Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2023 Sep 01; 11(B):714-719.
https://doi.org/10.3889/oamjms.2023.11572
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Endocrinology*

Duration of Type 2 Diabetes Mellitus Over 5 Years, HbA1c Levels Over 7%, Alkaline Phospatase Over 130 IU/L, and C-Reactive Protein Over 3 mg/dL as Risk Factors for Osteoporosis in Type 2 DM Patients

Gede Mahardika Putra[1]*, Ketut Siki Kawiyana[2], Gede Eka Wiratnaya[2], Ketut Suyasa[2]

[1]Department of Orthopedic and Traumatology, Faculty of Medicine, Udayana University, RSUP, Sanglah General Hospital, Bali, Indonesia; [2]Department of Orthopedic and Traumatology, Faculty of Medicine, Udayana University, Sanglah General Hospital, Denpasar, Bali, Indonesia

Edited by: Ksenija Bogoeva-Kostovska
Citation: Putra IGM, Kawiyana KS, Wiratnaya IGE, Suyasa IK. Duration of Type 2 Diabetes Mellitus Over 5 Years, HbA1c Levels Over 7%, Alkaline Phospatase Over 130 IU/L, and C-Reactive Protein Over 3 mg/dL as Risk Factors for Osteoporosis in Type 2 DM Patients. Open Access Maced J Med Sci. 2023 Sep 01; 11(B):714-719. https://doi.org/10.3889/oamjms.2023.11572
Keywords: Diabetes mellitus; Osteoporosis; Duration of diabetes; Hemoglobin A1c; Alkaline phosphatase; C-reactive protein
***Correspondence:** Gede Mahardika Putra, Department of Orthopedic and Traumatology, Faculty of Medicine Udayana University, RSUP, Sanglah General Hospital, Bali, Indonesia. E-mail: mahardikaputra3192@gmail.com
Received: 24-Feb-2023
Revised: 18-Aug-2023
Accepted: 25-Aug-2023

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Type 2 diabetes mellitus (DM) may increases the risk of osteoporosis due to impaired osteoblast and osteoclast function, which affects the morbidity and mortality rates of DM patients. Not many studies investigating the relationship of DM with osteoporosis.

AIM: The purpose of this study was to evaluate the duration of DM, hemoglobin A1c (HbA1c), alkaline phosphatase (ALP), and C-reactive protein (CRP) levels as risk factors for osteoporosis.

METHODS: Case control study was performed on a total of 44 samples that consist of ostoporosis group and non-osteoporosis group. Difference of HbA1c, ALP, and CRP between groups was evaluated using Chi-square test.

RESULTS: Based on statistical analysis, we found that the duration of DM Type II ≥5 years (p = 0.002, odds ratio [OR] 11.08), HbA1c levels ≥7% (p = 0.027, OR 5.4), ALP ≥130 IU/L (p = 0.045, OR 5.2), and CRP ≥3 ng/dL (p = 0.033, OR 4.67) were significant risk factors for osteoporosis. Based on multivariate analysis with logistic regression, we found that risk factors for the duration of DM Type II ≥5 years had the greatest strength of association with osteoporosis.

CONCLUSION: In DM patients, duration of DM ≥5 years, HbA1c levels ≥7%, ALP ≥130 IU/L, and CRP ≥3 ng/dL are predictor factors for osteoporosis that can be used in clinical practice. These risk factors can be used as evaluation parameters for DM patients who are suspected to have osteoporosis.

Introduction

Diabetes mellitus (DM) especially Type 2 is known to be closely related with bone metabolic disorders such as osteoporosis and pathologic fractures. This will not only result in increased medical costs, but also on the morbidity and mortality of patients with type 2 diabetes mellitus (T2DM). Assessing the factors that influence the incidence of osteoporosis in patients with T2DM is very important. Knowing and predicting these factors will be very helpful for clinicians in preventing the incidence of osteoporosis as well as counseling to patients and their families.

Osteoporosis is a systemic skeletal disorder in the form of low bone mass and abnormal microarchitecture changes that increase the risk of fracture. As the most common bone metabolic disorder, data from the Ministry of Health of Republic of Indonesia show that the incidence of osteoporosis is increasing from year to year [1]. In 2013, an increase in the prevalence of osteoporosis in women aged 50–80 years was found by 23%. Statistical data shows that the prevalence of hip fractures related to osteoporosis in 2050 will increase to 6.3 million people, with more than half of them in Asia [2].

