Advances in Research on the Effects of Neurological Diseases and Related Therapeutic Drugs on Osteoporosis (Postprint)

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Abstract

Patients with osteoporosis (OP) often suffer from multiple comorbidities. In addition to general risk factors for OP such as age, sex, and race, both comorbid diseases and their associated treatments can exert influences on bone metabolism. Currently, research on neurological diseases comorbid with OP remains relatively limited. This paper intends to provide a comprehensive review from four aspects: epidemiological characteristics, features of bone mass loss, related pathogenic mechanisms, and diagnostic and therapeutic advances, with the aim of offering insights into bone damage mechanisms, OP prevention, and anti-osteoporotic treatment for patients with neurological diseases.

Full Text

Research Progress on the Influence of Nervous System Diseases and Related Therapeutic Drugs on Osteoporosis

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Abstract

Patients with osteoporosis (OP) often suffer from a variety of diseases. In addition to general risk factors such as age, gender, and race, comorbidities and

related treatments can affect bone metabolism. Therefore, this article reviews the epidemiological characteristics, bone loss features, related pathogenesis, and progress in diagnosis and treatment to provide reference for understanding the mechanism of bone damage, OP prevention, and anti-osteoporosis treatment in patients with nervous system diseases.

Key words: Osteoporosis; Secondary osteoporosis; Stroke; Spinal cord injury; Multiple sclerosis; Parkinson's disease; Alzheimer's disease; Epilepsy; Treatment; Review

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Osteoporosis (OP) can be classified into primary and secondary types. Secondary OP is typically caused by bone mass loss, decreased bone mineral density (BMD), and destruction of bone microarchitecture due to certain diseases, medications, or other factors, leading to increased bone fragility and susceptibility to fragility fractures. Among OP patients, up to 50%-80% of men, >50% of premenopausal women, and 30% of postmenopausal women have secondary OP [1]. Patients with secondary OP are numerous, and their symptoms are often masked by the primary disease, leading to scattered visits to other specialties, which makes early identification of bone damage difficult and delays diagnosis and treatment. Currently, the topic of nervous system diseases combined with OP is receiving increasing attention. This article reviews common nervous system diseases that cause bone metabolism disorders from four aspects: epidemiological characteristics, pathogenesis, changes in bone turnover markers and bone microarchitecture, and current treatment progress, aiming to provide feasible references for clinical management of OP in these patients.

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1. Stroke and Spinal Cord Injury

1.1 Epidemiological Characteristics

Due to the frequent occurrence of limb movement disorders in stroke and spinal cord injury (SCI) patients, this population is at high risk for disuse OP. Statistics show that the prevalence of SCI-related OP is 43.8%, with a fragility fracture rate of 9.4% [2], while the incidence of OP in ischemic stroke patients can reach 40% [3], with a fracture incidence of 5.7% within 2 years [4]. Conversely, the incidence of stroke after osteoporotic fracture is approximately 25% [5]. Early studies indicate that SCI patients reach peak bone loss at about 3 months post-injury, with monthly bone loss of 2%-4% in the first year, stabilizing after 1.5-2 years [6]. Similarly, stroke patients have the highest incidence of OP at 3-6 months of disease course, with the lowest at 9-12 months [7].

1.2 Related Risk Factors or Possible Mechanisms

The primary cause of disuse OP in SCI and stroke patients is long-term limb immobilization, leading to loss of mechanical stress on bone [8]. Additionally, factors include swallowing difficulties and gastrointestinal dysfunction causing impaired absorption of vitamin D and calcium, loss of neurotrophic support to bone, hypercalciuria in the acute phase, hyperparathyroidism stimulating osteoclast activation, and limited sex hormone synthesis and secretion after SCI [9-10]. Bile acid metabolism and secretion also participate in bone homeostasis regulation. Elevated lithocholic acid levels have been observed in disuse OP patients, accompanied by decreased abundance of Firmicutes, Proteus, Akkermansia, and Rothia [11].

