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Review

The skeletal renin-angiotensin system: A potential therapeutic target for the treatment of osteoarticular diseases

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ABSTRACT

The classical renin-angiotensin system (RAS) is known to be a key regulator of blood pressure as well as fluid and electrolyte homeostasis. Additionally, it is now evident that components of the RAS are produced and act locally in many tissues, including liver, kidney, heart, lung, eye, bone, reproductive organ, adipose, and adrenal tissue, and these components are collectively known as tissue RAS. Recently, several studies have shown that local bone RAS is directly involved in bone metabolism, and activation of skeletal RAS plays an important role in bone diseases, such as osteoporosis, arthritis, and deterioration as well as in fracture healing. Based on the identification of RAS components in bone, we examined a new therapeutic approach to attenuate bone diseases through RAS inhibitors: renin inhibitor, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. In this paper, we provide a systematic review of the skeletal RAS in the pathophysiology of bone diseases and the beneficial effect of RAS inhibitors on bone tissue.

1. Introduction

The renin-angiotensin system (RAS) is known as a circulating endocrine system that has powerful effects on blood pressure and sodium homeostasis [1]. In general, the RAS consists of angiotensin II (AngII), angiotensin-converting enzyme (ACE), the angiotensin receptor, ACE structural homolog ACE2, angiotensin-(1–7) peptide, and Mas receptor. Renin produced by the kidney cleaves liver-produced angiotensinogen to produce angiotensin I, which is further cleaved by ACE to generate Ang II (Fig. 1). As the major biologically active hormone generated by this system, Ang II binds to specific receptors, triggering a broad range of biological actions impacting virtually every system in the body including the brain, heart, kidney, vasculature, and immune system [2]. The primary role of the RAS is to control blood pressure and fluid balance within the body. However, abnormal activation of the RAS is a major risk factor for cardiovascular disease [3], renal disease [4], and liver disease [5]. Consequently, ACE inhibitors (ACEIs) and angiotensin type 1 receptor blockers (ARBs) have proven extremely effective and are widely used for the treatment of hypertension, heart failure, and kidney disease [6–9]. Moreover, an increasing number of small prospective human studies have demonstrated beneficial effects of ACEIs or ARBs in the treatment of hepatic fibrosis [10–13].

In addition to the systemic RAS, there is now evidence that components of the RAS are produced and act locally in many tissues (e.g., liver, kidney, heart, lung, eye, bone, reproductive organ, adipose, and adrenal tissue) [14,15], and these components are collectively known as tissue RAS. It has been revealed that the local tissue RAS plays a pivotal role in bone metabolism that is independent of the systemic RAS, and has been shown to regulate regeneration, cell growth, apoptosis, inflammation, and angiogenesis [16]. In this study, we explore recent findings pertaining to the involvement of the skeletal RAS in bone metabolism and the progression of bone metabolism and diseases. We also elaborate on how pharmacological interventions aimed at modulating the RAS may be therapeutically useful in osteoarticular diseases.

2. Local RAS in skeletal physiology

The RAS influences bone density and microenvironments, and the link between the RAS and bone structure and metabolism has recently received greater attention. In 1997, Hatton et al. [17] demonstrated that bone might contain a tissue RAS that is likely to play a role in the regulation of bone resorption. The major proteins and receptors of the RAS are expressed locally within bone tissue and significantly regulate bone remodeling and metabolism [18] (Table 1). Angiotensin type 1 and 2 receptors (AT1R and AT2R) are expressed in cultured osteoblasts and osteoclasts [18]. Furthermore, renin and ACE have been shown to be expressed in bone cells in vivo [18]. It is well known that Ang II

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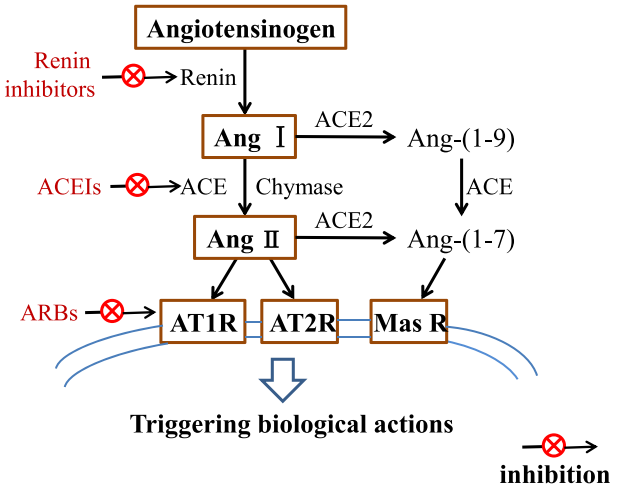

