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The effectiveness of estrogen therapy and aerobic exercise combined with resistance training therapy in postmenopausal women's osteoporosis

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Abstract. Postmenopausal osteoporosis (PMOP) usually happens five to ten years following a woman's menopause, and some women over 50 in China suffer from PMOP. Hormone replacement therapy (HRT) and aerobics combined with resistance training are the two promising osteoporosis interventions, but few studies have compared their efficacy. The mechanisms by which exercise treatment and hormone replacement therapy affect bone mineral density (BMD) are examined in this review and other health parameters in postmenopausal osteoporosis patients. As studied in this paper, estrogen improves osteoporosis. However, risks such as venous thromboembolism limit the long-term use of HRT. In terms of exercise therapy, a direct comparison of aerobic exercise combined with resistance exercise and HRT showed that supervised exercise improved BMD more than HRT and that exercise also boosted metabolism and avoided the risks of HRT. In conclusion, aerobic and resistance training provides a safer alternative to HRT for managing postmenopausal osteoporosis, and further studies should optimize exercise regimens.

Keywords: Postmenopausal osteoporosis, oestrogen, aerobic exercise, resistance training, review

1. Introduction

Osteoporosis is a diagnosable, treatable, systemic bone disease due to multiple causes of decreased bone mass, density, and bone deterioration microstructure, increasing the fragility of the bone and making it more prone to breaking. Primary osteoporosis and secondary osteoporosis are the two basic types of osteoporosis. There are three types of primary osteoporosis: idiopathic osteoporosis, senile osteoporosis, and postmenopausal osteoporosis. Typically, postmenopausal osteoporosis develops five to ten years following menopause, and the perimenopausal period (from the clinical features, endocrinology and biology of the beginning of menopausal tendency signs until one year after menopause) and the five years after menopause are the critical period to treat and prevent osteoporosis [1]. The osteoporosis prevalence in women over 50 in China is 32.1% [2]. The main reason is that after women enter

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perimenopause, the secretion of estrogen decreases. Its binding to estrogen receptors on the membrane of osteoblasts decreases, resulting in a significant increase in the activity of osteoclasts because bone resorption, which accelerates the loss of bone mass and causes a major drop in bone density, is more significant than bone synthesis [3]. Clinical manifestations include low back pain, fracture, spinal deformation and multiple organ dysfunction, seriously affecting quality of life. The 2018 epidemiological survey of osteoporosis in China's population showed that the prevalence of postmenopausal osteoporosis was 32.5%. In postmenopausal women, the risk of osteoporotic fracture has increased to 50%. Therefore, Chinese postmenopausal women's osteoporosis prevention and treatment should be completed on time, and the standardization of diagnostic and treatment protocols for postmenopausal osteoporosis has also received increasing attention.

Various factors may lead to postmenopausal osteoporosis, such as old age, long years of menopause, no calcium supplementation, and symptoms of bone pain [3]. Regarding the treatment of this disease, there are a variety of clinical treatments, such as bisphosphonates, RANKL signalling pathway therapy, etc., which can improve the symptoms to a certain extent. However, there are certain limitations, such as high costs and side effects. Estrogen-based therapy can promote osteoblast proliferation and inhibit osteoclast apoptosis to a certain extent, thus playing a role in preventing and treating postmenopausal osteoporosis. At the same time, aerobic exercise combined with exercise therapy has gradually come to people's attention and begun to be applied in the intervention of postmenopausal osteoporosis. Estrogen therapy and aerobic exercise combined with resistance exercise therapy are relatively gentle in the treatment process, can effectively improve menopause, relieve patients' mental stress, and are very helpful in preventing osteoporotic fractures. At the same time, they cost less and are less damaging to patients' bodies. However, treating these two options in postmenopausal osteoporosis has not yet been widely discussed, and there are fewer studies to observe the difference in comparative efficacy between the two. Therefore, this paper analyses the therapeutic mechanisms of estrogen therapy and aerobic exercise combined with resistance exercise therapy for postmenopausal osteoporosis to provide more evidence-based evidence for diagnosing and treating this disease.

