Association between Vitamin D and Calcium Level and BMD Alteration in Post-Menopausal Osteoporosis Patients Treated with Bisphosphonate Therapy for at Least 1 Year in Saiful Anwar Hospital Malang

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Abstract

Post-menopausal osteoporosis is a degenerative disease among post-menopausal women. In Indonesia, women over 50 years old get post-menopausal osteoporosis.The therapy should be comprehensive and continous. Bisphosphonate therapy is one of the most preferable therapeutic option for maintaining bone density. Calcium and vitamin D have a role in increasing osteoblastic activity. The objective of this study was to describe the vitamin D and calcium in bone mineral density (BMD) of hip and spine in postmenopausal woman with biphosphonat therapy. This study is a cross-sectional, observational analytic. The subject were female patients with post-menopausal osteoporosis treated in clinic of RSUD dr. Saiful Anwar Malang, who had received routine bisphosphonate for at least 1 year. The method was collecting the patient data, who received oral and injectie bisphosphonate therapy, serial BMD test,hip and spine, vitamin D and calcium level in serum test. Total sample 25 participan, the association between BMD change (Δ BMD), vitamin D and calcium level, were analyzed.with Chi Square test then continued using Spearman correlation test. Vitamin D levels in Δ BMD Spine in participants was less <30 ng/mL, mean 16.8+6.95 14 respondents (56%), and 6 respondens (24%) 10.05+5.28, normal vitamin D levels were 5 respondents (20%) mean 34.16+5.10. Vitamin D levels in Δ BMD Hip in participants was less <30 ng/mL, mean 15.19+7.7 12 respondents (48%), and 8 respondens (32%) 12.30+5.57, normal vitamin D levels were 5 respondents (20%) 33.66+5.40. Calcium levels in BMD spine 9.60+0.45, 14 respondents (56%), and 11 respondens (44%) 9.59+0.52. There is a significant and moderate relationship between vitamin D levels with Δ BMD spine (p=0.009, r=0.564) and Hip (p=0.039, r= 0.480) T Blood calcium levels with Δ BMD changes unrelated (normal). There is a significant association between vitamin D levels spine and Hip Δ BMD. Blood calcium levels with Δ BMD changes unrelated.

Keywords: *Osteoporosis, Bisphosphonate, Vitamin D levels, Calcium levels.*

INTRODUCTION

Postmenopausal osteoporosis is a degenerative disease in post-meno-pausal women, affecting bone structure and architecture. World Health Organization (WHO) defines osteoporosis as a condition where the bone mineral density (BMD) score was

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≤-2.5 compared to the standard deviation of mean score in young adult (Hania, 2008; Lin, *et al*., 2015; Indonesian Ministry of Health, 2015; Jeremiah, *et al.*, 2015; Mithal, *et al*., 2009). The Indonesian Osteoporosis Association in 2007 suggested that the proportion of individuals affected by osteoporosis aged over 50 years was 32.3% in women and 28.8% in men. The incidence of upper femoral fractures due to osteoporosis at the age of 40 in Indonesia is around 200 out of 100,000 cases (Indonesian Ministry of Health, 2015). The increase in bone mineral density by bisphosphonate with active vitamin D analog is associated with the serum calcium level in postmenopausal osteoporosis (Kinoshita, *et al.*, 2019).

Biphosphonate therapy can maintain bone mass and density, by suppressing osteoclast work so that bone resorption does not occur excessively even after the patient is no longer undergoing such therapy (Maraka, *et al*,. 2015; Watts, *et al*., 2010; Harmanjit, *et al*., 2013; Malaysian Osteoporosis Society, 2012). In addition, calcium and vitamin D in the body also has a role in increasing osteoblastic activity. Therefore, vitamin D levels and calcium levels in the blood must be optimized, because they can synergistically assist the process of bone formation by increasing osteoblastic activity (Silva, *et al*., 2015; Eastell, *et al*., 2016; Taha, *et al*., 2015; Reszka, *et al*., 2003).

There are few studies on bisphosphanates therapy in postmenopausal osteoporosis patients to measure calcium and vitamin D levels in Indonesia. This study aims to determine the change in BMD in postmenopausal menopausal patients treated with bisphosphonates as well as the relationship to vitamin D and calcium levels at the Regional General Hospital (RSUD) dr. Saiful Anwar, Malang City.

