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RESEARCH ARTICLE

Parathyroid Hormone-25(OH)D and Calcium-Phosphorus Ratio as Osteopenia Risk Factors in Women with Central Obesity

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Abstract

BACKGROUND: Central obesity has a close association with inflammation and the state of bone mass. Osteopenia is an abnormal condition of bone density. Bone mass density is influenced by several factors, such as 25(OH)D, parathyroid hormone (PTH), calcium (Ca) and phosphorus (P). The aim of this study was to evaluate the role of PTH-25(OH)D and Ca-P ratio as risk factors for osteopenia in women with central obesity.

METHODS: A cross-sectional study was conducted in September 2020 to March 2021. The total subjects were 130 women aged 25-50 years old with central obesity. The diagnosis of osteopenia was done using dual X-ray absorptiometry (DXA) to measure bone mineral density. Enzyme linked fluorescent assay (ELFA) method was done to measure PTH and 25(OH)D levels, ion selective electrode method to measure Ca, and photometer method to measure P level. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value and calculated prevalence ratio (PR) for osteopenia risks, followed by logistic regression analysis.

RESULTS: The PR of PTH level was 10.18 (95% CI: 1.15–5.85; p=0.01); the PTH-25(OH)D ratio was 5.12 (95% CI: 1.13–23.19; p=0.04); Ca level was 6.0 (95% CI: 1.33–27.14; p=0.02) and Ca-P ratio was 4.89 (95%CI: 1.33–17.97; p=0.02). The PR for PTH together with Ca level was 18.71 (95% CI: 2.17–160.40; p=0.008).

CONCLUSION: The PTH-25(OH)D ratio and the Ca-P ratio are risk factors for the incidence of osteopenia in women with central obesity. A high PTH-25(OH)D ratio and a high Ca-P ratio would have a higher risk of developing osteopenia in this population.

KEYWORDS: CRP, PTH-25(OH)D, Ca-P, osteopenia, central obesity, women

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Introduction

Detection of osteopenia according to the World Health Organization (WHO) was based on bone mineral density (BMD) using the dual energy X-ray absorptiometry (DXA) assessment with T-score between -1 and -2.5.(1,2) Osteopenia, which is affected by gender, age, genetic factors, nutritional status, menstrual status, and physical activity (3), can lead to irreversible osteoporosis. If osteoporosis is not early detected, it may lead to bone fractures, hence making osteoporosis an important health problem. In Southeast Asian countries, osteoporosis is still under-diagnosed and under-treated.(4) Previous study showed that the incidence of osteoporosis-related fractures was higher in women than men.(5,6)

In 2018, the prevalence of obesity and central obesity women in Indonesia was 29.3% and 31% respectively.(7) Visceral adipose tissue (VAT) is a strong risk factor for osteoporosis, and is inversely related to BMD.(8,9) Based on International Diabetes Federation (IDF), for South East Asian women, central obesity is determined when the waist circumference (WC) is above 80 cm. The waist to height ratio (WHtR) is the latest and better anthropometric measurement compared to WC, and it is said that the value of WHtR >0.5 is a risk for metabolic disease.(10-12) Visceral fat produce adipokines associated with inflammation, including interleukin-6 (IL-6), which can stimulate the production of liver C-reactive protein (CRP) and also can increase bone resorption or suppress bone formation. CRP is an acute-phase protein that has been widely studied, which is related to VAT and body fat percentage (BFP) as well as BMD.(13-16)

Vitamin D plays a role in bone metabolism by increasing calcium (Ca) and phosphorus (P) levels, regulating osteoblast and osteoclast activity, and stimulating parathyroid hormone (PTH) secretion. High level of bone metabolism is one of the risk factors of osteopenia and osteoporosis.(17,18) There is an association between 25(OH)D and bone turnover markers, *i.e.*, bone formation and bone resorption (19), but other studies concluded inversely (20,21), thus, further investigation is needed. Decreased Ca levels will stimulate secretion of the PTH, which plays a role in the change of 1,25(OH)2D that affects intestinal calcium absorption into the blood.(22) However, a study in 2017 showed there was no correlation between PTH and BMD.(18)

