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Review Article

Development of Osteoarthritis in Post-menopausal Women and Different Ways to Manage it

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Abstract

Menopause is a natural, gradual transition between active and inactive ovarian functions that last several years in women's lives and involves changes in both the body and the mind. Women enter an estrogen-deficient phase during menopause, which speeds up the ageing process. They are more likely to develop osteoarthritis compared to men, and the prevalence of the condition rises dramatically during menopause for women. As a result, this article aims to understand the connection between menopause and osteoarthritis, followed by various strategies for managing arthritis symptoms in postmenopausal women.

Keywords: Menopause; Estrogen; Osteoarthritis; Joint pain; Arthritis.

Introduction

Menopausal arthritis is osteoarthritis (OA) that causes joint pain and inflammation early in menopause and may persist even after other menopausal symptoms have gone away [1,2]. Women are more likely than men to develop OA after menopause, with rates that are 3.5 times higher in women between 50 and 60 than in men of the same age. Between 50 and 75, the risk of OA among women increases rapidly with incidence and severity [3]. According to the Women's Health Initiative, 44% of the participating postmenopausal women reported having osteoarthritis [4]. Within five years of natural menopause or a hysterectomy, 64% of females with knee osteoarthritis experienced symptoms [5,6]. The occurrence of OA after menopause suggested that postmenopausal women are more likely to develop OA than

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premenopausal women [2,7]. The hypothesis that estrogen deficiency may increase the risk of OA received epidemiological support from a large Italian study [2,8]. As a result, the most important question is whether women's osteoarthritis onset and progression are influenced by menopause. This review aims at discussing the connection between menopause, estrogen, and osteoarthritis, followed by varied ways that could manage arthritis symptoms in post-menopausal women.

The connection between menopause, estrogen, and osteoarthritis

Menopause is a natural, gradual transition between active and inactive ovarian functions that lasts several years in women's lives and involves changes in their biological and psychological makeup [5]. Women typically experience an inevitable onset of the ageing process by entering an estrogen-deficient phase when they reach menopause, accelerating the ageing process [5]. Considering differences between women living in different countries, the typical age of menopause is between 50 and 51 [9,10]. Genetics, ethnicity, smoking, socioeconomic status, and pregnancy history impact menopausal age [11]. When estrogen levels drop during menopause, symptoms such as hot flashes, night sweats, mood swings, fatigue, weight gain, and dryness in the vagina would occur. One of the less well-known effects is increased inflammation which causes joint pain, swelling, and stiffness [1]. This condition is known as "menopausal arthritis". It is common knowledge that estrogen reduces inflammation in women and that low estrogen levels are linked to arthritis, though the exact mechanism is still unclear [1]. The immune system is affected by estrogens in both a stimulatory and inhibitory manner [9]. Postmenopausal loss of ovarian function (disuse atrophy) is linked to OA, according to growing evidence that estrogen plays an important role in maintaining the homeostasis of articular tissue. Therefore, estrogen protects against joint degeneration [3]. The regulation of adult bone turnover and the growth and maturation of bone are both influenced by estrogen [5]. BMI primarily influences endogenous estrogen levels. Estradiol (E_1) and estrogen (E_2) levels are thought to be higher in women with a higher BMI, which can delay menopause [1]. Glycosaminoglycan synthesis, an essential component of connective tissue, is one reason estrogen has chondroprotective effects. In addition, estrogen prevents chondrocyte damage caused by reactive oxygen species by inhibiting cyclooxygenase 2 mRNA expression in other tissues and bovine articular chondrocytes. Therefore, cartilage damage is reduced by estrogens [4].

