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Recent discoveries of oral substances' effects on osteoporosis treatment - novel markers and pathways

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Summary

The search for optimal osteoporosis treatments continues, as the medications currently used in clinical therapy carry a risk of rare but acute side effects. New knowledge about etiopathogenetic pathways and osteoporosis biomarkers enabled the exact examination of various oral substances, often previously recognised for their positive impact on bone mass growth. A cross-section of novel reports from this year on the applications of many orally administered substances is presented. Diet, gut microbiota aspect, functional food, diabetes drug – empagliflozin and a variety of substances known from Chinese traditional medicine are now characterized in the context of the possible mechanism of treating or preventing osteoporosis. The progress of bone mass density and quality-regulating pathways recognition led to the finding of multiple orally administered substances with favorable mediation properties. The precise diagnosis of the substances' working mechanisms approves their potential use in new formulations of clinical treatments. Presently only used in diet supplementation, the orally administrated antiosteoporotic substances are potential core ingredients of modernized medications, provided their presumptive adverse effects are ruled out.

Keywords: osteoporosis, treatment, signaling pathway, biomarkers, medicaments

Introduction and purpose

Advances in osteoporosis diagnosis and treatment need optimization of existing therapies, especially that the current way of medication treatments such as bisphosphonates, or estrogen antagonists seems outdated concerning their rare but severe side effects [1]. The reported increase in the newfound factors influencing osteoporosis progression will potentially lead to a breakthrough in the current therapy methods. The discovery of the etiopathogenetic pathways and osteoporosis biomarkers enabled the exact examination of many various oral substances, often previously recognised for their positive impact on bone mass growth. This review presents a variety of reports from this year on the applications of many orally administered substances. All reports are the results of advanced laboratory studies employing new technologies.

Description of the state of knowledge

Diet

Despite numerous new medications emerging, the diet remains a crucial element of most common disease treatments. However, the impact of diets not specifically containing obvious bone-strengthening elements such as calcium, phosphorus, magnesium, and vitamins C and D on bone density and osteoporosis treatment [2] has only been explored recently. A study on the elderly Chinese population investigated the association between dietary patterns and BMD and vertebral fracture risk in both men and women [3]. They compared 'carnivorous', 'vegetarian', 'dairy fruit and egg', and 'beverage and fried food' diets. An association between the first three and a higher BMD at the total hip femoral neck, and lumbar spine was observed. Relatively lower BMD levels were attributed to the 'beverage and fried food' diet. At the same time, the “carnivorous diet" contributed to a nearly 40% reduced risk of clinical fracture over the studied period of 5 years. Incidentally, postmenopausal women presented an increased sensitivity to the benefits of 'carnivorous' and 'vegetarian' diets in terms of BMD and a decrease in fractures. The elderly women appeared to be strongly affected by lower BMD levels when following the 'beverage and fried food diet' compared to the rest of the study group. Hence, the appropriately nutritive diet enhances the effectiveness of osteoporosis treatment and prevention, especially in the elderly and postmenopausal women.

Gut microbiota

The interaction of the microflora of guts with the immune and endocrine systems, as well as the release of products of metabolic processes, such as the short-chain fatty acids (FFA), and bile acids are suspected to contribute to bone health. Studies reported disruption of the gut microbiome triggered by postmenopausal estrogen deficit, which is being linked with the response from the immune system negatively affecting bone remodelling. The microbiome imbalance produced by antibiotic therapy have a detrimental effect on skeletal maturation and growth. A deeper analysis of the estrogen deficiency relationship with the gut microflora and its general effects on the immunity systems’ functioning could appoint clear recommendations

for the dietary requirements and supplementation related to gut health and its interlinkage with bone state deterioration [4].

Functional Foods

Peptides

Functional foods commonly deliver food-derived peptides as they are easily digested, and absorbed while their toxicity is very low. Some of them, apart from nutritional function, may boost osteoporosis treatment. The peptides interacting with arginine-glycine-aspartic acid-binding active sites in integrin were found to interact with integrin while easing osteoporosis and suggested to be used not only in functional foods as osteogenic peptides but also theoretically integrated into bone materials [5].