The PTH-25(OH)D ratio is one of a parameter to determine the condition of insulin sensitivity in obese and metabolic syndrome patients.(23) This ratio has not been widely examined as a risk factor of decreased bone quality. This study was aimed to investigate the role of the PTH-25(OH)D ratio as a risk factor for osteopenia, while the results of several studies on PTH and 25(OH)D are still yielding conflicted results. Previous study stated that there was a correlation between Ca and BMD, on the contrary, there was an inverse relationship between P and BMD. (24) In addition, increased P levels in a normal population will affect bone health and it is associated with the risk of osteoporosis.(25)

The serum Ca-P ratio is an inexpensive parameter to support the diagnosis of hyperparathyroidism with the sensitivity of 86% and a specificity of 87%.(26) So far, the use of Ca-P ratio to detect the risk of osteoporosis or bone density disorders, is still limited by the patient's Ca and P intake. Previous studies have analyzed that high intake of P with low Ca will lead to a low Ca-P ratio and is associated with osteoporosis, as well as other bone parameters. (27,28) So, this study will be done to analyze the role of PTH-25(OH)D ratio, and Ca-P ratio in osteopenia among centrally obese women.

Methods

Study Design and Subject Recruitment

A cross-sectional observational study was conducted at the Diponegoro National Hospital, Semarang, between September 2020 and March 2021. The subjects of this study were 130 centrally obese women (waist circumference >80 cm and WHtR >0.5), ages 25-50 year-old, had regular menstruation for the last 6 months, creatinine levels within the reference value range (0.55-1.3 mg/dL) and serum glutamic pyruvic transaminase (SGPT) levels <2x the upper reference limit value (female: 42 U/L). Women with a history of fracture in the last 6 months, a history of joint pain, pregnant/breastfeeding, taking birth control pills and corticosteroids were excluded from the study.

All subjects filled out questions regarding age, UV exposure, physical activity, exercise, milk, milk snacks, yogurt and cheese intake. This study was conducted after obtaining ethical clearance from the Health Research Ethics Commission, Faculty of Medicine, Universitas Diponegoro/ Dr. Kariadi Hospital Semarang (No. 2424/EC/KEPK/FK UNDIP/X/2020). Informed consent was obtained from all participants.

Osteopenia Diagnosis

The diagnosis of osteopenia was carried out using the GE Lunar Prodigy-iDXA (GE Healthcare, Chicago, IL, USA) based on the interpretation of the BMD results by the radiologist. Osteopenia is defined as T score/Z score between (-1) and (-2.5) on one or more BMD examinations of the femoral, femoral neck and lumbar.

Laboratory Examination

The levels of intact PTH (iPTH/ PTH 1-84) and 25(OH)D were measured by enzyme linked fluorescent assay (ELFA) principle using MINI VIDAS® compact multiparametric immunoanalyzer (Biomerieux Clinical Diagnostic, Marcy-I'Etoile, France), Biomerieux VIDAS® PTH (1-84) (Biomerieux Clinical Diagnostic), and VIDAS® 25 OH Vitamin D TOTAL reagent (Biomerieux Clinical Diagnostic) PTH-25(OH) ratio calculation was done manually.

Calcium ion levels were measured by the ion selective electrode (ISE) method with Cornley-K-Lite 5 automatic electrolyte analyzer (Meizhou Cornley Hi-Tech Co Ltd, Shenzhen, China). Serum P levels were measured by the photometric method using an automatic clinical chemistry analyzer (Indiko TM, Thermo Fisher Scientific, Waltham, MA USA). Ca-P ratio calculation was done manually.

