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OSTEOARTHRITIS AND MENOPAUSE

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***Abstract* : Osteoarthritis (OA) is the most frequent joint disease encountered in the clinical practice and is the most common cause of locomotor disability in the elderly. OA strikes women more often than men and it increases in prevalence and incidence after menopause. Females are found to have more severe OA, more number of joint are involved, have more symptoms and increased hand and knee OA. Many experimental, clinical and epidemiological studies suggest that loss of estrogen at the time of menopause increases a woman's risk of getting osteoarthritis and use of HRT did seem to be associated with not only relieving of symptoms but also reduced rate of progression of osteoarthritis. Moreover, antiresorptive drugs like alendronate may also protect against the development of bone abnormalities associated with knee OA. On the contrary few studies have proposed that estradiol mediates the damage to cartilage tissue and estrogen is chondrodestructive suggesting that HRT is associated with a higher prevalence of clinical OA. Furthermore, polymorphisms in the ER alpha gene have been suggested to be associated with radiographic OA of the knee. Hence with the current level of evidence, HRT can not be recommended as a first-line treatment against progression of OA, but the fact can not be denied that if somebody is taking estrogen therapy for some other reason may get benefited. Otherwise treatment will include conventional non-pharmacological and pharmacological treatment.**

***Key words*: Osteoarthritis, menopause, HRT**

Osteoarthritis (OA) is the second most common rheumatological problem and is most frequent joint disease encountered in the clinical practice[1]. This is the most common cause of locomotor disability in the elderly. OA[2] 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.

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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 however arthroscopy, ultrasound, MRI, CT scan etc. are used specially for experimental studies and not recommended for routine clinical use. Radionucleide studies, may detect abnormalities before radiographic signs. Arthrocentesis and laboratory testing may help identify an underlying cause of secondary OA.

OA strikes women more often than men and it increases in prevalence, incidence and severity after menopause[3,4]. Therefore, million dollar questions arises, Is menopause associated with the onset and progression of osteoarthritis in women and can HRT

render help in such patients. The present review is aimed to reveal these facts.

Relation of Estrogen / Menopause and Osteoarthritis

Preclinical studies

Ovariectomy (OVX)-induced acceleration of cartilage degradation and erosion in rats indicate that estrogen deficiency accelerates cartilage turnover and increases cartilage surface erosion[5]. Whereas, estrogen supplementation may play an important role in delaying the development of osteoarthritis in OVX induced osteoarthritis in female rats both biochemically and histologically [6]. Not only estrogen but even levormeloxifene, a (SERM), can prevent the OVX-induced changes in cartilage degradation in both rodents and humans, suggesting potential therapeutic benefits in the prevention of destructive joint diseases such as osteoarthritis[7].

OVX may also have a detrimental effect on the intrinsic material properties of the articular cartilage of the knee and treatment with estradiol implants ameliorate these deleterious effects and help to maintain the tissue's structural integrity[8]. One recent study provide direct experimental prove that long-term estrogen replacement therapy may be beneficial in OA by increase insulin-like growth factor binding protein (IGFBP-3) levels in articular cartilage which appears to be synthesized by articular cartilage chondrocytes in a well-characterized monkey model of naturally occurring (OA)[9].

Clinical and epidemiological studies:

The Framingham Knee Osteoarthritis study suggests that knee osteoarthritis increases in prevalence throughout the elderly years, more so in women than in men[3]. Females are found to have more severe OA, more number of joints is involved, and have more symptoms and increased hand and knee OA[4]. These observations and others reporting a painful form of hand osteoarthritis after the menopause suggest that loss of estrogen at the time of menopause increases a woman's risk of getting osteoarthritis[10]. Polyarticulars osteoarthritis also has strong female inheritance, frequent onset around menopause and an association with previous hysterectomy and gynecological surgery leading to suggestion that hormonal factors are important in this subgroup[11]. A large epidemiological study was conducted in Italy, gave epidemiological support to the hypothesis that estrogen deficiency may increased the risk of OA[12].

In a prospective cohort study, use of estrogen replacement therapy did seem to be associated with a reduced rate of progression of knee osteoarthritis[13]. Similarly long term hormone replacement therapy increases bone mineral density in women who have experienced natural menopause, and protects against bone loss in surgically postmenopausal women[14]. Combined estrogen and progestin replacement therapy can relieve the knee OA symptoms of postmenopausal women. Significant differences on pain at night and tenderness around knee were seen in the treatment group compared with the control group after 1 months of treatment[15, 16]. One of the most recent studies focused on women who were taking bone antiresorptive agents, primarily estrogen or alendronate. Women taking either alendronate or estrogen had significantly fewer bone abnormalities associated with severe knee OA - including subchondral bone thickening, osteophytes, and bone marrow edema-like lesions than the women not taking these medications. "This finding is particularly important because the MRI bone marrow abnormality score which is a strong predictor of progression of structural deterioration in knee OA, was used. In addition, women using alendronate experienced less knee pain, according to the WOMAC scores, than nonusers. However, researchers found no association of either alendronate or estrogen use with changes in cartilage detected by MRI or radiographic changes of OA of the knee. Thus suggesting that alendronate and estrogen may protect against the development of bone abnormalities associated with knee OA, which may have

a beneficial effect on the overall course of the disease[17]. Furthermore, one recent review suggest that HRT for the menopause seems to be associated with a decrease in the prevalence of symptoms and radiological alterations related to hip and knee osteoarthritis[18].Not only this but in menopausal women and the elderly, populations most often affected by osteoarthritis (OA), estrogen levels are lower than normal[19], which strongly suggests that estrogen may be an important regulator of OA.

