Correlation between the morphometric parameters of the anterior cruciate ligament and the intercondylar width: gender and age differences.** *Knee Surg Sports Traumatol Arthrosc* 2009, **17:**812-817.
47. Varadarajan KM, Gill TJ, Freiberg AA, Rubash HE, Li G: **Gender differences in trochlear groove orientation and rotational kinematics of human knees.** *J Orthop Res* 2009, **27:**871-878.
48. Fayad LM, Rosenthal EH, Morrison WB, Carrino JA: **Anterior cruciate ligament volume: analysis of gender differences.** *J Magn Reson Imaging* 2008, **27:**218-223.
49. Ding C, Martel-Pelletier J, Pelletier JP, Abram F, Raynauld JP, Cicuttini F, Jones G: **Meniscal tear as an osteoarthritis risk factor in a largely non-osteoarthritic cohort: a cross-sectional study.** *J Rheumatol* 2007, **34:**776-784.
50. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, Felson DT: **Incidental meniscal findings on knee MRI in middle-aged and elderly persons.** *N Engl J Med* 2008, **359:**1108-1115.
51. Lange AK, Fiatarone Singh MA, Smith RM, Foroughi N, Baker MK, Shnier R, Vanwanseele B: **Degenerative meniscus tears and mobility impairment in women with knee osteoarthritis.** *Osteoarthritis Cartilage* 2007, **15:**701-708.
52. Stehling C, Lane NE, Nevitt MC, Lynch J, McCulloch CE, Link TM: **Subjects with higher physical activity levels have more severe focal knee lesions diagnosed with 3T MRI: analysis of a non-symptomatic cohort of the osteoarthritis initiative.** *Osteoarthritis Cartilage* 2010, **18:**776-786.
53. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, Li W, Hill C, Gale D: **Bone marrow edema and its relation to progression of knee osteoarthritis.** *Ann Intern Med* 2003, **139:**330-336.
54. Hunter DJ, Zhang Y, Niu J, Goggins J, Amin S, LaValley MP, Guermazi A, Genant H, Gale D, Felson DT: **Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis.** *Arthritis Rheum* 2006, **54:**1529-1535.
55. Kothari A, Guermazi A, Chmiel JS, Dunlop D, Song J, Almagor O, Marshall M, Cahue S, Prasad P, Sharma L: **Within-subregion relationship between bone marrow lesions and subsequent cartilage loss in knee osteoarthritis.** *Arthritis Care Res (Hoboken)* 2010, **62:**198-203.
56. Davies-Tuck ML, Wluka AE, Wang Y, English DR, Giles GG, Cicuttini F: **The natural history of bone marrow lesions in community-based adults with no clinical knee osteoarthritis.** *Ann Rheum Dis* 2009, **68:**904-908.
57. Tanamas SK, Wluka AE, Pelletier JP, Martel-Pelletier J, Abram F, Wang Y, Cicuttini FM: **The association between subchondral bone cysts and tibial cartilage volume and risk of joint replacement in people with knee osteoarthritis: a longitudinal study.** *Arthritis Res Ther* 2010, **12:**R58.
58. Cibere J, Zhang H, Garnero P, Poole AR, Lobanok T, Saxne T, Kraus VB, Way A, Thorne A, Wong H, Singer J, Kopec J, Guermazi A, Peterfy C, Nicolaou S, Munk PL, Esdaile JM: **Association of biomarkers with pre-radiographically defined and radiographically defined knee osteoarthritis in a population-based study.** *Arthritis Rheum* 2009, **60:**1372-1380.
59. Hunter DJ, Li J, LaValley M, Bauer DC, Nevitt M, DeGroot J, Poole R, Eyre D, Guermazi A, Gale D, Felson DT: **Cartilage markers and their association with cartilage loss on MRI in knee osteoarthritis: The Boston Osteoarthritis Knee Study.** *Arthritis Res Ther* 2007, **9:**R108.
60. Elliott AL, Kraus VB, Luta G, Stabler T, Renner JB, Woodard J, Dragomir AD, Helmick CG, Hochberg MC, Jordan JM: **Serum hyaluronan levels and radiographic knee and hip osteoarthritis in African Americans and Caucasians in the Johnston County Osteoarthritis Project.** *Arthritis Rheum* 2005, **52:**105-111.
61. Mouritzen U, Christgau S, Lehmann HJ, Tanko LB, Christiansen C: **Cartilage turnover assessed with a newly developed assay measuring collagen type II degradation products: influence of age, sex, menopause, hormone replacement therapy, and body mass index.** *Ann Rheum Dis* 2003, **62:**332-336.
62. Kojima T, Kojima M, Noda K, Ishiguro N, Poole AR: **Influences of menopause, aging, and gender on the cleavage of type II collagen in cartilage in relationship to bone turnover.** *Menopause* 2008, **15:**133-137.
63. Clark AG, Jordan JM, Vilim V, Renner JB, Dragomir AD, Luta G, Kraus VB: **Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity: the Johnston County Osteoarthritis Project.** *Arthritis Rheum* 1999, **42:**2356-2364.
64. Jordan JM, Luta G, Stabler T, Renner JB, Dragomir AD, Vilim V, Hochberg MC, Helmick CG, Kraus VB: **Ethnic and sex differences in serum levels of cartilage oligomeric matrix protein: the Johnston County Osteoarthritis Project.** *Arthritis Rheum* 2003, **48:**675-681.
65. Kelman A, Liu L, Yao W, Krumme A, Nevitt M, Lane NE: **Association of higher**

