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Research progress on the correlation between primary aldosteronism and bone metabolism

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Abstract: *Primary aldosteronism is a clinical syndrome characterized by hypertension, with or without hypokalemia, low renin and hyperaldosteronism, which is a common endocrine hypertension due to adrenal cortical lesions and excessive autonomic aldosteronism, resulting in increased retention of sodium and potassium and volume load. Studies have shown that aldosterone overdose increases the risk of cardiovascular disease, renal insufficiency, diabetes, metabolic syndrome and even death. In recent years, studies have pointed out that patients with primary aldosteronism have increased urinary calcium and elevated parathyroid hormone, and the prevalence of osteoporosis and fracture is higher than that of essential hypertension and healthy people. Primary aldosteronism may be a secondary cause of osteoporosis, but the specific pathogenesis remains unclear. This article reviews the correlation of bone metabolism and possible pathogenesis of primary aldosteronism.*

Keywords: *primary aldosteronism; parathyroid hormone; osteoporosis; fracture*

Primary aldosteronism (PA) is the most common cause of secondary hypertension, the prevalence of PA varies from 3% to 15%[1] , Aldosteronoma (APA) and idiopathic aldosteronism (IHA) are the most common types. Hypertension, hypokalemia and adrenal tumor or hyperplasia are important clinical manifestations of typical PA. Clinical studies[2-5] have found that aldosterone overdose increases the risk of cardiovascular adverse events (heart failure, left ventricular hypertrophy, atrial fibrillation, stroke, myocardial infarction, etc.), diabetes, metabolic syndrome, kidney disease, and even death independent of blood pressure. Secondary osteoporosis is due to diseases, drugs or other reasons caused by low bone mass, bone microstructure damage, resulting in increased bone fragility, prone to fracture of the systemic bone disease. Osteoporosis has become the second major health hazard after cardiovascular disease. In recent years, studies have shown[6] that compared with essential hypertension and healthy people, PA patients have increased urinary calcium, increased parathyroid hormone (PTH), and increased prevalence of osteoporosis and fracture. Excessive aldosterone may be a risk factor for bone metabolism, and PA is a secondary cause of secondary osteoporosis. Therefore, this article reviews the research progress of primary aldosteronism in bone metabolism by summarizing the studies published at home and abroad in recent years, so as to improve clinical workers' understanding of the correlation between primary aldosteronism and bone metabolism.

1. Correlation between primary aldosteronism and bone metabolism

1.1. Primary aldosteronism and bone metabolism serological indexes

Studies have shown that elevated PTH and increased urinary calcium are common features in patients with primary aldosteronism. As early as 1985, Resnick[7] discovered the phenomenon of elevated PTH in patients with primary aldosteronism. Subsequently, a large number of studies have proved that PTH is increased in aldosteronism patients or rats, and PTH can be decreased after treatment. In a meta-analysis involving 15 foreign studies[6] , 283 PA patients were compared with 475 essential hypertension (EH) patients, and the results showed that the serum PTH level of PA patients was higher than that of EH patients (MD= 21.50pg/ml, 95%CI (15.63, 27.37)). $P < 0.00001$); A meta-analysis of five studies involving 273 PA patients and 293 EH patients showed a slight increase in urinary calcium in PA patients

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(MD = 1.65mmol/ 24 h, 95% CI (1.24, 2.06), P<0.00001). However, there was no significant difference in serum calcium levels between PA and EH patients (MD = 0.00mmol/L, 95%CI (−0.08, 0.08), P = 1.0). The same conclusion has been reached in studies[8-10] comparing PA patients with healthy subjects (HS). Although there are few relevant researches in China, the results of the researches[11] are consistent.

Research on vitamin D has been inconsistent. The GECOH study carried out by Pilz[12] included 10 PA patients and 182 EH patients and concluded that there was no difference in vitamin D levels between groups. The same conclusion has also been reached in the studies of others [13-16] . However, Petramala et al.[10] concluded that PA patients showed a lower serum 25 (OH) -vitamin D3 level and a higher prevalence of vitamin D deficiency (65% vs 25% and 25%) in their study comparing 73 PA patients with 73 EH patients and 40 healthy subjects. Ismail[17] et al. found that among 17 PA patients, more than half of PA patients (71%) were vitamin D deficient, while only 29% of PA patients had adequate vitamin D levels. According to the existing studies, it is believed that the difference of vitamin D and blood calcium levels may be related to the corresponding compensatory difference of the body in order to maintain the balance of bone metabolism.