METHODS

This study was a cross-sectional, observational analytic study.The subjects were post-menopausal osteoporosis female patients visiting the osteoporosis clinic of Saiful Anwar Hospital Malang in 2016 and had been treated with bisphosphonate for at least 1 year. This study was conducted from August to September 2017, including preparation, data analysis, and report.

The dependent variable of this study was the change of BMD score, the level of calcium and vitamin D, while the independent variable were biphosphonat therapy.

The population of this study between 2016-2017, 362 patients, therefore this study used total sampling method, where all subjects who met the inclusion criteria were included into this study. The inclusion criteria were patients diagnosed with post-menopausal osteoporosis with BMD examination at Osteoporosis Clinic of Saiful Anwar Hospital Malang, had undergone at least once BMD examination at Osteoporosis Clinic of Saiful Anwar Hospital Malang in 2016, had been in regular bisphosphonate therapy for at least 12 months, and agreed to participate in the study. The exclusion criteria were longterm steroid therapy, estrogen therapy, heavy smoker, daily coffee, and alcohol consump-tion, and patients with other comorbidities (renal impairment, malignancy, and chronic infection).

Between 2016 and 2017, 362 osteoporosis patients attended Saiful Anwar Hospital Malang. Of 362 patients, 150 had postmenopausal osteoporosis in which 35 of whom were taking regular bisphosphonate therapy. Of 35 patients, 25 patients regularly visited the osteoporosis clinic at dr. Saiful Anwar Hospital. A total of 25 patients receiving bisphosphonates and regularly visited the osteoporosis clinic were included in the study.

Oral bisphosphonates were the most commonly used drug (14 patients or 56%). Bisphosphonates taken with the composition of oral risendronate was used by 13 patients (52%) who were taken once a week, and oral ibandronate as many as 1 patient (4%) taken once a month. While injection of bisphosphonates was used by 11 patients (44%), with details of 9 patients using ibandronate injection (which is injected every 3 months) and 2 patients using zolendronate injection.

Preparation

The medical record of patients who met the inclusion criteria were studied for thehistory of post-menopausal osteoporosis, bone mineral density (BMD) examination, and therapy given.

Sampling

Serial BMD of patients who agreed to participate in this study were examined. The level of calcium and vitamin D were also examined (approxiamety 15-20 minutes) through laboratory blood test.

Measurement

Chi square test was used for data analysis. The analysis was then continued using Spearman correlation test to find out the association between bisphosphonate therapy and BMD score, calcium level,and vitamin D level in post-menopausal osteoporosis patients treated with bisphosphonate. Analysis was done using SPSS version 20.00 software.

RESULT

The characteristics of patients according to age is presented in Table 1. From the total of 25 participants, participants who were <60 years old as many as 7 respondents (28.0%), who had the age of 61 - 70 as many as 9 respondents (36%), who had ages 71 to 80 as 7 respondents (28%), and who have age> 80 as many as 2 respondents (8%).

Table 1. Distribution of patients with postmenopausal osteoporosis treated with bisphosphonates.

Age	Frequency	Percentage
<60 y	7	28.00
61-70 y	9	36.00
71-80 y	7	28.00
>80 y	2	8.00
Total	**25**	**100**

From a total of 25 participants based on changes in BMD (Δ BMD) Spine can be found that has Δ BMD Spine worsened as many as 14 respondents (56%) mean 16.8+6.95, Δ BMD Spine improved by 11 respondents (44%) (6 respondens (24%) mean 10.05+5.28 , normal vitamin D levels were 5 respondents (20%) mean 34.16+5.10 (Table 3)

Table 2. The distribution of the use of bisphosphonate therapy in the year 2016-2017.

Number of patient	Oral Biophosphonat	Injection of Biohosphonat
13	One tablet per week	-
1	One tablet per month	-
11	-	Injection every 3 months

While from the total 25 participants, based on the change Δ BMD stated that those who have Δ Based on the result of Table 3, it is found that Chi Square with *p* value is 0.009, because *p*=0.009 <0.05 (α=5%), so it can be concluded that there is significant correlation between vitamin D and Δ BMD Spine. Then, spearman correlation value of 0.564 with value *p*=0.009. This suggests that the relationship of spine BMDs with vitamin D levels belongs to moderate and significant categories. The direction of a positive relationship indicates that decreased vitamin D levels are associated with changes in BMD (Δ BMD) of the worsening spine.

