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Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: informahealthcare.com/journals/irnf20

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To cite this article: Seyit Ahmet Ay, Murat Karaman, Mustafa Cakar, Sevket Balta, Erol Arslan, Fatih Bulucu, Seref Demirbas, Turgay Celik, Mehmet Ilkin Naharci, Sait Demirkol, Omer Kurt & Ergun Bozoglu (2013) Amlodipine Increases Vitamin D Levels More Than Valsartan in Newly Diagnosed Hypertensive Patients: Pointing to an Additional Effect on Bone Metabolism or a Novel Marker of Inflammation?, Renal Failure, 35:5, 691-696, DOI: 10.3109/0886022X.2013.780976

To link to this article: https://doi.org/10.3109/0886022X.2013.780976

Published online: 08 Apr 2013.

Renal Failure, 2013; 35(5): 691–696

ISSN 0886-022X print/1525-6049 online
DOI: 10.3109/0886022X.2013.780976

informa
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CLINICAL STUDY

Amlodipine Increases Vitamin D Levels More Than Valsartan in Newly Diagnosed Hypertensive Patients: Pointing to an Additional Effect on Bone Metabolism or a Novel Marker of Inflammation?

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Abstract

Hypertension is a major challenge for public health. Appropriate antihypertensive treatment seem to provide a better life with lower morbidity and mortality rates. Another pathologic condition, osteoporosis, mainly affects postmenouposal women, and constitutes a growing body of risks after a particular age. As bone is a dynamic organ system that is directly related to calcium and phosphor metabolism, imbalance in these two parameters upon aging or menopause finally may lead to osteoporosis. Today, both osteoporosis and high blood pressure are major morbidities, especially in the elderly population. There are some intriguing results on the effects of antihypertensive agents on bone metabolism in the literature. In this study, we aimed to investigate the effects of widely used antihypertensive agents, valsartan and amlodipine on vitamin D levels in newly diagnosed hypertensive population. We found that amlodipine increased vitamin D levels significantly in patients with a newly diagnosed hypertension on a 12-week treatment duration compared to valsartan.

Keywords: hypertension, vitamin D, amlodipine, valsartan, inflammation

INTRODUCTION

Hypertension is a major challenge for public health. Appropriate antihypertensive treatment seems to provide a better life with lower morbidity and mortality rates. Another pathologic condition, osteoporosis, mainly affects postmenopausal women and constitutes a growing body of risks after a particular age. As bone is a dynamic organ system that is directly related to calcium and phosphor metabolism, imbalance in these two parameters upon aging or menopause finally may lead to osteoporosis. Today, both osteoporosis and high blood pressure (BP) are major morbidities, especially in the elderly population. However, it has been shown by researchers that high BP in the elderly is statistically associated with decreased bone mineral content at the femoral neck, which may increase the susceptibility to fractures.[1]

A number of clinical and experimental studies report that the effects of calcium channel blockers (CCB) are not limited only to the cardiovascular system but might also be associated with skeletal calcium metabolism due to the presence of L-type calcium channels in osteoblastic cells. There are some intriguing results on the effects of antihypertensive agents on bone metabolism in the literature. Recent studies demonstrated that some antihypertensive drugs reduced the risk of bone fracture in elderly patients. In contrast, some authors report that there is no evidence that CCB prevent osteoporosis although they are widely used as first-line antihypertensive agents. Some animal studies reported that cilnidipine (L-/N-type CCB) ameliorated osteoporosis in ovariectomized hypertensive rats and speculated that antihypertensive drugs such as cilnidipine and carvedilol

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Received 3 December 2012; Revised 22 February 2013; Accepted 26 February 2013

might provide additional benefits in the treatment of hypertensive postmenopausal women.[2]

Bioactive vitamin D or calcitriol is a steroid hormone that has long been recognized for its important role in regulating the levels of calcium and phosphorus, and in mineralization of bones. In recent years, an association between vitamin D levels and high BP has been demonstrated. The underlying mechanism of this situation is not fully understood. Antihypertensive treatment, especially angiotensin-converting enzyme (ACE) inhibitors, is shown in several studies to have positive effects on bone metabolism. However, the relevant information is not sufficient. Another point of discussion is that vitamin D levels may be a part or a marker of inflammation in hypertensive patients. According to a growing body of data, vitamin D levels are associated with metabolic syndrome risk factors and decreased levels may be the indicator of ongoing inflammation in hypertensive patients.[3] The levels of inflammatory markers are known to improve with antihypertensive treatment.[4] In this study, we aimed to investigate the effects of widely used antihypertensive agents, valsartan and amlodipine, on vitamin D levels in newly diagnosed hypertensive population.