Notably, in patients with traumatic brain injury (TBI) combined with fractures, accelerated fracture healing can be observed, which is related to multiple factors including nerves, blood vessels, bone tissue regeneration-related growth factors, hormones, neuropeptides, and stem cells [12]. However, in a repetitive mild TBI rat model, micro-CT analysis of the fracture callus area after 9 weeks of intervention showed reduced bone volume and 40% lower callus connectivity density in the repetitive stimulation group compared with the control group [13]. This may be related to hypothalamic-pituitary axis dysfunction caused by trauma. The most common manifestation of hypothalamic-pituitary dysfunction after TBI is reduced growth hormone (GH) secretion, and GH is a key regulator of bone metabolism. GH supplementation can reverse trabecular bone loss caused by TBI, unloading, or TBI+unloading [14].

In pure traumatic brain injury, bone mass loss can result from lack of movement or immobilization after brain injury. Animal experiments have shown that rats with brain trauma have significantly lower lumbar BMD at 1 week post-surgery and bilateral distal femur BMD and femoral neck bone strength at 3 weeks post-surgery compared with blank controls [15].

1.3 Changes in Bone Metabolism Markers or Bone Damage Characteristics

In SCI patients during the acute phase of immobilization, enhanced bone resorption is the main manifestation, while bone formation remains unchanged or even decreases [8]. However, some studies have observed increased levels of both bone resorption and formation markers in acute phase patients [16]. During this period, patients also have increased urinary calcium excretion and decreased serum vitamin D levels [8], and this high calcium loss cannot be offset by higher calcium intake. In the late stage of immobilization, the above changes in bone metabolism biochemical markers gradually normalize [16].

In the acute phase, bone loss in the tibia and femur of SCI patients is mainly characterized by decreased cortical BMD, while in the chronic phase, cortical bone loss in these areas is mainly attributed to reduced cortical bone cross-sectional area [9]. Trabecular bone loss in acute SCI is more rapid than cortical

bone [8], and this remains true even in the late stage of disease [9].

1.4 Progress in Diagnosis and Treatment

For patients in the early disease stage, despite observed increased urinary calcium excretion and decreased vitamin D levels, vitamin D/calcium supplementation is not recommended to avoid aggravating hypercalcemia. Bone nutrition therapy should be initiated after disease stabilization [17]. Anti-osteoporosis drugs have shown good effects in improving BMD in SCI patients. For example, bisphosphonates can effectively slow bone loss in both acute and chronic SCI patients and reduce fracture incidence in OP patients [18]. Studies have also shown that early bisphosphonate treatment after SCI is safe and can increase hip and lumbar BMD [19]. Teriparatide treatment in patients with late-stage SCI injury can increase BMD in the spinal region [20], while denosumab treatment can increase lumbar and femoral BMD in early SCI patients, with no serious adverse reactions observed during follow-up [21].

The route of administration should also be selected based on the patient' s general condition. When patients cannot maintain a sitting or standing position and have difficulty swallowing, intravenous or subcutaneous injection formulations can be chosen. If conditions permit, patients with stable conditions should be encouraged to undergo rehabilitation exercise early to maintain mechanical loading on bone and muscle, while monitoring the hypothalamic-pituitary hormone axis to identify pituitary dysfunction and initiate hormone replacement therapy promptly.

2. Parkinson' s Disease (PD)

2.1 Epidemiological Characteristics

A nationwide longitudinal follow-up study indicated that PD patients have a 31% increased risk of developing OP compared with the general population [22]. PD is more common in male patients (male:female 2:1). However, in gender subgroup analysis, compared with normal controls, female PD patients had decreased BMD, while male PD patients showed no significant difference in BMD changes. Nevertheless, male PD patients have a higher risk of OP fractures than female patients [23].

2.2 Related Risk Factors or Possible Mechanisms

PD-related OP and osteopenia are directly or indirectly related to the following factors: female gender, reduced sunlight exposure, low body weight, nutritional status (vitamin D, vitamin B12, and folate deficiency), hyperhomocysteinemia (caused by vitamin B12, folate reduction, or levodopa treatment), disease duration and severity, reduced physical activity, and decreased muscle strength [24]. Additionally, PD may affect bone health through the hypothalamic-pituitary axis. In untreated PD patients, hypothalamic dysfunction can be observed,

with decreased secretion of hypothalamic regulatory peptides, leading to reduced blood levels of growth hormone, adrenocorticotropic hormone, and cortisol [25].