Bone turnover markers (BTM) in patients with PA were only mentioned in four studies. Ceccoli et al.[18] showed that compared with 110 patients with essential hypertension, 116 patients with PA had higher carboxy-terminal collagen crosslinks(CTX-1) and lower bone-specific alkaline phosphatase (B-ALP). After follow-up, CTX-I decreased and ALP increased in 40 PA patients treated with drugs or surgery. However, these differences were not statistically significant. Notsu[19] pointed out that there was no significant difference in the level of CTX-1 in 56 PA patients compared with 56 control group. However, in a prospective case-control study conducted by Loh[20] , it was found that compared with 17 EH patients, 18 PA patients had higher levels of bone formation markers intact procollagen I N-terminal propeptide (PINP) and CTX-1, which were significantly reduced after 3 months of treatment, suggesting that early PA patients may have shown increased bone turnover. Adolf[21] showed that 36 postmenopausal women with PA showed only a slight increase in osteocalcin, a bone formation parameter, and no change in tartrate resistant acid phosphatase 5b (TrAP), a bone resorption marker, when compared with 18 matched controls at baseline. After follow-up, B-ALP, osteocalcin, PINP, and TrAP were significantly lower in patients with bilateral PA treated with aldosterone receptor antagonist (MRA), but not in patients with unilateral PA treated with adrenal excision (ADX), consistent with the Loh conclusion. The reason for the heterogeneous results of BTM may be that bone turnover markers can only reflect short-term bone transition state, rather than chronic cumulative loss. It may also be related to the treatment of included PA patients. Studies have pointed out that MRA has a potential osteoprotective effect, and changes in bone turnover markers may be observed if more patients received MRA treatment in the included patients.

1.2. Primary aldosteronism and osteoporosis

Increased aldosterone may increase the prevalence of osteoporosis. Studies have reported conflicting results for BMD values. In 2004, animal studies[22-24] showed decreased bone mineral density (BMD) and cortical bone strength in rats with increased aldosterone compared with control rats, and the adverse effects of excessive aldosterone on bone metabolism were first reported. In 2012, Salcuni et al.[14] proposed that primary aldosteronism was related to osteoporosis for the first time through clinical trials. Compared with 15 nPA patients, 11 PA patients had lower BMD values of lumbar vertebrae, femoral neck and total hip joint, and an increased prevalence of osteoporosis (72.7% vs. 20.0%), lumbar BMD increased significantly after 1 year of treatment. Petramala et al. [10] compared 73 PA patients with 73 EH patients and 40 HS, and the prevalence of osteopenia/osteoporosis in PA subjects (38.5% and 10.5%) was significantly higher than that in EH patients (28% and 4%) and HS (25% and 5%). However, some studies [19, 25] showed no difference in BMD between PA patients and nPA group. Researchers speculated that bone embrittlement caused by excessive aldosterone may be due to bone deterioration, which may involve the deterioration of cancellous bone microstructure. Therefore, trabecular bone score (TBS) was introduced as a parameter representing microstructure. A few studies showed a significant reduction in lumbar TBS in women with PA. Aldosterone concentration was negatively correlated with lumbar TBS in women, and the results were significant after accounting for multivariable and confounding factors, while no such association was found in men. The application of TBS in the correlation between PA and bone metabolism needs more data support or more accurate methods to evaluate bone condition. The results of BMD improvement were consistent. After an average follow-up of 24 months for 40 PA patients treated with drugs or surgery by Ceccoli[18] , BMD of lumbar spine, femoral neck and total hip were significantly improved. Loh[20] also found that lumbar BMD improved after 3 months of follow-up in 18 PA patients.

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1.3. Primary aldosteronism and fracture

Excess aldosterone increases the risk of fracture. Salcuni et al. [14] first reported that the prevalence of vertebral fracture (VF) in PA patients was higher than that in the control group (45.5% vs 13.3%). Notsu[19] showed that the prevalence of VF in 56 PA patients (44.6%) was significantly higher than that in 56 control group (23.2%); Severe fractures occurred more frequently in PA patients than in controls; There was no difference in BMD at any site between PA patients with and without fractures. Yokomoto[26] showed that the prevalence of VF in PA patients (29%, 44/152) was higher than that in nPA patients (12%, 7/58), and the prevalence of VF in unilateral PA (46%, 17/37) was higher than that in bilateral PA (20%, 15/76). There was no significant difference in fracture prevalence with or without osteoporosis. All the above studies used the semi-quantitative Genant method[27] to evaluate morphometric vertebral fractures rather than clinically symptomatic fractures. Although bone mineral density reports are within osteopenic or normal limits, the risk of vertebral fracture is increased, suggesting that aldosterone excess may be a disruption of bone microstructure rather than bone mineral density[28] . Therefore, in patients with PA, it is recommended to evaluate the presence of fracture by X-ray examination, even if they show normal BMD. A longitudinal population database evaluation of clinically symptomatic fractures from the National Health Insurance System[29] showed consistent results, 2533 PA patients having a higher fracture rate at any site than 10132 EH patients(8.8% vs. 4.3%). However, MRA treatment has not been found to be effective in reversing the fracture risk of PA patients, which may be caused by the insufficient effect of MRA due to the increased amount of aldosterone induced by drug therapy. Regarding the change of fracture risk after PA treatment and whether there are differences in fracture risk among patients with different types of PA, it is impossible to draw a unified conclusion in limited studies, which needs the support of multicenter prospective data with large samples.

