jraas

Journal of the Renin-Angiotensin-Aldosterone System
July-September 2019: 1–6

DOI: 10.1177/1470320319862741
journals.sagepub.com/home/jra
SAGE

Effects of telmisartan and losartan treatments on bone turnover markers in patients with newly diagnosed stage I hypertension

Berna İ Aydoğan[1], Emrah Erarslan[1], Uğur Ünlütürk[1,2] and Sevim Güllü[1]

Abstract

Introduction: Telmisartan is an angiotensin-II receptor type-1 blocker and a partial agonist for peroxisome proliferator-activated receptor-γ. The aim of this study was to determine the potential effects of telmisartan on bone metabolism and turnover markers.

Methods: Forty-two patients with newly diagnosed stage I hypertension who were prescribed telmisartan 80 mg/day or losartan 100 mg/day were included. Serum levels of calcium, phosphorus, 25-hydroxy vitamin D, bone-specific alkaline phosphatase, osteocalcin, interleukin 6 and 24-hour urinary N-terminal telopeptide were measured at the beginning and after 12 weeks of treatment.

Results: When treatment arms were evaluated together, significantly increased 25-hydroxy vitamin D levels (p=0.01), and decreased parathormone (PTH) ($p<0.001$), bone-specific alkaline phosphatase (p=0.01), osteocalcin (p=0.045), urinary N-terminal telopeptide ($p<0.001$) and interleukin 6 levels (p=0.006) were observed. After eliminating the 25-hydroxy vitamin D effect, significant changes were not observed at any of the parameters. None of the levels of parameters were different between groups.

Conclusions: Neither telmisartan, despite its partial peroxisome proliferator-activated receptor-γ agonistic effect, nor losartan treatment had significant effects on bone turnover markers in newly diagnosed stage I hypertensive patients.

Keywords

Telmisartan, losartan, bone turnover markers, osteoporosis, fracture risk

Date received: 5 February 2019; accepted: 10 June 2019

Introduction

Hypertension is an independent risk factor for osteoporosis,[1] and frequently coexists with it, especially in the elderly population.[2] Different groups of antihypertensive drugs have been reported to have variable effects on bone mineral density and fracture risk.[3–6] In addition, recent cohort studies have showed that antihypertensive medications were associated with an increased risk of serious fall injuries.[7,8] On the other hand, there are data pointing to the beneficial effects of the renin-angiotensin system (RAS) blocking on bone metabolism[6,9] Therefore, the pleiotropic effects of antihypertensive drugs on bone metabolism can affect drug selection.

Peroxisome proliferator activated receptor-γ (PPAR-γ), a member of the DNA-binding nuclear receptor family, is expressed in haematopoietic stem cells and involved in osteoclastogenesis.[10,11] PPAR-γ also has regulatory effects on mesenchymal stem cells by causing a shift to adipocyte differentiation rather than osteoblasts.[12] Thiazolidinediones (TZDs), a group of oral hypoglycaemic drugs, are agonists for PPAR-γ receptors, and it is well known that this group of drugs have depressing effects on bone metabolism via

[1]Department of Endocrinology and Metabolism, Ankara University School of Medicine, Turkey
[2]Department of Endocrinology and Metabolism, Hacettepe University School of Medicine, Turkey

Corresponding author:
Berna İmge Aydoğan, Department of Endocrinology and Metabolism, Ankara University School of Medicine, Ibn-i Sina Hospital, Ankara, 06100, Turkey.
Email: imgehalici@gmail.com

PPAR-γ receptors and are associated with an increased risk of non-traumatic bone fractures.[13–15] Telmisartan is an angiotensin-II (Ang-II) receptor type-1 (AT1) blocker and a partial agonist for PPAR-γ with 25–30% of maximal receptor activation.[16] However, the data on the clinical effects of telmisartan treatment on human bone metabolism is quite limited.[17]

Therefore, in this study, we aimed to evaluate the effect of telmisartan treatment on bone metabolism and compare its effect with losartan, an AT1 blocker without any PPAR-γ agonistic effect.

