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Research Article

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Investigating the relationship between physical activity, diet and osteoporosis treatment (Study of postmenopausal women)

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ABSTRACT

Aim: This research aims to investigate the relationship between physical activity, diet and treatment of osteoporosis among postmenopausal women in 2024.

Methodology: The method of this research is based on the purpose, applied and based on descriptive-survey data collection method of cross-sectional type. The data collection tool is a sample of library sources and studies and a researcher-made questionnaire, and the range of answering the questions is based on a 5-point Likert scale (very high, high, medium, low and very low). The statistical population of this research consists of postmenopausal women in the 11th district of Mashhad city, 80 of whom were selected by purposive sampling.

Results: The findings of this research show that movement along with natural foods can be effective in dealing with the reduction of bone density and loss of bone tissue, especially during estrogen deficiency, lack of anti-inflammatory control and lack of antioxidants in postmenopausal women. The results of this research have shown a positive relationship with the increase of combined interventions, but some data do not show any additional and additional effects and effectiveness, which may be influenced by the choice of exercise and training regime and the consumption dose of natural foods. Therefore, the effect and mechanism of combination therapy still require further research with extensive experimental data.

Conclusion: Exercise and physical activity and natural foods have a lot of potential and advantages at a very low cost, while being non-toxic and have other advantages, which are widely considered and valued by the medical community.

Keywords: Physical activity, Natural food, Osteoporosis, Menopause

INTRODUCTION

Osteoporosis is a condition in which the bone becomes brittle and the possibility of breaking with small blows increases. Osteoporosis is one of the most common problems in human societies, osteoporosis usually has various reasons, and the process of reducing bone mass begins at the beginning of the 30s, and with age, bone mass is lost faster than it is created. The probability of developing osteoporosis depends partly on the amount of bone mass in youth. Maximum bone mass is partly heritable and varies by ethnic group. The higher the peak bone mass, the more bone you have in the bank, and with increasing age, the probability of developing osteoporosis decreases 5.

One of the late complications of menopause is the occurrence of osteoporosis, and several risk factors such as nutrition pattern, physical activity level, and body mass index play a role in the occurrence of this disease, all of which can be prevented 26. Osteoporosis is a public health problem that affects the quality of life of postmenopausal women. Several factors are involved in the occurrence of osteoporosis, one of which is the lack of physical activity. It also mentions postmenopausal osteoporosis in women due to ovarian atrophy, functional degeneration, and lack of estrogen secretion, which causes a decrease in bone mass, changes in trabecular bone structure, bone fragility, and systemic bone metabolic disease with rapid fragility 22.

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The old prevention method for PMOP mainly uses estradiol and bisphosphonates, but long-term use of such drugs may increase the risk of cancer and osteoporosis. Currently, 200 million women worldwide suffer from osteoporosis. It is expected that by 2050, the number of patients suffering from fractures caused by osteoporosis will double be compared to today, which shows the huge and widespread medical care and high economic burden3. Based on these cases, a proposed study explores the effect of exercise and physical activity along with natural extracts on postmenopausal osteoporosis.

DISCUSSION AND REVIEW

Mechanism of Osteoporosis Formation after Menopause

Bone is a multifunctional and changing organ that can support the activities of the motor system and maintain the metabolic balance of minerals such as calcium and Phos- phase. In order to ensure the homeostasis of the bone mi- confinement and meet the needs of body activities, bone tissue should be ablated and regenerated continuously, which is called bone remodeling. Bone remodeling is mainly completed by osteoclasts (OC), osteoblasts (OB), and so hemocytes in the bone remodeling cavity. Bone cells in the deep layer of bone can sense the microcracks caused by external force or growth and development, or respond to hormone changes such as estrogen deficiency, transmit signals to the bone surface, and then cause osteoclasts and osteoblasts to function. Osteoclasts are developed from blood-derived mononuclear precursor cells. They are the only bone re- sorption cells. They can produce enzymes related to the acid dissolution of mineral salts in bone tissue and the degras- dation of organic matter. They will adhere to the surface of the bone matrix for bone resorption, such as eliminating bone tissue microcracks. In this process, the bone matrix will release a variety of growth factors. Osteoblasts differentiate from bone marrow mesenchymal stem cells and are the main functional cells of bone formation . Stimulated by the direct contact of osteoclasts or cytokines, osteoblasts continue to mature, mineralize, and deposit to form new bone (1, 4). In this process, osteoblasts can negatively regulate the in- tensity of osteoclast bone resorption by secreting Osteoprotegerin (OPG). Bone remodeling is a dynamic coupling process of bone resorption and bone formation. Therefore, estrogen is very important for the balance of the bone remodeling coupling process2.

