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OSTEOARTHRITIS IN MENOPAUSAL WOMEN: CONCEPTS AND MANAGEMENT

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ABSTRACT
Hormonal changes that begin during the menopausal transition affect many biological systems. In postmenopause, long term manifestations of definite estrogen deprivation ensue, among which Osteoarthritis (OA) is one. Osteoarthritis is a chronic degenerative joint disease involving multiple physiopathological mechanisms. OA strikes women more often than men and it increases in prevalence, incidence and severity after menopause. Among the multiple physiopathological mechanisms involved in OA, those related to sex hormones have been attracting much attention, in particular those involving estrogens. The manifestation of osteoarthritis after the decline of estrogen in menopause has a different pathology compared to the osteoarthritis that occur as degenerative joint disease. The postmenopausal osteoarthritis is a subtype of osteoarthritis and it is considered as osteoporotic phenotype. This type of osteoarthritis demands anti-resorptive agents along with conventional line of management. There is increasing evidence that estrogen fulfil a relevant role in maintaining the homeostasis of articular tissues and, hence, of the joint itself. It also has anti-resorptive property. The dramatic rise in OA prevalence among post-menopausal women, presence of estrogen receptors (ERs) in chondrocytes, subchondral bone cells and sinoviocytes, suggest a link between OA and loss of ovarian function. A better understanding of the role that estrogen and its deficiency plays in the molecular mechanisms of menopause induced osteoarthritic changes that affect the different joint structures will help further development of new and precise therapeutic strategies to prevent and/or restore damaged articular tissues in OA.

KEYWORDS: Osteoarthritis, estrogen, menopause, subchondral bone, articular cartilage, menisci.

INTRODUCTION
Menopause is a physiological process universally affects all women who reach midlife. Studies indicate that women complete the transition to menopause, an estimated 85% report one or more symptoms, of which about ten percent seek medical help[1], necessitating the need to find effective and safe alternatives. Osteoarthritis, the most common articular disorder begins asymptomatically after menopause in the 2nd and 3rd decades and is extremely common by age 70. Almost all persons by age 40 have some pathologic change in weight bearing joint.[2]

OA is estimated to be the 10th leading cause of nonfatal burden[3,4] and fourth leading cause of Year Lived with Disability (YLD), accounting for 3.0% of total global YLDs.[5] It is also a disease that, at least in middle-aged and elderly persons, is much more common in women than in men, and sex differences in prevalence increase with age.[6]

Osteoarthritis is an abnormality of the synovial joints characterized by softening, splitting and fragmentation of articular cartilage not attributable to direct contact with inflammatory tissue. This is usually accompanied by subchondral sclerosis and bony cysts, joint space narrowing and bony outgrowths at tissue joint margins.[7]

OA is a chronic degenerative disorder of multifactorial etiology characterized by loss of articular cartilage and peri-articular bone remodeling. It is probably not a single disease but represents the final end result of various disorders as joint failure. OA may cause joint pain, bony or soft tissue swelling, tenderness, bony crepitus, peri-articular muscle atrophy, bony hypertrophy, deformity and marked loss of joint motion. It commonly affects the hands, feet, spine, and large weight-bearing joints, such as the hips and knees. It can present as localized, generalized or as erosive osteoarthritis.[8]

Primary osteoarthritis is not only related to aging but also to uncoupling of balance between cartilage degeneration

and regeneration whereas, secondary osteoarthritis is caused by another disease or condition. The diagnosis of OA is essentially clinico-radiological. X-rays are still the main diagnostic tool.[9]

OA strikes women more often than men and it increases in prevalence, incidence and severity after menopause.[10] Radiographic generalized OA is three times more common in women aged 45-64 years compared to their male counterparts. 64% of females with knee osteoarthritis suffered the onset of symptoms either peri menopausal or within 5 years of natural menopause or hysterectomy.[11]

Therefore, a million dollar question arises, is menopause associated with the onset and progression of osteoarthritis in women, and is there any difference in the OA occurring in postmenopausal women. The present article aims at differentiating the pathogenesis and treatment protocols of OA and post menopausal OA.