Sheep bone proteins

The animal-sourced proteins could also possibly alleviate osteoporosis. The effects of sheep bone protein hydrolysates (SBPHs) on calcium absorption and intestinal flora composition were investigated as a form of SBPHs + CaCl2 treatment in calcium-deficient rat models. The study showed that it significantly increased bone calcium content, BMD, trabecular bone volume, and thickness, reduced trabecular separation, and changed the bone turnover markers levels. The treatment not only can significantly improve the bone's mechanical strength and microstructure but also has an impact on gut microbiota. It was observed to reduce the abundance of Proteobacteria and Verrucomicrobiota, increase the abundance of Firmicutes, and promote the production of FFA. All of these are crucial factors considering the inflammatory and hyperlipidemic background of osteoporosis [6].

Antioxidants

Astaxanthin - SIRT1 signaling pathway

Astaxanthin (ATX) may inhibit palmitic acid (PA) -induced bone loss in ovariectomized (OVX) rats. Rats treated with ATX were observed to have increased bone mass and elevated activity of genes SIRT1 and SOD2 in bone tissue. The ATX intervention was able to significantly restore the osteogenic differentiation and cause up-regulation of osteoclast

differentiation with PA therapy. PA damage to cells is caused by increased oxidative stress, and ATX can target and modulate the activity of SIRT1 to regulate the levels of oxidative stress in cells. ATX may inhibit PA-induced bone loss through its antioxidant properties via the SIRT1 signaling pathway [7].

Caffeic acid (coffee, wine, tea, propolis) - inhibition of lysine-specific demethylase

Inhibition of lysine-specific demethylase 1 (LSD1) was proposed as a promising and attractive therapy for treating osteoporosis. Experimental novel Caffeic acid analogues (TCP-(MP)-CA) as potential LSD1 inhibitors exert inhibitory effects on osteoclastogenesis. Among them, TCP-MP-CA (11a) demonstrated osteoclastic bone loss both in vitro and in vivo, showing a significant improvement in the in vivo effects compared to the LSD1 inhibitor GSK-LSD1. 11a and its precursor 11e directly bind to LSD1/CoREST complex to inhibit LSD1 demethylation activity and influence its downstream IκB/NF-κB signaling pathway, and thus regulate osteoclastic bone loss. These findings suggested 11a or 11e as potential novel candidates for treating osteoclastic bone loss, and a concept for further development of TCP-(MP)-Caffeic acid analogs for therapeutic use in osteoporosis clinics [8, 9].

Berberine - SLC7A11/GSH/GPX4 signaling pathway

Nonalcoholic fatty liver disease (NAFLD) may contribute to osteoporosis. Berberine is a traditional Chinese medicine and was recently shown to be beneficial in NAFLD. Mice were fed a high-fat high-fructose high-glucose diet for 16 weeks and were then administered berberine (300 mg/kg/d). Berberine ameliorates bone loss induced by NAFLD by activating the SLC7A11/GSH/GPX4 signaling pathway and inhibiting ferroptosis. Therefore, berberine may serve as a therapeutic agent for NAFLD-induced bone loss [10].

Quanduzhong

Quanduzhong capsule (QDZ) is a single preparation composed of Eucommia ulmoides Oliv. used to treat OP in clinical practice. Differences in amino acid metabolism were identified between the OP 30 patients cohort and the healthy control group, as well as between OP patients before and after QDZ treatment. Compared with healthy controls, the serum levels of 14 amino acids in OP patients changed. Kynurenine, arginine, citrulline, methionine, and their combinations are expected to be potential biomarkers for OP diagnosis. Notably, QDZ reversed the changes in levels of 10 amino acids in the serum of OP patients and significantly impacted numerous metabolic pathways during the treatment of OP [11].

Eucommia ulmoides

Eucommia ulmoides is an ingredient used in the traditional Chinese medicine (TCM), a tertiary and monophyletic relict tree customarily credited with a strengthening impact on bones and muscles as well as general support of the liver and kidneys. The osteoporosis-prohibiting qualities of Eucommia ulmoides have been scientifically proven alongside its role in arthritis prevention and refinement of bone defects and fractures. A study presented evidence of the validity of total flavonoids from Eucommia ulmoides leaves (TFEL), being considered in the formulation of a conventional osteoporosis medication. The thirteen weeks of TFEL oral administration of young female rats resulted in a decrease of the serum level of TRACP-5b, a bone resorption marker [12], improvement in microstructural parameters, and, even at low dosage (50 mg/kg/d), elevation of the BMD. The potential reason for Eucommia ulmoides flavonoids to inhibit the rise of osteoporosis is targeting signaling pathways for calcium, cytokines VEGF, IL-17, and NF-κB, while AKT1, EGFR, PTGS2, VEGFA, and CALM are likely target genes conditioning their osteoprotectiveness. The TFEL was suggested to be used for elevation of the peak bone mass in young women preventing further postmenopausal osteoporosis and a supplementary food additive boosting bone strength [13].