Both OC and OB are target cells of estrogen, which activates hormone response elements if combined to the estrogen receptor (ER) within OC, can reduce the transcription factor c-jun activity in OC precursors and OC, inhibit osteogenesis induced by RANKL and M-CSF, and attenuate bone resorption. Binding of estrogen to ER also causes upregulation of the apoptosis-associated factor ligand (FASL) of OC that binds to Fas on OC in an autocrine manner and induces OC apoptosis through the Fas/FasL pathway7. In OB, estrogen can induce GSK3β phosphorylation which blocks β-catenin degradation, activates the Wnt/β-catenin pathway, binds to the TCF/LEF transcription factor family, and initiates cell cycle genes such as downstream cyc D and c-myc to mediate OB proliferation; and it also upregulates BMP-2 expression, which phosphorylates Smad1/5/8, activates the intranuclear gene ex- pression, and promotes osteogenic differentiation 6. Estrogen is also able to regulate many transcription factors' activity that in turn inhibits OB apoptosis through activation of Src/Shc/ERK signaling. Less estrogen caused by menopause leads to enhanced OC differentiation and reduced surface FasL expression, and OC escapes apoptosis. It also leads to decreased OB proliferation and differentiation capacity and increased apoptosis. Ultimately, bone resorption capacity is greater than bone formation, causing osteoporosis9.

Research method/statistical population and sample size

The method of this research is based on the purpose, applied and based on descriptive-survey data collection method of cross-sectional type. The data collection tool is a sample of library sources and studies and a researcher-made questionnaire, and the range of answering the questions is based on a 5-point Likert scale (very high, high, medium, low and very low). The statistical population of this research consists of postmenopausal women in the 11th district of Mashhad city, 80 of whom were selected by purposive sampling.

The OPG-RANKL-RANK

Signaling System Influences the Bone Remodeling Mechanisms

The OPG-RANKL-RANK signaling system is very important for the process of bone remodeling. Before the discovery of this system, people could not explain the regulatory mechanism of bone re- sorption and metabolism. Until 1997, Tsuda found a glycoprotein that can specifically inhibit the differentiation of osteoclasts. In the same year, Simonet found a secretory protein that can inhibit the differentiation of osteoclasts and increase bone mineral density. Later, different students found substances with similar functions. After identification, these molecules are the same substance, named osteoprotegerin. The relationship between osteoprotegerin (OPG), nuclear factor-κB receptor activation factor ligand (RANKL), and nuclear factor-κB receptor activation factor (RANK) was found in the subsequent study. In the stable state, the contents of OPG and RANKL are in a balanced state, and their relative contents maintain the number of osteoclasts and support the normal

level of bone resorption. When the change of one or more upstream factors excessively tilts this balance to the function of RANKL, the number of active osteoclasts increases and bone resorption is too strong; when the balance tilts too much to the function of OPG, the number of osteoclasts decreases and bone formation is too strong 15.

