RESEARCH ARTICLES

Comparison of panoramic mandibular cortical bone quality indexes in amlodipine users and healthy individuals

Aga Satria Nurrachman*✉, Lusi Epsilawati**, Azhari**, Suhardjo Sitam**

*Department of Dentomaxillofacial Radiology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia
**Department of Dentomaxillofacial Radiology, Faculty of Dentistry, Padjadjaran University, Bandung, West Java, Indonesia
*Jl Mayjen Prof. Dr. Moestopo No.47, Surabaya, East Java, Indonesia; ✉ correspondence: aga.satria@fkg.unair.ac.id

ABSTRACT

Hypertension and osteoporosis are believed to be linked to to each other. Previous studies have suggested that the imbalance of calcium metabolism in hypertensive condition and the use of calcium channel blockers such as amlodipine may lower the density and quality of bone. Panoramic radiography has been widely used as a reliable tool in assessing bone quality. One indicator of bone quality in panoramic radiograph is the macrostructure evaluation of mandibular cortical bone by using various indexes such as mandibular cortical index (MCI) and antegonial index (AI). This research aimed to compare the bone quality of hypertensive patients with amlodipine and healthy individuals using MCI and AI. In this study we used sixty panoramic radiographs of hypertensive patients with amlodipine and healthy individuals, thirty for each group, with various aspects of demography. The MCI analysis was done by dividing the mandibular cortical shape into three different qualitative categories and the AI analysis was done quantitatively by measuring the width of mandibular cortical bone in antegonial region using ImageJ software. There were statistically significant differences in the results between the two groups in terms of both AI (p = 0.000) and MCI (p = 0.001) in which hypertensive group had lower score. Based on this research, there were differences of mandibular bone quality of hypertensive patients with amlodipine and healthy individuals, particularly in its macrostructure.

Keywords: amlodipine; cortical bone; hypertension; mandible; radiography

INTRODUCTION

Hypertension or high blood pressure is a chronic condition where blood pressure increases in the arteries. This disease is classified either as primary hypertension when there is no definite medical causes or as secondary hypertension when it is caused by other pathologic conditions in kidney, heart, or endocrine system.[1] Hypertension becomes a prevalent medical issue in developing countries, nearly 75% of hypertensive persons live in developing countries and these regions are projected to have the largest increase in the prevalence of hypertension by 2025. Various factors such as poor lifestyle, high illiteracy rates, limited access to health care system, poverty, and the high cost of medicine are suspected to contribute to this condition. Hypertension affects 26.5-31.7% of Indonesian individuals (18 years and older), in which only 7.7-9.5% of those with hypertension are aware of their condition and 2.3% take antihypertensive medication.[2,3]

Hypertension and osteoporosis have been reported to be linked to each other. Osteoporosis is characterized by a fragile condition of bone that may cause bone fracture. Low calcium intake, a lack of vitamins D and K, and a high sodium consumption are known to be linked to both osteoporosis and hypertension.[4] Previous studies have shown that hypertension influences bone mineral density (BMD) through blood pressure regulation and calcium metabolism. High blood pressure is reported to cause the imbalance of calcium metabolism, leading to the leakage of bone calcium. This change then causes a secondary hyperparathyroidism where parathyroid hormone (PTH) increases bone turnover yet decreases BMD and bone quality.[1,5,6]

The use of antihypertensive medications has also been known to affect bone. These drugs may induce osteoporosis directly or indirectly by affecting bone metabolism, strength, and density. There are many classes of antihypertensive

agents with different working mechanisms in reducing blood pressure. One of the most widely used antihypertensive drugs in Indonesia is the calcium channel blocker (CCB) group, specifically amlodipine, because it can easily be obtained in hospitals and pharmacies, making it widely used as the first-line antihypertensive agents. For a dozen years, this drug has occupied the top ten best-selling drugs in the world. In 2006, amlodipine became the second best-selling drug in Indonesia and in 2010 it ranked 5th of the top 10 most widely prescribed drugs.[7] As the name implies, this class of drug works by inhibiting calcium absorption in the body and may have an influence on bone density and quality.[1,5,6,8,9]