2. Mechanism of primary aldosteronism affecting bone metabolism

2.1. Secondary hyperparathyroidism

In PA patients, a large amount of aldosterone is autonomic secreted by the adrenal cortical globule, resulting in sodium preservation and potassium excretion, and the amount of extracellular fluid is increased, resulting in decreased reabsorption of Na2+, Ca2 + and Mg2 + in proximal tubules. However, aldosterone can act on the principal cells of distal tubules and collecting ducts to promote reabsorption of Na2+, but less reabsorption of Ca2 + and Mg2 +. At the same time, blood potassium decreased, urine potassium increased, causing metabolic alkalosis, Ca2 + reabsorption also decreased; Finally, the excretion of Mg2 + and Ca2 + in the kidney increases, and the blood Mg2 + and Ca2 + decrease. In order to maintain the balance of calcium in the body, the secretion of PTH increases[30]. In addition, some studies have shown[31] that aldosterone can directly act on MR (halocorticoid receptor) present in parathyroid parenchymal cells and regulate PTH biosynthesis. Increased PTH acts on PTH1R receptors in bone and kidney, promotes bone calcium mobilization and renal tubule reabsorption of calcium, also promotes the conversion of 25(OH)D3 into 1,25(OH)2D3 in kidney, and acts on vitamin D receptors to promote intestinal calcium reabsorption and increase blood calcium concentration[32] . If PA is not detected early and treated in a timely manner, aldosterone continues to be secreted, PTH level increases for a long time, and continues to act on osteocytes, increasing RANKL receptor activator and WNT/β-catenin signaling pathway inhibitor, reducing bone formation and increasing bone resorption, leading to bone loss and bone mass loss，even osteoporosis and fragility fractures[33]。

Studies have shown [34] that hyperparathyroidism also contributes to the maintenance of aldosteronism in patients with primary aldosteronism. Adrenal cortical adenomas and hyperplastic nodules express type 1 PTH receptor[31]，PTH can act on adrenal globular zona cells through its receptor PTH1R and co-stimulate aldosterone biosynthesis with ANG II through the cAMP pathway.

2.2. Raising FGF23

Normal blood phosphorus concentration is the basic prerequisite for normal bone mineralization, and hyperphosphatemia is an important cause of abnormal calcium and phosphorus deposition and calcification. Hypophosphatemia can lead to incomplete bone mineralization, osteoporosis and even pathological fracture. Fibroblast growth factor-23 (FGF23) is a bone-derived phosphate and vitamin D regulatory hormone secreted by osteocytes and osteoblasts. FGF23 reduces phosphate reabsorption in urine by directly downregulating sodium phosphate cotransporter in renal proximal tubular epithelial cells. FGF23 can also inhibit the expression of renal 1α-hydroxylase in proximal tubules, reduce the

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production of active vitamin D, and reduce the absorption of intestinal calcium and phosphorus[35] . Experiments have shown that[36] after aldosterone treatment of UMR106(rat osteosarcoma cells), the expression of FGF23 is significantly increased. The increase of FGF23 promoted by aldosterone is related to SGK1 and NF-κB calcium ion channels, and this effect can be reversed by the halocorticoid receptor antagonist. Clinical studies[37] also found that blood phosphorus decreased and FGF23 increased in PA patients, and FGF23 showed an increasing trend with the increase of aldosterone level.