BMD HIP deteriorated as many as 12 respondents (48%) mean 15.19+7.7, Δ BMD HIP improved as much as 13 respondents (52%) (8 respondens (32%) 12.30+5.57, normal vitamin D levels were 5 respondents (20%) 33.66+5.40 (Table 4).

Furthermore, based on the results of Table 4 it is found that Chi square results with p-value of 0.039, because the value of *p*=0.039 <0.05 (*α*=5%), so it can be concluded that there is a significant relationship or linkage between vitamin D levels with Δ BMD of hip. The spearman correlation value was 0.480 with *p* value=0.039. This suggests that

Table 3. Cross-tabulation between vitamin D levels and BMD Spine.

Vitamin D Level	Δ BMD Spine			Δ BMD Spine			
	Worsening	%	Mean±SD	Improve	%	Mean±SD	%
	14	56	16.08+6.95	6	24	10.05+5.28	80
Normal	0	0	0	5	20	34.16±5.10	20
Total	14	56	0	11	44		100
p: 0.0009 *r*: 0.564							

the association of BMD HIP with vitamin D levels belongs to moderate and significant categories. The direction of a positive relationship indicates that decreased vitamin D levels are associated with a decrease in BMD (Δ BMD) of hip.

Next, based on the results of Table 5 it is found that Chi square results can not be calculated because all observations of calcium levels obtained the same results that all patients have normal calcium levels.

The relation between calcium levels and δ bmd is noted from chi square test. Based on the results of Table 6 it is found that Chi square results can not be calculated because all observations of calcium levels obtained the same results that all patients have normal calcium levels.

DISCUSSION

This research found some characteristic, sample age at most is 61-70 years old (36%), then 51-60 years (28%) and the rest are patients over 70 years (36%).

By using bisphosphonate therapy, it was not necessarily BMD patients increased even some patients experienced a worsening of BMD that is as much as 60% of patients on the value of BMD pelvis or spine after a year of treatment. The worsening of BMD is most prevalent in patients taking oral bisphosphonates of 10 patients (40%) versus 5 patients (20%) using bisphosphonate injections. This may be due to an ugly absorption factor (*ie* less than 1%) in oral preparation coupled with incorrect oral dosage consumption due to lack of patient knowledge of how to take this drug (Cairoli, *et al*., 2014; Colin, 2002; Grey & Reid, 2006; Kennedy, *et al*., 2007; Horikawa, 2015).

In this study, low vitamin D levels were found in approximately 80% of patients (20 people), this may be due to several factors including (1) low exercise activity (of all samples, only 16% of all patients performing regular exercise) which is associated with exposure of patients with sun rays (Indonesian Ministry of Health, 2015; Mithal, *et al*., 2009; Kinoshita, *et al*., 2019) and (2) low vitamin D supplementation in patients (only 16% of patients

Table 4. Cross tabulation between vitamin D levels and Δ BMD of hip.

Vitamin D	Δ BMD HIP						
	Worsening	%	Mean±SD	Improve	%	Mean±SD	%
Low	12	48	15.19±7.7	8	32	12.3±5.57	80
Normal	0	0	0	5	20	33.66±5.40	20
Total	12	48	0	13	52		100
P=0.0039 *r*=0.480							

Table 5. Cross tabulation between calcium levels and BMD Spine.

Calcium	Δ BMD Spine							
	Worsening	%	Mean±SD	Improve	%	Mean±SD	Total	%
Normal	14	56	9.60±0.45	11	44	9.59 ±0.52	25	100
Total	14	56	0	11	44	0	25	100
p= - *r*= -								

receiving vitamin D supplements) and (3) low intake of foods rich in vitamin D as in cheese, milk and fish. While the remaining patients about 20% (5 people) have normal vitamin D levels because these patients do regular exercise such as by doing elderly gymnastics and gymnastics osteoporosis and adequate vitamin D supplementation in these patients. This is in the prevailing circumstances in patients with vitamin D3 deficiency (Rosol, *et al*., 2008); Taha, *et al*., 2015; Colin, 2002; Grey & Reid, 2006).

Vtamin D plays a key role in preventing the initiation stage by exerting anti-inflammatory, antioxidant defenses and DNA damage repair processes (Feldman, *et al*., 2014). Multiple myeloma is the most common cancer to affect bone with up to 90% of patients developing bone lesions (Roodman, 2010). It is characterised by increased bone resorption and the majority of patients have pathological fractures at diagnosis (Croucher & Apperley, 1998). Secondary spread of prostate cancer and breast cancer frequently involves metastases to bone, resulting in debilitating pain, immobility, fractures and spinal compression syndromes (Mundy, 2002).