Fig. 1. The classical renin angiotensin system (RAS) and its inhibitors. Abbreviations: Ang I, angiotensin I; Ang II, angiotensin II; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme type 2; AT1R, angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; ACEIs, angiotensin-converting enzyme inhibitors; ARB, Ang II type 1 receptor blocker; Ang (1–9), angiotensin (1–9); Ang (1–7), angiotensin (1–7); Mas R, Mas receptor.

Table 1
Distribution of RAS components in bone cells and tissues in different species. Abbreviations: RAS, renin-angiotensin system; AT1R, angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; ACE, angiotensin-converting enzyme; Ang I, angiotensin I; Ang II, angiotensin II.

RAS components	Localization	Species	Years	References
Renin/AT1R/ AT2R/ACE	Osteoblasts/osteoclasts	Mouse	2009	[18]
Renin	Bone marrow cells	Mouse	2009	[18]
AT1R	Chondrocytes	Human	2012	[23]
AT1R	Fibroblast-like synoviocytes	Human	2007	[22]
Ang I/Ang II/AT1R	Synovium	Rat	2007	[58]
AT1R/ACE	Osteoblasts, osteoclasts, and bone marrow cells	Rabbit	2014	[30,101]

mediates biological responses through AT1R and AT2R; however, its main described effects are AT1R mediated [19]. In line with this hypothesis, a study found that Ang II stimulates the proliferation of osteoblast-rich populations of cells in calvariae through AT1R [20]. Hagiwara et al. [21] showed that Ang II suppressed osteoblastic cell differentiation and bone formation by binding specifically to AT1R. The expression of AT1R was also found in fibroblast-like synoviocytes and chondrocytes [22,23]. These findings suggest that Ang II may exert a direct effect on every kind of cell in bone tissue. According to a study by Schurman et al., Ang II may decrease calcium uptake in bone, as demonstrated using a bone disc bioassay system [24]. In addition, it was reported that blockade of AT1R by losartan positively influenced bone metabolism and structure [25]. Ang II was also shown to accelerate osteoclastic functions, which are mediated through the activation of receptor activator of NF-κB ligand (RANKL) [15]. Recently, it has been documented that activation of the skeletal RAS may cause bone metabolic disorders [26]. Thus, adjusting the counterbalance of Ang II in bones might be a valuable therapeutic approach to prevent bone loss [25]. Altogether, these results suggest that a local RAS exists in bone that is closely associated with bone metabolism [15] and bone metabolic disorders [27].

3. Skeletal RAS activation in bone diseases

3.1. Osteoporosis

3.1.1. RAS role in osteoporosis

The relationship between the RAS and bone health, structure, and metabolism has been established and has received increasing attention lately, with a variety of studies examining the role of various RAS components in bone density and fracture risk [26]. Functional studies have revealed that activation of RAS (angiotensinogen, renin and Ang II) induces osteoporosis through the acceleration of bone resorption [28] (Table 2). The local RAS (angiotensinogen, renin and Ang II) in bone was found to participate in age-related osteoporosis of aging mice [29]. Also, the RAS was reported to be involved in the development of glucocorticoid-induced osteoporotic rabbits [30] (see also Table 2). Strikingly, studies have shown that, in addition to causing osteoporosis, RAS activation reduces blood ionized calcium levels [28,31]. The RAS was also shown to be related to bone mineral density (BMD) in glucocorticoid-induced osteoporotic patients, suggesting that a local RAS might influence RANKL/Osteoprotegerin signaling to modulate bone metabolism [32]. As a key active peptide in RAS, Ang II increases the activity of osteoclasts and accelerates osteoporosis in ovariectomized rats [15]. Ex vivo cultures showed that Ang II acts on osteoblasts but not directly on osteoclast precursor cells, while up regulating osteoclastogenesis-supporting cytokines, such as RANKL and vascular endothelial growth factor, thereby promoting the formation of osteoclasts [15,28,33]. A previous study using an AT1a receptor-deficient mouse model demonstrated that the AT1a receptor negatively regulates bone turnover and bone mass [33]. Accordingly, the effect of Ang II on osteoblasts and osteoclasts is becoming uncovered. It should be noted that infusion of Ang II acutely raises circulating parathyroid hormone (PTH) [31,34]. PTH is a negative regulator of osteoblast function but a positive regulator of osteoclast function, which in turn reduces bone formation and increases bone resorption, respectively [35,36]. It is well documented that Ang II and PTH have prominent roles in inducing osteoclastogenesis [37,38]. Therefore, activated RAS and excess PTH have been associated with adverse clinical outcomes in skeletal diseases such as osteoporosis as well as bone fractures. However, additional studies are needed to explore in more depth the possibility of a clinically meaningful interplay between the RAS and PTH in bone diseases.