Contrary results:

Metabolism of estrogen—specifically the conversion of estrone into estradiol—has also been observed within osteoarthritic cartilage tissue.[4] Based on these results, some researchers have proposed that estradiol mediates the damage to cartilage tissue in osteoarthritis[20, 21].

Thus, with our expanding knowledge of osteoarthritis (OA) over the years, our concept of this "aging" disease has been re-evaluated to that which is the opposite of traditional views. To clinicians and scientists, OA is no longer the inevitable disease of aging. Epidemiological studies show a higher incidence of OA affecting polyarticular joints in women than age-matched men, particularly those over the age of 55. This discrepancy in sex difference in the OA incidence highlights the significance of sex hormones and their alterations in menopause. Evidence indicates that this alteration possibly occurs early in adult life and may well persist into menopause. As well, this hormonal perturbation is thought to be consequent to obesity in these women. Both in vivo and in vitro studies suggest that estrogen is chondrodestructive via the receptor-mediated mechanism. The finding of estrogen receptor in canine, rabbit, and human articular cartilage further confirms this hypothesis. Recent findings of elevated synovial estradiol level and higher estrogen receptor bindings in human osteoarthritic cartilage strongly suggest the importance of local uptake of estradiol (E2) and the possible up-regulation of estrogen receptors. Estrogen, like other hypothesized etiologies, is important in the development of OA in women[22].

One prospective cohort study to examine the effects of HRT on radiographic knee OA indicated that current use of HRT had a moderate but not statistically significant, protective effect against worsening of radiographic knee OA among elderly white women. These findings point fingers to studies suggesting potential benefits of HRT in prevention OA in women[13]. The study examining postmenopausal estrogen (PME) use and prevalence of clinical osteoarthritis (OA) at the hand, knee, and hip indicated, significantly larger proportion of women who used PME for at least 1 year had hip and hand OA compared with women not using PME (4.1% vs. 1.1%),indicating PME is associated with a higher prevalence of clinical OA[23].

Furthermore, polymorphisms in estrogen receptors have been suggested to play important roles in the pathopysiology of osteoarthritis. Polymorphisms in the ERalpha gene are suggested to be associated with radiographic OA of the knee, and in particular with osteophytosis, in both elderly men and elderly women[24].The study of Jin et al 2004 confirmed these findings[25].

Thus, findings regarding a correlation between estrogen and OA are inconsistent and inconclusive and range from estrogen protecting against OA to detrimental to cartilage[26].

Current management of osteoarthritis and place of HRT

Status of HRT in OA: Thus, researchers strongly implicates estrogen imbalances during menopause and/or estrogen deficiency following menopause as major hormonal risk factors for the disease Indeed, large-scale controlled studies have shown a reduced incidence of osteoarthritis in postmenopausal women who undergo long-term estrogen replacement therapy. On the contrary few results disfavoring its use are present suggesting worsening of OA with the use of postmenopausal estrogen use. Hence with the current

level of evidence, HRT can not be recommended as a first-line treatment against progression of OA, but the fact can not be denied that if somebody is taking estrogen therapy for some other reason may get benefited.

Otherwise treatment will include Non-pharmacological measure[2] in the form of education and behavioral intervention, weight loss, exercises, mechanical aids, transcutaneous nerve stimulation, local massage, acupuncture, pain management counseling and support groups. Assistive devices in knee osteoarthritis, physical therapy in form of knee sleeves, cone or walker and occupational therapy are other modalities which can be used.

Pharmacological treatment[2] in the form of drugs which can relieve symptoms like, acetaminophen, salicylates and traditional NSAIDs, COX-2 inhibitors, or NSAIDs with misoprostol as cotherapy. Opiods like tramadol, topical analgesia and intra-articular glucocorticoid injection can also be helpful. The second category of drugs includes symptomatic slow acting drugs for OA (SYSADOA) including nutraceutical like glucosamine and chondroitin sulfate or their combination. Therapeutic benefit of hyaluronan multiple intraarticular injectionsmay be utilized. However, routine use of it is not well established because of unclear mechanisms of action, multiple injections are required and latency of onset of action[27]. Hylan GF-20 (synvisc) is a high molecular weight cross-linked derivative of hyaluronan that has elastoviscous properties similar to healthy synovial fluid .Its efficacy for treatment of osteoarthritis knee pain, with low incidence of local adverse effects, has been demonstrated in recent clinical trial[28].

Therapy in the pipeline like structure modifying OA drugs (SMOADS) including metalloprotease inhibitors may have promising role in future. Moreover disease modification potential of agents like glcosamine, diacerhein and hyaluronan need further studies. Patients with persistent pain, progressive limitation of daily activities despite medical management, progressive joint damage and ankylosis may be the candidates for surgery[2].

In conclusion menopause is associated with the onset and progression of osteoarthritis in women and HRT can render help in such patients but with the current level of evidence, it can not be recommended as a first-line treatment.

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