This study also examined the parameters of liver function *i.e.*, SGPT level, which was measured by International Federation of Clinical Chemistry (IFCC) method using an automatic clinical chemistry analyzer Indiko TM (Thermo Fisher Scientific), as well as kidney function *i.e.*, creatinine level, which was measured by enzymatic colorimetric assay, using an automatic clinical chemistry analyzer Indiko TM (Thermo Fisher Scientific).

Statistical Analysis

The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value for PTH, 25(OH) D, Ca, P and CRP level, and also for PTH-25(OH)D and Ca-P ratio. The PR calculations were obtained from the 2x2 table for 2 groups of osteopenia and normopenia. Bivariate analysis was also conducted for all main and confounding independent variables which include: age, UV exposure, physical activity, exercise, milk intake, milk snacks, yogurt and cheese. Based on the bivariate analysis, the main and confounding independent variables with $p<0.25$ were then further analyzed with the logistic regression analysis with a backward system. This study employed a significance level of $p<0.05$.

Results

One hundred thirty subjects were included, a total of 60 subjects (46.2%) were overweight (BMI=25–29.9 kg/m^2) and 70 subjects (53.8%) were obese (BMI ≥30 kg/m^2). The results of BMD examination showed that 120 (92.3%) subjects had normal bones, and 10 (7.7%) subjects had osteopenia.

The best cut-off value from ROC curve for CRP, PTH, 25(OH)D, PTH-25(OH)D ratio, Ca, P and Ca-P ratio was as follows: 5.05 mg/L; 23.25 ng/mL; 10.55 ng/dL; 2.425; 1.52 mmol/mL; 1.245 mmol/mL and 1.185, respectively. The result of bivariate analysis for all risk factors both groups of normopenia and osteopenia was shown in Table 1.

Meanwhile, the calculation of prevalence ratio values for all laboratory parameters could be seen in Table 2 and Figure 1.

The analysis using logistic regression with a backward system was done to obtain the best model as can be seen in Table 3. Only 5 risk factors that met the requirements for logistic regression analysis, which were PTH, PTH-25(OH) D ratio, Ca, Ca-P ratio, UV exposure and exercise.

Several models were applied to adjust the risk factors, it was found that model No. 5 was the best. The determined value of it was PTH levels >23.25 pg/dL and Ca levels >1.52 mmol/L, with the following regression equation: y = -5.394 + 2.48 (PTH >23.25 pg/dL) + 1.95 (Ca >1.52 mmol/L).

The probability of a woman with central obesity with PTH levels >23.25 pg/dL and Ca >1.52 mmol/L to have osteopenia was 0.324. These results showed the role of high PTH along with high Ca levels for the occurrence of osteopenia in a woman with central obesity is 32.4%, while the remaining 67.6% is determined by other factors/ variables. From model No. 5, we calculated the PR for PTH >23.25 pg/dL together with Ca >1.52 mmol/L was 18.71 (95% CI: 2.17–160.40; p=0.008).

Discussion

In this study CRP level >5.05 mg/L was found not as osteopenia risk factor. It is necessary to consider the effect of cytokines that stimulate CRP release, such as IL-6, or other pro-inflammatory cytokines, such as IL-1 and TNFα. Previous study showed a different results, it may be due to the differences in study population. Another study showed that increased CRP levels were associated with decreased BMD.(29) A total of 23 study subjects (17.7%) had elevated CRP levels (>10 mg/dL), while the remaining 107 subjects (82.3%) were still within the reference range. This showed that most of the subjects were not in a state of inflammation. Most of the subjects were metabolically healthy obese, which has a low risk for metabolic disorders that could affect bone condition.(30)

The PTH level >23.25 pg/mL was a risk factor for osteopenia in productive women with central obesity (PR=10.18; 95%CI: 1.45–95.85). This was in accordance with previous studies that increased PTH levels were found in fracture patients due to osteoporosis.(18) Previous study in 2020 showed that there was a significant assiciation between PTH and BMD.(31) PTH played an important role in Ca metabolism, maintaining Ca levels in the blood. An increase in PTH levels or hyperparathyroid state could cause an increase serum Ca levels, through a direct mechanism, namely by bone resorption, especially in individuals with minimal Ca intake.(31,32)