Patients and methods

Patients

Patients with newly diagnosed stage-I hypertension (according to seventh Joint National Committee (JNC 7))[18] who were prescribed AT1 blocker treatment (telmisartan 80 mg/day or losartan 100 mg/day) were included in the study. The exclusion criteria of the study included: the use of agents or substances that affect Ca^{+2} homeostasis or metabolism (preparations containing Ca^{+2} or vitamin D, bisphosphonate, levothyroxine, corticosteroid, antidepressant, fibric acid derivate, non-steroidal anti-inflammatory drug, selective *oestrogen receptor modulator, antiepileptic*), serum creatinine levels ⩾1.5 mg/dl for males and ⩾1.4 for females, patients with any kind of malignancy, other conditions that may affect vitamin D or calcium metabolism (malabsorption syndromes, Cushing syndrome, renal or active hepatic disease, primary hyperparathyroidism, sarcoidosis), history of any hormonal treatments within the last three months, current pregnancy and lactation, smoking or drug abuse and premenopausal women. The study was approved by the Ankara University Local Ethics Committee for Human Studies and informed consent was obtained from each patient upon recruitment to the study.

Blood samples

Blood samples were obtained at 08:00 after overnight fasting and before starting antihypertensive treatments, and centrifuged at 5000 g for five minutes. Serum samples (at least 1.0 ml) were stored at −80°C. Serum levels of calcium (Ca), phosphorus (P), 25-hydroxy vitamin D (25-OHD), bone alkaline phosphatase (Bs-ALP) (IDS Ostase BAP EIA, UK), osteocalcin (OC) (DIA Source hOST-EASIA, Belgium), interleukin 6 (IL-6) (DIA Source IL-6-EASIA-CE, Belgium) as well as 24-hour urinary N-terminal telopeptide (NTx) (OSTEOMARK NTx Urine EIA, USA) levels were measured with micro-enzyme linked immunosorbent assay (ELISA) method (Versa Max microplate reader ELİSA and Versa Max ELISA washer devices). The measurement of PTH was made by the chemiluminescence method. The reference ranges were 14–72 pg/ml and 20–100 ng/ml for parathormone (PTH) and 25-OHD, respectively. At the end of a 12-week follow-up, all evaluations were repeated.

Statistical analyses

Categorical data were compared using the chi-square Fisher exact test. Group data with a normal distribution were compared using the Student *t*-test or analysis of variance. The Mann-Whitney U test and Wilcoxon signed rank test were used appropriately to compare inter/intra-group nonparametric data. The Wilcoxon and paired *t*-test were used to explore the changes in ordinal and continuous variables during follow-up in each treatment groups. Correlations between bone turnover markers, IL-6 and other parameters were evaluated with the *Spearman* rank correlation. Partial correlation was used to evaluate relationship between PTH and other variables, adjusted for 25-OHD, and between 25-OHD and other variables, adjusted for PTH. Covariance analysis was performed to assess drug effects on variables (25-OHD and PTH were covariates). Factorial analysis of variance (ANOVA) test for changes in bone markers was performed. Independent variables were treatment arms, PTH and 25-OHD levels. Changes in PTH and 25-OHD levels at the end of the study period were grouped as 'low' and 'high' according to median levels. Values were expressed as mean ± standard deviation or median as appropriate. A value of $p<0.05$ was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 15.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Forty-two patients with newly diagnosed stage I hypertension were included in our study. In the telmisartan treatment arm there were 22 patients (mean age: 54.2±10.2 years) and in the losartan arm there were 20 patients (mean age: 49.3±9.9 years) completed the study. The basic characteristics of patients are summarised in Table 1.

When treatment arms were evaluated together; a statistically significant increase in 25-OHD levels and a significant decrease in PTH levels were observed. Bs-ALP, urinary NTx and IL-6 levels decreased significantly as well. Serum Ca and P levels were not different compared to the basal levels (Table 2). In the covariate analysis, after eliminating the effect of 25-OHD, there was no significant change at any of the measured parameters.

Mean values of blood pressure were not different between treatment arms at baseline (Table 1). At the end of study, mean systolic blood pressure was 126.5±6.7 mm Hg and 124.4±7.3 mm Hg in the telmisartan and losartan groups, respectively (p=0.25), and mean diastolic blood pressure was 79.8±4.7 and 78.9±5.6 mm Hg in the

telmisartan and losartan treatment groups, respectively (p=0.6).

The two study arms were similar in regarding the changes of the measured parameters during the follow-up period (Table 3). The decrease in mean IL-6 levels was only significant in the losartan group. Decreases in urinary NTx were statistically significant in both treatment arms (Table 3).

