Viewpoint

Generalised osteoarthritis: a hormonally mediated disease

TIM D SPECTOR^{1 2} AND GILES D CAMPION³

From the ¹Department of Rheumatology, St Bartholomew's Hospital, London; the ²Department of Epidemiology, The London Hospital Medical College, London; and the ³Sections of Rheumatology and Biochemistry, Rush-Presbyterian-St Luke's Medical Centre, Chicago, USA

A variety of clinical, pathological, and epidemiological data has suggested that generalised osteoarthritis may be hormonally mediated. This article studies the available evidence and possible mechanisms involved.

Osteoarthritis (OA) is a group of clinically heterogeneous disorders unified by the pathological features of hyaline cartilage loss and subchondral bone reaction. Population studies indicate the extremely high prevalence of OA (over the age of 70 up to 90% of the population have some radiological evidence of OA¹) and the sexual differences in its clinical presentation. Osteoarthritis in women more commonly affects multiple joints and is usually more severe than in men.¹ The apparent prominence of women presenting with polyarticular symptoms in middle age has fuelled speculation that there may be some relation between the onset of OA and the menopause. These ideas are not new; in 1805 Haygarth noted 'the nodosities of the joints are almost peculiar to women and begin when the menses naturally cease'.² The term 'menopausal arthritis' was first coined as early as 1920 and has been given various synonyms, including climacteric arthritis, endocrine arthritis, hypoglandular arthritis, and chronic villous arthritis.

Clinical studies

In 1925 Cecil and Archer reported a form of OA which they described as 'a chronic polyarthritis of obese middle-aged women, occurring at or just after the menopause and characterised by persistent pain and stiffness in the joints affected'. They described 50 women with this condition, which was associated

with the presence of Heberden's nodes, and named the disease menopausal arthritis.³ This form of OA was said to progress to degenerative joint disease after the initial symptoms of pain and swelling had subsided. In 1937 the term menopausal arthritis appeared in the official British classification of chronic arthritis. In 1938 Hall described 50 women with joint symptoms occurring soon after the menopause or hysterectomy. All had joint stiffness and swelling.⁴ The association of the menopause and the appearance of Heberden's nodes was further supported in a study of 99 women by Stecher *et al* in 1949.⁵

In 1952 Kellgren and Moore described a similar group of women with Heberden's nodes characterised by a rapid onset of symptoms and multiple joint involvement (hands, spine, and knees). The acute inflammatory nature of the condition was again emphasised. Although the mean age of onset was 52, they were unable to find a direct relation with the menopause, 20% of the cases occurring before the menopause, and they renamed it 'primary generalised osteoarthritis'.⁶ In 1956 Rogers and Lansbury reported a woman with arthritis mutilans, who developed exacerbations of her arthritis during the administration of large doses of chorionic gonadotrophin.⁷ In 1975 Ehrlich described a syndrome of erosive inflammatory OA which involved the digits of perimenopausal women.⁸

Because early workers believed generalised OA to be caused by a lack of oestrogens, several small trials of oestrogens were attempted in women with OA, without any significant signs of clinical improvement.^{3 6 9}

A number of workers have studied urinary and serum sex hormone concentrations in women with existing OA, but the results have been inconsistent.^{7 10-12} This might in part be explained by the

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Correspondence to Dr Tim D Spector, Department of Epidemiology, The London Hospital Medical College, London E1 1AD.

heterogeneous groups of patients studied or the variable nature of oestrogen concentrations or oestrogen receptor sensitivity.

Population studies

Epidemiological surveys have indicated that disease subsets in OA do exist, and most clinicians recognise nodal generalised OA to be one of these. This apparent subgroup of OA was found to have a marked female to male sex ratio. In the population surveys of Lawrence *x* ray evidence of nodal generalised OA was three times higher in women in the age range 45–64, and no difference was seen between men and women with the non-nodal forms.¹ Other hospital based studies have shown a female to male ratio as high as 10:1.⁷ In an analysis of age specific incidence rates from population data Wood found a marked peak of age of onset at 50 years in women for nodal generalised OA.¹³ The prevalence of Heberden's nodes has also been found to be greater in women than men at all ages, reaching 18.8% at 55 years.¹⁴ Epidemiological studies have confirmed the association between the presence of Heberden's nodes and polyarticular joint involvement.^{1 15} Strangely, the effect of the menopause on joints has not received much attention. Gynaecologists, however, regard joint symptoms as one of the principal components of the climacteric, with 49% of women in one study reporting symptoms of aching or stiffness in joints.¹⁶ Moreover, women experiencing symptoms at the menopause, other than flushes or changes in libido, have been found to have significantly higher concentrations of plasma oestradiol than asymptomatic women.¹⁷