In the other side, the incidence of T2DM is still considered a major public health problem. There were approximately 536.6 million (10.5%) people worldwide experience DM in 2021 [3]. The prevalence of T2DM in Indonesia is also increasing from year to year, with 6.9% in 2013 and increased to 8.5% in 2018 [4]. The previous studies reported that DM is a risk factor for osteoporosis [5], [6], [7]. Chronic hyperglycemia in DM is known as a direct or indirect cause that interferes with osteoblast function and impairs the process of bone formation [5].

Several factors that were reported increase the incidence of osteoporosis in patients with T2DM were

hemoglobin A1c (HbA1c) levels at initial diagnosis, insulin resistance, and inflammatory biomarkers [8]. Other study was also mentioned the significant association between of age at diagnosis, gender, menstrual status, body mass index, C-reactive protein (CRP) levels, alkaline phosphatase (ALP) levels, and HbA1c levels toward osteoporosis [9].

This multifactorial cause of osteoporosis in T2DM patients is very important to identify at the initial examination. This can facilitate the prevention of osteoporosis and low energy fractures in T2DM patients, which finally could improving the patient's quality of life. There were only few numbers of available study regarding osteoporosis in T2DM patients, and the result was still inconsistent. Moreover, no related studies have been carried out in Indonesia. This study aimed to identify the risk factors for osteoporosis in patients with T2DM. The results of this study are expected to provide fracture prevention in patients with T2DM and improve the patient's quality of life.

Materials and Methods

This research was conducted within Ethical Committee approval by Research Ethics Commission Faculty of Medicine, Universitas Udayana/Prof. Dr. I. G. N. G. Ngoerah Hospital Denpasar. All study participants were given an explanation regarding the study and were asked to fill out written informed consent before enrollment.

This is a case–control study to determine the effect of T2DM duration, HbA1c, ALP, and CRP toward the changes bone mineral density (BMD) levels which are markers of osteoporosis. The research was conducted at the diabetic center, radiology department, and clinical pathology laboratory at Prof. Dr. I. G. N. G. Ngoerah Hospital Denpasar from February 2022 to April 2022.

The study subjects were all patients with T2DM who visited diabetic center in our hospital during the study period. The inclusion criteria were: (1) Women aged <50 years or men aged <70 years; (2) patients with T2DM; (3) the patient is cooperative with the examinations performed; and (4) willing to participate in the research by signing an informed consent. The exclusion criteria were: Patients with comorbidities (hepatic dysfunction, human immunodeficiency virus disease, malignancy, chronic kidney disease, hyperthyroidism), patients with congenital bone disorders, taking long-term medications such as corticosteroids, patients with autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus), and patients with impaired mobility.

Minimum sample size calculation was performed using the two unpaired category formula, with minimum sample of 44 patients. The study subjects were recruited using purposive sampling technique. The case group was defined as osteoporosis patient (T score <−2.5 based on BMD) and control group was defined as non-osteoporosis patient (T score ≥2.5 based on BMD). The participant underwent DEXA examination for BMD measurement, continued with venipuncture for HbA1c, ALP, and CRP. There was no fasting or special diet requirement before venipuncture. We took minimum 1 mL of blood and stored it into ethylenediaminetetraacetic acid vacutainer, mix the tube, and immediately sent to clinical pathology laboratory.

Data analysis was performed using SPSS software. Descriptive analysis was used to describe samples characteristics in each group. Bivariat analysis was performed using Chi-square test to evaluate the odd of each osteoporosis risk factor. The data will be presented in odds ratio (OR) and 95% confidence interval (CI). $p < 0.05$ was considered as statistically significant. Multivariate analysis using logistic regression was performed to analyze the risk factors which were significant in bivariate analysis ($p < 0.2$).

Results

There were a total of 44 samples included in this study, consisting of 22 case and 22 control. The characteristics of the study subjects are shown in Table 1.