Table 1. Bivariate analysis for risk factors.

	n (%)		*p*- value
	Osteopenia	Normopenia	
Age			
≥40 y.o	5 (12.8)	34 (87.2)	0.28
<40 y.o	5 (5.5)	86 (94.5)	
UV exposure			
Never/rarely	6 (60.0)	43 (35.8)	0.24
Routine	3 (30.0)	28 (23.3)	
Physical activity			
Light	6 (12.2)	43 (87.8)	0.82
Moderate	4 (4.9)	77 (95.1)	
Exercise			
Never/rarely	8 (7.1)	104 (92.9)	0.01
Routine	2 (11.1)	16 (88.9)	
Milk intake			
Never/ <1 glass/week	7 (7.6)	85 (92.4)	1
>1 glass/week	3 (7.9)	35 (92.1)	
Milk snack intake			
Never/ <1 portion/ week	1 (3.1)	31 (96.9)	0.46
>1 portion/ week	8 (80.0)	66 (55.0)	
Yoghurt intake			
Never/ <1 portion/ week	5 (5.9)	80 (94.1)	0.47
>1 portion/ week	5 (11.1)	40 (88.9)	
Cheese intake			
Never/ <1 portion/ week	5 (6.7)	70 (93.3)	0.86
>1 portion/ week	5 (9.1)	50 (90.9)	
CRP			
>5.05 mg/dL	6 (10.9)	49 (89.1)	0.24
≤5.05 mg/dL	4 (5.3)	71 (94.7)	
PTH			
>23.35 pg/mL	9 (14.8)	52 (85.2)	0.01
≤23.35 pg/mL	1 (1.4)	68 (98.6)	
25(OH)D			
≤10.55 ng/mL	4 (5.6)	67 (94.4)	0.53
>10.55 ng/mL	6 (10.2)	53 (89.8)	
PTH-25(OH)D ratio			
>2.196	8 (14.0)	49 (86.0)	0.04
≤2.196	2 (2.7)	71 (97.3)	
Ca			
>1.52 mmol/L	8 (15.4)	44 (84.6)	0.19
≤1.52 mmol/L	2 (2.6)	76 (97.4)	
P			
<1.24 mmol/L	5 (50.0)	71 (59.2)	0.57
≥1.24 mmol/L	5 (50.0)	49 (40.8)	
Ca-P ratio			
>1.185	7 (16.7)	35 (83.3)	0.02
≤1.185	3 (3.4)	85 (96.6)	

The test was considered significant if $p<0.05$.

Table 2. Ratio prevalence of all laboratory parameters.

Parameters	PR	Lower 95% CI	Upper 95% CI	*p-value*
CRP (>5.05 mg/L)	2.05	0.61	6.9	0.4
PTH (>23.25 ng/mL)	10.18	1.45	95.85	0.01
25(OH)D (<10.55 ng/dL)	0.55	0.16	1.87	0.53
PTH-25(OH)D ratio (>2.196)	5.12	1.13	23.19	0.04
Ca (>1.52 mmol/mL)	6	1.33	27.14	0.02
P (<1.25 mmol/mL)	0.71	0.22	2.33	0.82
Ca-P ratio (>1.185)	4.89	1.33	17.97	0.02

The test was considered significant if $p<0.05$.

The level of 25(OH)D >10.55 ng/mL was not a risk factor for osteopenia. Vitamin D either in the form of D2 or D3, need to be activated into 25(OH)D in the liver and 1,25(OH)2D in the kidneys. The conversion of 25(OH)D to 1,25(OH)2D was affected by the the cytochrome P450 (CYP450) and 25-hydroxyvitamin D-1α-hydroxylase (1α-OHase) enzymes in the kidney. Another cytochrome enzyme, P27B1 (CYP27B1), 1α-hydroxylase also affects the activity of bone cells, both osteoblasts and osteocytes. Local production of 1,25(OH)2D in osteocytes promotes maturation of osteoblasts and osteocytes and affects bone formation.(33) This explanation could support that 25(OH) D levels was not a risk factor for osteopenia, because there was still the possibility of the influence of the enzyme that converts 25(OH)D to 1,25(OH)2D which actively played a role in bone formation.