Empagliflozin - therapy for diabetic osteoporosis

Adipose-derived stem cells (ASCs) from diabetic osteoporosis (DOP) mice showed impaired osteogenic differentiation capacity. Antidiabetic drugs, sodium-glucose co-transporter inhibitor-2 (SGLT-2), and empagliflozin can play multipotent roles through various mechanisms of action. Osteogenic differentiation potential and autophagy activity weakened in DOP-ASCs when compared to healthy controls. However, empagliflozin enhanced autophagy flux by promoting the formation of autophagosomes and acidification of autophagic lysosomes, increasing LC3-II gene expression and decreasing SQSTM1 gene expression. Furthermore, empagliflozin contributed to the reversal of osteogenesis inhibition in DOP-ASCs induced by a diabetic microenvironment. When 3-methyladenine was used to block autophagy activity, empagliflozin could not exert its protective effect on DOP-ASCs. Nonetheless, this study demonstrated that the advent of cellular autophagy attributed to the administration of empagliflozin could ameliorate the impaired osteogenic differentiation potential of ASCs in DOP mice [14].

Proteomics

The developing field of proteomics focuses on disease processes and therapy responses based on the analysis of total proteins in the cell, proposing more targeted curations or disease modeling methods. The proteomic approach served the more profound recognition of factors invading bone metabolism and causing orthopedic-related diseases such as osteoporosis. After verification of more than 400 proteins, 22 of them such as apolipoproteins, zymoproteins, complement proteins, and binding proteins synthase (PHLD), cAMP protein kinase regulator chain (SAMP), pigment epithelium-derived factor (PEDF), transcriptional regulatory protein HptR (HPTR), apolipoprotein A-1 (APOA1), sex hormone binding globulin (SHBG), complement C6 (CO6), alpha-2-macroglobulin (A2MG), carboxypeptidase N catalytic chain (CBPN), Apolipoprotein D (APOD), and Thyroxine-Binding Globulin (THBG) were identified as the most promising biological targets for therapeutic intervention of OP. They still need clinical verification but could serve as indicators of bone age and markers of disease severity [15].

Traditional Chinese medicine in OP treatment

Traditional Chinese medicine (TCM) active ingredients with their long history of use and attribution of bone repair scaffold activation properties have just recently been explored as a possible ingredient of clinically approved medications for osteoporosis. The list of ingredients includes the deer antler, Astragalus radix, Herba Epimedii, naringin, Eucommiol, isopsoralen, icariin, Astragalus polysaccharides, and chondroitin sulfate, contained in Drynariae Rhizoma, Eucommiae Cortex, and Psoralea corylifolia. The current knowledge of signalling molecules lets us verify if and why these substances can be beneficial for bone structure and BMD. They increase levels of phosphorus, calcium, and alkaline phosphatase, enhance bone density, and reduce the trabecular gap, which results in bone formation stimulation and bone resorption inhibition. These qualities make them promising candidates for introduction into more conventional osteoporosis healing strategies [16].

Psoralea corylifolia L.

Psoraleae Fructus (Bu Gu Zhi) is the fruit of Psoralea corylifolia L. (PCL) and has been used for centuries in TCM formulas to treat OP. A new drug called "BX" has been developed from PCL, To explore the mechanism of action of BX in the treatment of ovariectomy-induced OP-based function-oriented multi-omics analysis of gut microbiota and metabolites.

BX improved OP in (OVX) mice by increasing bone parameters (BMD, BV/TV, Tb. N and Tb. Sp) and bone formation markers in serum, procollagen type I amino-terminal peptide (PINP) and bone-specific alkaline phosphatase (BALP). A total of 59 differential metabolites were identified, and 9 metabolic pathways, including arachidonic acid metabolism, glycerophospholipid metabolism, purine metabolism, and tryptophan metabolism, were found to be involved in the progression of OP. The enzymes related to purine and tryptophan metabolism, which are from the Lachnospiraceae NK4A136 group, Blautia, Rs-E47 termite group, UCG-009, and Clostridia UCG-014, were identified as the intrinsic link between gut microbiota and metabolites. The regulation of gut microbiota and restoration of metabolic disorders may be the mechanisms of action of BX in alleviating OP [17].