Furthermore, small intestinal bacterial overgrowth can be observed in PD patients. Due to increased intestinal bacteria, bile acids are decomposed, causing reduced lipid absorption and affecting vitamin D absorption, leading to OP and fractures [26].

2.3 Changes in Bone Metabolism Markers or Bone Damage Characteristics

A small-sample case-control study suggested that PD patients have lower serum levels of bone formation marker procollagen type 1 amino-terminal propeptide (P1NP) and bone resorption marker beta-C-terminal telopeptide (β-CTX) than normal controls [27]. PD patients also have lower BMD at the hip, lumbar spine, and femoral neck than healthy individuals [23], and low BMD and low serum vitamin D levels can appear in early disease stages (H-Y stage 1-1.5) and mark disease progression [28].

Another PD mouse model study showed that micro-CT analysis of trabecular bone in the distal femoral metaphysis revealed reduced trabecular bone volume/tissue volume, trabecular thickness, connectivity density, and BMD in PD mice compared with controls [29]. The study also found significantly decreased mRNA expression levels of early osteoblast differentiation marker Runx2 and late differentiation marker osteocalcin (OC) in the PD mouse model [29].

2.4 Progress in Diagnosis and Treatment

Given that PD patients are primarily characterized by resting tremor, bradykinesia, muscle rigidity, and postural balance disorders, after proper medication control of motor symptoms, attention should be paid to the role of physical activity in improving muscle strength, balance ability, and BMD [30]. Levodopa can cause OP by inducing hyperhomocysteinemia, so supplementation with vitamin B12 and folate is recommended [31], along with monitoring blood homocysteine levels. Since PD can cause orthostatic hypotension and attention deficits, fall prevention nursing should be strengthened to avoid fractures.

Currently, there are no large-scale studies on anti-osteoporosis drugs in PD patients. Therefore, anti-osteoporosis treatment can refer to primary OP guidelines. In PD patients treated with alendronate combined with Caltrate D, increased BMD at the femoral neck, trochanter, and total hip was observed, with lower hip fracture incidence than the control group and Caltrate D alone group [32]. A home-based zoledronic acid trial for fracture prevention in patients with parkinsonism is currently ongoing [33]. Other anti-osteoporosis drugs such as teriparatide and denosumab currently have no clinical studies confirming their safety and efficacy in PD patients.

3. Multiple Sclerosis (MS)

3.1 Epidemiological Characteristics

A meta-analysis of 13,906 MS patients indicated that the pooled prevalence of OP in MS patients is 17%, and osteopenia is 43% [34]. A matched cohort study showed that compared with normal individuals, MS patients have significantly increased hip fracture incidence (47.4% vs. 34.2%) [35].

3.2 Related Risk Factors or Possible Mechanisms

The specific mechanism of MS combined with OP still needs further exploration, but MS patients develop OP related to immobilization, vitamin D deficiency, glucocorticoid (GC) treatment, and inflammatory factor levels [36-37]. MS can cause visual, balance, and coordination impairments and muscle weakness, thereby increasing the risk of falls and fractures [38].

3.3 Changes in Bone Metabolism Markers or Bone Damage Characteristics

MS patients have significantly reduced serum OC levels [39], and the most significant BMD decreases occur at the femoral neck, lumbar spine, and hip [40]. However, in studies investigating bone microstructure changes, no significant alterations in trabecular bone index were observed in MS patients [41].

3.4 Progress in Diagnosis and Treatment

Screening indications for OP in MS patients include postmenopausal status and clinical expanded disability status scale scores $ $6.0. Those with scores <6.0 but with previous fracture history, long-term GC use, and anticonvulsant medication use are also candidates for screening [40]. Although MS patients have statistically significant 10-year osteoporotic fracture risk as predicted by FRAX, FRAX underestimates the osteoporotic fracture risk in MS patients by 3%-5% regardless of whether BMD is included in the assessment. This indicates that FRAX does not adequately reflect fracture risk in MS patients, and other bone health parameters need to be integrated for evaluation [42].