2. Effect of oestrogen on postmenopausal osteoporosis

Estrogen is closely related to osteoblasts, osteoclasts, chondrocytes and some inflammatory factors and can regulate the transcription and translation of target genes through the action of estrogen receptors (ER) in bone tissue cells. ER mainly includes ERα, ERβ and ERγ, etc., and there is a heterogeneous expression of ER in osteoclasts and osteoblasts lineages, with ERα being highly expressed in the bone cortex, while ERβ is highly expressed in the trabeculae, indicating that it might have many purposes in bone tissues [4]. ERα is highly expressed in the bone cortex, whereas ERβ is highly expressed in the trabeculae, suggesting that it may have different functions in bone tissue [4]. Estrogen can not only act directly on bone cells by binding to ER but also indirectly by regulating immune cells and immune factors, thus promoting the proliferation and osteoblasts to differentiate, osteoclasts to undergo apoptosis, osteoclast activity to be inhibited, and thus maintaining the harmony between bone the balance between bone resorption and bone formation and protecting the bone tissues [5]. Women's ovarian function declines with age, especially after menopause, when the ovaries rarely secrete estrogen and estrogen levels plummet. Studies have shown a significant negative correlation between the average oestrogen level and the time of menopause in postmenopausal women ($r=-0.423$, $P<0.01$), and the significant decrease in oestrogen leads to the frequent occurrence of osteoporosis symptoms [6]. Epidemiological investigations have shown that the prevalence of PMOP can be up to 32.5%. The reason for this may be that oestrogen has the effect of inhibiting bone resorption and suppressing inflammation. This may lessen pain responses that are triggered by inflammation and prevent the development of neuroinflammatory diseases. However, the exact mechanism is not fully understood [7].

Estrogen may also affect the level of serum ferritin, a class of iron-containing proteins with a molecular weight of 450,000, which contains more than 20% iron and is one of the primary forms of iron storage in the body. Serum ferritin is widely found in the body, such as bone marrow, liver and spleen, and its essential role is to provide iron for the synthesis of haemoglobin [8]. Studies have shown

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that serum ferritin levels in premenopausal and postmenopausal women were 39.4 (17.8-72.2) μg /L and 104.2 (48.9-172.7) μg /L, respectively, and that oestrogen levels in premenopausal and postmenopausal women were 145.5 (101.0-19.25) ng /L and 22.0 (13.0-40.0) ng /L, respectively. Oestrogen and serum ferritin had a negative correlation, which can be speculated that iron and oestrogen together have an effect on bone mineral density in postmenopausal women and that there are conflicting effects between the two [9].

2.1. Estrogen Replacement Therapy Programme

The results of current studies have shown that HRT has advantages not found in other treatments for PMOP, which are closely associated with age, dosage, and route of administration [10,11]. 2023 Chinese Guidelines for Menopausal Management and Menopausal Hormone Therapy suggests that, for women <60 years of age or in the ten years following menopause, without contraindications, menopausal hormone therapy is used to alleviate vasodilator symptoms (The benefit-risk ratio of menopausal hormone therapy for relieving vasomotor symptoms (VMS), slowing down bone loss and preventing fractures is the highest in women aged <60 years or with contraindications for menopause within ten years. For bone protection, the duration of use of the therapy needs to be at least 3 to 5 years, with the effects fading after discontinuation. Recently, a large-sample RCT shown that reduced dosages of medroxyprogesterone acetate, either alone or in combination with low levels of mixed oestrogens, showed that HT prevented loss of BMD in the spine and hip, reduced bone conversion, and improved vasodilatory symptoms [10]. The A meta-analysis encompassing 15 RCTs with 13,280 patients examined the use of estrogen in the management of postmenopausal osteoporosis. The findings demonstrated the effectiveness of estrogenic medications in modifying the mineral density of the lumbar vertebrae, vertebral fracture incidence [OR=0.61, 95% CI (0.52, 0.71), P<0.001], serum osteocalcin [MD=- 16.03, 95% CI (-18.68, -13.67), P < 0.001] were specific. The reticulated meta-results showed that bazedoxifene among estrogens was the most effective in increasing lumbar BMD. Serious adverse effects are rare with estrogen therapy, and the frequency of typical side effects (such as cramping in the muscles and hot flashes) is minimal [12].