Further evidence for the effect of gynaecological and hormonal factors comes from a recent case-control study of women with OA. These women were found to have had double the number of hysterectomies compared with age matched controls with rheumatoid arthritis and from the population. The association between OA and hysterectomy was strongest for those with polyarticular disease. Dilatation and curetage procedures and gynaecological problems were also more prevalent in the women with OA.¹⁸ The commonest indication for hysterectomy was dysfunctional uterine bleeding or fibroids, both of which have been attributed to an absolute or relative excess—that is, unopposed—of oestrogens.¹⁹

The clinical and population studies of generalised OA suggest that onset of the disease is related either to the perimenopausal period or to an episode of hormone imbalance.

High concentrations of unopposed oestrogens are normally found for several years before and after the clinical menopause as progesterone concentra-

tions fall earlier and disappear completely at the menopause. Thus it may be the ratio of oestrogen to progesterone concentrations, rather than the absolute oestrogen concentration, that is of importance in precipitating generalised OA.

Osteoarthritis, obesity, and osteoporosis

A correlation between obesity and OA of the knee and generalised OA has been found in women.²⁰ This has also been shown for a number of non-weight-bearing sites, and the association appears to be stronger in women than men²³ and to be related to excess body weight rather than muscle bulk. Obesity in women is a known cause of hyperoestrogenism, occurring through the peripheral formation of oestrogen from androstenedione in the fat tissue. After the menopause this route becomes the principal source of oestrogens. Thus the association between OA and obesity also suggests a role for endocrine influences in the development of OA. Interestingly, smoking, which has antioestrogenic effects, appears to have a mildly protective effect on the development of knee OA, independent of body weight.²⁵

The possible association between oestrogens and OA is also suggested by the apparently 'negative association' between OA and osteoporosis. This is indicated by a number of pathological and radiographic studies, which found OA to be rare in cases of hip fracture due to osteoporosis.^{26–29} These findings are also more consistently found in women than men. Conflicting results have been reported from assessments of bone mass in patients with OA, some showing an increase^{30 31} and others no difference from controls matched for height and weight. As loss of oestrogen is now accepted as being the major contributory factor in postmenopausal osteoporosis, and bone loss can be halted by its administration, the inverse relation between osteoporosis and oestrogen also suggests a role for oestrogen in the pathogenesis of OA.

Experimental studies

Several investigators have examined the possible relation between OA and oestrogens in a number of studies using animal models. In 1963 Silberberg using male mice with a genetic predisposition to OA found that oestrogen treatment caused a decrease in incidence and severity of lesions.³³ This conflicted somewhat with one of their earlier studies, where female mice undergoing oophorectomy had a reduction of their disease.³⁴ The effect of oestrogens on sulphate metabolism has also been studied. It causes depression of metabolism in both normal rat hyaline

costal cartilage³⁵ and in rabbit epiphyseal cartilage.³⁶ Oestrogens were also found to suppress chondrocyte proliferation in chondrocyte cultures.³⁷ Rosner *et al* used experimentally induced OA (partial meniscectomy) in rabbits as a model of OA. They found no improvement in the OA with oestrogen valerate and, in addition, found that oestradiol suppressed proteoglycan synthesis in both normal and osteoarthritic cartilage. Proteoglycan concentration, however, was not altered, suggesting suppression of proteoglycan catabolism.³⁸ In further studies they found that oestradiol administration led to a worsening of osteoarthritic lesions,³⁹ but that tamoxifen, an oestrogen receptor blocker, was associated with an improvement in the disorder.⁴⁰ More recently, Mason's group has reported inhibition of [³⁵S]proteoglycan synthesis by pharmacological doses of oestradiol (10^{-5} mol/l) in explant cultures of bovine chondrocytes and in cell cultures of Swarm rat chondrosarcoma.⁴¹ Similar doses inhibited cell division in the log growth phase. Oestrogens had no effect in physiological doses (10^{-9} – 10^{-8} mol/l), however, on either [³⁵S]proteoglycan synthesis or articular cartilage growth, and neither physiological or pharmacological doses of oestrogens affected [³⁵S]proteoglycan turnover.⁴²