MATERIAL AND METHODS

Patients

The study was conducted in a tertiary referral center. A total of 61 newly diagnosed hypertensive patients from internal medicine, geriatrics, and cardiology outpatient clinics were included in the study. Newly diagnosed hypertensive patients were defined as those who were diagnosed with hypertension during the period of the study and were not on any antihypertensive therapy. The patients were asked to sit down for 10 min before the BP was recorded using a manual mercury sphygmomanometer. The mean of two BP measurements was taken. Patients with evidence of any target organ damage from high BP, diabetes, secondary hypertension, osteoporosis, thyroid or parathyroid dysfunction, and other chronic diseases, inflammatory conditions, alcoholism, and smoking, and those who were receiving any medications were excluded. Twenty-eight of these patients were prescribed amlodipine and 33 were prescribed valsartan. Oral antihypertensive preparations were started until the regulation of the BP with dose escalation, with valsartan (80–320 mg) or amlodipine (5–10 mg). These treatments were independently and randomly started in mentioned outpatient clinics. The patients were questioned in terms of osteoporosis, osteopenia, fracture, or fall history and symptoms of imbalance. The patients were followed through a total of 12 weeks. A complete blood count, renal and hepatic function tests, electrolytes, serum lipid levels, thyroid hormones, 25-hydroxy (OH) vitamin D, calcium, phosphorus, magnesium, and parathyroid hormone (PTH) levels of the patient groups were measured before treatment and on the 12th week. At the start point of the study, the patients having lower levels of vitamin D according to the laboratory normal ranges and vitamin D deficiency symptoms, such as instability, falls, and hip fracture, were given vitamin D replacement and excluded from the study. Asymptomatic patients with lower vitamin D levels were followed through the study period. At the end of the study, replacement with vitamin D preparations to the patients with lower vitamin D levels was performed. The patients lived in the same city center, and they were followed in the same season (summer) period, so we excluded the possible different seasonal and latitude effects on vitamin D levels. None of the patients had any regular medication other than mentioned antihypertensive drugs. All participants gave written informed consent. The study protocol was approved by The Research and Ethics Committees of Gulhane Military Medical Academy. A part of data was published elsewhere.

Anthropometric Measurements

Weight (in kilograms) and height (in centimeters) were measured and body mass index (BMI) was calculated as body weight/height^2 (kg/m^2).

Blood Sample Collection and Analysis of Parameters

For biochemical analyses, all blood samples were drawn in the morning after at least 10 h of fasting. The samples were promptly centrifuged, the plasma and serum were separated, and all plasma samples were run in the same assay. Fasting plasma glucose, total cholesterol (TC), triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels were measured by the enzymatic colorimetric method with an Olympus AU2700 auto analyzer using reagents from Olympus Diagnostics (GmbH, Hamburg, Germany). Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula.[5] The vitamin D levels were measured by radioreceptor assays. Serum FT4 and FT3 were measured by radioimmunoassay and serum TSH by immunoradiometric assays. PTH levels were measured by biointact assays.

Statistical Analysis

SPSS 15.0 (Statistical Package for the Social Sciences ver. 15.0, SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Quantitative variables were expressed as mean $\pm$ standard deviation. The Kolmogorov–Smirnov test was used to determine the distribution characteristics of variables, and Levene's test was used to determine the equality of variance. The differences between groups were studied for significance by independent samples t-test as appropriate. Categorical variables were compared by Chi-square test. Spearman correlation analysis was used to evaluate the relationship between variables. The differences and correlations were considered significant at $p < 0.05$.

RESULTS

In total, 61 patients were recruited in the study. Two patients in the amlodipine group were excluded because of ankle edema, one patient had extensive dermatitis on hands, and one patient could not use the drug due to intolerance. In the valsartan group, two patients stopped the drug due to cough and one patient was excluded from the study because of the lack of informed consent. Thus, a total of 54 patients (amlodipine: 24 patients, valsartan: 30 patients) completed the study.

At the beginning of treatment, 10 patients (18.5%) had serious hypovitaminosis D (<10 ng/mL), but none of them was symptomatic; therefore, vitamin D supplementation to these patients was not considered. At the end of the study, while significant improvements were seen in four of these patients (40%), five patients (50%) had partial improvements and one had no improvement, and treatment with vitamin D was started to these six patients. In other patients, the vitamin D levels were increased significantly compared to baseline levels and did not require any additional treatment.