Calcium levels in this study showed normal levels in all patients (25 people), whereas it should be noted that the complications of bisphosphonates are the occurrence of hypocalcemia. This may be due to the following factors, (1) homeostatic factor, this factor maintains the levels of calcium in the blood through hormonal mechanisms, in which the hormones associated with calcium levels are parathormone and calcitonin, so that by the mechanism of homeostasis the calcium in the blood will be maintained within normal limits, especially accompanied by (2) almost all patients in this study using calcium supplementation.

Based on Table 3 it can be concluded that there is a significant relationship or association between vitamin D levels and Δ BMD of the spine and, shows a moderate and significant category relationship. The direction of a positive relationship indicates that with decreasing levels of Vitamin D it is related to the value of Δ BMD of the spine will get worse and vice versa.

From statistical analysis indicated that there was a hip Δ BMD relationship with vitamin D levels included in moderate and significant categories. The

Table 6. Cross tabulation between calcium levels and Δ BMD of hip.

Calcium	Δ BMD Spine							
	Worsening	%	Mean±SD	Improve	%	Mean±SD	Total	%
Normal	12	48	9.71±0.58	13	52	9.49 ±0.34	25	100
Total	12	48	0	13	52	0	25	100
p= - *r*= -								

direction of a positive relationship indicates that with decreasing vitamin D levels associated with Δ the worsening of pelvic BMD. This is consistent with some references that suggest that vitamin D is an integral part of post-menopausal osteoporosis prevention programs. The mechanism of vitamin D that can affect Δ BMD spine and Δ pelvic bone BMD binds to the VDR in the osteoblast to stimulate increased osteoblast activity, indirectly inhibit osteoclast work, vitamin D also increases calcium absorption in the digestive tract and balances calcium plasma and phosphate concentration to ensure bone mineralization (Silva, *et al*., 2015; Malaysian Osteoporosis Society, 2012; Pawel & Mary, 2011; Eastell, *et al*., 2016; Cairoli, *et al*., 2014; Colin, 2002).

The association of calcium levels with changes in BMD in both spine and pelvis is shown by 2 tables, namely Table 5 and Table 6. Both tables are directly discussed together because both tables present data with normal calcium levels all. Because of that the calculation with chi-square test can not be done. So the next test is spearman test also can not be done calculation. In this study calcium levels in all normal patients may be caused by all patients having adequate calcium intake, in addition there is a mechanism of homeostasis that serves to stabilize blood calcium levels (Rosol, *et al.*, 2008; Cairoli, *et al*., 2014).

CONCLUSION

There is a significant relationship or association between vitamin D levels spine BMD and Hip BMD, where the relationship falls into moderate and significant categories (less than normal vitamin D levels (<30) have a positive correlation with worsening BMD). Blood calcium levels with BMD changes unrelated.

SUGGESTION

It is highly recommended for the patients to know the importance of the increased level of vitamin D in the blood in the success of osteoporosis treatment process including those with menopausal post osteoporosis given bifosfonat.

REFERENCES

Cairoli, E., Eller-Vainicher, C., Ulivieri, F.M., Zhukouskaya, V.V., Palmieri, S., Morelli, V., Beck-Peccoz, P., and Chiodini, I., 2014, Factors Associated with bisphosphonates treatment failure in post menopausal women with primary Osteoporosis, *Osteoporosis International*, **25**, 1401-1410.

Colin, E.M., 2002, Studies on the interaction between the estrogen and vitamin D endocrine system. Rotterdam: Department of Internal Medicine of the Erasmus MC.

Croucher, P.I., and Apperley, J.F., 1998, Bone disease in multiple myeloma, *Br J Haematol*, **103**(4), 902-910.

Eastell, R., O'Neil, T.W., Hofbauer, L.C., Langdahl, B., Reid, I.R., Gold, D.T., and Cummings, S.R., 2016, Postmenopausal Osteoporosis, *Nat Rev Dis Primers*, **2**, 16069.

Feldman, D., Krishnan, A.V., Swami, S., Giovannucci, E., and Feldman, B.J., 2014, The role of vitamin D in reducing cancer risk and progression, N*at. Rev. Cancer,* **14**(5), 342–357.