The outcomes of controlled, randomized experiments and meta-analyses in women of different age groups suggest that HRT reduces The use of HRT in women over ten years of menopause or at age 60 is more likely to increase the prevalence of breast cancer than heart attacks and all-cause deaths among women who have been menopausal for more than ten years is likely to increase the effects related to the adverse aspects of coronary heart disease receiving HRT before those milestones [10]. Therefore, it has been suggested that in menopausal women under 60 years old or up to ten years after menopause, oestrogen should be administered for early osteoporosis treatment and prevention, especially in those with VMS [11].

3. Effects of aerobic and resistance exercise therapy on PMOP

Exercise has been in the spotlight as one of the few non-pharmacological treatments for osteoporosis. Multiple evidence-based pieces evidences have been shown to indicate that exercise not only increases bone mass, mechanical properties, bone strength and BMD but also improves osteoporosis symptoms or prevent osteoporotic fractures by inhibiting osteoclastogenesis and bone resorption through the OPG/RANKL pathway secreted by mesenchymal stem cells, osteoclasts and osteoblasts, as well as proinflammatory cytokines [13]. Similar therapies are available in postmenopausal osteoporosis. Standard exercise therapies include aerobic and resistance exercises.

3.1. Effects of aerobics on PMOP

Aerobic exercise is defined as physical activity that requires the body's metabolic system to use oxygen to produce energy through repetitive, regulated movement. Aerobic exercise increases the cardiovascular system's capacity to take in and move oxygen. There are many different types of aerobic exercise that may be done, but they all include elevating the heart rate over where it should be. One can

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engage in a variety of aerobic exercises, but they all include increasing heart rate to 70 to 80% of age-appropriate maximum.

Tianshu Shi et al. developed a PMOP model by performing ovariectomy on ten-week-old female rats and found that PMOP model mice had lower serum levels of myogenic kynurenine and reduced levels of kynurenine aminotransferase in gastrocnemius muscle [10]. They were able to increase the level of kynurenine aminotransferase in the muscle and serum concentration of kynurenine in PMOP model mice after a month-long treadmill aerobic exercise in postmenopausal osteoporosis model mice and alleviate bone loss [10]. Also, in the study by Li Liang et al., 40 90-day female unproductive rats were divided into four groups: sham operation group (A group), ovariectomized group (B group), estrogen control group (C group) and medium intensity running group (D group) groups [14]. After eight weeks, the diameter of the right and left femoral head of D group was thicker than that of B group (left: about 2.69%, right: about 3.34%), and the trabecular area, trabecular thickness, and number of trabeculae of the femoral head of D group were higher than that of B group by 34.1% ($P<O.05$), 16.0%, and 59.7%, respectively. Regarding trabecular separation, D group was 17.0% lower than B group [14].

Additionally, a study of 94 postmenopausal osteoporosis women assigned to a 12-week exercise programme showed that aerobic exercise had a significant improvement in fat mass (mean decrease of 0.094%, $p<0.05$) and BMI but little effect on BMD and estradiol and muscle mass [15]. Apart from that, it has been demonstrated that menopausal women with a mean age of 61 years, a BMI of 29 kg/m^2, and who were predominately Caucasian (91%) saw a 10% decrease in total oestradiol after engaging in an average of 178 minutes of exercise per week for a year [16]. In the study by Dowsett et al., postmenopausal women were found to have lower oestradiol concentrations when they were physically active. In a study by Singh M. A., it was shown that Aerobic and endurance training by themselves can lower central fat deposits but have minimal impact on total body composition [17]. Therefore, it is still controversial as to whether aerobic training is effective in alleviating osteoporosis in addition to affecting fat mass and BMI on other body compositions such as oestrogen, and it needs to be investigated.