The demographic characteristics and baseline biochemical results of the study groups are shown in Table 1. The study was performed on 54 patients with newly diagnosed essential hypertension (amlodipine $n = 24$ and valsartan $n = 30$). 14 (42%) of the amlodipine group and 24 (80%) of the valsartan group patients were female ($p = 0.083$). The patients of the two groups were matched for age and BMI. The mean SBP and DBP were 155.63 ± 9.37 and 91.71 ± 8.5 mmHg in the amlodipine group and 155.57 ± 11.33 and 93.57 ± 7.58 mmHg in the valsartan group, respectively. The work was designed to study increased BP that is described as newly diagnosed aiming at the smaller time from the start point. At the baseline measurements, fasting plasma glucose, serum total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, urea, creatinine, uric acid, aspartate aminotransferase, alanine aminotransferase and hemoglobin levels, white blood cell counts, and mean corpuscular volumes of the two groups were similar.

Systolic as well as diastolic BPs were significantly decreased after treatment in both groups. The mean systolic BP before and after treatment were 155.59 ± 10.4 and 126.87 ± 7.18 mmHg, respectively ($p < 0.001$). The mean diastolic BP before and after treatment were 92.74 ± 7.98 and 75.68 ± 6.95 mmHg, respectively ($p < 0.001$).

Table 1. Demographics, anthropometrics, baseline characteristics, and laboratory results of the newly diagnosed hypertensive patients on amlodipine and valsartan treatment groups.

Parameter	Amlodipine	Valsartan	p
n	24	30	
Age (years)	53.54 ± 11.33	51.2 ± 13.67	0.503
Sex (M/F) (n)	10/14	6/24	0.083*
BMI (kg/m^2)	30.03 ± 3.78	30.09 ± 4.83	0.963
Systolic blood pressure (mmHg)	155.63 ± 9.37	155.57 ± 11.33	0.984
Diastolic blood pressure (mmHg)	91.71 ± 8.5	93.57 ± 7.58	0.407
WBC (/mm^3)	6941.67 ± 1435.24	7376.67 ± 1452.15	0.276
Hemoglobin (g/dL)	14.64 ± 1.3	14.26 ± 1.12	0.265
Hematocrit (%)	41.96 ± 3.69	41.55 ± 3.31	0.674
Platelet count (10^3/mm^3)	248.96 ± 69.45	261 ± 50.75	0.481
MCV (fl)	88.04 ± 4.68	85.74 ± 11.9	0.338
Fasting plasma glucose (mg/dL)	100.13 ± 10.54	95.27 ± 13.26	0.14
Urea (mg/dL)	31.04 ± 10.08	28.33 ± 7.8	0.285
Creatinine (mg/dL)	0.9 ± 0.12	0.88 ± 0.12	0.451
Na	139.98 ± 2.11	140.92 ± 2.1	0.11
K	4.36 ± 0.29	4.48 ± 0.38	0.206
Uric acid (mg/dL)	5.05 ± 0,9	5.02 ± 1.03	0.894
ALT (IU/mL)	26.04 ± 10.4	21.17 ± 13.43	0.139
AST (IU/mL)	23.46 ± 5.06	21.47 ± 5.44	0.17
Total cholesterol (mg/dL)	218.08 ± 56.79	224.72 ± 30.39	0.61
Triglyceride (mg/dL)	140.65 ± 52.28	143.9 ± 54.89	0.827
HDL (mg/dL)	51.74 ± 10	52.55 ± 14.26	0.811
LDL (mg/dL)	145.37 ± 38.84	142.8 ± 26.69	0.788
Vitamin D3 (ng/mL)	15.01 ± 6.01	17.35 ± 7.19	0.216
PTH (pg/mL)	50.92 ± 16.15	55.34 ± 18.23	0.416
Calcium (mg/dL)	9.85 ± 0.44	9.64 ± 0.47	0.107
Magnesium (mg/dL)	2.13 ± 0.19	2.07 ± 0.11	0.201
Phosphorus (mg/dL)	3.64 ± 0.5	3.54 ± 0.46	0.54
TSH	1.8 ± 1.66	1.88 ± 1.36	0.844

Notes: Values are given as mean ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PTH, Parathormone; WBC, white blood cell count; PLT, platelet count; Cr, creatinine; Hb, hemoglobin; Hct,hematocrit; TSH, thyroid stimulating hormone.
*χ^2 test; otherwise independent samples t-test.