Erzhi Wan

Erzhi Wan (EZW), a classic TCM prescription for the liver and the kidney, is composed of Ligustri Lucidi Fructus and Ecliptae Herba, which has the potential effect on treating OP. Serum levels associated with bone turnover markers were detected by enzyme-linked immunosorbent (ELISA) assay. In proteomics study on OVX rats EZW alleviated a variety of metabolites and proteins among the kidney, bone and bone marrow, primarily in amino acid metabolism, carbohydrate metabolism, nucleotide metabolism and lipid metabolism, thus leading to improvements of OP, which provided theoretical basis for clinical treatment of EZW on OP [18].

Ligustri Lucid

Calcium sensing receptor (CaSR) has become the novel target for treating osteoporosis with herbal medicine Ligustri Lucidi Fructus (LLF). The newly discovered natural product ligands towards CaSR, including olenuezhenoside and ligustroflavone, will be the candidates for the treatment of osteoporosis. Cellular results showed that both compounds exhibited distinct osteogenic activity by enhancing the proliferation, differentiation and mineralization of osteoblastic cells [19].

Ginsenosides

Ginsenoside, a traditional Chinese medicament extracted from ginseng plants, is widely investigated for osteoporosis preventive effects in search of a theoretical confirmation of its place in clinical treatments and bone tissue creation. Different types of ginsenosides were proven to influence bone remodeling through interactions with osteoclasts, osteoblasts, and mesenchymal stem cells [20]. The monomers of ginsenoside stimulate osteoblast

generation and differentiation by regulation of signaling pathways WNT/β-catenin, FGF, and BMP/TGF-β. Moreover, the substance evinced anti-inflammatory and antibacterial values alongside vascular remodeling, and angiogenic properties, counteracting the osteoporosis background conditions [21].

Zhuang-Gu-Fang

Senile osteoporosis (SOP) is an age-related systemic metabolic bone disorder. Zhuang-Gu-Fang (ZGF) modulates myokines, stimulates osteogenic differentiation, and mitigates osteoporosis via myoblast and myoblast exosomal microRNAs (miRNAs). ZGF may enhance the osteogenic differentiation of the bone marrow-derived mesenchymal stem cells (BMSCs) through myoblasts and myoblast-derived exosomes. Moreover, the mice experiment corroborated these findings, which revealed that ZGF not only up-regulated the expression of miR-5100, miR-450b-5p and miR-126a-3p in muscle and bone tissues but also concurrently down-regulated the expression of miR-669a-5p in these tissues. Thus the myoblast exosomes miR-669a-5p and miR-450b-5p are novel targets for the regulation of osteoblastic differentiation and the treatment of SOP. ZGF can promote osteogenic differentiation of osteoblasts, regulate bone metabolism, and thereby delay the process of SOP [22].

Gynecology - phytoestrogens

Blackcurrant

Osteoporosis risk increases in menopausal individuals owing to the decrease in estrogen secretion. Blackcurrant extract (BCE) ameliorates osteoporosis thanks to its phytoestrogenic activity. After treating mouse MC3T3-E1 preosteoblast with BCE for 48 h, cell proliferation had increased. BCE treatment increased alkaline phosphatase (Alp) activity and total collagen content. Moreover, the expression of Col-I, Alp, Bglap, and Runx2 increased in BCE-treated cells. Furthermore, when MC3T3-E1 cells were treated with BCE for 21 days, the levels of calcified nodules increased. Alp staining intensity was stronger in the epiphyses on the femoral tissue of OVX rats treated with 3% BCE than in those of untreated OVX rats. The results suggest that BCE may promote osteogenesis by inducing osteoblast differentiation [23].