Table 2
Summary of studies that have investigated the importance of the RAS in bone diseases. Abbreviations: RAS, renin-angiotensin system; GIOP, glucocorticoid-induced osteoporosis; RA, rheumatoid arthritis; AT1R, angiotensin type 1 receptor.

Clinical setting	Years	Species	Main finding	References
Osteoporosis	2008	Rat	Ang II directly accelerates estrogen-deficiency-induced osteoporosis independently of blood pressure	[15]
Osteoporosis	2009	Mouse	Activation of RAS induces osteoporosis independently of hypertension	[28]
Osteoporosis	2014	Mouse	RAS plays an important role in the pathology of age-related osteoporosis	[29]
Osteoporosis	2014	Rabbit	Local RAS is involved in GIOP	[30]
Osteoporosis	2015	Human	Local RAS is associated with bone mineral density of GIOP patients	[32]
RA	2007	Rat	Targeting the AT1Rs have significant therapeutic potential in experimental arthritis	[58]
RA	2010	Rat	RAS activation is involved in vascular damage in a model of RA	[68]
Femur fracture	2010	Mouse	Local RAS in bone influences the process of fracture healing	[96]
Renal osteodystrophy	2012	Mouse	The local RAS in bone is involved in bone deterioration of mice with obstructive nephropathy	[102]
Osteonecrosis	2014	Rabbit	Osteonecrosis is strongly associated with the activation of the local bone RAS	[101]

Table 3
Previously reported effects of RAS inhibitors on bone diseases. Abbreviations: RAS, renin-angiotensin system; ACEI, ACE inhibitor; BMD, bone mineral density; ARB, Ang II type 1 receptor blocker; TRAP, tartrate-resistant acid phosphatase; OVX, ovariectomy; OP, osteoporosis; AT2R, Ang II type 2 receptor; GIOP, glucocorticoid-induced osteoporosis.

Drug class	Drug	Reported pharmacological effects	References
ACEI	Quinapril/enalapril	Reduce BMD loss, increase calcium and vitamin D levels in hypertensive subjects	[45]
ACEI	Imidapril	Increase bone density and decrease TRAP activity and urinary deoxypyridinoline in OVX-induced OP in rat	[42]
ACEI	Perindopril	Increase bone formation rate and serum osteocalcin in GIOP in rabbit	[30]
ACEI	Captopril	Improve lumbar vertebral bone strength in aged OVX rats	[52]
ARB	Olmesartan	Increase bone density and decrease TRAP activity and urinary deoxypyridinoline in OVX-induced OP in rat	[15]
ARB	Losartan	Increase strength, mass and trabecular connections of ovariectomized rat femurs	[47]
ARB	Telmisartan	Reduce BMD loss in OVX-induced OP in mice	[48]
ARB	Losartan	Improve bone strength at the material level in diabetic rat	[49]
AT2R blocker	PD123319	Increase bone mass in adult mice	[18]
Renin inhibitor	Aliskiren	Increase bone mass and improved trabecular bone structure in OVX-induced OP mice	[50,51]
ACEI	Ramipril/captopril	Exert anti-inflammatory effect in rats with adjuvant arthritis	[88,89]
ACEI	Quinapril	Exert anti-inflammatory effect in mice with collagen-induced arthritis	[90]
ACEI	Ramipril	Exert the effect of immunomodulatory, anti-inflammatory and antioxidant potentials in adjuvant arthritis in rats	[91]
ARB	Losartan	Reduce knee joint swelling in rats with adjuvant monarthritis	[58]
ARB	Olmesartan	Suppress immune responses and the development of severe arthritis and joint destruction in mice with collagen-induced arthritis	[92]
ARB	Losartan	Exert anti-inflammatory actions and improved joint function in antigen-induced arthritis mice and adjuvant arthritis rats	[93]
ARB	Losartan	Increase the efficacy of methotrexate therapy in adjuvant arthritis rats	[94]
ARB	Losartan	Upregulate AT2R in adjuvant-induced arthritis rats	[95]
ACEI	Perindopril	Accelerate bone healing and remodeling in mice femur fracture model or ovariectomized rats	[96,97]
ACEI	Enalapril	Promotion of fracture repair in rat fracture model	[98]
ACEI/ARB	Enalapril/losartan	Slow the thinning of bone trabeculae and increased quality of fractures healing in OVX rats	[100]