Table 1: Subjects characteristics

Variable	n (%)	
	Osteoporosis	Not osteoporosis
Gender		
Male	13 (59.1)	8 (36.4)
Female	9 (40.9)	14 (63.6)
Duration of T2DM		
≥5 years	19 (86.4)	8 (36.4)
<5 years	3 (13.6)	14 (63.6)
HbA1c		
≥7%	18 (81.8)	10 (45.5)
<7%	4 (18.2)	12 (54.5)
ALP		
≥130 IU/L	12 (54.5)	3 (13.6)
<130 IU/L	10 (45.5)	19 (86.4)
CRP		
≥3 ng/dL	17 (89.5)	11 (44.0)
<3 ng/dL	2 (10.5)	14 (56.0)

HbA1c: Hemoglobin A1c, ALP: Alkaline phosphatas, CRP: C-reactive protein, T2DM: Type 2 diabetes mellitus.

Based on bivariate analysis using Chi-square test, we found that the duration of DM Type II ≥5 years ($p = 0.002$, OR 11.08), HbA1c levels ≥7% ($p = 0.027$, OR 5.4), ALP ≥130 IU/L ($p = 0.045$, OR 5.2), and CRP ≥3 ng/dL (p 0.033, OR 4.67) were significant risk factors for osteoporosis (Table 2).

Based on multivariate analysis with logistic regression, we found that Type 2 diabetes mellitus (T2DM) duration ≥5 years had the greatest association with osteoporosis compared to other variables (Table 3).

Table 2: Bivariate analysis

Variable	T2DM Group		p	OR (95% CI)
	Osteoporosis (%)	Not osteoporosis (%)		
Duration of T2DM				
≥5 years	19 (86.4)	8 (36.4)	0.002	11.08 (2.48–49.46)
<5 years	3 (13.6)	14 (63.6)		
HbA1c				
≥7%	18 (81.8)	10 (45.5)	0.027	5.4 (1.37–21.26)
<7%	4 (18.2)	12 (54.5)		
ALP				
≥130 IU/L	12 (54.5)	3 (13.6)	0.045	5.2 (1.20–23.15)
<130 IU/L	10 (45.5)	19 (86.4)		
CRP				
≥3 ng/dL	16 (72.7)	8 (36.4)	0.033	4.66 (1.29–16.76)
<3 ng/dL	6 (27.3)	14 (63.6)		

DM: Diabetes mellitus, OR: Odd ratio, HbA1c: Hemoglobin A1c, ALP: Alkaline phosphatas, CRP: C-reactive protein, CI: Confidence interval

Table 3: Multivariate analysis

Risk factors	Exp (B)	95% CI for Exp (B)	
		Lower	Upper
T2DM duration ≥5 years	0.621	0.128	3.008
HbA1c ≥7%	0.194	0.031	1.208
ALP ≥130 IU/mL	0.000	0.968	1.031
CRP ≥3 ng/L	0.219	0.036	1.347

T2DM: Type 2 diabetes mellitus, HbA1c: Hemoglobin A1c, ALP: Alkaline phosphatas, CRP: C-reactive protein, CI: Confidence interval.

Discussion

Association between T2DM duration with osteoporosis

In this study, it was found that DM Type II ≥5 years was a risk factor for osteoporosis in patients with DM Type II. Until now, various studies have found different findings regarding the relationship between the duration of T2DM and the incidence of osteoporosis. Research by Jang *et al*. in 2018 in South Korea measured BMD levels in different locations to compare between participants with a DM duration of 5 years and those with a duration of DM >5 years. It was found that the group with a longer DM duration had a lower total hip and femoral neck BMD compared to those with a shorter DM duration, even after adjusting for other risk factors, such as age, body mass index (BMI), and serum Vitamin D levels [10]. Another study with similar results also found that the risk of hip fracture due to osteoporosis increased with a longer DM duration and found that women with Type 2 diabetes (T2D) duration of more than 10 years had a 2.30 times higher risk (95 CI 1.39–3.81) multivariate adjustment for hip fracture compared to women without diabetes [11]. Similar results were also obtained in a study in Australia which found a longer duration of diabetes and was significantly associated with an increased risk of osteoporotic fractures. Furthermore, this study suggests that the associations found may be due to the increased severity of the disease and increased microvascular and macrovascular complications in patients with a longer duration of DM [12].