Table 2. The measurements of biochemical parameters that may influence vitamin D levels before and after treatment in amlodipine and valsartan groups. The increase in vitamin D levels was statistically significant in the amlodipine group.

	Amlodipine			Valsartan		
	Baseline	12th week	*p*	Baseline	12th week	*p*
Vitamin D3 (ng/mL)	15.21 ± 6.25	22.25 ± 11.05	**0.012**	17.56 ± 7.3	20.93 ± 11.56	0.130
PTH (pg/mL)	49.54 ± 15.94	48.29 ± 13.52	0.757	52.33 ± 15.21	48.17 ± 12.24	0.242
Ca (mg/dl)	9.71 ± 0.46	9.66 ± 0.81	0.787	9.61 ± 0.51	9.65 ± 0.29	0.705
Mg (mg/dl)	2.16 ± 0.22	2.12 ± 0.15	0.625	2.06 ± 0.12	2.05 ± 0.12	0.769
P (mg/dl)	3.55 ± 0.55	3.16 ± 0.25	0.232	3.6 ± 0.31	3.49 ± 0.42	0.441
TSH (mIU/mL)	1.59 ± 0.84	1.74 ± 1.15	0.308	1.67 ± 1.48	1.4 ± 0.72	0.225

Notes: Values are given as mean ± standard deviation. PTH, Parathormone; TSH, thyroid stimulating hormone.
Paired samples *t*-test.

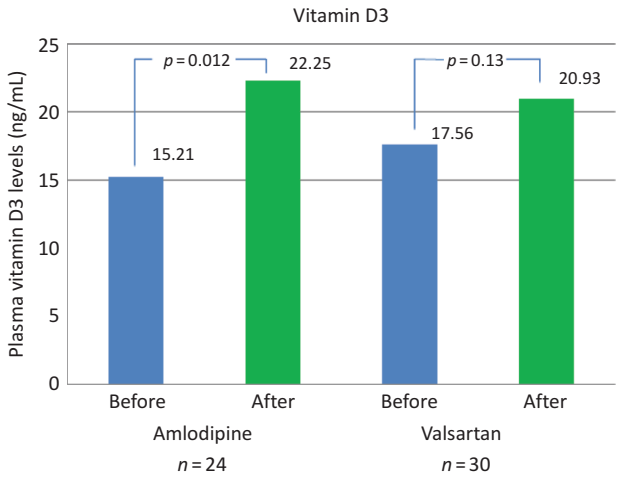

Figure 1. Chart showing the changes in plasma vitamin D levels in amlodipine and valsartan treatment groups of newly diagnosed hypertensive patients before and after 12 weeks of antihypertensive treatment.

In the total group, vitamin D levels were 16.32 + 6.73, 21.89 + 10.87 at the start point and after treatment, respectively, and the increase was statistically significant ($p = 0.003$). In the amlodipine group, there was a significant increase in the levels of vitamin D (median vitamin D levels before/after 15.21 ± 6.25/22.25 ± 11.05 ng/mL, respectively; $p = 0.012$) (Table 2; Figure 1). The effect of 12 weeks of antihypertensive therapy with amlodipine and valsartan on parameters that may interfere with bone metabolism is shown in Table 2. There was no change in calcium, magnesium, phosphorus, parathormone, and thyroid hormones at both groups after treatment.

In the valsartan group, there was an increase in the levels of vitamin D on the 12th week, but the change was not statistically significant (Table 2).

DISCUSSION

In the present study, antihypertensive treatment has been found to increase serum vitamin D levels in newly diagnosed hypertensive patients. It is true that we can say amlodipine had a greater effect in increasing vitamin D levels in these patients compared to valsartan on a 12-week treatment duration. The increase was significant in the amlodipine group, but valsartan failed to show any significance.