The mechanisms by which osteoblasts regulate the differentiation and maturation of osteoclasts are influenced by three cytokines, OPG, RANKL, and RANK. RANK belongs to the type I transmembrane receptor protein and is the only receptor for OC surface-mediated RANKL activity, a critical gate for differentiation and activation signaling pathways. RANKL is a member of the tumor necrosis factor (TNF) superfamily that can be secreted by OB, T cells, and endothelial cells and has a role in regulating OC proliferation and differentiation 14. It has been shown that anti-RANKL treatment can enhance skeletal mechanical properties. Osteoprotegerin, a member of the tumor necrosis factor receptor superfamily, is an osteoclast repressor secreted during OB differentiation and is able to negatively regulate the bone resorption process. OPG acts as an inhibitor of RANK activation by binding to RANKL with a higher affinity, blocking the OC precursor differentiation, inhibiting the function of OC, and preventing excessive bone resorption. Osteoprotegerin presented significant regulation of bone metabolism, with evidence of greater advantage for maintenance of skeletal and muscle function compared to gene deletion or selective inhibition of RANKL, a single treatment with OPG sup- plementation. Thus, the proportion of OPG/RANKL is the lever that regulates the balance between bone resorption and bone formation. Estrogen downregulates RANKL, induces OC formation, and also promotes OB OPG 18. The sudden decrease in estrogen secretion after menopause triggered increased RANKL secretion, reduced OPG synthesis, active OC, enhanced bone resorption, and a dynamic imbalance of bone remodeling.

Effects of the Inflammatory Response on Bone Mass

Cells in the bone marrow are functionally divided into cells involved in bone metabolism and hematopoietic cells involved in the immune response, and both share the same microenvironment in the bone marrow and interact to perform functional activities of the skeletal system. It has been clear that osteoclasts and immune cells have common progenitor cells and are also regulated by many common regulators. T cells, B cells, cytokines, chemokines, and costimulatory molecules interact with immune cells under physiological and pathologic conditions, with the OPG- RANKL-RANK signaling system as a bridge to regulate bone formation and bone resorption, and then affect the bone remodeling process. Several studies have shown that almost all chronic diseases are linked to inflammation and that inflammation and immunity are complementary processes, with many immunoactivity substances and immune cells involved in the inflammatory response19.

B cells and T cells in immune cells are involved in bone formation and bone resorption processes. B lymphocytes were shown to secrete OPG to maintain OPG/RANKL balance and promote bone formation. Interferon c (I FN-c) secreted by helper T lymphocytes 1 (Th1) are important anti-inflammatory factors that have been clinically used in the treatment of severe osteoporosis 25. IFN-c is able to bind to the OC surface receptor IFNGR, activate TRAFA6, inhibit downstream NF-κB, JNK, and exert antibone resorption; in OB, IFN-c upregulates Runx2, Osterix expression, and osteocalcin and ALP synthesis, which confirmed that the number of OB was significantly decreased in IFN-c receptor gene knockout mice. In contrast to this effect, interleukin 4 (IL-4), mainly secreted by Th2 cells, suppresses OB differentiation by upregulating and downregulating RANKL expression (10). The specific IL-17 secreted by Th17 in subsets of CD4+ cells can stimulate OB and fibroblasts and also mediate the secretion of the inflammatory factors IL-1, TNF-α, and IL-6, further promoting bone resorption and inhibiting bone formation. Furthermore, other inflammatory factors are also involved in the regulation of bone remodeling, and binding of the tumor necrosis factor α (TNF-α) as a ligand to OC surface receptors can either cooperate with RANKL to induce OC formation or directly activate TRAFA2/6 to upregulate OC expression without RANKL dependence: Smad6/7 activated by TNF-α within OB can inhibit Smad1/5/8, to further inhibit BMP-mediated OB differentiation processes. IL-1 is able to bind to OC surface IL1R, which indirectly activates TRAF6, which upregulates OC gene expression through multiple pathways and promotes the bone resorption process. It has also been shown that IL-6 promotes OB-mediated osteogenic differentiation through the activation of JAK 2 and RANKL, and also cooperates with IL-1 and TGF-β to induce T cell differentiation into Th17. There are estrogen targets on T cells that can be directly regulated by the latter, and estrogen can also inhibit the expression of bone resorption factors like TNF-α, IL-1, and IL-6 at the gene level, increase the expression of ostia organic factors such as TGFβ, and then initiate OC apoptosis and prevent bone loss. Sub menopausal estrogen reduction leads to T cell expansion, significantly increased content of proinflammatory factors IL-1, IL-6, IL-17, TNF-α, and IFN- c, enhanced OC function, reduced OB bone deposition capacity, and bone resorption greater than bone formation, resulting in reduced bone mass and osteoporosis formation.