However, different results have been shown by several other studies. Brown and Sharpless in 2004 stated that there was no correlation between BMD and duration of diabetes or current glycemic control (by HbA1c) in postmenopausal women or children [13]. Research by Goldshtein *et al*. also found the duration of diabetes was not a significant indicator of an increased incidence of fractures with a Hazard Ratio value of 1.12 and 95% CI 0.94–1.33 [14]. In fact, a meta-analysis by Vestergaard found that duration of diabetes was not a significant risk factor for osteoporosis [15]. This is also similar to a study conducted by Leidig-Bruckner *et al*., which found that diabetes has no correlation with the occurrence of BMD and osteoporosis [16]. Another study conducted in Turkey also has the same conclusion that there is no relationship between the duration of diabetes and bone density [17].

Association between HbA1c levels in T2DM patients with osteoporosis

In this study HbA1c level ≥7% was found to be a risk factor for osteoporosis in patients with T2DM. Several risk factors for osteoporosis have been identified, some of which are highly complex due to the multiple mechanisms involved, such as in T2D. T2D affects sugar, fat, and protein metabolism as well as causing dysregulation of calcium, phosphorus, and magnesium, which in turn triggers a series of complications, such as neuropathy, cardiovascular disease, peripheral blood vessels, retinopathy, and metabolic bone disease [18].

Results from our research is in accordance with the study of Lin *et al*. which stated that T2DM patients with HbA1c levels of more than 7% had a higher risk of osteoporosis 1.49 times significantly higher than those with HbA1c <7% [19]. Long-term exposure to diabetes induces changes in bone metabolism and impairs bone microarchitecture through various mechanisms, including increased insulin levels, hypercalciuria, decreased renal function, obesity, further glycation end products in collagen, angiopathy, neuropathy, and inflammation. Specifically, insulin stimulates osteoblast proliferation and differentiation, whereas high glucose levels directly affect osteoblast metabolism and maturation by altering gene expression and reducing bone mineral quality [18].

Different results were obtained in the study of Oei *et al*. It was found that patients with diabetes had higher BMD values when compared to patients without diabetes in the lumbar spine and neck of the femur ($p < 0.05$). Despite a higher BMD and a thicker femoral cortex over narrower bones, the risk of fracture remains higher in diabetic patients. Oei *et al*. argued that the fragility of bones that appear to be “strong” in the uncontrolled diabetes group may result from the accumulation of microcracks and/or cortical porosity, reflecting disturbances of bone homeostasis [20]. This similarity was also found in another study in Rotterdam where patients with HbA1c >7% had higher BMD values than patients without diabetes [21]. In line with these findings, research from Melton *et al*. also found no correlation between HbA1c >7% and BMD values [22].

The association of ALP levels in T2DM patients with osteoporosis

The results of this study indicate that ALP levels >130 IU/mL were a risk factor for osteoporosis in patients with T2DM. As is known so far, ALP plays a role in bone formation. The increase in ALP in the collagen matrix phase during the production phase has a unidirectional correlation in the process of bone formation. Most studies suggest that in diabetic patients, there is an imbalance between bone formation and bone resorption in diabetes [23].

According to previous research by Park, *et al*., serum ALP levels >120 IU/L were associated with lower BMD compared to serum ALP <120 IU/L [24]. Another study from Chen *et al*. in 2018 found that total BMD decreased significantly when ALP increased [9]. Research from Kang *et al*. found that in patients with a mean ALP of 120.67 ± 10.6 IU/L, there was a significant decrease in BMD [25]. Bergman *et al*. also showed results that increased ALP affected a decrease in BMD. However, this is in contrast to a study by Lumachi *et al*. which evaluating ALP together with other markers of bone formation (osteocalcin, collagen Type I, and BMD) in elderly men without a history of fracture. They found no association at all between ALP and BMD in this population [26]. Another study from Malluche *et al*. stated that the relationship between BMD and ALP was not significant after adjusting for age, sex, and BMI [27].