2.3. Mineralocorticoid receptors

Osteoporosis is the result of the interaction between intrinsic genetic predisposition factors and external environmental factors. Scholars at home and abroad have studied the related genes of osteoporosis, tried to find the direct cause, sought sensitive genetic markers, predicted the risk of osteoporosis, and developed drugs to prevent bone loss and reverse osteoporosis. One of these genome-wide association studies focused on identifying novel candidate genes for osteoporosis [38] showed a strong association between osteoporosis and genes involved in aldosterone signaling in epithelial cells. NR3C2 and PIK3R12 of aldosterone signaling genes have been shown to be involved in bone metabolism, and PRKCH is a new potential candidate gene affecting bone metabolism. NR3C2 encodes a halocorticoid receptor (MR) expressed in osteocytes, osteoblasts and osteoclasts, which promotes osteoblast differentiation after MR activation. PIK3R1 encodes the subunit of phosphatidylinositol kinase 3, which is involved in osteoblast and osteoclast differentiation. PRKCH gene expression in osteoblasts correlates with the differentiation and maturation of bone markers (osteocalcin, bone salivary protein and alkaline phosphatase).

2.4. Boost cortisol production

Studies have shown that the harmful effects of excess aldosterone on bone may be related to the co-secretion of aldosterone and cortisol. In 2017, a study[39] analyzed steroid metabolic components based on mass spectrometry in 174 PA patients and controls, and found that the excretion of cortisol and total glucocorticoid metabolites increased significantly in PA patients, which was at least similar to subclinical Cushing's syndrome. Several parameters indicating adverse metabolic risk in primary hyperaldosteronism, including waist circumference, high-density lipoprotein, and diastolic blood pressure, as well as body mass index and insulin resistance, were associated with glucocorticoid excess but not with halocorticoid output, suggesting that previously unrecognized glucocorticoid excess in primary aldosteronism may be a major determinant of metabolic risk, including bone metabolism. Other studies[34] have shown that PTH receptors and vitamin D receptors in normal adrenal cortex and aldosteronproducing cells can promote cortisol production by upregulating the mRNA expression levels of steroidogenic enzymes (including CYP11B2, CYP17A1 and CYP11B1). Excessive cortisol has adverse effects on bone metabolism, and glucocorticoids can indirectly affect gonadal hormones, neuromuscular system and local bone tissue RAS, and then affect vascular endothelial cells, interfere with bone metabolism, and increase the risk of fracture[40] . It can also directly increase the expression of nuclear factor-κB ligand RANKL receptor activator, increase the number of bone resorptive osteoclasts, reduce the recruitment of osteoblasts, accelerate the apoptosis of osteoblasts, stimulate the apoptosis of osteocytes, and the imbalance of bone formation and resorption leads to osteoporosis [41].

2.5. Oxidative stress

Reactive oxygen species (ROS) are small molecules derived from oxygen through mitochondrial electron transport mechanism. Regulated ROS regulate cell proliferation, differentiation, survival and apoptosis through important signaling pathways. During oxidative stress, the production of reactive oxygen species exceeds that of the antioxidant system, inhibiting WNT/β-catenin signaling pathway leads to the decrease of osteoblast activity and number, inducing the increase of RANKL expression in osteoclasts and promoting osteoclast differentiation cytokine TNF-α. Activation of MAPKs/NF-κB/NLRP3 signaling pathway can promote osteoclast formation and increase osteoclast activity[42], and reduce bone mineral density. Studies have found that[43-45] rats with increased aldosterone have increased urinary calcium and magnesium excretion, decreased ionized calcium and magnesium in blood, and stimulated PTH secretion. Elevated circulating PTH promotes excessive intracellular calcium accumulation, and calcium ions directly enter mitochondria through endoplasmic reticulum and induce oxidative stress in PBMC (lymphocytes and monocytes) through NADPH oxidase. The formation of superoxide, which overwhelms antioxidant defenses and leads to oxidative stress; Plasma α1 antiprotease activity, which is inversely related to oxidative stress, decreased.

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3. Discussion and outlook

Excessive aldosterone can increase urinary calcium, increase PTH, and increase the prevalence of osteoporosis and fracture. Excessive aldosterone may regulate bone metabolism by upregulating the level of FGF23, acting on MR receptors on the surface of osteocytes and co-secreting with cortisol, leading to oxidative stress and secondary hyperparathyroidism. PA may be one of the causes of secondary osteoporosis. Secondary osteoporosis is reversible, and only treatment can delay the progression of the disease to the greatest extent, reduce the occurrence of fractures, and improve the quality of life. Therefore, it is necessary to look for the presence of PA in the face of unexplained osteoporosis combined with hypertension in clinical work. But less relevant research at home and abroad, the existing research is also more attention to the aldosterone excess of electrolyte and the effect of PTH, in the majority with cross-sectional study, the pathogenesis is still unclear, so still need to be more rigorous experimental design and larger sample size of prospective clinical study further defined the relationship between them and possible mechanism of effect.

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