Panoramic radiography is one of the most general diagnostic examinations that are regularly referred by practitioners in any dental treatments. Various techniques have been proposed and developed in assessing bone quality and density using panoramic radiograph. The qualitative analysis of cortical bone morphology, known as mandibular cortical index (MCI), has been proven to successfully identify osteoporotic conditions. Mandibular cortical index qualifies mandibular cortical shape and groups it into three categories which represent a state of the decreased bone quality. In addition, there is also AI that measures cortical thickness in the anterior to the gonion region of mandible. These two parameters have been widely used to measure bone quality and to see the signs of resorption, which can describe the state of osteoporosis.[8,10–13] The aim of this study was to describe the condition of bone in hypertensive patients, particularly in amlodipine users, by assessing the quality of mandibular cortical bone through MCI and AI analysis, and comparing it with healthy non-hypertensive individuals.

MATERIALS AND METHODS

This study used a descriptive and analytical cross-sectional design which assessed the quality of mandibular cortical bone in hypertensive patients who took amlodipine and compared it with that in normal individuals. The population and sample used in this study were secondary data in the form of panoramic radiographs of 30 hypertensive patients who took amlodipine and 30 non-hypertensive individuals, including male and female subjects whose age range was between 40-75 years old from the database of Universitas Padjadjaran Dental Hospital. The samples were selected using a purposive sampling technique. The selected samples were all radiographs that met the following criteria: 1) patients who had hypertension for at least 1 year, 2) patients who took amlodipine drugs with a daily dose of 5-10 mg, 3) no pathological conditions that affected the mandibular cortical bone, 4) radiographic data that had a good quality so an assessment could be carried out. This research received approval from the health research ethics committee of Universitas Padjadjaran Bandung where this study was conducted. The quality assessment of the mandibular cortical bone was done with two types of index, MCI and AI.

Mandibular cortical index (MCI) is a qualitative index that classifies mandibular cortical shape from the right to left mental foramen into one of the three classifications according to the method proposed by Klemetti et.al.: C1 – endosteal margin of the cortex looks sharp and firm on both sides, the cortex is in normal condition and no changes occurred; C2 - endosteal margins have semilunar defects or form residues (one to three layers) on one or both sides (mild to moderate cortex erosion); C3 - the cortical layer forms an endosteal layer with thicker and more severely eroded cortex residues.[10,11,14–16]

Antegonial Index (AI) measures mandibular cortical thickness in the anterior area at the gonial angle, in the form of a line perpendicular to the cortex on the line connecting the anterior border of the ramus ascendens to the mandibular lower border. Measurement was done using ImageJ software (ImageJ 2.0.0-rc-69/1.52p, Wayne Rasband, National Institutes of Health USA) that had been calibrated in a scale of millimeter (mm) and carried out on both the right and left sides of the mandible, and the mean score was then calculated as the final result.[8,12,13]
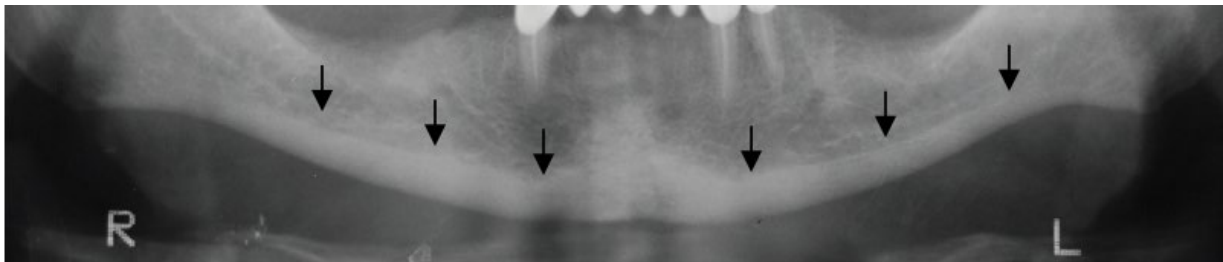
Figure 1. C1 type of mandibular cortical bone in MCI. The mandibular cortex looks sharp, intact, and homogenously radiopaque on both sides which represents a normal condition.[11]
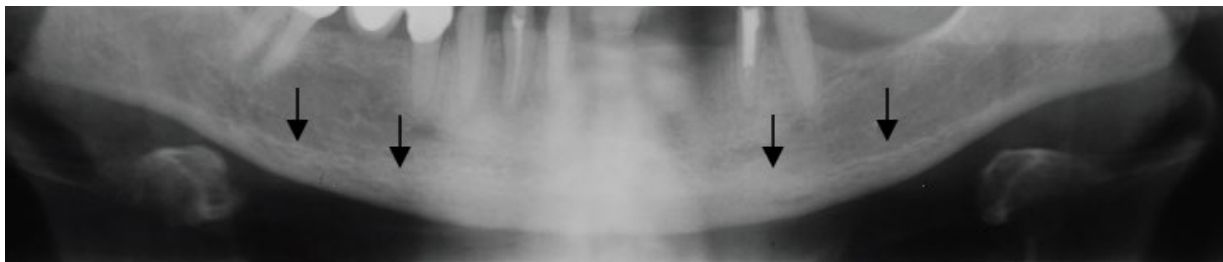