The association between CRP levels in patients with T2DM and osteoporosis

The results of this study indicate that CRP levels ≥3 ng/dL was a risk factor for osteoporosis in patients with T2DM. In DM patients with osteoporosis, inflammatory factors such as CRP were found to be increased compared to DM patients who did not have osteoporosis [28]. The association between increased CRP levels in patients with DM and the incidence of osteoporosis was reported by Mitama *et al*. that CRP levels can predict the risk of fracture in men with HR 1.47 (95% CI 1.02–1.98) and in women with HR 1.47 (95% CI 1.04–1.92) [29].

This is also in line with research conducted by Ishii *et al*. that each increase in CRP is associated with a decrease of 0.16–0.22 SD in the bone strength index and at CRP levels above 3 mg/L; each doubling of CRP is also associated with a 42% of relative increase in the non-traumatic fracture rate [30]. The Italian study investigating 919 Italian men and women between the ages of 40 and 79 found that higher CRP levels were strongly associated with future non-traumatic fractures, with a relative risk of 9.4 (95% CI, 3.6–24.8) for the highest T-score (≥2.5 ~ 3 mg/L) compared to the lowest T-score (<1.1 mg/L) [31]. Research from Berglundh *et al*. states that women with CRP >3 mg/L at ages 75 and 80 have significantly higher rates of bone loss compared to women with CRP <3 mg/L during 10 years of follow-up [32].

In contrast to the previous study, Bhupathiraju *et al*. found no relationship between CRP concentration and trabecular bone in postmenopause women with peripheral quantitative CT [33]. In line with this, an Australian study conducted among 444 women aged 65 years also found no correlation between CRP concentrations and BMD as measured by DXA [34]. One previous study even found high CRP to be associated with high BMD [35]. Another study by Ganesan *et al*. found no correlation between CRP inflammatory markers and the incidence of osteoporosis, cancer, and frailty [36].

Conclusion

In T2DM patients, duration of DM ≥5 years, HbA1c levels ≥7%, ALP ≥130 IU/L, and CRP ≥3 ng/dL are predictor factors for osteoporosis that can be used in clinical practice. These risk factors can be used as evaluation parameters for T2DM patients to prevent osteoporosis and pathological fracture.

References

1. Kementerian Kesehatan Republik Indonesia. Profil Kesehatan Indonesia Tahun 2020. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020.
2. Cheung CL, Ang SB, Chadha M, Chow ES, Chung YS, Hew FL, *et al.* An updated hip fracture projection in Asia: The Asian Federation of Osteoporosis Societies study. Osteoporos Sarcopenia. 2018;4(1):16-21. https://doi.org/10.1016/j.afos.2018.03.003
   PMid:30775536
3. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, *et al.* IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119. https://doi.org/10.1016/j.diabres.2021.109119
   PMid:34879977
4. Kementerian Kesehatan RI. Riset Kesehatan Dasar 2018. Indonesia: Kementerian Kesehatan RI; 2018.
5. Leidig-Bruckner G, Ziegler R. Diabetes mellitus a risk for osteoporosis? Exp Clin Endocrinol Diabetes. 2001;109 Suppl 2:S493-514. https://doi.org/10.1055/s-2001-18605
   PMid:11460594
6. Montagnani A, Gonnelli S, Alessandri M, Nuti R. Osteoporosis and risk of fracture in patients with diabetes: An update. Aging Clin Exp Res. 2011;23(2):84-90. https://doi.org/10.1007/BF03351073
   PMid:21743287
7. Raška I Jr., Rašková M, Zikán V, Škrha J. Prevalence and risk factors of osteoporosis in postmenopausal women with Type 2 diabetes mellitus. Cent Eur J Public Health. 2017;25(1):3-10.