The PTH-25(OH)D ratio >2.425 was a risk factor for osteopenia in productive women with central obesity. Increased levels of PTH could stimulate the release of Ca^{2+} from bone, as well as decreased levels of 25(OH)D could interfere with Ca^{2+} absorption. The calculation of the increasing PTH/25(OH) ratio, allowed an increased risk of bone disorders.(31,32)

The Ca levels >1.52 mmol/L was a risk factors for osteopenia in reproductive women with central obesity. These results were in line with another study, which show that Ca levels that were within the upper limit of the reference value are at risk for osteoporosis compared to patients with normal Ca levels.(34) There was a significant association between levels of serum Ca with BMD in postmenopausal women.(35) The Phosphorus level <1.245 mmol/mL was not a risk factor for the incidence of osteopenia in reproductive women with central obesity. This result was consistent with a previous study which show that P levels were significantly associated with BMD in men's lumbosacral, but not in women.(25) High phosphorus diet was positively associated with BMD in adolescent girls, but had no effect if the individual consumes a high Ca diet. (36) This study did not investigate about the impact of food and drink intake that may affects serum phosphorus levels.

The Ca-P ratio >1.185 was a risk factor for the incidence of osteopenia in women of reproductive age with central obesity. This study was in accordance with previous study that the Ca-P ratio may play a role in the diagnosis of primary hyperparathyroidism which results in decreased bone density due to increased Ca serum levels.(26) Several studies have shown a relationship between the Ca-P ratio of diet with bone health. Ca-P ratio of intake was inversely related to whole body BMD and femoral neck region, in both pre and postmenopausal women. A decrease in the Ca-P ratio from intake can stimulate PTH production, causing an increase in bone reabsorption.(27)

Several factors that influence the incidence of osteopenia that were taken into account in this study included

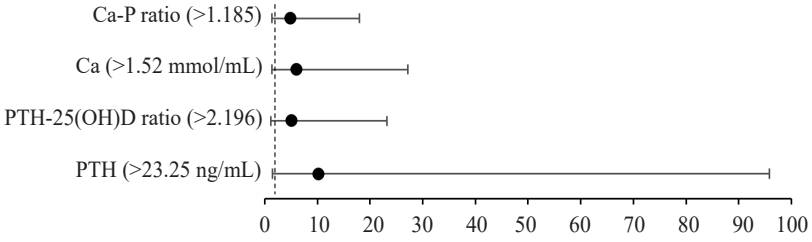

Figure 1. Forest plot ratio prevalence for risk factors.

Table 3. Adjusted model of risk factor analysis of all parameters.