Oestrogen receptors in the articular cartilage of the dog, rabbit, and baboon have been reported by various workers.^{43–45} Mason's group, however, has been unable to isolate oestrogen receptors in bovine articular chondrocytes and commented that receptor levels reported by other authors were low.⁴² They conclude that although high doses of oestrogen can affect proteoglycan metabolism, turnover is unlikely to be under the direct physiological control of oestrogen, suggesting that second messengers may be involved.

That oestrogens may be chondrodestructive is supported by the apparent increase in osteoarthritic change associated with oestrogen administration in the meniscectomy model performed in oophorectomised female virgin rabbits, whereas the study on genetically determined OA in male mice suggests the opposite. The conflicting results of the animal studies perhaps emphasise the heterogeneous nature of OA and also cast doubt on the possibility that any existing animal model can reflect the clinical situation of generalised OA in humans. Moreover, it may not be appropriate to compare a genetic model of OA with a surgical model, or male mice with oophorectomised virgin rabbits.

The gross physiological effects of oestrogens on the musculoskeletal system are well known. They accelerate cartilage maturation, diminish linear bone growth, stimulate endochondral ossification, and induce cartilage matrix dehydration with apparently

increased collagen.⁴⁶ Thus it is likely that they will have an important role in chondrocyte function. Whether that role is direct or indirect via a secondary messenger is not clear, but the presence of cellular receptors for oestrogen in human articular cartilage would be strong evidence in support of a direct role.

Apart from effects on cartilage, oestrogens have been shown to have potent effects on bone metabolism. After the menopause or oophorectomy there is a steady decline in bone mass, which may be prevented by oestrogen treatment^{47 48} or even reversed.⁴⁹ On oestrogen administration there is inhibition of bone resorption, followed some months later by a suppression of bone formation.⁵⁰

The mechanism by which oestrogen acts on bone is far from clear. Until recently, evidence for a direct action on bone via a receptor mediated system was lacking. Two independent groups, however, using sensitive new receptor assays, have reported the presence of low levels of oestrogen receptors in human and rat osteoblast-like osteosarcoma cells and in several strains of normal human osteoblast-like cells.^{51 52} In addition, enhanced levels of mRNA of type I procollagen and transforming growth factor β were found in cultured human osteoblast-like cells treated with 1 nM oestradiol. It has been postulated that oestrogen may control the transcriptional activity of the transforming growth factor β gene. Transforming growth factor β is one of a family of regulatory polypeptides and acts on a variety of connective tissues, including bone. There is now evidence that it is involved in the coupling of osteoclastic and osteoblastic activity in the regulation of normal bone turnover.⁵³ Moreover, transforming growth factor β has been found to be closely related to cartilage inducing factor A, which induces the formation of type II collagen and cartilage proteoglycans from undifferentiated mesenchymal cells 'in vitro'.⁵⁴

Discussion

The observations that generalised OA occurs predominantly in perimenopausal women and is associated with obesity, the presence of fibroids, or dysfunctional uterine bleeding and negatively associated with osteoporosis can be explained on the basis of an absolute or relative oestrogen excess. Women with high endogenous oestrogen concentrations, for whatever reason, are therefore predisposed to generalised OA, the effect being greatest around the menopause when the ratio of oestrogen to progesterone is high. This hypothesis is supported by some animal models, which show a worsening of lesions with oestrogens and improvement with tamoxifen. Oestrogen may act on subchondral bone

and cartilage receptors via receptors and second messengers such as the regulatory polypeptides transforming growth factor β or cartilage inducing factor A, interfering with osteoclast and osteoblast coupling and cartilage turnover.

Thus although generalised OA undoubtedly has a multifactorial aetiology involving evolutionary, mechanical, and genetic influences on the articular surfaces, there is little doubt that generalised OA can be precipitated hormonally in certain predisposed individuals at critical times in life. By studying these subgroups, both at the cellular level and in populations, we will gain insight into the way in which minor hormonal alterations affect the joint environment in most cases of OA.

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