https://doi.org/10.21101/cejph.a4717
PMid:28399348

8. Li KH, Liu YT, Yang YW, Lin YL, Hung ML, Lin IC. A positive correlation between blood glucose level and bone mineral density in Taiwan. Arch Osteoporos. 2018;13(1):78. https://doi.org/10.1007/s11657-018-0494-9
PMid:30009330
9. Chen H, Li J, Wang Q. Associations between bone-alkaline phosphatase and bone mineral density in adults with and without diabetes. Medicine (Baltimore). 2018;97(17):e0432. https://doi.org/10.1097/MD.0000000000010432
PMid:29702995
10. Jang M, Kim H, Lea S, Oh S, Kim JS, Oh B. Effect of duration of diabetes on bone mineral density: A population study on East Asian males. BMC Endocr Disord. 2018;18(1):61. https://doi.org/10.1186/s12902-018-0290-y
PMid:30185190
11. Nicodemus KK, Folsom AR, Iowa Women's Health Study. Type 1 and Type 2 diabetes and incident hip fractures in postmenopausal women. Diabetes Care. 2001;24(7):1192-7. https://doi.org/10.2337/diacare.24.7.1192
PMid:11423501
12. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ, Blue Mountains Eye Study. Diabetes and risk of fracture: The blue mountains eye study. Diabetes Care. 2001;24(7):1198-203. https://doi.org/10.2337/diacare.24.7.1198
PMid:11423502
13. Brown SA, Sharpless JL. Osteoporosis: An Under-appreciated complication of diabetes. Clin Diabetes. 2004;22(1):10-20. https://doi.org/10.2337/diaclin.22.1.10
14. Goldshtein I, Nguyen AM, dePapp AE, Ish-Shalom S, Chandler JM, Chodick G, *et al.* Epidemiology and correlates of osteoporotic fractures among Type 2 diabetic patients. Arch Osteoporos. 2018;13(1):15. https://doi.org/10.1007/s11657-018-0432-x
PMid:29502187
15. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with Type 1 and Type 2 diabetes--a meta-analysis. Osteoporos Int. 2007;18(4):427-44. https://doi.org/10.1007/s00198-006-0253-4
PMid:17068657
16. Leidig-Bruckner G, Grobholz S, Bruckner T, Scheidt-Nave C, Nawroth P, Schneider JG. Prevalence and determinants of osteoporosis in patients with Type 1 and Type 2 diabetes mellitus. BMC Endocr Disord. 2014;14:33. https://doi.org/10.1186/1472-6823-14-33
PMid:24721668
17. Anaforoglu I, Nar-Demirer A, Bascil-Tutuncu N, Ertorer ME. Prevalence of osteoporosis and factors affecting bone mineral density among postmenopausal Turkish women with Type 2 diabetes. J Diabetes Complications. 2009;23(1):12-7. https://doi.org/10.1016/j.jdiacomp.2007.06.004
PMid:18413190
18. Murray CE, Coleman CM. Impact of diabetes mellitus on bone health. Int J Mol Sci. 2019;20(19):4873. https://doi.org/10.3390/ijms20194873
PMid:31575077
19. Lin HH, Hsu HY, Tsai MC, Hsu LY, Chien KL, Yeh TL. Association between Type 2 diabetes and osteoporosis risk: A representative cohort study in Taiwan. PLoS One. 2021;16(7):e0254451. https://doi.org/10.1371/journal.pone.0254451
PMid:34255803
20. Oei L, Zillikens MC, Dehghan A, Buitendijk GH, Castaño-Betancourt MC, Estrada K, *et al.* High bone mineral density and fracture risk in Type 2 diabetes as skeletal complications of inadequate glucose control: The Rotterdam Study. Diabetes Care. 2013;36(6):1619-28. https://doi.org/10.2337/dc12-1188
PMid:23315602
21. Garg R, Chen Z, Beck T, Cauley JA, Wu G, Nelson D, *et al.* Hip geometry in diabetic women: Implications for fracture risk. Metabolism. 2012;61(12):1756-62. https://doi.org/10.1016/j.metabol.2012.05.010
PMid:22726843
22. Melton LJ 3rd, Leibson CL, Achenbach SJ, Therneau TM, Khosla S. Fracture risk in Type 2 diabetes: Update of a population-based study. J Bone Miner Res. 2008;23(8):1334-42. https://doi.org/10.1359/jbmr.080323
PMid:18348689
23. Bandeira F, Costa AG, Soares Filho MA, Pimentel L, Lima L, Bilezikian JP. Bone markers and osteoporosis therapy. Arq Bras Endocrinol Metabol. 2014;58(5):504-13. https://doi.org/10.1590/0004-2730000003384
PMid:25166041
24. Park JC, Kovesdy CP, Duong U, Streja E, Rambod M, Nissenson AR, *et al.* Association of serum alkaline phosphatase and bone mineral density in maintenance hemodialysis patients. Hemodial Int. 2010;14(2):182-92. https://doi.org/10.1111/j.1542-4758.2009.00430.x
25. Kang KY, Hong YS, Park SH, Ju JH. Increased serum alkaline phosphatase levels correlate with high disease activity and low bone mineral density in patients with axial spondyloarthritis. Semin Arthritis Rheum. 2015;45(2):202-7. https://doi.org/10.1016/j.semarthrit.2015.03.002
PMid:25895696
26. Lumachi F, Orlando R, Fallo F, Basso SM. Relationship between bone formation markers bone alkaline phosphatase, osteocalcin and amino-terminal propeptide of Type I collagen and bone mineral density in elderly men. Preliminary results. *In vivo*. 2012;26(6):1041-4.
27. Malluche HH, Davenport DL, Cantor T, Monier-Faugere MC. Bone mineral density and serum biochemical predictors of bone loss in patients with CKD on dialysis. Clin J Am Soc Nephrol. 2014;9(7):1254-62. https://doi.org/10.2215/CJN.09470913
PMid:24948144
28. Chen Z, Zhao GH, Zhang YK, Shen GS, Xu YJ, Xu NW. Research on the correlation of diabetes mellitus complicated with osteoporosis with lipid metabolism, adipokines and inflammatory factors and its regression analysis. Eur Rev Med Pharmacol Sci. 2017;21(17):3900-5.
29. Mitama Y, Fujiwara S, Yoneda M, Kira S, Kohno N. Association of Type 2 diabetes and an inflammatory marker with incident bone fracture among a Japanese cohort. J Diabetes Investig. 2017;8(5):709-15. https://doi.org/10.1111/jdi.12632
PMid:28122172
30. Ishii S, Cauley JA, Greendale GA, Crandall CJ, Danielson ME, Ouchi Y, *et al.* C-reactive protein, bone strength, and nine-year fracture risk: Data from the Study of Women's Health Across the Nation (SWAN). J Bone Miner Res. 2013;28(7):1688-98. https://doi.org/10.1002/jbmr.1915
PMid:23456822
31. Schett G, Kiechl S, Weger S, Pederiva A, Mayr A, Petrangeli M, *et al.* High-sensitivity C-reactive protein and risk of nontraumatic fractures in the Bruneck study. Arch Intern Med. 2006;166(22):2495-501. https://doi.org/10.1001/archinte.166.22.2495
PMid:17159016
32. Berglundh S, Malmgren L, Luthman H, McGuigan F, Åkesson K. C-reactive protein, bone loss, fracture, and mortality in elderly women: A longitudinal study in the OPRA cohort. Osteoporos Int. 2015;26(2):727-35. https://doi.org/10.1007/s00198-014-2951-7