Figure 2. C2 type of mandibular cortical bone in MCI. Note the erosion on both sides of the mandibular cortex. The mandibular cortex looks more porous, thus producing a mixed density radiographic appearance of bone.[11]
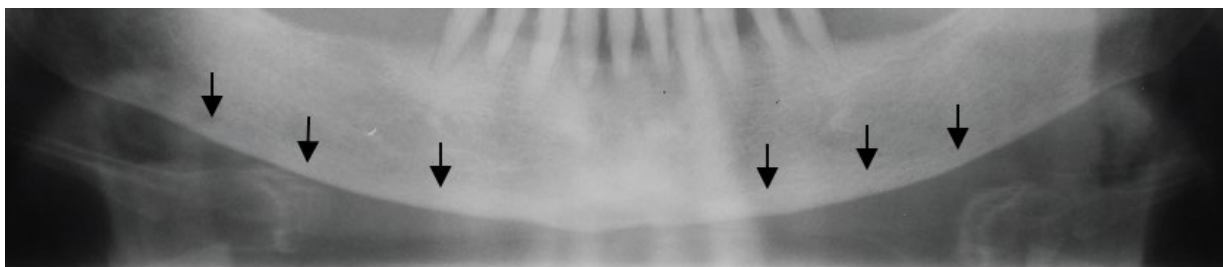

Figure 3. C3 type of mandibular cortical bone in MCI. The mandibular cortex is lost and could not be traced clearly on both sides of the mandible due to severe erosion and thinning.[11]
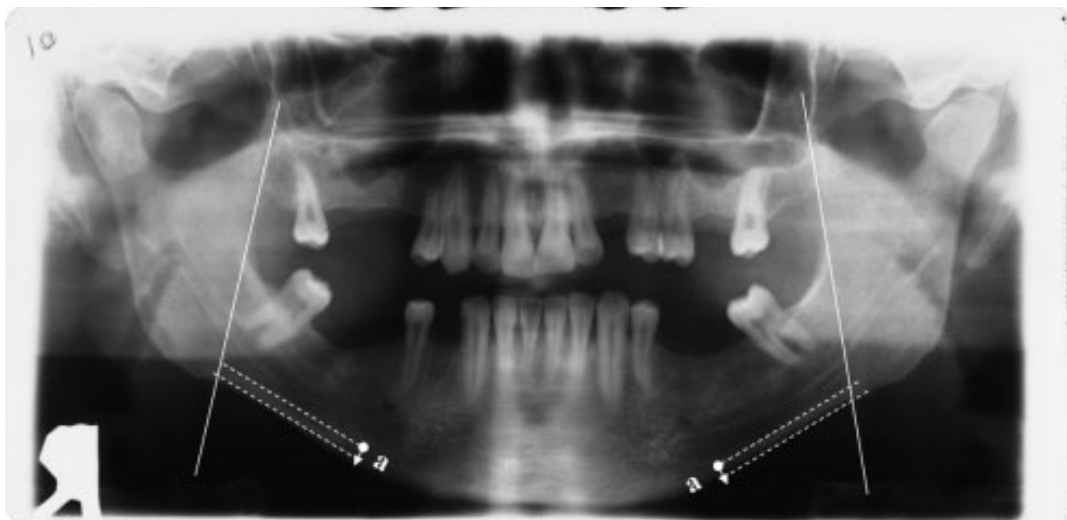

Figure 4. AI measurements and distances used in this study[12]