In treatment for the primary disease, short-term high-dose intravenous GC treatment (1,000 mg methylprednisolone intravenously for 5 consecutive days, followed by 60 mg prednisone orally daily, gradually reduced within 21 days) appears to have no long-term negative impact on BMD in young and newly diagnosed MS patients, with only a non-statistically significant decrease in P1NP levels observed initially (day 4) [43]. However, this study only included 25 subjects, all of whom received concurrent active vitamin D supplementation. Due to the increased risk of OP, falls, and fractures in MS patients, the Canadian MS Society recommends that MS patients achieve and maintain minimum serum 25-(OH)D levels for vitamin D bone nutrition therapy [44].

Currently, there is a lack of research data on the application of anti-osteoporosis drugs in MS patients, and their exact effects in this population need to be further clarified. However, supplementation with short-chain fatty acids can increase OC and decrease β-CTX levels in MS patients, suggesting that nutritional supplementation plays an important role in maintaining bone health [45]. Melatonin therapy can normalize bone formation in MS model mice, reversing the reduction in serum 25-(OH)D3, calcium, and OC levels in the MS mouse model [39].

4. Alzheimer' s Disease (AD)

4.1 Epidemiological Characteristics

There are currently no clear epidemiological data on the incidence of AD combined with OP. A meta-analysis on the association between cognitive impairment and OP indicated that individuals with cognitive impairment have a 1.56-fold increased risk of OP compared with normal individuals. In subgroup analysis by type of cognitive impairment, AD patients showed a 1.7-fold increased risk of OP [46], and their hip fracture risk increased by nearly 2-fold [47].

4.2 Related Risk Factors or Possible Mechanisms

The accumulation of abnormally folded amyloid beta peptide (Aβ) in the brain is a pathological hallmark of AD. A$ 42$can promote degradation of inhibitor of nuclear factor \kappa B, enhance nuclear$ regulated kinase phosphorylation, stimulate calcium oscillation signaling pathways, thereby enhancing receptor$ \kappa B ligand (RANKL)-induced osteoclast bone resorption[48]. The neurodegenerative cascade in AD causes chron$ products (AGEs)[49]. In vitro experiments have found that A $ enhances RANKL-induced osteoclastogenesis through AGEs [50]. Animal studies have observed that MiR-483-5p in AD model mice promotes the shift of bone marrow mesenchymal stem cells from osteogenic differentiation to adipocyte generation by inhibiting insulin-like growth factor 2 and mediating brain-derived extracellular vesicles, inducing bone-fat imbalance [51].

The nervous system is indispensable for maintaining bone metabolism homeostasis. AD patients exhibit increased sympathetic activity and decreased parasympathetic activity. Sympathetic signals in osteoblasts inhibit their own proliferation through circadian clock genes, while the sympathetic nervous system can also promote bone resorption by increasing RANKL expression [52]. Additionally, AD patients begin to reduce activity in middle age [53], weakening mechanical stimulation to the skeletal system and gradually developing sarcopenia, which plays an important role in maintaining bone remodeling.

4.3 Changes in Bone Metabolism Markers or Bone Damage Characteristics

A case-control study observed that AD patients have reduced vitamin D and osteocalcin levels compared with healthy controls [54]. In early-stage male AD

patients, bone resorption markers urinary deoxypyridinoline/creatinine ratio and urinary calcium/creatinine ratio, and bone formation marker serum osteocalcin levels were significantly higher than in healthy controls [55]. Additionally, in mild AD patients, bone resorption marker carboxy-terminal cross-linked telopeptide of type 1 collagen (CTX) and bone formation marker OC levels were increased compared with normal controls [56], indicating increased bone turnover rate in early and mild AD patients.

Regarding bone microstructure changes in AD, a study on AD transgenic 5xFAD mouse model bone damage found that compared with wild-type mice, 5xFAD mice showed lower volumetric bone density (vBMD) on micro-CT, with bone microstructure damage primarily in bone cortex, manifested as increased endosteal diameter and increased bone loss, while trabecular bone parameters showed no significant differences. Mineralization levels were significantly reduced, with decreased bone mineral crystal size and lattice spacing [49].

4.4 Progress in Diagnosis and Treatment

Biochemical improvement is important for controlling the primary disease and improving bone metabolism in AD patients. Given that AD patients may stop exercising or maintain a sedentary lifestyle due to their condition, maintaining physical activity not only enhances bone quality and protects bone but also improves cognitive function in AD patients. However, high-frequency physical activity does not show greater improvement than low-frequency exercise, so the primary disease should be effectively controlled as soon as possible, early activity should be promoted, and fall prevention should be emphasized [57].