3.1.2. Therapeutic potential of RAS inhibition for osteoporosis

The systemic RAS has shown therapeutic value as a target of anti-hypertensive medications including ACEIs and ARBs [39]. Currently, besides their application in the prevention and treatment of hypertension, RAS inhibitors, such as ACEIs, ARBs, and renin inhibitors (Fig. 1), are widely used clinically to treat tissue injury due to locally high RAS activity, as associated with renal and cardiovascular disease [40]. More recently, RAS-inhibiting drugs have been confirmed to have beneficial effects on bone tissue [41] (see also Table 3). Pharmacological results demonstrate that inhibiting local skeletal RAS activity could prevent bone loss in animals [15,18,28,42]. Meanwhile, several clinical studies on the general population suggested that ARB/ACEI decrease the risk of bone fracture. To control blood pressure and preserve cardiac function, ACEIs and ARBs are used widely in patients with chronic kidney disease. Treatment with ACEI/ARB was associated with a lower rate of hospitalization due to fracture in hemodialysis patients with secondary hyperparathyroidism [43]. Hypertension and osteoporosis are two major chronic diseases affecting the elderly. ACEI use has been associated with higher femoral neck BMD in older women, and higher femoral neck, total hip, and lumbar spine BMD in older men [44]. Thus, ACEIs may be beneficial to elderly people who are at risk not only for hypertension but also osteoporosis [44]. ACEIs also have a beneficial effect on BMD and changes in calcium metabolism in hypertensive subjects [45]. In fracture patients, treatment with ACEI was associated with a 7% reduction in risk of any fracture and a 14% reduction in risk of hip fracture [46]. Subsequent experimental studies further confirmed the beneficial effects of ACEI and ARB on maintenance of bone health in ovariectomized rat [15,42,47] and mouse models [18,48], which were established to reduce circulating estrogen levels. Additionally, perindopril remarkably blocked the activation of local RAS and partially reversed glucocorticoid-induced osteoporosis in rabbits [30]. It was recently reported that losartan has a therapeutic effect on the physicochemical properties of diabetic bone, resulting in improvement of bone strength at the material level [49]. Moreover, the renin inhibitor aliskiren markedly increased bone mass and improved trabecular bone structure in ovariectomy-induced osteoporotic mice, suggesting its potential role in treating postmenopausal osteoporosis [50,51]. A study by Liu et al. [52] demonstrated that captopril dose-dependently increased secretion of alkaline phosphatase and the expression of collagen I mRNA in rat osteoblasts in vitro. Therefore, ACEIs, ARBs, and renin inhibitors, three ideal RAS-inhibiting drugs, have been suggested to have beneficial effects on osteoporosis (see Table 3). Further work is required to elucidate the mechanisms underlying this apparent advantage. However, the routine anti-hypertension dosage of ACEIs may not have influence on bone loss in osteoporosis models, so higher-dose ACEIs should be used for patients with osteoporosis [52]. In addition, all of current researches are based almost entirely on observational studies or a handful of trials with surrogate measures of bone turnover [53], and focused mostly on animal models. So, these findings need much more support from clinical studies in the future. At the same time, more basic and translation work needs to be done to better understand the links between cardiovascular disease (in particular hypertension) and osteoporosis.