3.2. Effects of resistance training on PMOP

Resistance training, also known as weight or strength training, involves using resistance to increase muscle strength, growth, and endurance.

Yu Yuan et al. showed that mechanical loading from exercise, as well as Bone Morphogenetic Protein and Wnt-Catenin, seem to play a significant role in activities that promote bone formation and that resistance training is an inducer of differentiation of MSCs to osteoblasts [13]. In comparison to aerobic exercise, Amna Aamir Khan et al. showed that anaerobic exercise in the resistance category had a positive effect on muscle mass (rise of 0.068%, $p=0.063$), BMD ($p<0.05$) and estradiol levels (mean increase of 16.42%, $p<0.05$) [15]. Additionally, deep squat training outperformed estradiol hormone replacement treatment in ovariectomized rats, attenuating the detrimental effects of ovariectomy on muscle mass, metabolic parameters, BMD, and adiposity [18].

Resistance exercise dosage, frequency, movements, and duration that are most healthy for osteoporosis patients' bones are still being researched today, and the likelihood differs from person to person. Therefore, it is advised that postmenopausal osteoporosis patients exercise while paying attention to their bodies' real-time physiological data.

4. Comparison

By analyzing the two aspects separately, estrogen has the effect of inhibiting bone resorption and suppressing inflammation, which can reduce the pain response caused by inflammation and reduce the occurrence of neuroinflammatory diseases, and influencing serum ferritin levels has an effect on BMD in postmenopausal women, but the use of HRT modality in women over the age of 60 or menopausal for more than ten years has the potential to increase the adverse effects associated with off-coronary heart disease [10]. Therefore, it has been recommended that oestrogen be used, especially in menopausal women with VMS, for the early PMOP in women under 60 or for up to 10 years following menopause.

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Anaerobic exercise can enhance muscle mass, metabolic parameters, and other factors, while aerobic exercise has a significant impact on fat mass and BMI characteristics.

4.1. Comparative experiment between resistance training (TR) and 17β-estradiol treatment (HR)

4.1.1. Comparison differences in performance of resistance training and 17β-estradiol treatment on human body composition and biochemical parameters. According to the study by Rodrigo Mello Gomes et al., ovariectomy enhanced the body weight of the OVX groups as compared to the Sham group increased by 22.3% [18]. Hormone replacement, nevertheless, resulted in a reduction in body weight by about 20.3%. The value of this variable remained the same in TR animals as it did in OVX animals. The OVX group had a more significant amount of white adipose tissue (WAT) storage than the Sham group. On the other hand, strength training and hormone replacement have been demonstrated to be effective in raising plasma Ca2+ and decreasing total cholesterol and triglycerides compared to unintervened OVX animals [14]. In addition, there was a higher HOMA-IR index, lower blood glucose decreased by about 24.2%, and lower blood insulin levels in the TR control group compared to the control group [18]. Reduced indices of both cholesterol (HR 99.9 mg/dL; TR was 119.4 mg/dL;) and cholesterol (HR 158.5 mg/dL; TR value 171.5 mg/dL). Serum Ca2+ levels in the TR and HR groups were also more significant than in the Sham group. Comparing the TR and HR groups to the sham-operated group, plasma ALP levels were likewise comparable (254.3 U/L in the sham-operated group compared with. 449.9 U/L in the OVX group) [18].

4.1.2. Comparing the effects of resistance training and 17β-estradiol treatment on BMD. Spinal and femoral BMD loss was seen in animals in the OVX group at 0.2g/cm^2 of OVX, 0.1g/cm^2 of Sham [18]. The spine and femoral BMD in TR animals were comparable to that of Sham animals in terms of total values and t-scores despite the harmful effects of lower circulating estrogen. Hormone treatment decreased the severity of HR t-scores, but it did not normalize BMD, and bone loss continued [18].