Oxidative Stress Affects Bone Metabolism

Oxidative stress (OS) is also an important pathogenetic factor of postmenopausal osteoporosis. Active oxygen species, such as hydrogen peroxide and hydroxyl groups are

produced during cell metabolism, and antioxidant enzyme lines in the body, including catalase (CAT), glutathione catalase (GPX), and superoxide dismutase (SOD), are responsible for re- moving free radicals from protected cells. Under the dual effects of aging and estrogen reduction, the body's oxidative stress response is enhanced, leading to an imbalance of bone remodeling. In physiological states, intracellular ROS can indirectly activate JNK and serine/ threonine kinase (MST1), which then phosphorylates the fork head transcription factor (FOXO) to nucleate, induce DNA expression, and activate activities like DNA repair, cell cycle, apoptosis, and autophagy. ROS inhibits OB occurrence and reduces its lifespan, so during OB transcription maturation, the transcription factor FOXO protects against increased ROS caused by inducing autophagy and reducing enhanced mitochondrial respiration in osteoblasts. Moreover, FOXO also prevents oxidative stress within OB by increasing SOD, CAT expression, and accumulation of GPX. On the contrary, ROS is required for OC pro- duction, function, and survival. ROS can activate JNK and p38 to phosphorylate AP-1 and, in turn, enhance OC differentiation. suggesting that FOXO may inhibit bone resorption in an ant reactive oxygen species manner. Studies have shown that estrogen can remove reactive oxygen species and protect bone health by fighting body oxidation. Estradiol can significantly enhance autophagy to reduce OB apoptosis through the ERs/ERK/mTOR pathway. RANKL can increase ROS. estrogen in osteoclast progenitors can induce the effect of OPG secretion to inhibit RANKL and attenuate the function of OC. Higher serum levels of inflammatory factors and prooxidative biomarkers in menopausal women mean a state of high oxidative stress. Estrogen deficiency increases NADPH oxidase (NOX) on the membrane, decreasing antioxidant system capacity, and ROS accumulation triggers oxidative stress. At the same time, this process exacerbates OB apoptosis and OC differentiation, with bone resorption greater than bone formation and eventually PMOP 12.

Exercise Affects the Postmenopausal Osteoporosis Mechanism

In recent years, exercise has attracted much attention as a nondrug treatment of osteoporosis. Studies show that exercise effectively controls and prevents osteo- porosis and is also a potential intervention strategy to overcome postmenopausal complications due to changes in metabolic hormones, especially estrogen levels. Exercise regulation of the postmenopausal female estrogen secretion mechanism is not clear; the existing studies show the following associations: sports cause the hypothalamus-pituitary-gonadal axis, a study in strict accordance with the ASCM standard for postmenopausal women showed that 12 weeks of exercise can effectively improve female estradiol levels, and compared with aerobic exercise, anaerobic exercise has a more significant effect on bone density. However, the impact of exercise on estrogen secretion is somewhat contradictory. Past studies have shown that adipose tissue can synthesize estrogen, while exercise is conducive to reduce fat quality, so it helps to reduce estrogen levels .Previous studies believe that aerobic exercise has negative effects on estrogen levels, and the effect of resistance exercise is unknown 4. Another study of postmenopausal obese women showed that estrogen levels increased in aerobic, resistance, and control groups, but there were no significant differences. In short, exercise has a regulatory effect on estrogen, but the specific mechanism and effect results have not been uniformly determined and may be affected by the individual physiological state, exercise strength, and other factors 16.