Siwu decoction

Siwu decoction (SWD) is widely used in gynecological diseases, such as peripheral menopause syndrome, premature ovarian failure, and menstrual disorders. SWD promoted the proliferation of osteoblasts and regulated the protein expressions of the ER/PI3K/AKT pathway in vitro. SWD improved the morphological structure, bone mineralization and bone mineral density of femurs and suppressed osteoclastogenesis in postmenopausal osteoporosis (PMOP) rat model via ER/PI3K/AKT pathway in vivo. In addition, SWD regulated the mRNA expressions of osteogenesis-related genes. SWD exerts a phytoestrogen osteoprotective on PMOP by regulating the ER/PI3K/AKT pathway, which marks it as a valuable medicine or supplement of PMOP [24].

Mijiao

The Mijiao (MJ) formula, a traditional herbal remedy, that incorporates antlers as its primary constituent, can effectively treat osteoporosis (OP), anti-ageing, enhance immune activity, and change depression-like behavior. MJ formula promoted osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) and moderated osteoporosis in OVX rats by regulating the NAT10-mediated Runx2 mRNA ac4C modification. The expression of osteogenic differentiation-related proteins in BMSCs was detected in vivo, indicating their role in promoting bone formation. In addition, the potential mechanism of its bone protective effect was explored via in vitro experiments. MJ formula significantly mitigated bone mass loss highlighting its potential as an OP therapeutic agent. MJ formula can treat estrogen deficiency OP by stabilizing Runx2 mRNA through NAT10-mediated ac4C acetylation, promoting osteogenic differentiation and protecting bone mass. Conceivably, MJ formulation could be a safe and promising strategy for the treatment of osteoporosis [25].

Andrology

Epimedii Folium - NLRP3/cleaved caspase-1/IL-1β signalling pathway

The decoction from the plant Epimedium brevicornu Maxim (EF) is prevalent in TCM as a bone-strengthening medicament. Its effect on the molecular mechanisms in guts is expected to play a role in the „gut-bone axis”, and hence, to bear upon osteoporosis. The EF decoction (EFD) tested on osteoporotic mice was found to increase the femur length, uterine weight, abdominal fat weight, insulin-like growth factor 1 (IGF-1) levels, and weight.

Growth in the four latter respects was significant, amounting to 69.86%, 61.14%, 59.48%, and 14.06% respectively. The EFD simultaneously reduced the serum type I collagen cross-linked carboxy-terminal peptide (CTX-I) levels by 15.02%. The EFD activity was attributed to control of the NLRP3/cleaved caspase-1/IL-1β signaling pathway supporting the bone metabolism and intestinal tight junction proteins. Furthermore, the EFD regulated the gut microflora communities' (Coriobacteriaceae, Lactobacillus, Clostridiales, Prevotella, and bacteria of family S24-7) size and led to a butyrate and propionate amount increase. Additional analysis showed a beneficial effect of the EFD on gut microbiome restoration after antibiotic-therapy-caused gut bacteria imbalance, preventing its osteoporotic consequences [26].

Icarin

Herba Epimedii derived total active flavonoid glucosides include icariin (ICA) and its structurally similar metabolic products (icaritin, icariside I, and icariside II). Apart from the antiosteoporotic functions followed by bone loss prevention in postmenopausal women, Epimedium was also clinically confirmed to provide hormone-regulative and erectile function-enhancing properties, as customarily claimed by the TCM alongside anti-oxidation, anti-tumour and immunoregulatory effects. The bioactivity of epimedium-derived compounds on the male reproductive system has not been entirely understood so far, however, the mechanisms of pathway modulation were examined. ICA treatment significantly elevated gene expression of osteogenic markers and increased alkaline phosphatase (ALP) activity in MC3T3-E1 and C3H10T1/2 cells. RNA sequencing revealed that the expression of several genes involved in the Notch pathway was decreased following ICA treatment. Real-time PCR further demonstrated that the mRNA levels of Notch ligands Jagged-1 (Jag1), lunatic fringe (Lfng), and Notch signaling downstream target gene Hey-1 were significantly decreased following ICA treatment. In addition, the constitutive activation of Notch signaling through overexpression of the intracellular domain of Notch (NICD) fully blocked ICA-induced osteoblast differentiation. Moreover, inhibiting Notch signaling markedly enhanced osteogenic differentiation following ICA treatment. The mRNA levels of Notch pathway molecules (Lfng, Notch1, Rbpjk and Nfatc1) were increased in OVX mice, and administration of ICA significantly decreased the expression of these genes. ICA promotes osteogenic differentiation in vitro and alleviates osteoporosis in vivo through inhibition of the Notch signaling pathway [27].