Regarding dietary recommendations, the Mediterranean diet can reduce oxidative damage and inflammatory factor levels associated with AD pathogenesis [58]. For pharmacological treatment, AD patients have reduced vitamin D levels, and vitamin D supplementation is recommended. Adequate vitamin D levels can also reduce the risk of AD onset [59].

Currently, few studies have evaluated the exact efficacy of anti-osteoporosis drugs in AD patients. The only available study found that in elderly populations (including AD patients), bisphosphonate users had a 17% lower risk of hip fracture compared with calcitonin users, but the study did not compare the efficacy of different bisphosphonate preparations [60]. A study evaluating the effectiveness of denosumab, teriparatide, and zoledronic acid in frail elderly individuals (including AD patients) found that all three can prevent hip fracture occurrence in frail elderly people [61]. Additionally, elevated plasma sclerostin levels were found in cognitively normal older adults at high risk for AD, which positively correlated with brain Aβ load [62]. As a sclerostin monoclonal antibody, romosozumab may improve bone damage in AD patients, but caution is needed regarding its potential to increase cardiovascular events in elderly patients [63].

Studies on the effects of anti-osteoporosis drugs on AD have found that bis-

phosphonates appear to have beneficial effects on AD. Zameer et al. [64] developed alendronate chitosan nanoparticles (CS-ALN-NPs) that deliver alendronate directly to the brain via intranasal administration. Animal experiments observed that this approach improved Aβ deposition in the hippocampus and reduced brain inflammatory factor levels in intracerebroventricular streptozotocin-induced AD mice, suggesting potential neuroprotective effects. Therefore, if no contraindications exist, bisphosphonates are more recommended for AD patients.

5. Epilepsy

5.1 Epidemiological Characteristics

It is estimated that anti-epileptic drug treatment can increase fracture risk by 4%-6% annually [65]. Epilepsy events, enzyme-inducing and non-enzyme-inducing anti-epileptic drugs are independently associated with OP development [66]. The risk of OP increases with epilepsy duration, and compared with monotherapy, dual therapy and triple therapy increase OP risk by 1.3-fold and 2.2-fold, respectively [67]. In patients previously using enzyme-inducing anti-epileptic drugs or non-enzyme-inducing anti-epileptic drugs for $ $2 years, vertebral fracture incidence rates were 27.0% and 19.0%, respectively [68].

5.2 Related Risk Factors or Possible Mechanisms

Based on whether they have enzyme-inducing effects, anti-epileptic drugs can be divided into enzyme-inducing types (including phenytoin, phenobarbital, carbamazepine, etc.) and non-enzyme-inducing types (including valproic acid, lamotrigine, gabapentin, ethosuximide, levetiracetam, etc.).

Anti-epileptic drugs can affect bone metabolism through multiple pathways [64,69]: (1) downregulating sex hormone-binding globulin, reducing bioactive testosterone and estradiol levels; (2) phenobarbital and phenytoin can induce cytochrome P450 activity, accelerating catabolism of vitamin D and its metabolites and inhibiting calcium absorption; (3) phenytoin can reduce serum vitamin K levels, affecting Gla protein and OC carboxylation; (4) inhibiting calcitonin secretion and affecting PTH function; (5) upregulating leptin and homocysteine levels (carbamazepine); (6) directly interfering with bone cells, affecting osteoblast differentiation and increasing osteoclast activity.

5.3 Changes in Bone Metabolism Markers or Bone Damage Characteristics

Some studies have observed that both enzyme-inducing and non-enzyme-inducing anti-epileptic drugs can lead to decreased vitamin D levels and increased PTH levels, but calcium and phosphorus levels are mostly normal. A meta-analysis pointed out that changes in serum bone turnover markers in epilepsy patients are not significantly correlated with the degree of BMD

changes [70]. In studies observing anti-epileptic drug effects on rat bone microstructure, valproic acid reduced bone volume fraction by 19%, apparent bone density by 14%, and increased structural model index by 41%, while carbamazepine, eslicarbazepine, and levetiracetam had smaller adverse effects on bone biology [70]. Additionally, valproic acid and phenytoin can reduce BMD and bone mineral content at multiple sites, while levetiracetam has no significant effect [71].

