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Potential of renin-angiotensin system inhibition to improve metabolic bone disorders

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ABSTRACT

Metabolic bone disorder is an abnormality of bones indicated by reduced bone mass and high risk of fractures. Several lines of evidence have demonstrated that the local bone tissue renin-angiotensin system (RAS) is directly involved in bone metabolism and influences the bone health. This review aimed to assess the role of RAS in bone metabolism and comparative effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in reducing the bone fractures. In summary, the clinical trials, in vivo studies, and functional - pharmacological experiments suggested that the RAS regulates bone marrow metabolism and influences the bone health. Hence, it warrants further investigation on the role of ACEIs and ARBs in reducing risk fractures.

Implication for health policy/practice/research/medical education:
Several studies have demonstrated that the local bone tissue renin-angiotensin system (RAS) is directly involved in bone metabolism and influences the bone health.

Introduction

Metabolic bone disorder (MBD) is an abnormality of bones characterized by the reduced bone mass and high risk of fractures (1). MBD is the most common endocrine dysfunction after diabetes and thyroid disease. The common MBD includes osteoporosis, osteomalacia, fluorosis, and primary hyperparathyroidism, while the rare MBDs include Paget's disease, tumor-induced osteomalacia, fibrous dysplasia, and osteogenesis imperfect (2). MBD is usually caused by abnormalities in minerals such as calcium and phosphorus and hormones interfering with mineral metabolism such as parathyroid hormone (PTH) and vitamin D (1). Recent studies demonstrated that the bone tissue renin-angiotensin system (RAS) is directly involved in bone metabolism (3). The RAS is an endocrine system that controls blood pressure, blood volume, and fluid balance. The dysfunction of RAS system induces various disorders such as hypertension,

nephropathy, preeclampsia, polycystic ovary syndrome, and kidney allograft dysfunction (4). The elements of RAS include angiotensinogen (AGT), renin, angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and the angiotensin II receptor 1 (AT1) and angiotensin II receptor 2 (AT2). The RAS include three main components such as renin, angiotensin, and aldosterone. Angiotensin II as the major biologically dynamic hormone which is created by the successive cleavage of peptides derived from AGT. AGT is synthesized and secreted from the liver and converted to angiotensin I (Ang I) by renin that released from the juxtaglomerular cells of the kidney. Then, Ang I is effectively activated to Ang II by angiotensin-converting enzyme (ACE), which predominantly exists in high levels on the endothelial cells' surface within the pneumonic circulation (3,4).

As the best dynamic component of the RAS, Ang II can act on certain receptors. The RAS blockade may

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protect organs through inhibiting ACE and blocking the angiotensin II receptor. The beneficial effects of RAS-inhibiting drugs, on the quality of bone have been documented in some studies. RAS inhibitors such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are examined more closely to evaluate the possible role on bone quality and metabolism in diabetes-related bone disorders. Some studies have investigated the beneficial effects of these drugs on expanding bone mass and reducing bone fractures (1,5). This review evaluated the viability of the dual blockade of the RAS to prevent MBDs.

Method of the study

Relevant articles published during 2005 – 2019 were searched in Medline, OVID, Embase, and the Cochrane Central Register of Controlled Trials databases. The following search terms such as "Metabolic bone disorder, renin-angiotensin system, and dual blockade", were used to retrieve articles published on the topic.

Osteoblasts and adiponectin

Adiponectin is a hormone secreted exclusively from adipocytes. Adiponectin receptors, AdipoR2 and AdipoR1 have been detected in human osteoblasts. In vitro, adiponectin promotes osteoblast proliferation and resulted in an increase of alkaline phosphatase (ALP) activity, osteocalcin, type I collagen production, and mineralized matrix. Adiponectin induces human osteoblast proliferation and differentiation respectively through AdipoR/JNK and AdipoR/p38 pathways. Further, adiponectin is known to induce bone morphogenic protein (BMP)-2 expression in osteoblastic cells (6,7).