When interactions between changes in Bs-ALP, urinary NTx, OC and IL-6 levels were assessed, only the NTx level was positively correlated with IL-6 (r=0.33, p=0.03). The levels of PTH and 25-OHD were inversely correlated at the beginning and the end of the study, respectively (p=0.045, r=−0.31 and p=0.02, r=−0.36)

In the covariate analysis after eliminating the effect of the changes in 25-OHD levels, there was no statistically significant difference in Ca, P, PTH, Bs-ALP, OC, NTx and IL-6 levels after 12-week follow-up in both groups. The covariate analysis, which was made to eliminate the PTH effect, did not show any significant changes in Ca, P, PTH, Bs-ALP, OC, NTx and IL-6 levels after 12-week follow-up in both groups.

Table 1. Basic characteristics of patients.

Parameter	Telmisartan (n=24)	Losartan (n=21)	p Value
Female	11 (50%)	8 (40%)	NS
Male	11 (50%)	12 (60%)	NS
Age (years)	54.2±10.2	49.3±9.9	NS
SBP (mm Hg)	149.7±4.4	149.6±4.6	NS
DBP (mm Hg)	94.4±2.8	95.1±2.8	NS
BUN (mg/dl)	12.9±2.9	14.1±2.7	NS
Creatinine (mg/dl)	0.78±0.09	0.82±0.17	NS
Na (mEq/l)	141.2±1.86	141.6±1.73	NS
K (mEq/l)	4.54±0.39	4.46±0.31	NS
Total ALP (U/l)	81.1±18.35	77.7±20.46	NS

ALP: alkaline phosphatase; BUN: blood urea nitrogen; DBP: diastolic blood pressure; K: potassium; *n*: number of patients; Na: sodium; NS: non-significant; SBP: systolic blood pressure; SD: standard deviation.
Age and laboratory parameters are given as mean±SD.

The factorial ANOVA analysis showed that changes in IL-6 and NTx levels during the study period, had interactions with the change in PTH level (p=0.023 and p=0.025, respectively). There was no interaction between changes in Bs-ALP, OC, NTx and IL-6 levels and treatment arms.

Discussion

In the present study, we evaluated and compared the effects of telmisartan and losartan on bone metabolism. After eliminating the effect of the changes in 25-OHD levels; neither losartan nor telmisartan were found to have significant effects on bone turnover markers during a 12-week treatment period in newly diagnosed hypertensive patients.

Both osteoblasts and osteoclasts are shown to have AT1, Ang-II receptor type-2 (AT2) and Ang-II converting enzyme expression.[19–22] Ang-II was shown to induce the expression of receptor activator of NF-kappa B ligand (RANKL) in osteoblasts, leading to the activation of osteoclasts.[19] Treatment with AT2 receptor blockage resulted in an increase in bone mass due to enhancement of osteoblastic activity and a suppression of osteoclastic activity *in vivo*.[23]

Regarding the effects of angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEI) on bone metabolism, clinical studies point out favourable outcomes of osteoporosis in patients treated with these groups.[6,24–26] However, most of the available data about the effects of ARBs on bone turnover have come from animal model and cell culture studies. Telmisartan was shown to promote fracture healing in the mice model and alleviate rosiglitazone-induced bone loss in ovariectomised spontaneous hypertensive rats.[27,28] A favourable effect of telmisartan was also shown on bone loss in oestrogen-deficient mice.[29] In addition, after telmisartan treatment, recovery in lumbar and femoral bone mineral density (BMD), positive biomechanical changes in lumbar spine, amelioration in microarchitecture of tibial metaphysis and normalization of serum OC and deoxypyridinoline/creatinine ratio were observed. In the present

Table 2. Changes in bone turnover markers, vitamin D, PTH and interleukin 6 (IL-6) levels during follow-up period in whole group.

Parameter	Basal	12th week	p
Ca (mg/dl)	9.12±0.31	9.11±0.32	NS
P (mg/dl)	3.41±0.51	3.38±0.58	NS
25-OHD (µg/ml)	16.3 (10.2–41.9)	17.9 (10.4–49.1)	**0.01**
PTH (pg/ml)	52.2±25.1	43.1±22.6	**<0.001**
Bs-ALP (µg/l)	16.8±5.1	15.4±3.5	**0.01**
OC (ng/ml)	11.3±5.3	9.3±5.8	**NS**
NTx (nM BCE/mM creatinine)	100.9±64.4	44.1±36.5	**<0.001**
IL-6 (pg/ml)	17.9 (2.3–196.9)	10.4 (0.8–137.6)	**0.006**

25-OHD: 25-hydroxy vitamin D; BCE: bone collagen equivalents; Bs-ALP: bone-specific alkaline phosphatase; Ca: calcium; NTx: N-terminal telopeptide; OC: osteocalcin; P: phosphorus; PTH: parathormone.