5.4 Progress in Diagnosis and Treatment

Currently, enzyme-inducing anti-epileptic drugs have greater impact on bone metabolism. For epilepsy patients at high risk for OP, enzyme-inducing anti-epileptic drugs should be avoided as much as possible based on epilepsy treatment guidelines, with monotherapy preferred and combination therapy used when appropriate. Patients taking anti-epileptic drugs are recommended to supplement vitamin D and calcium to prevent bone loss. Research on whether bisphosphonates can be added is limited, but existing results support using bisphosphonates to prevent OP in these patients [64]. Currently, there is no clear evidence for the safety and efficacy of anti-osteoporosis drugs such as teriparatide and denosumab in epilepsy patients. However, it is worth noting that hypocalcemia can trigger epileptic seizures, so adverse reactions such as hypocalcemia should be monitored when using anti-osteoporosis drugs, and electrolyte levels should be dynamically monitored.

6. Other Nervous System Diseases

6.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

Currently, there are no reliable comorbidity data on ADHD and OP. In child/adolescent ADHD patients, fracture prevalence was observed to be 4.83%, 2.55 times higher than in those without ADHD, with upper limbs being the main fracture site (69.62%), lower limbs accounting for 22.85%, and other sites 7.53% [72].

Methylphenidate (MP) is a commonly used treatment drug for ADHD patients. However, recent studies have found it may cause early-onset OP and higher fracture risk. In cell experiments, although MP did not change the activity of chondrocyte precursor cells, it reduced the expression of cartilage extracellular matrix-related genes (type II collagen and aggrecan) and increased the expression of growth plate calcification-related genes (Runx2, type I collagen, and osteocalcin), leading to premature growth plate closure and affecting skeletal development and peak bone mass acquisition [73]. Additionally, MP can stimulate osteoclast differentiation and activity in male rats in a dose- and sex-dependent manner [74].

Many ADHD patients often use antipsychotic drugs such as selective serotonin reuptake inhibitors like fluoxetine (FLX) for depression and anxiety. Animal

experiments observed that combined MP and FLX treatment in adolescent rats resulted in shorter femur and tibia lengths, thinner tibial growth plates, more disordered chondrocyte arrangement, reduced trabecular number, thickness, bone volume fraction, and increased separation at the proximal tibia on micro-CT, and decreased femoral ultimate strength compared with blank and single-drug groups [75]. Therefore, antipsychotic drugs also play an important role in their bone metabolism disorders.

Currently, there are no studies on the efficacy and safety of anti-OP drugs in ADHD patients with OP, so treatment can refer to primary OP guidelines. However, why the drugs for treating the primary disease produce gender differences remains unclear, so more attention should be paid to bone protection during treatment of male ADHD patients.

6.2 Myasthenia Gravis (MG)

MG patients require GC therapy to suppress autoimmune responses, and GC is an important cause of OP. According to surveys, the prevalence of OP in MG patients is 14% in the lumbar spine and 2.5% in the femur. However, the impact of the primary disease on bone metabolism is not yet clear, and there are no studies on bone microstructure in MG patients, so bone damage characteristics still need to be explored.

MG patients require anticholinesterase drugs to relieve symptoms and immunosuppressive therapy. For patients with surgical indications, thymectomy is the preferred treatment option. Thymectomy can cause changes in various cytokine secretions, such as tumor necrosis factor (TNF) and interleukin (IL)-7, which are involved in OP pathogenesis [76]. Patrizia et al. [77] found that after thymectomy, although the number of TNF-producing CD4+ T cells decreased, serum TNF levels did not change significantly. While increased IL-7 and RANKL levels were observed postoperatively, there was no significant effect on the RANKL/OPG ratio or bone metabolism markers.

In studies on anti-OP treatment for MG patients, after treatment with alendronate on the basis of alfacalcidol combined with calcium, patients' average BMD increased by 3.4% in the lumbar spine, 1.8% in the femoral neck, and 2.6% in the hip, with bone resorption marker β-CTX levels significantly decreased. In contrast, patients treated with alfacalcidol alone showed decreased BMD in the lumbar spine, femoral neck, and hip [78]. This demonstrates that alendronate combined with alfacalcidol is more effective than alfacalcidol alone in preventing bone loss in MG patients initiating GC treatment.