Relationship between RAS cascade and bone metabolism

Bone is exceedingly vascularized connective tissue. Skeletal vasculature plays a considerable role in bone improvement, recovery, and remodeling. Several lines of evidence demonstrated the presence of RAS components in the bone marrow microenvironment. The effect of RAS on bone digestion system can be related to the control of blood flow (1). Hagiwara et al indicated the impact of Ang II on the separation of rodent calvarial osteoblastic cells and found the diminishing impact of Ang II on the regulation of calcium in cells and the network layer (8).

Circulatory system of RAS

Although a variety of signaling factors is involved in bone metabolism and homeostasis, the cyclic adenosine monophosphate (cAMP) serves as the key intracellular signaling factor (9). Increased levels of cAMP were found in plasma and urine samples of osteoporotic and hypertensive patients (10). This abnormal cAMP signaling pathway may aggravate hypertension-related osteoporosis. Angiotensin II can increase intracellular cAMP. Further, increased downstream signaling pathway induces the metabolism of low-density lipoprotein by increasing intracellular cAMP, controlling homocysteine and nitrous oxide (N2O), and altering core binding factor α1 (Cbfa1) expression (11). Studies using Tsukuba hypertensive mouse that expressing both the human renin and human AGT genes, showed that the activation of RAS induces high turnover osteoporosis with accelerated bone resorption. Furthermore, Ang II may regulate calcium metabolism by decreasing ionized calcium and increasing PTH levels (1,12).

Local tissue RAS

In addition to circulating components of the RAS, tissue-specific RAS has been identified in numerous tissues such as fat tissue, bone marrow, heart, blood vessels and kidney. The tissue-specific RAS plays a major role in mediating inflammation, angiogenesis, cell proliferation, and apoptotic cell death (13). Local bone marrow RAS plays a major role in the growth and differentiation of hematopoietic cells (1,14). Studies of knockout mice mutant for ACE and other RAS components have further implicated a regulatory role for the RAS in hematopoiesis (15). Presence of increased expression of renin and AGT in bone samples of the aged mice indicates that angiotensin II plays a major role in the pathogenesis of age-related osteoporosis (16). Therefore, angiotensin II may affect its receptors on osteoprogenitor bone cells through RAS, thereby guiding the separation of osteoclasts and influences bone metabolism.

Dual RAS blockade

The concept of the dual blockade of the RAS began through the synergistic lowering impact of angiotensin II by the co-administration of ACEIs and ARBs (17). Ang II signals through AT1R and AT2R receptors and their expression were found in cultured osteoblasts and osteoclasts. Further, the expression of renin and ACE in bone cells was also documented. Pharmacological blockade of Ang II by losartan (AT1R inhibitor) can positively influence bone metabolism and growth. In addition, it has been indicated that Ang II could accelerate osteoclastic functions by activating the receptor activator of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) ligand (RANKL). Several sources confirm that activation of skeletal RAS plays an important role in bone metabolic disorders. Thus, some therapeutic approaches may be provided through the RAS inhibition to prevent bone loss by adjusting the balance of Ang II (18). Overall, the available evidence strongly suggested that the local RAS in bone is more closely associated with bone metabolism and bone metabolic disorders (19). In this regard, a study by Izu et al reported that the AT2R blockade causes an increase in the bone mass of adult mice. In addition, the AT2 knock-out mice enhanced the bone mass in adult

mice. Furthermore, in vivo studies demonstrated that the AT2 receptor was implicated in the basal suppression of osteoblastic activity. Similarly, the AT2 receptor blockade also suppresses bone resorption in vivo. Observations on the presence of the renin, ACE and AT2R in the bone microenvironment revealed that local RAS regulates the bone and angiotensin functions through the AT2 receptor (19).