Table 3. Change in bone metabolism and turnover markers according to treatment groups.

	Telmisartan			Losartan			Between treatment arms
	Basal	12th week	*p*	Basal	12th week	*p*	*p*
Ca (mg/dl)	9.12±0.31	9.06±0.25	NS	9.12±0.30	9.16±0.38	NS	NS
P (mg/dl)	3.45±0.52	3.45±0.61	NS	3.36±0.48	3.34±0.52	NS	NS
25-OHD (µg/ml)	15.1 (10.3–41.9)	18 (10.4–49.1)	NS	16.7 (10.2–41.9)	17.7 (10.7–41.6)	NS	NS
PTH (pg/ml)	51.4±24.3	46.9±23.8	NS	52.9±25.6	42.8±23.5	**0.04**	NS
Bs-ALP (µg/l)	17.2±5.3	16.2±4.9	NS	16.1±5.0	15.3±3.3	**NS**	NS
OC (ng/ml)	11.4±5.5	8.9±5.7	NS	10.9±4.8	8.3±6.1	NS	NS
NTx (nM BCE/mM) creatinine)	108.1±78.3	46.8±43.2	**0.002**	92.8±44.2	39.9±26.9	**0.001**	NS
IL-6 (pg/ml)	14.0 (2.3–196.9)	11.5 (0.8–137.6)	NS	20.3 (3.8–149.6)	9.9 (3.4–42.2)	**0.01**	NS

25-OHD: 25-hydroxy vitamin D; BCE: bone collagen equivalents; Bs-ALP: bone-specific alkaline phosphatase; Ca: calcium; IL-6: interleukin 6; NTx: N-terminal telopeptide; OC: osteocalcin; P: phosphorus; PTH: parathormone.

study, we observed statistically significant decreases in levels of NTx in both treatment arms. Additionally, there was an increase in 25-OHD levels and coexisting decrease in PTH levels in the whole group and treatment arms. After eliminating the effect of the changes in 25-OHD and PTH levels, there was no statistically significant difference in Ca, P, PTH, Bs-ALP, OC, NTx and IL-6 levels after 12-week follow-up. Nevertheless, favourable effects of telmisartan on bone metabolism have not been confirmed in all studies,[30] and a neutral effect on bone remodelling markers in hypertensive patients was also reported.[17]

A causal relationship between RAS activation and vitamin D insufficiency due to decreased production of vitamin D receptors (VDRs) was previously proposed.[31,32] RAS activation was also reported to induce PTH secretion in a previous study.[33] However, changes in PTH and 25-OHD levels in our study could be related to seasonal variations, as the study began at the end of winter and was completed at the end of spring in the home country of the study. No significant changes at any of the measured markers for remodelling were observed after eliminating the 25-OHD and PTH effects. We observed an interaction between the changes in PTH and NTx levels. Therefore, suppression of bone remodelling in the present study may be a result of decreased PTH levels. The direct effects of 25-OHD on bone homeostasis are complex. Stimulation of mineralization and resorption of bone were both reported.[34,35] However, when Ca supply is sufficient, 25-OHD improves mineral deposition indirectly. In our study, the effects of 25-OHD may explain why suppression of formation was not as significant as resorption. Furthermore, the strong suppressor effect of 25-OHD changes on PTH, even in small quantities (2.4 µg/ml) was remarkable in this study.

IL-6 was shown to activate osteoclastogenesis in submaximal doses.[36] Telmisartan and losartan were reported to decrease IL-6 levels in rat aorta cell cultures and patients with heart failure, respectively.[37,38] Also, there is a close relationship between vitamin D and the immune system. Inhibition of IL-6 production by monocytes/macrophages with vitamin D treatment was demonstrated previously.[39] PPAR-γ activators have been shown to inhibit the inflammatory markers such as IL-6. In the present study, although levels of IL-6 decreased in both treatment arms during the follow-up period, these changes reached statistical significance only in the losartan group, suggesting a mechanism other than the effect of PPAR-γ agonism. In both treatment arms, changes in IL-6 levels were related with changes in 25-OHD levels. Therefore, favourable effects of 25-OHD on turnover markers may be explained, at least in part, by the decrease in IL-6 levels in the present study.