PATHOGENESIS OF OA[12]

Initially, osteoarthritis has been considered to be a disease of articular cartilage, but recent research has indicated that the condition involves the entire joint. The loss of articular cartilage has been thought to be the primary change, but a combination of cellular changes and biomechanical stresses causes several secondary changes, including subchondral bone remodeling, the formation of osteophytes, the development of bone marrow lesions, change in the synovium, joint capsule, ligaments and periarticular muscles, and meniscal tears and extrusion.

Normal adult articular cartilage is made up of extracellular matrix (water, collagen, proteoglycans and a very small component of calcium salt) and chondrocytes. The turnover rate of collagen is relatively slow, whereas proteoglycan turnover is rapid. The normal turnover of this matrix components is mediated by the chondrocytes, which synthetize these components and the proteolytic enzymes responsible for their breakdown.

Osteoarthritis result from failure of chondrocytes to maintain homeostasis between synthesis and degradation of these extracellular matrix components.

Trauma causing a micro fracture or inflammation causing a slight increase in enzymatic activity may allow the formation of “wear” particles, which could be then engulfed by resident macrophages. At some point in time, the production of these “wear” particles overwhelms the ability of the system to eliminate them and they become mediators of inflammation, stimulating the chondrocyte to release degradative enzymes.

Osteoarthritic cartilage is characterized by an increase in anabolic and catabolic activity. At first, compensatory mechanisms such as increased synthesis of matrix molecules and proliferation of chondrocytes in the deeper layers of the cartilage, are able to maintain the integrity of the articular cartilage, but in the end loss of chondrocytes and changes in extracellular matrix predominate and osteoarthritic changes develop.

Initial degenerative changes in the articular cartilage lead to cartilage softening, fibrillation zone of the superficial layers, fissuring and diminished cartilage thickness, but these changes become more pronounced with time, when articular cartilage thins to total destruction, eventually leaving the underlying subchondral bone plate completely exposed. All these changes in the articular cartilage are referred to as chondropathy.

It is not yet clear whether changes within subchondral bone precede changes in the articular cartilage or whether they occur in the disease progression, secondary to adaptation processes after changes in the biomechanical properties of the overlying articular cartilage.

Subchondral bone properties are modified through the cell mediated process of remodeling and modelling. Bone remodeling includes the cupling of mechanisms that resorb bone and form new bone on a previously resorbed surface, whereas bone modeling is a mechanism that drives changes in the architecture and volume of bone via direct apposition to existing bone surfaces. During the osteoarthritic process all of these mechanisms may be altered at some point in time resulting in subchondral bone structure changes.

Changes in the bone include sclerotic changes and the development of bone marrow lesions that can be visualized by magnetic resonance imaging (MRI). Thus, there is a progressive increase in the subchondral bone plate thickness, a modification in the architecture of subchondral trabecular bone, formation of new bone at the joint margins - osteophytes.

In later stages, severe remodelling processes take place in particular in areas of advanced cartilage destruction, apart from extensive bone sclerosis (osteoid deposition), significant aseptic bone necrosis is a common feature of late-stage. In areas of total cartilage destruction (the eburnated bone plate), synovial fluid gets access to the bone marrow and presumably leads to the bone cysts frequently seen in late stage disease. Growth factors from the synovial fluid are probably involved in inducing fibrocytic and even chondrometaplastic changes, which lead to the “cartilage nodules” characteristic for late-stage disease. In osteoarthritic subchondral bone, type I of collagen is elevated, but this collagen content is abnormal and this leads to abnormal mineralization. Thus osteoarthritic subchondral bone has an increased osteoid collagen matrix and an abnormal mineralization resulting in a hypomineralization of this tissue. Although the subchondral bone tissue is hypomineralized in osteoarthritis, the increase in trabecular number and

volume compensates for this situation, thus providing an apparent stiffer structure. With alteration in its properties, subchondral bone may be less able to absorb and dissipate energy, thereby increasing forces transmitted through the joint and predisposing the articular surface to deformation. Subchondral bone attrition may be caused by altered mechanical loading resulting in subchondral remodeling and is associated with concomitant bone marrow lessions. Bone attrition is evaluated at conventional radiography as loss of bone density or, at MRI, as flattening/depression of the articular cortex. MRI studies have demonstrated that these bone lesions themselves are associated with development and worsening of cartilage loss.