Women typically experience decreased bone density due to the dramatic drop in estrogen levels during menopause [12]. Due to the ovaries' ageing process, ovarian estrogen release would gradually decrease. When compared to women of reproductive age, menopausal women have extremely low levels of estradiol [9]. An average annual bone loss of 2-3% in the first few years and 0.5-1% after that is the overall effect of menopause [12]. As a result, key changes in the subchondral bone, such as bone biomechanical structural damage, occur simultaneously with or before cartilage degeneration in postmenopausal women,

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followed by advancing OA [5]. In postmenopausal OA patients, estrogen deficiency may result in elevated serum IL-6, which has been shown to accelerate OA progression [5]. Compared to controls, the serum concentrations of free and total estradiol significantly decreased in postmenopausal women. Post-menopausal women had significantly higher levels of 2-hydroxy estradiol. In addition to free and total estradiol deficiency, the authors found a correlation between a decreased serum level of 2-hydroxy estrone in premenopausal women and an increased serum level of total 2-hydroxy estrone in postmenopausal women with OA [4].

Effect of progesterone and estrogen on the development of knee inflammation in postmenopausal OA

In women, estrogen and progesterone receptors were found in the synovial cell lining [13]. Estrogens affect inflammatory processes, as revealed by the rise in inflammatory reactions to infection and sepsis [14]. Similarly, progesterone may also contribute to maintaining cartilage volume by controlling matrix metalloproteinase (MMPs) production, which is mainly responsible for articular cartilage degradation [13].

Low serum levels of estradiol and progesterone in post-menopausal women were associated with the rise in knee effusion-synovitis followed by other OA-related structural changes [13]. Due to the lack of estradiol after menopause, the higher levels of IL-1, IL-6, TNF-α and other inflammatory factors in synovial fluid and cartilage may stimulate the pathogenesis of OA [15]. Higher IL-1 levels may lead to OA by affecting the microenvironment of articular cartilage, accelerating the progress of the synovial membrane inflammation, repressing the cartilage matrix synthesis, supporting the cartilage matrix degradation, and decreasing the restorative ability of cartilage [15]. Higher IL-6 triggers the loss of matrix moisture, affects the matrix composition, and degrades the microenvironment of chondrocytes, creating a vicious cycle between matrixes and chondrocytes degradation, followed by resorption of subchondral bone [15]. TNF-α, an early mediator of local inflammation, activates neutrophils, induces prostaglandin E2 production by synovial cells, promotes the synthesis of matrix metalloproteinase in cartilage, and accelerates articular cartilage degeneration, thereby aggravating osteoarthritis [15]. However, research on the association between progesterone and the pathogenesis of knee osteoarthritis is very limited, thus highlighting the need for immediate research [13]. Hence, menopause plays a more significant role in the progression of cartilage degeneration, while estrogen deficiency is a risk factor for cartilage degeneration [4]. Fortunately, early intervention with lifestyle changes, menopausal hormone therapy, nutritional supplements, and Orth biologics treatment such as platelet-rich plasma (PRP) therapy, bone marrow aspirate concentrate (BMAC), etc., can reduce the severity of many menopausal diseases.

Management of OA symptoms

Physical therapy

Women, who engage in regular physical activity, are reported to gain muscle strength

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and fitness balance. Additionally, practicing knee protection behaviors would increase bone density. Several international guidelines suggest health interventions that include physical activity and exercise recommendations for non-pharmacological management. Although education and treatment interventions reduce osteoarthritis symptoms and clinical outcomes, their efficacy is short-lasting since the failure to adhere to behaviour change is the primary cause of such interventions' ineffectiveness over the long term. However, long-term adherence to the recommendation and constant behaviour modification is required to maintain the benefits of physical activity [11].

Regular exercise

Regular exercise was reported to prevent weight gain and improve mobility, range of motion, and joint support. It is recommended for adult women in good health to exercise for at least 150 minutes per week at a moderate level or 75 minutes per week at a vigorous level. Women should focus on gentle muscle-strengthening exercises like stretches, yoga, or Pilates alongside low-impact aerobics like walking [1].