The main limiting factors were the relatively short follow-up period, small sample size of study and lack of bone mineral density measurements. Healthy controls were not included and the design of the study was not randomised.

In conclusion, neither telmisartan, which also has a partial agonistic effect on the PPAR-γ receptor, nor losartan had significant effects on bone turnover markers. Randomised controlled clinical studies are needed to assess the effects of AT1 receptor blockers on other bone turnover markers, BMD and fracture risk in special groups of patients, especially in postmenopausal women.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Ankara University Medical Foundation.

ORCID iD

Berna İmge Aydoğan https://orcid.org/0000-0001-9806-3891

References

1. Cappuccio FP, Meilahn E, Zmuda JM, et al. High blood pressure and bone-mineral loss in elderly white women: A prospective study. Study of Osteoporotic Fractures Research Group. *Lancet* 1999; 354: 971–975.
2. Perez-Castrillon JL, Justo I, Silva J, et al. Bone mass and bone modelling markers in hypertensive postmenopausal women. *J Hum Hypertens* 2003; 17: 107–110.
3. Perez-Castrillon JL, Silva J, Justo I, et al. Effect of quinapril, quinapril-hydrochlorothiazide, and enalapril on the bone mass of hypertensive subjects: Relationship with angiotensin converting enzyme polymorphisms. *Am J Hypertens* 2003; 16: 453–459.
4. Reid IR, Ames RW, Orr-Walker BJ, et al. Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: A randomized controlled trial. *Am J Med* 2000; 109: 362–370.
5. Solomon DH, Mogun H, Garneau K, et al. Risk of fractures in older adults using antihypertensive medications. *J Bone Miner Res* 2011; 26: 1561–1567.
6. Rejnmark L, Vestergaard P and Mosekilde L. Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: A nationwide case-control study. *J Hypertens* 2006; 24: 581–589.
7. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA Intern Med* 2014; 174: 588–595.
8. Butt DA, Mamdani M, Austin PC, et al. The risk of hip fracture after initiating antihypertensive drugs in the elderly. *Arch Intern Med* 2012; 172: 1739–1744.
9. Gebru Y, Diao TY, Pan H, et al. Potential of RAS inhibition to improve metabolic bone disorders. *Biomed Res Int* 2013; 2013: 932691.
10. Maurin AC, Chavassieux PM and Meunier PJ. Expression of PPARgamma and beta/delta in human primary osteoblastic cells: Influence of polyunsaturated fatty acids. *Calcif Tissue Int* 2005; 76: 385–392.
11. Wu H, Li L, Ma Y, et al. Regulation of selective PPARgamma modulators in the differentiation of osteoclasts. *J Cell Biochem* 2013; 114: 1969–1977.
12. Shimizu M, Yamashita D, Yamaguchi T, et al. Aspects of the regulatory mechanisms of PPAR functions: Analysis of a bidirectional response element and regulation by sumoylation. *Mol Cell Biochem* 2006; 286: 33–42.
13. Wan Y, Chong LW and Evans RM. PPAR-gamma regulates osteoclastogenesis in mice. *Nat Med* 2007; 13: 1496–1503.
14. Bilezikian JP, Josse RG, Eastell R, et al. Rosiglitazone decreases bone mineral density and increases bone turnover in postmenopausal women with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2013; 98: 1519–1528.
15. Xiao WH, Wang YR, Hou WF, et al. The effects of pioglitazone on biochemical markers of bone turnover in the patients with type 2 diabetes. *Int J Endocrinol* 2013; 2013: 290734.
16. Kurtz TW. Treating the metabolic syndrome: Telmisartan as a peroxisome proliferator-activated receptor-gamma activator. *Acta Diabetol* 2005; 42: S9–S16.
17. Perez-Castrillon JL, De Luis D, Inglada L, et al. [Telmisartan effect's on remodelling bone markers in hypertensive patients.] *Nutr Hosp* 2012; 27: 276–280.
18. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 2003; 289: 2560–2572.
19. Shimizu H, Nakagami H, Osako MK, et al. Angiotensin II accelerates osteoporosis by activating osteoclasts. *FASEB J* 2008; 22: 2465–2475.