It remains unclear whether the morphological changes that occur in the osteoarthritic synovial membrane are primary or whether they are the result of joint inflammation, cartilage degradation and lesions of the subchondral bone. Histologically, the synovial membrane of osteoarthritic joints commonly exhibits hyperplasia of the lining cell layer occasionally accompanied by focal infiltration of lymphocytes and monocytes in sublining layers. Synovitis is belived to be induced at first by the cartilage matrix proteolytic degradation products that produce wear particles and soluble cartilage-specific neo-antigens, as well as other factors including microcrystals and abnormal mechanical stress. These components are released into the synovial fluid and are phagocyted by synovial lining macrophages, perpetuating the inflammation of the synovial membrane through the synthesis of mediators, which in turn diffuse through the synovial fluid into the cartilage, and create a vicious circle, with increased cartilage degradation, and subsequently produce more inflammation.

Patients with osteoarthritis experience thickening of the synovial lining cell layer, increased vascularity and inflammatory cell infiltration of the synovial membranes, with the most marked changes occurring in advanced osteoarthritis.

Meniscal degeneration is commonly seen in osteoarthritis, where menisci appear torn, fissured, fragmented, macerated or completely destroyed. Degeneration of menisci initiates within the substance of the tissue rather than surface. Tissue fibrillation and disruption is first seen at the inner rim, which spreads to the articular surfaces of the meniscus over time, and progresses to total disruption or loss of meniscus tissue mainly in the avascular zone.

The meniscus is less able to withstand loading and force transmission during normal movements of the joint, further leading to degenerative tears. Meniscal tears are often accompanied by varying degrees of meniscal extrusion. The tear might be a preceding feature of incipient osteoarthritis, and meniscus damage and extrusion often have a key role in the structural progression of the disease.

In conclusion, osteoarthritis is a multifactorial disease of whole joint, with a complex pathomechanism involving interaction between the multiple joint tissue. Knowing of this complex process of producing osteoarthritis is essential for development of new methods of diagnostic and treatment.

POST MENOPAUSAL OA- THE SUBSET OF OA

The Framingham Knee Osteoarthritis study suggests that knee osteoarthritis increases in prevalence throughout the elderly years, more so in women than in men.[13]

Estrogen plays an important role in the growth and maturation of bone as well as in the regulation of bone turnover in adult bone. During bone growth estrogen is needed for proper closure of epiphyseal growth plates both in females and in males. Also in young skeleton estrogen deficiency leads to increased osteoclast formation and enhanced bone resorption. In menopause estrogen deficiency induces cancellous as well as cortical bone loss. Highly increased bone resorption in cancellous bone leads to general bone loss and destruction of local architecture because of penetrative resorption and microfractures. In healthy individuals, bone mass is maintained by the balanced activity of bone-forming osteoblasts and bone-resorbing osteoclasts. These two cell types, although derived from mesenchymal and hematopoietic precursors, respectively, affect each other's differentiation and activity. In addition, bone, particularly the trabecular component closely associated with bone marrow, is a rich microenvironment in which many cell types have the opportunity to influence osteoblast/osteoclast dynamics.[14]

Depending on the ratio between formation and resorption, sub-chondral bone remodelling can culminate in either a sclerotic or an osteoporotic phenotype.[15] Estrogen deficiency in post menopausal or perimenopausal women culminates in OA which is a Osteoporotic phenotype. Increasing numbers of experimental and human studies have demonstrated the existence of remodelling abnormalities in the subchondral bone, with increased bone turnover and subsequent bone loss in early stages of OA. These changes are followed by reduced bone turn over and further subchondral sclerosis in the late stages of OA.[16,17,18] Estrogen deficiency may lead to increased serum IL-6 in postmenopausal patients with OA, which has been found to promote OA progression.[19] Thus, in a post-menopausal women key changes in the subchondral bone include high bone turn over with decreased BMD and bone biomechanical structural damage in the early stages of OA, which either coincide with or precede cartilage degeneration. Subchondral bone degeneration may be the trigger for changes in the cartilage biomechanical and biochemical microenvironment, thus

promoting cartilage erosion and ultimately OA progression.[20,21]