A large number of current studies point to the significant positive effect of mechanical loads generated by exercise on maintaining bone mass and that amputation leads to accelerated bone loss in the affected limb. Mechanical stimulation mainly fights the PMOP from several aspects 1. On the one hand, mechanical load can directly stimulate the ER response and slow down the ER reduction due to estrogen deficiency. Experiments showed that ERK is not activated by pulling tension in OB and osteocytes that knocked down the ERα and ERβ genes, suggesting that ERs are ligand-independent and are directly involved in the conversion of mechanical forces into mechanical signals in osteocytes. On the other hand, mechanical stress may modulate bone remodeling by regulating osteogenic differentiation of myeloid marrow mesenchymal cells 17. Fluid hydrodynamic regulation of osteogenic differentiation of bone marrow mesenchymal cells is reported to upregulate Runx2 expression in mouse bone marrow mesenchymal cell lines by both classical and nonclassical Antipathy's, whereas mechanical unloading reduces β-catenin expression and sup- presses OB proliferation (24, 26). In addition, exercise also showed upregulation of collagen expression in OB, and mechanical stress affects collagen arrangement upon the formation of new bone, thereby enhancing bone strength. Without physical activity, bed rest or weightlessness negatively affects the bone by inhibiting OB activity and/or enhancing OC activity. In conclusion, the mechanical load induced by exercise has a positive effect on the proliferation and activity of osteoblasts, thereby promoting bone formation under physiological and pathological conditions 24.

Exercise may cause amelioration of inflammatory cytokines by upregulating anti inflammatory cytokines, which in turn affect bone metabolism (22,23). Low impact, high in tensity interphase exercise has been reported to stimulate responses to bone transformation markers and cytokines such as IL-1, IL-6, and TNF-α which are significantly above baseline, suggesting a correlation between this form of exercise and immune and skeletal responses. The body is in motion. It can also affect the OPG/RANKL/RANK system. Endurance treadmill exercise increases OPG expression and decreases

RANKL levels in rats. Resistance exercise increases OPG in adult rats and then upregulates the OPG/ RANKL ratio to inhibit bone resorption. Several animal experiments reported similar effects on other forms of exercise: reduced RANKL levels and increased OPG levels were observed in osteoblast experiments in acutely trained mice. Diabetic model rats showed significant OPG in bone and serum and decreased mRNA and protein expression of RANKL after forced swimming training. However, another study found that exercise may not change the level of RANKL and OPG and their expression: a 12-week joint exercise experiment for healthy female college students showed that the bone metabolic response of OPG/RANK/ RANKL signaling is not obvious 8. This speculation is due to the way of exercise. Long-term low-intensity exercise is not enough to improve body function, so the role of the RANKL signaling system is also limited. Long and moderate- intensity regular physical exercise can reduce bone ab- sorption and increase bone mass in healthy people and pathological patients. From the above discussion, it can be concluded that OPG/RANKL changes may be affected by motor mode, motor intensity, and cycle, but still need to be further confirmed by more evidence.

Effects of Natural Plant Extracts on Postmenopausal Osteoporosis

It has been proved that the effective components of various natural plants and Chinese herbal medicines have significant prevention and control effects on PMOP, and the toxic side effects of traditional drug treatment have not been found, which is considered as a potential alternative therapy for traditional drugs for PMOP. It was found that multiple natural components control PMOP as dependent on their estrogen-like effects. It was shown that echinoid (ECH), a novel phytoestrogen, effectively reverses uterine atrophy in ovariectomy (OVX) rats by enhancing in utero ER expression and upregulating OB proliferation and differentiation via ER-mediated OPG/RANKLER. At the same time, ECH can promote osteogenesis and differentiation of bone marrow mesenchymal cells through activation of the classical Wnt pathway and autophagy; EHC can also regulate the NF-κB pathway and MAPK pathway to inhibit RANKL-induced osteogenesis and reduce bone loss. Similarly, XSPS can promote the nuclear accumulation of β-catenin in bone marrow stromal cells without affecting BMP signaling, inducing osteogenic differentiation while inhibiting RANKL induced osteoclast differentiation. Naringin modulates the classical Wnt pathway, upregulates OB differentiation, and downregulates ERK activity, which in turn suppresses bone resorption. Glycyrrhizate directly attenuates OC specific genes and inhibits OC maturation induced by the NF-κB, ERK and MAPK pathways. In addition, Glenavon, soy isoflavone, and resveratrol are also phytoestrogens that can replace estrogen to promote mesenchymal cell osteogenic differentiation and regulate bone remodeling balance.