Table 1. Mandibular cortical index classifications in both groups

		MCI			All
		C1	C2	C3	
Healthy individuals	Amount	10	20	0	30
	Percentage	33.3	66.7	0	100.0
Amlodipine users	Amount	6	13	11	30
	Percentage	20	43.3	36.7	100.0
All	Amount	16	33	11	60
	Percentage	26.7	55	18.3	100.0
		p = 0.001	x^2 = 13.485		

Table 2. Results of antegonial index measurement in both groups

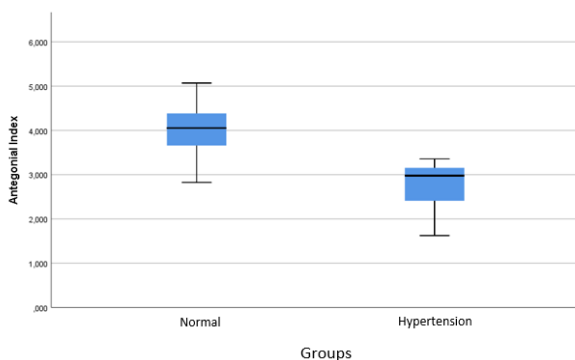|	Mean	SD	Minimum	Maximum	p
Healthy individuals	4.008	0.553	2.824	5.068	
Amlodipine users	2.775	0.505	1.623	3.355	0.000

Figure 5. The result diagram of antegonial index measurements in both groups

The quality of MCI for each sample was deliberated together by two oral and maxillofacial radiology specialists to decide the final category, while the quantitative AI measurements were conducted individually three times by each observer to get the final mean score. The data were then tested statistically with a Mann-Whitney test to compare the mean score of AI between the two groups, and tested with a Chi-square test to compare the qualitative data in the MCI assessment. A p value less than 0.05 was considered statistically significant.

RESULTS

In total there were 60 samples in this study with 30 samples in each group. The results of the MCI assessment showed that most of the samples in the hypertension group had C3 cortical bone shape, whereas none in the normal group had this category (Table 1). Based on the Chi-square test, there were significant differences between the two groups (p = 0.001).

Lower AI was found in the hypertension group (2.775 ± 0.505) compared to the normal group (4.008 ± 0.553). The results of the Mann-Whitney statistical test also showed that there were significant differences in the values between the two groups (p = 0.000).

DISCUSSION

Patients with hypertension are known to have a higher risk of fracture and decreased bone density than healthy individuals. Some studies have shown that hypertensive samples have lower BMD and bone magnesium levels than the normal condition, in which the disruption of calcium metabolism possibly becomes a main causative factor. Hypertension is known to be associated with high levels of sodium chloride (NaCl) in the body, disrupting calcium absorption and increasing urinary calcium excretion (hypercalciuria). In a condition of high levels of NaCl, calcium in blood cannot be filtered in the kidney to be reabsorbed back into the bloodstream in the proximal distal

tubule and Henle's arch so it must be excreted. As shown in previous studies, the two ions have the same binding site, namely the claudin-2 protein in the proximal tubule of the kidney, which causes them to compete with each other to bind. In addition, the reabsorption process is also regulated by hormones such as parathyroid hormone (PTH). The removal of calcium from the body through urine lowers blood calcium levels and causes activation of the PTH hormone. The elevation of PTH will then increase bone turnover, reduce BMD, and bone quality.[1,17]

Amlodipine is a dihydropyridine calcium channel blocker with an antihypertensive effect that works by inhibiting the entry or absorption of calcium when entering the L-type calcium channel membrane which then causes a decrease in intracellular calcium concentration and relaxation of smooth muscle cells in peripheral and coronary arteries.[18] Several other theories state that amlodipine can reduce bone quality by reducing the production of steroid hormones, thus reducing bone formation and decreasing mandibular trabecular and cortical volume. A study conducted by Adelaja et al. discovered the impaired morphology of the bone marrow in adult Wistar rats treated with 5-15 mg of amlodipine besylate.[19] Another study also stated that this class of drugs inhibits osteoclast function which then may cause either positive or negative effects. Several studies have shown that amlodipine can inhibit bone resorption and reduce the risk of osteoporosis if it occurs in the intact bone, but it can disrupt a healing process if it occurs in a fractured bone.[8,20,21]