MANAGEMENT APPROACH

An OA subset of high remodelling and/or/ low subchondral bone mineral density (BMD) may benefit from management with anti-resorptive agents to inhibit OA progression.[22] Subchondral bone is a potential therapeutic target, and drugs acting on subchondral bone represent disease modifying OA drugs. Similarly the main pathological changes in OA is degeneration of the articular cartilage that promotes subchondral bone lesion during progression of OA, particularly in late OA stages when cartilage erosion is extensive. Therefore subchondral bone and cartilage are strongly dependent on each other during the progression of OA. In short, OA disease-modifying drugs must be able to act on both of these joint tissues to prevent the development and progression of OA.[16,17,18]

Estrogen-related drugs that act on both subchondral bone and cartilage are good candidates for early-stage OA treatment, especially osteoporotic OA because of its anti-resorptive property.[15] These drugs are potent in antagonizing bone resorption, which can effectively decrease bone remodeling and prevent subchondral bone loss and the deterioration of microarchitecture and biomechanical properties. Thus, the protective effect of these drugs on articular cartilage may be an indirect effect through protection of the subchondral bone. Additionally, these drugs directly target cartilage tissue, preventing cartilage damage and maintaining healthy cartilage. In addition to the direct or indirect protective role of these drugs on articular cartilage, subchondral bone, and the surrounding joint tissues, including the synovium and muscle, the joint tissues themselves interact with each other, thus maintaining joint organ homeostasis as a whole and finally delaying joint degeneration.[15]

Effects of estrogen-related drugs on joint tissues are as shown in the table.[15]

Effects of estrogen-related drugs on joint tissues:

Tissue	Main effects
Articular cartilage	Reduction of articular cartilage turnover and destruction, regulation of cartilage metabolism, improvement of mechanical properties
Subchondral bone	Regulation of bone growth and remodeling, promotion of matrix production and mineralization, regulation of osteoblast and osteoclast development and function
Synovial membrane	Decrease of the proliferation of rheumatoid arthritis-like synovial cells, decrease of proinflammatory cytokine production, reversion of experimental arthritis
Muscle	Promotion of myoblast proliferation and differentiation, reduction of muscle cell apoptosis, reversion of muscle atrophy and contractile dysfunction

DISCUSSION

According to the ratio of osteoclasts and osteoblast activity, the subchondral bone remodelling can culminate as osteosclerotic and osteoporotic subtype.[15] These two can be considered as the subtypes of osteoarthritis. In a postmenopausal women, due to estrogen deficiency, osteoporotic phenotype marks the early stage of OA, which is followed by reduced bone turnover and subchondral sclerosis as late stage OA.[23] An emerging concept is that estrogen could decrease bone turnover and may have potential beneficial effects for early-stage OA. Conversely, the prevention of bone loss may result in effects that are not beneficial or are even harmful for late-stage OA, with some studies showing an association between high bone density and radiographic OA changes. Estrogen may have a beneficial effect on only certain subtypes of OA.[15]

CONCLUSION

In summary, estrogen may have different effects on the initiation and progression of OA. Increasing numbers of experimental and human studies have demonstrated the existence of remodeling abnormalities in the subchondral bone, with increased bone turnover and subsequent bone loss in early stages of OA. These changes are followed by reduced bone turnover and further subchondral sclerosis in the late stages of OA.[15] Consequently, estrogen could decrease bone turnover and may have potential beneficial effects for early-stage OA. Conversely, the prevention of bone loss may result in effects that are not beneficial or are even harmful for late-stage OA. Second, estrogen may have a beneficial effect on only certain subtypes of OA. Depending on the ratio between formation and resorption, subchondral bone remodeling can culminate in either a sclerotic or an osteoporotic phenotype. Patients with osteoporotic OA may thus achieve clinical and structural benefit from estrogen intervention.

Taken together, the identification of OA patient phenotypes and specific OA stages should be considered alongside therapeutic interventions, which may lead to clearer conclusions regarding role of antiresorptive therapy on post menopausal OA and its progression.

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