Other native components can also improve bone remodeling imbalance by regulating the OPG/RANKL axis: salidroside suppresses bone turnover and upregulates bone OPG/ RANKL expression, thus increasing bone density in OVX rats. Ginsenoside, the main active ingredient of TCM panax ginseng, significantly suppresses RANKL in diced IKK activity and NFATc1 activity, as well as inhibition of OC synthesis, cathepsin K, MMP, and TRACP, suggesting that ginsenoside can inhibit osteoclast by inhibiting the RANKL-induced NF-κB pathway and Ca2+ pathway. Violoxin not only inhibits RANKL mediated expression of OC specific marker genes such as NFATc1 and TRACP, but also promotes expression of factors in OB, thus alleviating bone loss in OVX rats. There is additional evidence that calycosin inhibits the RANKL mediated MAPK pathway and downregulates ALP and TRACP expression. Mountain seed polysaccharide from cypress roots can upregulate OPG to downregulate RANKL expression and regulate the latter-mediated PI3K/Akt pathway. Both components significantly fight osteoporosis in OVX rats, suggesting use as a potential surrogate for PMOP.

Plant components have antioxidative and anti inflammatory effects, and they realize the prevention of PMOP by preventing inflammation and inhibiting oxidative stress 22. Epimedii prevents IL-1-induced apoptosis through the PI3K/AKT pathway and also inhibits STAT3 activation and reduces Th-17 cells. Melon polyphenols and lutein are all-natural antioxidants, which have positive effects on protecting bone loss in OVX rats, and lutein can also inhibit OC-specific protein expression and bone resorption. Plant active components can influence oxidative stress levels by upregulating the expression of antioxidant enzyme lines, such as cocoa and lycopene, which can all upregulate GPX and SOD activity within OB and inhibit bone turnover in OVX rats to restore bone strength and microstructure. The advantage of natural ingredients is that there are no toxic side effects. Studies show that pomegranate seed oil extract is rich in phytoestrogens and antioxidants, which have therapeutic effects on osteoporosis and have no adverse effects on blood lipids, uric acid, liver, and kidney function. In conclusion, the estrogen-like effects and antioxidant and anti-inflammatory effects of natural components make them of great research value in the prevention and control of PMOP.

Anti menopausal Osteoporosis Effects of Exercise Combined with Natural Extracts

The PMOP effects of exercise control were limited, and studies showed that exercise intervention in OVX rats could not prevent bone loss after OVX but alleviated the dramatic reduction in estrogen- dependent physiological processes due to estrogen deficiency, and the motor effects were much lower in estradiol than in the OVX rat group. Early studies found that estrogen and mechanical stimulation

synergistically inhibit OC generation, suggesting that they may work better against PMOP. Alendronate was reported to prevent bone loss in low-intensity whole-body vibration groups in OVX rats, but the combined intervention group was better, suggesting that low intensity vibration enhances the effect of alendronate on OVX rats by further improving bone trabecular structure. However, high-frequency loading combined with bisphosphonate intervention in OVX rats indicate that a single factor improved bone microstructure, but the combination had no additive effect. The above findings suggest that the effect of the combined intervention may be affected by the exercise mode or exercise intensity as well as the drug type 21. But traditional pharmacological treatment has limitations and disadvantages, such as estrogen, calcitonin increases the risk of cancer, bisphosphonate has a very low likelihood of jaw necrosis, and new drugs such as catapsin K inhibitors and clinical application sclerosis inhibitors have side effects and deficiencies. Long-term effectiveness research data, leading to patients low acceptance and poor compliance with such drug treatments. Natural plant ingredients replace traditional drugs, and in combi- nation with exercise, they may be highly potential and valuable therapies against PMOP.