20. Bandow K, Nishikawa Y, Ohnishi T, et al. Low-intensity pulsed ultrasound (LIPUS) induces RANKL, MCP-1, and MIP-1beta expression in osteoblasts through the angiotensin II type 1 receptor. *J Cell Physiol* 2007; 211: 392–398.
21. Garcia P, Schwenzer S, Slotta JE, et al. Inhibition of angiotensin-converting enzyme stimulates fracture healing and periosteal callus formation – role of a local renin-angiotensin system. *Br J Pharmacol* 2010; 159: 1672–1680.
22. Hatton R, Stimpel M and Chambers TJ. Angiotensin II is generated from angiotensin I by bone cells and stimulates osteoclastic bone resorption in vitro. *J Endocrinol* 1997; 152: 5–10.
23. Izu Y, Mizoguchi F, Kawamata A, et al. Angiotensin II type 2 receptor blockade increases bone mass. *J Biol Chem* 2009; 284: 4857–4864.
24. Lynn H, Kwok T, Wong SY, et al. Angiotensin converting enzyme inhibitor use is associated with higher bone mineral density in elderly Chinese. *Bone* 2006; 38: 584–588.
25. Yamamoto S, Kido R, Onishi Y, et al. Use of renin-angiotensin system inhibitors is associated with reduction of fracture risk in hemodialysis patients. *PloS One* 2015; 10: e0122691.
26. Choi HJ, Park C, Lee YK, et al. Risk of fractures in subjects with antihypertensive medications: A nationwide claim study. *Int J Cardiol* 2015; 184: 62–67.
27. Ma L, Ji JL, Ji H, et al. Telmisartan alleviates rosiglitazone-induced bone loss in ovariectomized spontaneous hypertensive rats. *Bone* 2010; 47: 5–11.
28. Zhao X, Wang JX, Feng YF, et al. Systemic treatment with telmisartan improves femur fracture healing in mice. *PloS One* 2014; 9: e92085.
29. Kang KY, Kang Y, Kim M, et al. The effects of antihypertensive drugs on bone mineral density in ovariectomized mice. *J Korean Med Sci* 2013; 28: 1139–1144.
30. Kolli V, Stechschulte LA, Dowling AR, et al. Partial agonist, telmisartan, maintains PPARgamma serine 112 phosphorylation, and does not affect osteoblast differentiation and bone mass. *PloS One* 2014; 9: e96323.
31. Ferder M, Inserra F, Manucha W, et al. The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system. *Am J Physiol Cell Physiol* 2013; 304: C1027–C1039.
32. Garcia IM, Altamirano L, Mazzei L, et al. Role of mitochondria in paricalcitol-mediated cytoprotection during obstructive nephropathy. *Am J Physiol Renal Physiol* 2012; 302: F1595–F1605.
33. Brown JM, Williams JS, Luther JM, et al. Human interventions to characterize novel relationships between the renin-angiotensin-aldosterone system and parathyroid hormone. *Hypertension* 2014; 63: 273–280.
34. Gardiner EM, Baldock PA, Thomas GP, et al. Increased formation and decreased resorption of bone in mice with

elevated vitamin D receptor in mature cells of the osteoblastic lineage. *FASEB J* 2000; 14: 1908–1916.
35. Sooy K, Sabbagh Y and Demay MB. Osteoblasts lacking the vitamin D receptor display enhanced osteogenic potential in vitro. *J Cell Biochem* 2005; 94: 81–87.
36. Tai H, Miyaura C, Pilbeam CC, et al. Transcriptional induction of cyclooxygenase-2 in osteoblasts is involved in interleukin-6-induced osteoclast formation. *Endocrinology* 1997; 138: 2372–2379.
37. Ogino K, Kato M, Furuse Y, et al. Addition of losartan to angiotensin-converting enzyme inhibitors improves insulin resistance in patients with chronic heart failure treated without beta-blockers. *Circ J* 2010; 74: 2346–2352.
38. Tian Q, Miyazaki R, Ichiki T, et al. Inhibition of tumor necrosis factor-alpha-induced interleukin-6 expression by telmisartan through cross-talk of peroxisome proliferator-activated receptor-gamma with nuclear factor kappaB and CCAAT/enhancer-binding protein-beta. *Hypertension* 2009; 53: 798–804.
39. Zhang Y, Leung DY, Richers BN, et al. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol* 2012; 188: 2127–2135.