3.2. Arthritis

3.2.1. RAS role in arthritis

In previous studies, it was found that plasma renin activity was substantially elevated in patients with rheumatoid arthritis (RA) [54,55] and osteoarthritis [56], which may reflect RAS activation. Researchers have also identified the presence and upregulation of AT1R in the synovium of patients with RA [57,58] (see also Table 1), suggesting that this receptor may participate in chronic inflammatory joint diseases. Likewise, Kawakami et al. [23] found that AT1R and AT2R are expressed in articular chondrocytes in RA patients and are regulated by IL-1. Previous reports have also demonstrated that ACE activity in synovial fluid was increased in patients with arthritis [59–61], and that ACE was increased in the pleural fluid of patients with RA [62]. In addition, the RAS and its primary mediator Ang II have a direct influence on the progression of the arthritic process through inflaming synovial vasculature and inflammation. Several studies demonstrated that Ang II has effects on synovial fibroblasts and synovial vasculature, and stimulates synovial angiogenesis via autocrine and paracrine mechanisms [59,63–66]. Furthermore, higher AngI/II protein content was found in inflamed synovium [58] (see also Table 1). Recently, it is reported that the Ang II concentration in plasma of rats with adjuvant-induced arthritis (AIA) was obviously elevated, and the densities of both AT1R and AT2R were also increased in the heart and kidney of these rats [67]. Moreover, the expression of AT1R and ACE was significantly increased in the vasculature of AIA rats, suggesting that local

activation of the RAS in the vasculature plays a critical role in the AIA model [68]. Olmesartan, an ARB, but not hydralazine, attenuated the hypertrophic differentiation of chondrocytes induced by Ang II, suggesting that the effect of Ang II on chondrocytes was independent of blood pressure [69]. Thus, the above-mentioned reports regarding the functions of the local synovial RAS in RA could offer alternative therapeutic approaches [70].

3.2.2. Therapeutic potential of RAS inhibition for arthritis

3.2.2.1. Human studies. In 1984, Martin et al. reported in a small open study that captopril, a thiol-containing ACEI, improved arthritis symptoms, clinical scores, plasma viscosity, and the C-reactive protein (CRP) level in patients with active RA [71]. However, the clinical benefit of captopril was subsequently attributed not to ACEIs per se but to the presence of a thiol group in the molecule, which is similar to that in the immunosuppressant penicillamine [72]. Although previous studies have failed to demonstrate beneficial therapeutic effects of non-thiol ACEIs in RA [72], this outcome could be merely insufficient to inhibit RAS in the local synovial microenvironment. Like patients with cardiovascular risk factors, RA patients are also characterized by impaired endothelial function compared with normal subjects [73–77]. Since RA patients have premature atherosclerosis and a life expectancy that is reduced up to 10 years due to cardiovascular comorbidities [78], any additional gain in maintaining endothelial integrity may indicate the potential of a therapeutic intervention such as ACEI or ARB in patients with RA [79,80]. It was previously reported that ACEI with 10 mg/day ramipril for 8 weeks of prevalent anti-inflammatory treatment markedly improved endothelial function in patients with RA [80]. Likewise, simvastatin 20 mg daily improves endothelial function in patients with RA through lowering CRP and TNF-α concentrations [79]. In fact, the precise etiology of RA remains unclear. However, it is known that inflammatory processes are involved in the pathogenesis of RA [81] and drive RA partly through upregulating complex cytokine networks [82]. Studies have shown that Ang II induces inflammation through AT1R and that losartan decreases the expression of pro-inflammatory cytokines [83–86] that may contribute to the pathogenesis of RA [58]. In vitro, losartan suppressed TNF-α production from inflamed human synovium in RA patients in a dose-dependent manner [58]. A similar study showed that the use of losartan was associated with reductions in CRP and erythrocyte sedimentation rate in patients with RA [87]. These studies suggest that tissue-specific ACEIs or ARBs would be beneficial for the clinical treatment of RA. Further research should focus on clinical trials to assess the side effects of RAS inhibitors for arthritis.