In comparing the bone quality of the groups of hypertensive patients taking amlodipine and healthy individuals, panoramic radiograph was used in this study because it is a common examination and often chosen by practitioners in diagnosing and screening the condition of the teeth. Several studies have described the usefulness of panoramic radiograph as a means of assessing the signs of resorption and osteoporosis. Some indices that may be used are MCIand AI as in this study.[22] The results of this study indicated a significant difference between the two groups in
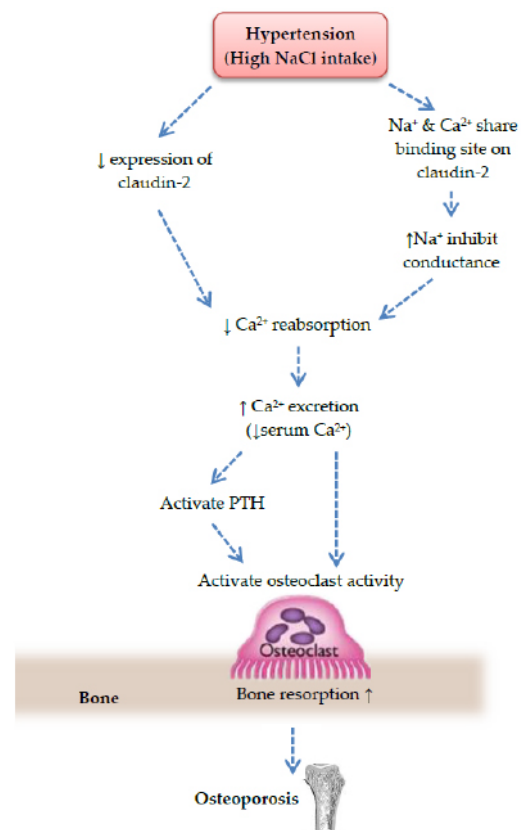

Figure 6. Pathway mechanism of osteoporosis in case of hypertension[17]

terms of the mandibular cortical quality based on both the MCI and AI indices.

Analysis of MCI is reported to have an excellent accuracy among other radiomorphometric indices in assessing osteoporosis signs.[12] MCI is a qualitative method for evaluating the morphological structure of the mandibular cortical layer by categorizing its shapes into several types. This study found that C3 (severe cortical erosion) was more dominant in the amlodipine group than the healthy group. This indicates that the samples in the amlodipine group had more porosity in the mandibular cortical layer due to reduced bone mass. The AI analysis that quantitatively assessed the cortical thickness in the anterior gonial region of the mandible also found a statistically significant difference between these two groups where the amlodipine group had lower mean score of cortical thickness than the healthy group. These results are in line with several previous studies that, in a condition of hypertension with a regular

antihypertensive drug therapy, there can be an alteration of bone quality due to the disruption of calcium metabolism.[1,8,17,18,20,21,23,24]

However, the effects of amlodipine on calcium metabolism and bone density themselves are still debated. There have been many studies that examined the relationship between these two and some of them concluded that the relationship is inconsistent and contradictory, including the result of this study. Several studies stated that taking antihypertensive medication raises the risk of fracture,[25,26] while others claimed that the blood-pressure-lowering effect indirectly increases bone density, which may lower the risk of fracture.[27] A research in Wistar rats given amlodipine showed insignificant changes in bone,[18] other stated amlodipine impairs the bone marrow morphology,[19] while some researchers wrote that amlodipine actually has an anti-osteoporosis effect through inhibition of L-type calcium channels by stimulating the inositol triphosphate receptor, releasing calcium intracellular, or stopping osteoclast activation and maturation.[18,28–30] This study only assessed and focused on the macrostructure of mandibular cortical thickness and shape. Therefore, further research using a microstructural or molecular approach is indispensable.