As a potential mechanism for these results, there may be some idea to think that antihypertensive treatment should change the bone metabolism. Bone is the largest store of calcium in the body, and the bone calcium content and mineralization may represent the whole body calcium balance. The changes in bone metabolism may lead to changes in calcium levels and especially antihypertensive drugs may have effects on bone metabolism through this way. Antihypertensive drugs have been investigated many times in terms of their effects on bone metabolism before. As an example, treatment with beta-blockers, angiotensin-converting enzyme inhibitors, and CCB was found to be associated with a small but significantly reduced risk of fracture,[6] and Rejnmark et al. concluded that the use of more than 2000 defined daily antihypertensive dosage was associated with a 19% (95% CI: 10–27%) decreased hip fracture risk.[7] However, risk of fracture in patients treated with non-diuretic cardiovascular drugs is largely unknown. In another point, calcium metabolism disturbances such as increased urinary calcium, vitamin D insufficiency, and decreased bone mineral density have been associated with cardiovascular diseases. In a study by Mcgreevy et al., vitamin D deficiency has lately been associated with myocardial infarction, stroke, hypertension, and other cardiovascular and related diseases such as atherosclerosis and endothelial dysfunction. There has also been increasing evidence on vitamin D showing roles in renin–angiotensin system (RAS) regulation and directly affecting cardiac muscle and regulating the immune system.[8] Such an effect has been described in a late study by Kota et al. that there should be an association between low plasma 25(OH)D levels, high BMI, and upregulation of the RAS.[9]

At first, the findings of the present study may indicate the previously mentioned role of vitamin D as an inflammatory marker that decreases with ongoing inflammation. It is true that antihypertensive medication is expected to decrease the ongoing inflammation and so vitamin D levels should increase as the inflammation gets lower.

This finding supports the previous studies giving vitamin D a role indicating metabolic syndrome and risk factors.[3] On the other hand, the exact mechanisms responsible for the mentioned increase in vitamin D levels are not fully understood. However, it looks as if it is an effect that is independent from serum calcium, phosphorus, parathormone, magnesium levels, or thyroid function.

It was shown that abnormalities of calcium metabolism may play key roles in the pathophysiology of hypertension.[10,11] These changes may be at the systemic level in essential hypertension as well as in experimental hypertension. Previous studies on stroke-prone spontaneously hypertensive rats (SHRSP) showed various abnormalities in Ca metabolism, and SHRSP were proposed to be a good model for spontaneous osteoporosis in man.[12,13] This also means that there should be an association between hypertension and calcium metabolism. An increased urinary calcium excretion and a reduced bone density have been reported in hypertensive patients compared to normotensive controls by Cappuccio et al. in 1999 and Tsuda et al. in 2001.[1,14] Beyond this, hypertensive patients have been found to be in increased risk of osteoporosis and bone fractures.[15] Antihypertensive therapy reduced the risk of fracture in these patients in a recent case-controlled study.[16]

High BP is reported to be associated with abnormalities in calcium metabolism. As a possible mechanism, platelet cytosolic calcium levels correlated with systolic and pulse pressures in Sabra or Lyon rats.[17] In a previous study, it was demonstrated that there is a graded independent relation between higher levels of phosphate, PTH, Ca $\times$ P product, and the risk of nondipping in hypertensive patients with an estimated GFR of >60 mL/min and normal mineral metabolism.[18] Also, it was proposed that sustained calcium loss may lead to increased bone mineral loss in people with high BP, and a recent study suggested vitamin D supplementation to have a role in reducing BP in hypertensive patients and that it should be supplemented with the antihypertensive drugs.

CCB are effective antihypertensive agents, but they may affect many metabolic processes, including bone metabolism. In an ovariectomy-induced osteopenic rat model, amlodipine and lacidipine improved the bone loss.[19] In another study, amlodipine was found to be capable of mitigating the negative effects of orchiectomy and proposed to be a good way in the prevention of osteoporosis.[20] In a rat model, it was concluded that chronic use of amlodipine compromised bone neoformation in the repairing process of surgical defect in the mandibular ramus of rats, but no precluded occurrence of fracture consolidation was reported.[21] Amlodipine was speculated to exert its effect through a direct inhibition of osteoclast function and/or suppression of parathormone secretion and subsequent inhibition of osteoclast activity.[15] Our findings are also in favor of potent CCB such as amlodipine and lacidipine to have beneficial effects on bone metabolism and an antihypertensive effect.

Valsartan also led to increases in vitamin D levels, but the change was not statistically significant. The mechanisms underlying the difference between amlodipine and valsartan in terms of increasing vitamin D levels are not fully understood. But it may be associated with the CCB effect of the amlodipine itself or another effect at the receptor level.

The relatively small number of patients in study groups may be the limitation of our study to identify the whole mechanisms underlying why amlodipine resulted in a significant improvement in vitamin D levels.

CONCLUSION

In the present study, despite elevated levels of vitamin D with the use of both drugs, this increase was found to be more significant in the amlodipine group compared to valsartan. As a result, in hypertensive subjects with lower vitamin D levels, taking the preference of antihypertensive treatment regimens into account is important and these results require to be supported by studies on larger patient groups with the use of different treatment options.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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