However, recent studies regarding the effects of ARBs on bone function in humans and animals have indicated conflicting results since the administration of ARBs has generally no significant impact on bone loss among older men. Likewise, ARBs fail to cause significant changes in the bone properties of rats, diabetic mice, ovariectomized rats, or orchiectomized rats (20). Clinical studies recommend that ACEIs may lower bone fractures. Studies in hypertensive rat model suggested that the ACEIs attenuated osteoporosis through inhibition of RAS, not nitric oxide. In addition, ACEIs are in use for the treatment of hypertension, cardiac failure, and diabetic nephropathy (21). In addition, most of the clinical studies have illustrated that the patients treated with ACEIs have an appropriate bone mineral density (BMD) and low fracture risk.

Angiotensin receptor blockers and osteoporosis

In the USA, ARBs are prescribed only when a patient is not tolerated with the ACEIs. As a result the number of patients who used ARB are limited as well as restricted human studies about ABR and BMD or fracture risk in the literature (22). A cohort study on Medicare patients receiving single-drug treatment for anti-hypertension treatment suggested the progressively defensive impact of ARBs on relative fracture risk over time. Primary osteoblasts cultured with different doses of captopril demonstrated that captopril dose-dependently decreased ACE and increased the ALP level and expression of collagen I (23). These studies suggested that the RAS-inhibiting drugs including ACEIs, ARBs, and renin inhibitors, have beneficial effects on osteoporosis. However, further studies are warranted to elucidate the underlying mechanisms of these drugs. It is important to note that the use of routine anti-hypertension doses of ACEIs in osteoporosis models may not be effective to prevent the bone loss and hence higher dose should be used for the treatment of osteoporosis (24). Moreover, existing knowledge is entirely derived based on observational studies or trials conducted with small sample sizes and surrogate measures of bone turnover. Hence, it is recommended to perform further studies for better understanding of the relationship between osteoporosis and RAS-inhibiting drugs.

RAS inhibition to bone metabolic disorders

Studies in chimeric RAS model of transgenic mice showed that the high bone turnover is responsible for the advancement of osteoporosis. In these mice, silencing of the AT2 and AT1 receptors demonstrated the antagonistic effects on Ang-II activity of these receptors on the cell surface. Further, gene expression analysis suggests that the osteoblasts express AT1 and AT2 receptors, while bone marrow macrophages and pre-osteoclasts showed low-expression of AT1 receptors only (14). The other bone cell functions of Ang-II include inhibition of osteoblastic differentiation, collagen synthesis in osteoblasts and resorption of bone matrix by the osteoclasts (25). Although Ang-II had no impact on osteoclast arrangement or bone resorption through confined osteoclasts; however, co-cultures of osteoclasts with calvarial or MC3T3-E1 osteoblastic cells improved bone resorption (25). The interaction between AT1 and AT2 receptors was also observed in vivo pharmacological tests. Losartan treatment exacerbates osteoporosis despite an improvement of hypertension, which restricts the Ang-II union with a Pro-inhibitor that is required to correct the osteoporotic phenotype. Apparently, losartan can recover the muscles of myopathy mice by blocking transforming growth factor beta signaling in skeletal muscles (26).

There are three important steps in the RAS pathway that can regulate the primary and rate-limiting steps of RAS. Renin, and renin inhibitors that mediate the transformation of AGT to Ang I, can have a great potential in diminishing Ang-II activities on the bone. Aliskiren is a non-peptide renin inhibitor that binds to the active site of renin and inhibits the binding of renin to AGT (27). Ang-II stimulates the binding of DNA and collagen and reduces the activity of soluble phosphatase in bone cell of fetal rat periosteum and mature bone cells acquired from the human trabecular bone (27). In osteoclasts co-cultures with osteoblastic cells, Ang-II restores bone resorption, which can be inhibited by using ACEIs. In transgenic mouse models overproducing human renin and AGT or implantation of Ang-II in ovariectomized rats, overexpression of RAS causes osteoporosis (1, 14). In general, Ang II stimulates osteoporosis by osteoclasts via receptor activator NF-κB ligand (RANKL) induction. Ang II blockade may become a novel therapeutic approach to attenuate osteoporosis in hypertensive patients. Izu et al investigated the effect of AT2 receptor blockers on bone mass and found that AT2 receptor blockers improved bone mass by improving both osteoblastic movements and suppression of osteoclastic activity (28). Studies on the autonomic effects of ARBs on bone deformity in the elderly, showed that the use of pro inhibitors other than ARBs increased bone loss in the elderly. The other metabolic effects of the antihypertensive drug telmisartan, has been attributed to its action as an Ang-II receptor inhibitor and partial peroxisome proliferator-activated receptor γ (PPARγ) agonist. PPARγ plays a critical role in energy homeostasis and metabolic function (29). In addition, hormones and cytokines that affect both bone absorption and deposition