Diet

The study by Rajajei, et al., revealed that omega-3 fatty acids would effectively reduce joint inflammation [12,16]. Parvez, et al., [12,17] demonstrated that nightshade vegetables like eggplants and potatoes contain C-reactive protein known to cause joint inflammation. Ishibashi, et al., [12,18] concluded that the hydroxyl radical scavenger H_2 would successfully reduce oxidative stress in patients with arthritis, thereby reporting a significant improvement in arthritis symptoms.

Joint inflammation can be reduced by drinking more water daily. Sköldstam, et al., [12,19] reported that frequent fasting increased joint inflammation, while shorter fasting did not affect osteoarthritis. OA cannot be cured through diet change but can lessen its severity [12].

A menopause diet should include protein, healthy fats, and complex nutrient-rich carbs. Examples of phytoestrogens include soy, oats, mung beans, and alfalfa. Vitamin K-rich foods like kiwi, Swiss chard, kale, tomatoes, parsley, and bone and cartilage mineralization are helpful in joint pain treatment. Vitamin D-rich foods like eggs, mushrooms, tuna, salmon, and carrots can help seniors with vitamin D deficiency and alleviate pain in the hips, upper or lower extremity joints, and muscles [1].

Medications

Acute pain can be alleviated by consuming nonsteroidal anti-inflammatory drugs (NSAIDs) and other anti-inflammatory medications such as acetaminophen or ibuprofen. Corticosteroids can be injected into the affected joint or taken orally to reduce inflammation and alleviate pain and swelling. Although hormone replacement therapy (HRT) is effective, it comes with a higher risk of serious side effects and health risks, so it is recommended to be used by women experiencing severe symptoms [1]. HRT could reduce symptoms and progression, increase bone mineral density, and reduce radiological OA abnormalities

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[20]. Postmenopausal women can experience relief from knee OA symptoms with estrogen and progestin replacement therapy [2].

Follicle-stimulating hormone (FSH) and luteinising hormone (LH) would play a significant role in the regulation of bone mass in postmenopausal women, according to a Chinese study [1]. Due to their anti-resorptive properties, estrogen-related medications are ideal for early-stage OA treatment as they treat subchondral bone and cartilage. As a result, estrogen-related medications are reported to directly target cartilage tissue, preserve healthy cartilage, and prevent damage. Additionally, they protect articular cartilage, subchondral bone, and the surrounding joint tissues, such as synovium and muscle, and interact with the joint tissues, preserving joint organ homeostasis and ultimately preventing joint degeneration [5].

Orthobiologics

The use of orthobiologics (autologous biological products)-to treat various musculoskeletal conditions represents an emerging field in Orthopaedics and sports medicine. Orthobiologic treatments aim to improve symptoms and quality of life while possibly halting or preventing joint degeneration [21].

Prolotherapy

The researchers have proposed three potential mechanisms. Firstly, prolotherapy's fundamental premise is inflammation induction through irritants to promote tissue regeneration and repair. One study found that articular cartilage defects could be repaired with 10% dextrose [22,23]. Second, the pro-chondrogenic effect of dextrose prolotherapy needs to be better established. When measured by MRI, intra-articular dextrose prolotherapy did not slow down or reverse the loss of cartilage in patients with knee OA. However, a small study in patients with severe symptomatic knee OA found that intra-articular dextrose prolotherapy improved knee cartilage quality through direct arthroscopic visualization and cartilage biopsy, indicating chondrogenesis [22,24].

Dextrose's direct pain-reducing effect is the third proposed mechanism. In a double-blind RCT, patients with chronic low back pain and either gluteal or leg pain experienced a reduction in pain following the injection of epidural dextrose (5%) without local anesthetic. The hypothesis that dextrose may have a direct sensorineural effect is supported by the fact that analgesia began as early as 15 minutes after the injection [22,25].

Compared to blinded saline injections and at-home exercises, prolotherapy improved knee osteoarthritis pain, function, and stiffness scores in a clinically significant way [26].