RANKL modificators

Hyperoside

An active flavonoid glucoside Hyperoside is a compound isolable from many TCM medications suspected to have antiosteoporotic qualities. When orally administered for twelve weeks by a group of OVX mice, the hyperoside was found to increase the BMD, enhance bone strength and restore trabecular bone micro-architecture. The bone resorption markers (tartrate-resistant acid phosphatase 5b (TRAP-5b) and C-terminal telopeptide of type I collagen (CTX)) activity largely decreased and the bone formation markers (osteocalcin (OC) and bone-specific alkaline phosphatase (BALP)) activity highly increased upon the period of hyperoside intake. The expression of nuclear factor of activated T cell cytoplasmic 1 (NFATc1), TNF-receptor-associated factor 6 (TRAF6), receptor activator of nuclear factor-κB ligand (RANKL), phosphorylated inhibitor of nuclear factor-κB α (IκBα), and NF-kB p65 was diminished, while the expression of osteoprotegerin (OPG) was enhanced. The final hypothetical reason for hyperoside's antiosteoporotic activity was stated as the rise of the OPG/RANKL ratio, and the blocking of the TRAF-6 mediated RANKL/RANK/NF-κB signaling pathway. Altogether, the study reports substantiate the utility of hyperoside in osteoporosis treatment [28].

Puerarin

Elevated reactive oxygen species levels promote excessive osteoclastogenesis and bone resorption. Puerarin, a natural antioxidant, can prevent bone loss through its antioxidant effects by regulating the PI3K/AKT/FoxO1 signaling pathway. Puerarin strongly alleviated oxidative stress-induced bone loss in OVX rats in vivo owing to its antioxidant effects. Puerarin improved the oxidative stress status of cells and inhibited osteoclast formation in vitro. Moreover, the protein expression of FoxO1 and its downstream target, catalase, was upregulated by puerarin. Puerarin improved the OPG/RANKL ratio, upregulated the protein expression and transcriptional activity of FoxO1, and suppressed the differentiation of RAW264.7 cells into osteoclasts. FoxO1 is a pivotal target of puerarin to confer anti-osteoporosis effects [29].

Desertliving Cistanche

Desertliving Cistanche demonstrated efficacy in preventing and treating postmenopausal hyperlipidemic osteoporosis in rats modulating the PI3K/AKT signaling pathway [30]. After six weeks of treatment, compared to the normal control group, rats in the model group

exhibited blurred trabecular morphology, disorganized osteocytes, significantly elevated levels of bone-specific alkaline phosphatase (BALP), bone Gla-protein (BGP), total cholesterol (TC), tumor necrosis factor-α (TNF-α), and receptor activator of NF-κB ligand (RANKL). Also, the model group revealed significantly reduced levels of ultimate load, fracture load, estradiol (E2), BMD, osteoprotegerin (OPG), phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) in femoral tissue. The atorvastatin group presented with higher TC and TNF-α levels compared to the normal control group. Conversely, the treatment group demonstrated enhanced trabecular morphology, denser structure, smaller bone marrow cavities, and reduced BALP, BGP, TC, TNF-α, and RANKL levels. Furthermore, the treatment group exhibited higher levels of E2, BMD, OPG, PI3K and Akt in bone tissue compared to the model group. The treatment group also had lower TC and TNF-α levels than the atorvastatin group. Biomechanical analysis indicated that after administration of Desertliving Cistanche, the treatment group had reduced body mass, increased ultimate and fracture load of the femur, denser bone structure, smaller bone marrow cavities, and altered periosteal arrangement compared to the model group [31].

Conclusions

Thanks to the advances in recognising pathways regulating the density and quality of bone mass, a lot of beneficially mediating orally administered substances can be identified. Detailed determination of their mode of action supports their therapeutic significance and validates their use in safe clinical applications. Currently, the substances supply mainly pharmacotherapy and mechanotherapy, but their prevalence in standard clinical treatment methods is projected to grow. Especially if presumptive adverse effects can be outruled, the orally administered therapeutics might take the lead in osteoporosis treatment.

Disclosures

Author's contribution

Conceptualization: EL, RJ; Investigation: EL; Writing -rough preparation: ML, AR, BM; Writing -review and editing: EL, BM; Visualization: ML, RJ; Supervision: AR.

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