PMid:25410434

33. Bhupathiraju SN, Alekel DL, Stewart JW, Hanson LN, Shedd KM, Reddy MB, *et al.* Relationship of circulating total homocysteine and C-reactive protein to trabecular bone in postmenopausal women. J Clin Densitom. 2007;10(4):395-403. https://doi.org/10.1016/j.jocd.2007.06.002

PMid:17662632

34. Pasco JA, Kotowicz MA, Henry MJ, Nicholson GC, Spilsbury HJ, Box JD, *et al.* High-sensitivity C-reactive protein and fracture risk in elderly women. JAMA. 2006;296(11):1353-5. https://doi.org/10.1001/jama.296.11.1353

PMid:16985226

35. Nakamura K, Saito T, Kobayashi R, Oshiki R, Oyama M, Nishiwaki T, *et al.* C-reactive protein predicts incident fracture in community-dwelling elderly Japanese women: The Muramatsu study. Osteoporos Int. 2011;22(7):2145-50. https://doi.org/10.1007/s00198-010-1425-9

PMid:20936400

36. Ganesan K, Teklehaimanot S, Tran TH, Asuncion M, Norris K. Relationship of C-reactive protein and bone mineral density in community-dwelling elderly females. J Natl Med Assoc 2005;97(3):329-33.