levels of serum Cartilage Oligomeric Matrix Protein and N-telopeptide crosslinks with the development of radiographic hip osteoarthritis in elderly women. *Arthritis Rheum* 2006, **54:**236-243.

66. Chaganti RK, Kelman A, Lui L, Yao W, Javaid MK, Bauer D, Nevitt M, Lane NE, Study Of Osteoporotic Fractures Research Group Sof: **Change in serum measurements of cartilage oligomeric matrix protein and association with the development and worsening of radiographic hip osteoarthritis.** *Osteoarthritis Cartilage* 2008, **16:**566-571.
67. Kraus VB, Kepler TB, Stabler T, Renner J, Jordan J: **First qualification study of serum biomarkers as indicators of total body burden of osteoarthritis.** *PLoS One* 2010, **5:**e9739.
68. Rego-Perez I, Fernandez-Moreno M, Fernandez-Lopez C, Arenas J, Blanco FJ: **Mitochondrial DNA haplogroups: role in the prevalence and severity of knee osteoarthritis.** *Arthritis Rheum* 2008, **58:**2387-2396.
69. Pagura SM, Thomas SG, Woodhouse LJ, Ezzat S, Marks P: **Circulating and synovial levels of IGF-I, cytokines, physical function and anthropometry differ in women awaiting total knee arthroplasty when compared to men.** *J Orthop Res* 2005, **23:**397-405.
70. Nelson AE, Fang F, Shi XA, Kraus VB, Stabler T, Renner JB, Schwartz TA, Helmick CG, Jordan JM: **Failure of serum transforming growth factor-beta (TGF-beta1) as a biomarker of radiographic osteoarthritis at the knee and hip: a cross-sectional analysis in the Johnston County Osteoarthritis Project.** *Osteoarthritis Cartilage* 2009, **17:**772-776.
71. Nelson AE, Golightly YM, Kraus VB, Stabler T, Renner JB, Helmick CG, Jordan JM: **Serum transforming growth factor-beta 1 is not a robust biomarker of incident and progressive radiographic osteoarthritis at the hip and knee: the Johnston County Osteoarthritis Project.** *Osteoarthritis Cartilage* 2010, **18:**825-829.
72. Loughlin J, Dowling B, Chapman K, Marcelline L, Mustafa Z, Southam L, Ferreira A, Ciesielski C, Carson DA, Corr M: **Functional variants within the secreted frizzled-related protein 3 gene are associated with hip osteoarthritis in females.** *Proc Natl Acad Sci U S A* 2004, **101:**9757-9762.
73. Valdes AM, Loughlin J, Oene MV, Chapman K, Surdulescu GL, Doherty M, Spector TD: **Sex and ethnic differences in the association of ASPN, CALM1, COL2A1, COMP, and FRZB with genetic susceptibility to osteoarthritis of the knee.** *Arthritis Rheum* 2007, **56:**137-146.
74. Valdes AM, Van Oene M, Hart DJ, Surdulescu GL, Loughlin J, Doherty M, Spector TD: **Reproducible genetic associations between candidate genes and clinical knee osteoarthritis in men and women.** *Arthritis Rheum* 2006, **54:**533-539.

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