4.2. Controlled experiments of resistance training and oestrogen treatment

4.2.1. Comparison of bone mineral density levels before and following therapy between the two study groups. According to the research by Chen Weixi et al.,[19], prior to treatment, the comparison of bone mineral density levels of lumbar vertebrae L2~4, hip joints, and femoral necks between the two groups of subjects was statistically insignificant because of the significant differences; following therapy, bone mineral density levels of lumbar vertebrae L2~4, hip joints, and femoral necks were all higher than before treatment [19]. Following therapy, the BMD levels of lumbar vertebrae L2~4, hip joint, and femoral neck of the study subjects in both groups increased compared with those before treatment [19]. Following therapy, the observation group's BMD levels for the hip joint, the femoral neck, and the L2~4 lumbar vertebrae were more significant than those in the control group. The statistics of the observation group control group were 0.73g/cm^2, 0.72g/cm^2, and following therapy were 0.90g/cm^2, 0.81g/cm^2. The lumbar spine L2~4 was treated. The results of the observation group and control group for the hip joint were 0.56g/cm^2, 0.55g/cm^2, and following the therapy, they were 0.74g/cm^2, 0.66g/cm^2, prior to the femoral neck therapy. After treatment, the values from the observation and control groups were 0.89g/cm^2 and 0.74g/cm^2, respectively [19].

4.2.2. Comparison of joint function before and after treatment between the two study groups. Prior to treatment, there was not a statistically significant distinction in the joint function ratings among the two study subject groups ($P > 0.05$); following treatment, the joint performance scores of both study subject groups rose in comparison to the pre-treatment period, with the observation group's joint function scores rising above those of the control group. Before therapy, the monitored and control groups had assessment scores of 55 and 56 points, respectively. These scores increased to 89.5 and 74.8 points following treatment, respectively [19].

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4.2.3. Comparison of the levels of bone metabolism indexes between the two study groups before and following therapy. Before treatment, there was virtually no difference between the blood Ga and BGP levels of the two groups of study participants (all $P > 0.05$); following therapy, the blood Ga level of the two groups of participants increased, and the BGP level decreased in comparison to that before treatment, and the blood Ga level of the study participants the observation group was higher than that of the control group BGP level was lower than that of the control group. The observation group and control were 1.95 and 1.96 mmol/L prior to therapy and 2.40 and 2.01 mmol/L post-treatment, respectively. The results for the observation and control groups are presented next; they were, respectively, 17.30 ng/ml and 17.28 ng/ml before treatment and 13.20 ng/ml and 16.80 ng/ml following therapy [19].

5. Conclusion

In summary, resistance training combined with aerobic exercise can be effective in treating injuries caused by estrogen deficiency in postmenopausal women, thereby alleviating osteoporosis. Exercises like resistance training and aerobics can help postmenopausal women feel better and spend less money on secondary symptoms that are mostly brought on by sarcopenia, muscle loss, and weight gain. Estrogen therapy can also significantly affect body composition biochemical parameters and have an inhibitory effect on osteoporosis. Overall, aerobic exercise combined with a resistance training programme can be more effective in promoting bone density, muscle strength and metabolism in menopausal women than oestrogen therapy, which has some side effects and is more effective in treating osteoporosis. In current research, estrogen therapy has been shown to have some risk of venous thrombosis, breast cancer, stroke, and other related diseases. Aerobic training and resistance exercise, in addition to fat mass, BMI and other indices, the impact on other factors is still controversial. Resistance training on the bones of osteoporosis patients, the most reasonable training aspects of the indicators, such as exercise frequency, time, and intensity of resistant training, are not yet widely determined. In the future, oestrogen therapy can be developed in the direction of natural oestrogen and natural progesterone-like hormones, strict criteria for the use of oestrogen should be formulated, attention should be paid to the prevention of oestrogen side effects, and oestrogen combination therapy should be adopted as much as possible to avoid the possibility of side effects. In the future, aerobic and resistance exercise can be further researched on the effects of exercise mode, exercise intensity and training interval on osteoporosis patients so that detailed and precise treatments can be organized for patients with different physical conditions.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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