Although the efficacy of bisphosphonate treatment for MG patients with OP has been validated, its safety requires further investigation. Some case reports have documented that alendronate, risedronate, and pamidronate can induce or exacerbate MG [79]. The authors suggest that the rare drug-related adverse reactions of bisphosphonates in MG patients may be related to acute inflammatory reactions caused by bisphosphonate-stimulated T cell activation and

cytokine release [80-81]. However, these studies are isolated case reports, and the interaction between MG and bisphosphonates requires further exploration. For patients choosing such drugs, adverse reactions should be carefully monitored. Due to the lack of research on other anti-OP drugs, their therapeutic effects in MG patients with OP cannot currently be evaluated.

6.3 Brain Tumors

Some studies suggest that among survivors who received brain tumor treatment in childhood, radiotherapy is associated with significant bone mineral loss. Isaac et al. [82] investigated young survivors of posterior fossa tumors (astrocytoma or medulloblastoma) or optic nerve glioma. The incidence of osteopenia was 67% in the radiotherapy group and 27% in the non-radiotherapy group, while OP prevalence was >40% and 0%, respectively. Due to local compression of brain tissue, some patients may have comorbid epilepsy, and as previously discussed, epilepsy medications are closely related to OP development. Additionally, GCs are commonly used to relieve tumor-related vasogenic brain edema, and GCs are undoubtedly important factors affecting bone metabolism. Patients with intracranial germ cell tumors are prone to OP due to intracranial irradiation and multiple hormone deficiencies. Kang et al. [83] observed that 25% of long-term survivors of intracranial germ cell tumors were diagnosed with OP, 42.9% had osteopenia, and low body weight and late initiation of growth hormone replacement therapy were negatively correlated with BMD. The pathogenesis of OP in brain tumor patients is complex, being related not only to local compression and related complications but also closely related to treatment regimens. Therefore, prevention of bone loss should begin while treating the primary disease. However, current research on anti-OP treatment in brain tumor patients is insufficient, and how to select initial and sequential treatment regimens remains to be explored.

6.4 Peripheral Nerve Injury

In addition to systemic diseases, local peripheral nerve injury can also lead to OP, which may be related to local immobilization and reduced neurotransmitter content such as neuropeptides caused by peripheral nerve injury [84]. In a rat model of chronic sciatic nerve ligation injury, the injured side showed reduced muscle weight and cross-sectional area compared with the healthy side, with a decreasing trend in calcium content. Micro-CT revealed significantly lower BMD, bone volume fraction, bone area fraction, trabecular number, connectivity density, and bone perimeter in the affected tibia than in the healthy tibia [84]. Additionally, M1 macrophage infiltration exacerbates muscle/bone atrophy after peripheral nerve injury. Shimada et al. [85] observed through animal experiments that compared with the control group, the peripheral nerve injury group had significantly reduced muscle weight and total BMD at 1 and 3 weeks, with M1 macrophage infiltration visible in muscles under microscopy. After inhibiting macrophage infiltration, muscle weight and total BMD were signifi-

cantly higher than in the untreated group. Therefore, both systemic and local factors can interfere with normal bone metabolism, and the key to treatment remains managing the primary disease and removing the root cause.

7. Conclusion

Nervous system diseases and related therapeutic drugs can induce or exacerbate OP. Prevention and treatment should target related risk factors and adjust medication appropriately. High-risk populations should undergo screening tests such as BMD and FRAX, and anti-osteoporosis treatment should be initiated when necessary. However, the primary task of treatment remains controlling the primary disease. Currently, treatment of OP related to nervous system diseases mostly follows primary OP diagnosis and treatment guidelines, and its efficacy and safety require further evaluation. Meanwhile, the impact of anti-osteoporosis drugs on the primary disease also needs to be clarified. This article briefly elaborates on the relationship between the two and proposes possible treatment measures, hoping to provide references for clinical management of OP related to nervous system diseases and ideas for multidisciplinary collaborative diagnosis and treatment models for secondary OP.

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