As the samples were collected randomly and the variables of age and sex were ignored in this study, there may be some limitations of the result. Several studies showed that the mandible reaches the greatest height at around 30-39 years old in both sexes. The height and quality of bone have also been known to decrease with aging, starting up to 40 years old. A greater bone damage has also been found in older menopausal women due to the decreasing estrogen levels. In addition, this study did not clearly distinguish and compare the exact duration of hypertension and the duration of taking amlodipine from each sample available in this study, which can affect the results obtained. Some studies stated that the longer the duration of hypertension and the longer the patients take amlodipine, the worse the reduce in bone mineral density. There are other factors that can affect the

decrease in bone mass such as reduced physical activity, diet, alcohol consumption, race, family history, heredity, and other secondary conditions that may cause osteoporosis.[1,12,14,27]

CONCLUSION

Based on the result of this study, it can be concluded that there are significant differences in the quality of mandibular bone between groups of healthy individuals and hypertensive patients who take amlodipine, especially in macrostructure, through AI and MCI index analysis on panoramic radiographs.

REFERENCES

1. Hussein MK, Fatah AA. The effect of hypertension and beta-blocker antihypertensive drug on bone mineral density value at the mandibular cortex in mental and gonial regions in hounsfield unite using computed tomographic study. Journal of Al Rafidain Univ Coll. 2016; (38): 33–47.
2. Ibrahim MM, Damasceno A. Hypertension in developing countries. Lancet. 2012; 380(9841): 611–619.
   doi: 10.1016/S0140-6736(12)60861-7
3. NIHRD. National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia, Jakarta. Kementerian Kesehatan RI. 2018.
4. Yang S, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Association between hypertension and fragility fracture: a longitudinal study. Osteoporos Int. 2014; 25(1): 97–103.
   doi: 10.1007/s00198-013-2457-8
5. Salam MHA. Effect of blocking L-Type calcium channels on bone in ovariectomy model of osteoporosis in rats. Med J Cairo Univ. 2017; 85(5): 1903–1910.
6. Kang KY, Kang Y, Kim M, Kim Y, Yi H, Kim J, Jung HR, Park SW, Kim HY, Ju JH, Hong YS. The effects of antihypertensive drugs on bone mineral density in ovariectomized mice. J Korean Med Sci. 2013; 28: 1139–1144.
   doi: 10.3346/jkms.2013.28.8.1139

7. Alegantina S, Isnawati A. Profil disolusi tablet amlodipin dan perbandingan kadar dua produk generik dengan produk inovator. J Kefarmasian Indones. 2015; 5(1): 11–18. doi: 10.22435/jki.v5i1.4081.11-18

8. Septiana F, Epsilawati L, Suhardjo, Dananjaya A. Analysis of the mandible cortical bone height in amlodipine user patient using panoramic radiograph. FDI-PDGI Contin Educ. 2017; 391–397.

9. Gradošová I, Živná H, Švejkovská K, Palička V, Tichý A, Živný P. Effects of amlodipine on bone metabolism in male albino Wistar rats Cardiovascular diseases are one of the leading causes of death for people in developed countries world-wide. The most common form is arterial hypertension, which can be reduced by sever. Acta Vet Brno. 2011; 80: 391–396.

10. Govindraju P, Chandra P. Radiomorphometric indices of the mandible – an indicator of osteoporosis. J Clin Diagn Res. 2014; 8(3): 195–198. doi: 10.7860/JCDR/2014/6844.4160

11. Hastar E, Yilmaz HH, Orhan H. Evaluation of mental index, mandibular cortical index and panoramic mandibular index on dental panoramic radiographs in the elderly. Eur J Dent. 2011; 5(1): 60–67.

12. Dagistan S, Bilge OM. Comparison of antegonial index, mental index, panoramic mandibular index and mandibular cortical index values in the panoramic radiographs of normal males and male patients with osteoporosis. Dentomaxillofacial Radiol. 2010; 39(5): 290–294. doi: 10.1259/dmfr/46589325

13. Tofangchiha M, Javadi A, Khorasani M, Shokrimozhdehi M. Diagnosis of osteoporosis using cortex mandibular indices based on cortex thickness and morphology in comparison with visual assessment of the cortex. Journal of Craniomaxillofacial Research. 2017; 4(2): 345–351.