Florencio-Silva, R., Sasso, G.R.D.S., Sasso-Cerri, E., Simoes, M.J., and Cerri, P.S., 2015, Biology of Bone Tissue: Structure, Function, and Factors that Influence Bone Cells, *BioMed Research International*, **2015**, 1-17.

Grey, A., and Reid, I.R., 2006, Differences between the bisphosphonates for the prevention and treatment of osteoporosis, *Ther Clin Risk Manag.*, **2**(1), 77-86.

Hania, H.M., Occurrence of Osteoporosis Among Menopausal Women in Gaza Strip. 2008. PhD Thesis. Islamic University-Gaza.

Harmanjit, S., Manoj G., and Jasbir, S., 2013, Osteoporosis: Current Management Guidelines, *Indian Journal of Clinical Practice*, **23**(12), 842-850.

Horikawa, A., Miyakoshi, N., Shimada, Y., Sugimura, Y., and Kodama, H., 2015, Comparative Study

between intravenous and oral alendronate administration for the treatment of Osteoporosis, *SpingerPlus*, **4**, 675.

Indonesian Ministry of Health, 2015, Data and Conditions of Osteoporosis Disease in Indonesia, Indonesian Ministry of Health data and information center, Jakarta.

Jeremiah, M.P., Unwin, B.K., Greenawald, M.H., and Casiano, V.E., 2015, Diagnosis and Management of Osteoporosis, *American Family Physician*, **962**(4), 216-268.

Kennedy, P., Jain, A., Srinivasan, R., and Chaudhry, S., 2007, Calcium Homeostasis and Osteoporosis, *N Engl J Med.*, **357**(3), 266-281.

Kinoshita, M., Ishijima, M., Kaneko, H., Liu, L., Nagao, M., Sadatsuki, R., *et al.*, 2019, The increase in bone mineral density by bisphosphonate with active vitamin D analog is associated with the serum calcium level within the reference interval in postmenopausal osteoporosis, *Mod Rheumatol*, **29**(1), 157-164.

Lin, X., Xiong, D., Peng, Y-Q., Sheng, Z-F., Wu, X-Y., Wu, X-P., *et al.*, 2015, Epidemiology and Management of Osteoporosis in The People's Republic of China: Current Perspectives, *Clinical Intervention in Aging*, **10**, 1017-1033.

Malaysian Osteoporosis Society, 2012, Clinical Guidance on Management of Osteoporosis, Malaysian Osteoporosis Society.

Maraka, S., and Kennel, K.A., 2015, Biphosphonate for The Prevention and Treatment of Osteoporosis, *British Medical Journal*, **351**, h3783.

Mary, E.E., 2015, Prevention and Management of Osteoporosis. JPSW March/April 2010 J., **1**(2), 48-52.

Mithal, A., Dhingra, V., and Lau, E., 2009, The Asian Audit: Epidemiology, Costs, and Burden of Osteoporosis in Asia 2009, *International Osteoporosis Foundation*, 56-57.

Mundy, G.R., 2002, Metastasis to bone: causes, consequences and therapeutic opportunities, *Nat Rev Cancer,* **2**(8), 584-593.

National Medicines Information Centre, 2013, Update on Osteoporosis, *NMIC Bulletin Update on Osteoporosis*, **19**(2).

Pawel, S., and Mary, L.B., 2011, Vertebral Fracture Initiative, International Osteoporosis Foundation.

Reszka, A.A., and Rodan, G.A., 2003, Mechanism of action of bisphosphonates, *Current osteoporosis reports*, **1**(2), 45-52.

Rosol, T.J., Chew, D.J., Nagode, L.A., and Capen, C.C., 2008, Patophysiology of calcium metabolism, *Vet Clin Pathol.*, **24**(2), 49-63.

Roodman, G.D., 2010, Pathogenesis of myeloma bone disease, *J Cell Biochem,* **109**, 283-291.

Taha, A., Al-Taki, M., and Taha, T., 2015, Vitamin D revisited: impact on osteoporosis, *Women Health Open J.,* **1**(2), 48-52.

Watts, N.B., and Diab, D.L., 2010, Long Term Use of Biphosphonates in Osteoporosis, *The Journal of Clinical Endocrinology and Metabolism*, **95**(4), 1555-1565.