The PMOP effect examined by motion along with natural extracts is at an exploratory stage, and existing studies show that the effect of natural composition and biomechanical stimulation has an incremental effect on bone. It has been found that hybrid intervention can significantly increase the expression of the sterix osteoblast transcription factor and inhibit GSK-3ß, thereby promoting the proliferation and differentiation of osteoblasts and strengthening osteoporosis. The combination of naringin combined with exercise has been reported to significantly increase bone strength, bone mass, end peptide of Type I collagen C (CTX) and osteocalcin expression in ovx rats and is superior to a single intervention. The combination of the Golden Finch isoflavone with resistance exercise alone prevented the loss of the femur caused by OVX compared to experiments. However, the mechanism of joint intervention in PMOP is not defined, and based on previous analysis, several course of action may include the following. On the one hand, estrogen-like effects of natural components can replace the mechanical stimulation produced by the synergistic motion of estrogen and improve bone loss due to hormone deficiency (11,13,23).

It has been reported for both phytoestrogen 8-prenylnaringenin (8-PN) and vibration to stimulate ERα expression in OVX rats, and it is speculated that vibrations combined with 8-PN stimulation have synergistic effects on OVX rat ERα, making the combined group have a more pronounced effect on bone than the 8-PN group. Experiments using rats intervening with the dye lutein (GEN) found a more pronounced reduction in bone mineral density than animals with voluntary exercise.

Through the antioxidant pathway another study showed that soybean isoflavone significantly improved GSH levels in OVX rats but had no SOD activity, while 12-week platform exercise enhanced SOD activity and H2O2 induced significantly increased DNA tail length, suggesting that moderate exercise binding soy isoflavone protected rats from oxidative stress through different pathways. In addition, isoflavone synergy with weekly aerobic and resistance training for six months reduced TNF-α and IL-6 levels in postmenopausal obese women and superior to exercise alone 21.

Furthermore, the combined means may also affect osteogenic differentiation or bone formation marker expression, which in turn affects bone metabolism. It was reported that β-catenin, Akt, ERα, and Runx2 expression were significantly increased in OB in the treadmill-bound Epimedii intervention group, compared with exercise alone.

Hybrid therapy significantly prevented bone loss caused by OVX and increased OB differentiation and mineral ability, some of which may be regulated by the era/Akt/β-catenin pathway, but whether hybrid intervention affects OC differentiation is uncertain. Laboratory experiments by in-house researchers have shown that icarine combined with exercise placenta stimulation may inhibit bone absorption by regulating NF-kB signaling and affect increased OB proliferation by the classic Wnt/β-catenin pathway. Soy isoflavone participatory treadmill exercise intervention can restore bone mass to fake surgical surfaces in ovx rats with the same effect as estradiol therapy. 26. However, the effect of soy protein combined with moderate endurance exercise in postmenopausal women showed that there was no intervention effect on bone density. In addition, it is speculated that exercise intensity and dosage may affect the combined effect, and the molecular mechanisms of maintaining bone mass may be different, not simply synergy.

CONCLUSIONS

In a summary, it is possible that motor binding to natural extracts may involve multiple pathways including mechanical signaling, estrogen deficiency-mediated OPG/ RANKL alterations, and anti-inflammatory and antioxidant control of PMOP. Most of the existing studies have shown the additive effect of combination interventions, but several data show no additional efficacy, which may be affected by the choice of exercise regimen and extract dosage. Therefore, the effect and mechanism of combination treatment still need to be further explored by extensive experimental data. Exercise and natural ingredients have great potential and advantages with their low cost, nontoxic, and other ad- vantages, which have been widely valued by the medical community. We are eager to select the best treatment scheme based on various

therapies in the future to greatly reduce the pain of patients with osteoporosis and help potential patients stay away from the threat of osteoporosis.

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CONFLICT OF INTEREST

According to the authors, this article has no conflict of interest.

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