regulate the bone digestion system. Further, it is hypothesized that, in the osteoblast/osteoclast co-culture system, Ang II receptors through the signals and cellular communication regulate the bone metabolism. Sub-analysis of a clinical study indicated that the osteoporosis fracture risk was reduced by the RAS inhibitors (30). In order to achieve a more successful blockade of the RAS, a combination of diverse classes of drugs can be used. This regard, aliskiren is a successful candidate drug that can control the dynamic renin and downstream components of the RAS in both subjects of with and without hypertension (27).

ACE inhibitors
ACE is the key enzyme involved in the conversion of inactive Ang I to active Ang II. ACE is distributed all over the body in membrane-bound, and soluble forms. The soluble form is derived from the membrane-bound form through the action of ACE secretase (31). Numerous researchers have illustrated that ACE acts as an endopeptidase on other substrates, such as substance P and the luteinizing-hormone-releasing hormone (31). Ang (1–12) also could be a substrate of ACE and has been identified as a propeptide of the RAS in plasma and tissues (31). Several lines of evidence revealed that the association of the ACE inhibitor with beneficial changes in bone mass, suggesting the possible detrimental effect of Ang II on the bone (32). However, some of the recent studies did not show the protective effect of ACE inhibitor (33). Comparison of high-risk fracture patients using ACEIS and ARBs with the patients without using these drugs indicated a significant difference in BMD. A subsequent study reported an increase in BMD in patients treated with ACE inhibitors while reducing the risk of fractures (34). In this regard, direct renin inhibitor, in contrast to ACEIs and ARBs, significantly reduces plasma renin activity by reducing renin synthesis by Ang-II.

Angiotensin II receptor blockers
Since ARBs exhibit effects that are similar to those of ACEIs, they often are used as alternatives in patients that are not tolerated by ACEIs. However, ACEIs and ARBs have different effects on angiotensin II and hence their effect on ACE2 levels and function may be different (35). The ARBs may offer more total angiotensin II inhibition by selective association with the site of the receptor. These drugs block the activation of the AT1 receptor and attenuate the adverse events of RAS activation on bone metabolism. Hence, ARBs will reduce the detrimental effects of Ang-II on the bone tissue and the direct effects of the receptor on bone metabolism. Several unique cohorts reported the association of ACEIs and/or ARBs with the risk of fractures. However, there was no evidence on the association of ACEIs or ARB use with the risk of fractures. Additionally, there is no significant association

between diuretic use or β-blocker use with the risk of fractures was noted. Some meta-analysis also revealed no association of the ACEIs or ARBs use with the risk of composite fractures. Nevertheless, summary of two large meta-analyses revealed that the ACEIs and ARBs use is associated with the reduced risk of hip fractures. A recent meta-analysis found that the association of ACEIs and ARBs use with the bone fractures remains inconsistent (35).

Conclusion
In summary, reviewing the above-mentioned topics and evaluating the clinical trials, in vivo studies, and functional - pharmacological experiments suggested that the RAS regulates bone marrow metabolism and influences the bone health. *Further investigations* warranted on the role of ACEIs and ARBs in reducing risk fractures.

Authors' contribution
MM was the principal investigator of the study. MM and MK were included in preparing the concept and design. MM and BVKSL revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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