Platelet rich plasma

Platelet-rich plasma (PRP), a type of orthobiologics, has received attention in recent clinical trials to treat knee OA. Compared to physiologic plasma, PRP has significantly higher platelet concentrations and associated growth factors. Various studies have shown that PRP functions better in pain relief than steroids or HA injections. PRP typically contains four to six times the patient's baseline concentration of platelets [27]. IGF-1 has anabolic effects on the joint,

encouraging the formation of type II collagen, proteoglycans, and other extracellular matrix components. PDGF, TGF-B, and other growth factors were typically present in the various solutions. These components could discourage proteolysis of the extracellular matrix microenvironment and promote adhesion between chondrocytes. PDGF stimulates chondrocyte production, and TGF-beta possesses an anabolic effect on chondrocytes. TGF-beta further aids the transformation of articular mesenchymal stem/stromal cells into chondrocytes. According to the findings of a randomized controlled trial conducted in 2014, intra-articular PRP knee injections in conjunction with therapeutic exercise may be more effective than therapeutic exercise on its own at reducing pain, reducing stiffness, and improving quality of life [27]. Chang, et al., compared 16 studies with 1543 patients and found that PRP was better at controlling pain than HA. The beneficial effects of PRP, which are more pronounced in patients with mild OA, can last up to a year. It was discovered that HA only worked for two months and steroids only for one month [28]. The minor side effects include pain at the injection site, joint stiffness, syncope, dizziness, headache, gastritis, sweating, and tachycardia. Pain relief with PRP may last six to twelve months after the injection [29].

Intra-articular mesenchymal Stem/Stromal Cell (MSC) injection

An additional product of orthobiologics, bone marrow mesenchymal stem cells (BM-MSCs), are thought to be multipotent because they can grow into various cell types, including type II chondrocytes, adipocytes, and osteoblasts/osteocytes. Mesenchymal stem cells have traditionally been isolated from autologous iliac crest samples. Still, it has been demonstrated that they can also be isolated from adult sources (skeletal muscle, synovium, adipose tissue) and embryonic sources (umbilical cord). Compared to the current treatments for translational OA therapy, mesenchymal stem cells offer several significant advantages. First, the risk of autoimmune rejection is eliminated due to these cells' autologous nature. Second, mesenchymal stem cells can be isolated in relatively large numbers and with high purity, maximizing their ability to differentiate into the damaged joint space's target tissue.

Thirdly, mesenchymal stem cells, like other regenerative medicine products, have strong anti-inflammatory properties because they express IL-1 Ra and can stop resident joint space macrophages from releasing pro-inflammatory cytokines. Fourth, human mesenchymal stem cells can be cultured and expanded ex vivo using Good Manufacturing Practices (GMP), making it possible to administer additional pharmacological treatments to boost cell proliferation and maturation and their capacity for repair. Lastly, the widespread application of mesenchymal stem cells in human clinical trials over the past ten years demonstrates their safety and efficacy as a translational therapy [29]. Orozco, et al., [30] reported that chronic knee osteoarthritis could be effectively treated with MSC therapy as an alternative. The treatment is straightforward, does not necessitate hospitalization or surgery, eases pain, and significantly raises cartilage quality. Ahmad et al. reported a 29% decrease from baseline in the WOMAC pain

scales and an increase in cartilage deposition. Self-limiting adverse effects included pain and edema [31]. In patients with moderate-to-severe KOA, a 12-month combination of BMC and AD-MSC was safe and effective in improving patient-reported outcomes [32]. In patients with knee osteoarthritis, BMAC and AD-MSC, which include mechanically treated (microfat/nanofat) injections and enzymatically treated stromal vascular fraction (SVF) injections, prove to be safer and more effective for a shorter duration of two years [33].

Conclusion

In conclusion, women's OA onset and progression are linked to menopause. Changes in diet and lifestyle, medication, regular exercise, and orthobiologics could help menopausal arthritis patients by reducing symptoms and progression, increasing bone mineral density, decreasing bone loss, and reducing radiological abnormalities.

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Conflicts of interest

The authors declare no conflict of interest.

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