3.2.2.2. Animal model studies. Consistent with human studies showing that blocking the RAS has therapeutic benefit for arthritis, several animal studies have revealed the beneficial effects of ACEIs and ARBs used in animal models of arthritis (see Table 3). Caspritz et al. demonstrated that ramipril confers potent anti-inflammatory effects by ameliorating the severity of AIA [88]. In addition, captopril has been shown to be beneficial in arthritis via its anti-inflammatory properties [89]. It has been suggested that quinapril has significant anti-inflammatory properties, sufficient to suppress the severity of collagen-induced arthritis (CIA) [90]. Recently, it was reported that ramipril use may represent a promising protective strategy against RA, and its effects are largely due to its immunomodulatory, anti-inflammatory, and antioxidant potential [91]. Moreover, the ARB olmesartan attenuated the development of severe arthritis in the CIA model clinically and pathologically, even when administered only at disease onset [92]. Accordingly, ARBs may be useful therapeutically in RA, and Ang II may be involved in the development of CIA [92]. It has been shown that acute joint inflammation is attenuated in a dose-dependent manner by losartan, and prophylactic administration of this agent substantially inhibited the development of adjuvant-induced monarthritis [58]. The study also found that losartan was able to decrease the production of TNF-α, IL-1β, and chemokine ligand 1 and ameliorate joint histological changes in both mouse and rat AIA [93]. Refaat et al. [94] demonstrated that combined therapy with methotrexate and losartan showed better treatment effects than either drug alone in AIA. Moreover, losartan increased the efficacy of methotrexate therapy in AIA rats, with no observed toxicity [94]. Generally, AT1R is thought to be responsible for most of the physiological and pathological actions of Ang II. However, Ang II can also act through AT2R, which has counter-regulatory action relative to AT1R. It was shown that losartan plays a therapeutic role in AIA rats, which might be mainly associated with the upregulation of AT2R and the downregulation of AT1R [95]. Additionally, intra-articular injection of AT2R agonist into AIA rats remarkably reduced the severity of arthritis [95]. Based on these reports, it is likely that losartan also exerts its therapeutic effects in AIA rats via upregulation of AT2R.

3.3. Other bone diseases and RAS inhibition

3.3.1. Fracture healing

A previous study on a mouse femur fracture model suggested that the RAS participates in the process of fracture healing [96] and indeed expression of RAS components has been observed in the fracture callus [96,97]. Epidemiological studies have demonstrated the benefit of RAS inhibitors for increasing bone mass and decreasing the risk of bone fractures [43–46]. Similarly, in an animal fracture model, administration of perindopril caused an increase in callus formation followed by stimulation of fracture healing [96,97]. Moreover, enalapril exerted significant positive effects on fracture repair in a rat femoral fracture model [98]. The therapeutic value of ARBs also has been extended to bone health. ARBs have been shown to enhance bone health and decrease the risk of fractures clinically [99] and in experimental models [15,48,100] (see also Table 3).

3.3.2. Bone deterioration

The RAS was reported to participate in the development of osteonecrosis by steroids in rabbits [101] (see also Table 2). In addition, the local RAS in bone was involved in bone deterioration of mice with obstructive nephropathy [102] (see also Table 2). Likewise, hyperglycemia was shown to cause bone deterioration due to the high activity of the skeletal RAS [103]. These studies provide compelling evidence that osteonecrosis is strongly associated with the activation of the local bone RAS.

4. Conclusion

There is growing evidence that the RAS in local bone tissue is directly involved in bone metabolism. Coincidently, several studies have also shown an association between bone diseases and RAS when renin, ACE, and AT1R were upregulated. Several drugs (ACEIs and ARBs) block Ang II production and its effects, preventing the development of osteoporosis and other bone diseases. There is also strong evidence that RAS inhibitors ameliorate osteoporosis through reduced BMD loss, increased bone mass and bone strength, and decreased tartrate-resistant acid phosphatase activity and urinary deoxypyridinoline. In addition, RAS inhibitors have proven effective in reducing knee joint swelling, inflammation, and autoimmunity. Taken together, these observations allow us to surmise that, along with improving joint function, ACEIs and ARBs may, at the very least, function as an effective adjunctive therapy for disease control in patients with arthritis. Furthermore, RAS inhibitors also accelerate bone healing and remodeling in animal fracture models. Thus, the use of RAS inhibitors is a promising new strategy for the prevention and treatment of osteoporosis, arthritis, fracture, and deterioration. In conclusion, this review examined the role of RAS in the development of bone disease and demonstrated the importance of ACEIs and ARBs as prospective candidates for treatment of bone

disease. The current data may encourage a clinical study to assess the side effects of RAS inhibitors in osteoarticular diseases. Further research is needed to elucidate the mechanistic pathways by which these RAS inhibitors act on bone tissue.

Conflict of interest

The authors declare that they have no competing interests.

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