14. Moeintaghavi A, Hosseinizarch H, Tabassi SM. The comparison of mandibular radiomorphometric indices in panoramic radiography between patients with chronic periodontitis and healthy individuals. The Journal of Contemporary Dental Practice. 2014; 15(4): 461–465. doi: 10.5005/jp-journals-10024-1563

15. Carmo JZB, Medeiros SF de. Mandibular inferior cortex erosion on dental panoramic radiograph as a sign of low bone mineral density in postmenopausal women. Rev Bras Ginecol Obstet. 2017; 39(12): 663–669. doi: 10.1055/s-0037-1606622

16. Alapati S, Reddy RS, Tatapudi R, Kotha R, Bodu NK, Chennoju S. Identifying risk groups for osteoporosis by digital panoramic radiography. Contemp Clincal Dent. 2015; 6(1): 253–257. doi: 10.4103/0976-237X.166833

17. Wong SK, Chin K, Suhaimi FH, Ahmad F, Ima-Nirwana S. The Relationship between Metabolic Syndrome and Osteoporosis: A Review. Nutrients. 2016; 8(6): 347. doi: 10.3390/nu8060347

18. Zivna H, Gradošová I, Zivny P, Cermakova E, Palicka V. Effects of Amlodipine on Bone Metabolism in Orchidectomised Spontaneously Hypertensive Rats. Pharmacology. 2018; 102(1-2): 67–73. doi: 10.1159/000489666

19. Adelaja A, Ghazali O, Ayantunji L, Omotoso G. Amlodipine besylate impairs the morphology of bone marrow in adult male wistar rats. Anatomy Journal of Africa. 2017; 6(2): 963–968. doi: 10.4314/aja.v6i2.160479

20. Moraes RB, Corrêa L, Luz JGC. Adverse effects of the amlodipine on bone healing of the mandibular fracture : an experimental study in rats. Oral Maxillofac Surg. 2011; 15(2): 93–101. doi: 10.1007/s10006-010-0237-6

21. Ağˇaçayak KS, Güven S, Koparal M, Güneş N, Atalay Y, Atılgan S. Long-term effects of antihypertensive medications on bone mineral density in men older than 55 years. Clin Interv Aging. 2014; 9: 509–513. doi: 10.2147/CIA.S60669

22. Varma B, David AP, Kurup S, Sam DM, Aravind M, Chandy ML. Assessment of panoramic radiomorphometric indices of mandible in diabetes mellitus patients and non diabetic individuals. Journal of Clinical and Diagnostic Research. 2017; 11(11): 35–39.

23. Gunawan G, Sitam S, Epsilawati L. Densitas tulang mandibula pengguna obat anti hipertensi calcium channel blocker (CCB) melalui radiograf panoramik. Jurnal Radiologi Dentomaksilofasial Indonesia. 2020; 4(2): 1. doi: 10.32793/jrdi.v4i2.527

24. Septina F, Sitam S, Epsilawati L. Analisis antegonion indeks dan mental indeks pada subjek hipertensi pengguna amlodipine yang di evaluasi menggunakan radiograf panoramik. E-Prodenta J Dent. 2020; 4(1): 284–292.

25. Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: self-controlled case series. Pharmacoepidemiol Drug Saf [Internet]. 2011; 20(8): 879–84. doi: 10.1002/pds.2176

26. Pinheiro M de M, Eis SR. Epidemiology of osteoporotic fractures in Brazil: What we have and what we need. Arq Bras Endocrinol Metabol. 2010; 54(2): 164–170. doi: 10.1590/S0004-27302010000200012

27. Kim SY, Kim S, Choi SE, Kim BS, Choi HR, Hwang D, Won CW. Number of daily antihypertensive drugs and the risk of osteoporotic fractures in older hypertensive adults: National health insurance service – Senior cohort. J Cardiol. 2017; 70(1): 80–5. doi: 10.1016/j.jjcc.2016.09.011

28. Zaheer S, Boer I De, Allison M, Brown JM, Psaty BM, Robinson-cohen C, et al. Parathyroid hormone and the use of diuretics and calcium-channel blockers: the multi-ethnic study of atherosclerosis. J Bone Miner Res. 2016; 31(6): 1137–1145. doi: 10.1002/jbmr.2779

29. Mao Y, Jiang L, Yan X, Ma H. Effects of antihypertensive drugs on bone metabolism in ovariectomized spontaneously hypertensive rats. Int J Clin Exp Med. 2016; 9(9): 17628–17635.

30. Ghosh M, Majumdar SR. Antihypertensive medications, bone mineral density, and fractures: a review of old cardiac drugs that provides new insights into osteoporosis. Endocrine. 2014; 46(3): 397–405. doi: 10.1007/s12020-014-0167-4