Model	Parameter	Reference	PR	95% CI		*p*-value
				Lower	Upper	
1	**PTH**					
	>23.25 pg/dL	≤23.25 pg/dL	8.02	0.85	75.58	0.89
	PTH-25(OH)D ratio					
	>2.196	≤2.196	3.14	0.51	19.38	0.22
	Ca					
	>1.52 mmol/L	≤1.52 mmol/L	9.45	0.59	150.11	0.11
	Ca-P ratio					
	>1.185	≤1.185	0.77	0.06	6.39	0.84
	UV exposure					
	Never/rarely	Routine	1.11	0.24	5.24	0.89
	Excercise					
	Never/rarely	Routine	1.01	0.16	6.35	0.99
2	**PTH**					
	>23.25 pg/dL	≤23.25 pg/dL	9.03	0.85	75.55	0.07
	PTH-25(OH)D ratio					
	>2.196	≤2.196	3.14	0.51	19.37	0.22
	Ca					
	>1.52 mmol/L	≤1.52 mmol/L	9.45	0.59	149.66	0.11
	Ca-P ratio					
	>1.185	≤1.185	0.76	0.06	9.03	0.83
	UV exposure					
	Never/rarely	Routine	1.19	0.24	5.23	0.89
3	**PTH**					
	>23.25 pg/dL	≤23.25 pg/dL	8.1	0.87	75.67	0.07
	PTH-25(OH)D ratio					
	>2.196	≤2.196	3.25	0.54	19.13	0.19
	Ca					
	>1.52 mmol/L	≤1.52 mmol/L	9.73	0.54	148.62	0.10
	Ca-P ratio					
	>1.185	≤1.52	0.77	0.07	9.02	0.83
4	**PTH**					
	>23.25 pg/dL	≤23.25 pg/dL	7.86	0.86	75.67	0.07
	PTH-25(OH)D ratio					
	>2.196	≤2.196	3.09	0.55	17.51	0.2
	Ca					
	>1.52 mmol/L	≤1.52 mmol/L	7.76	1.48	40.62	0.02
5	**PTH**					
	>23.25 pg/dL	≤23.25 pg/dL	11.97	1.43	99.95	0.02*
	Ca					
	>1.52 mmol/L	≤1.52 mmol/L	7.03	1.38	35.95	0.02*

The test was considered significant if $p<0.05$.

age, UV exposure, physical activity, exercise, milk intake, milk-contained snacks, yoghurt and cheese. Likewise, CRP, 25(OH)D and P levels were excluded from the multivariate analysis. This study did not investigate further about type of physical activity, duration and time of UV exposure.

The best results were model No. 5, which is the combination of PTH and Ca (as shown in Table 3). Chronic exposure to high parathyroid levels will cause a continuous bone resorption effect. Osteoblasts and bone marrow stromal cells mediate the action of PTH on osteoclasts through several types of cytokines by increasing differentiation of osteoclast precursors and stimulation of resorption activation in mature osteoclasts. This could lead to an increase in blood Ca levels.(22)

Previous studies had shown an association between PTH and fat mass in overweight young adult women. Parathyroid hormone and Ca intake increase Ca levels in adipocytes leading to decreased lipolysis and increased lipogenesis through the mechanism of increasing fatty acid synthesis in cells.(37) Ca levels within the upper limit of the reference value were at risk of developing osteoporosis compared to patients with low levels of Ca. More than 50% of women with high Ca levels meet the criteria for osteoporosis and need further BMD examination.(34)

Further study is needed to investigate the impact of food and drink intake that may affects serum P levels, physical activity, duration and time of UV exposure, and other inflammatory markers, such as TNF-α, IL-1, and IL-6.

Conclusion

This study found that reproductive age, central obesity women with a PTH level >23.25 ng/mL, PTH-25(OH)D ratio >2.425, Ca level >1.52 mmol/mL and a Ca-P ratio >1.185 had 10.18 times; 5.12 times; 6 times; and 4.89 times greater risk of osteopenia, respectively. The PTH level >23.25 ng/mL accompanied with Ca >1.52 mmol/mL is the best risk factor for osteopenia in women with central obesity. This expected parameter can be used to prevent a person from falling in osteoporosis and fractures due to osteoporosis.

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Authors Contribution

MH were involved in planning and supervised the work, processed the experimental data, performed the analysis, drafted the manuscript and designed the figures. LB and TIW designed and supervised the study, giving the critical input, revised and finalized the manuscript. SHT performed the calculations and statistical analysis and giving critical input especially in the methods section of the manuscript. BR, IM and BM giving the critical input for the study.

References

1. Jeremiah MP, Unwin BK, Greenawald MH. Diagnosis and management of osteoporosis. Am Fam Physician. 2015; 92(4): 261-8.
2. Cooper C, Ferrari S. IOF Compendium of Osteoporosis. Nyon: International Osteoporosis Foundation; 2019.
3. Sözen T ÖL, Başaran NC. An overview and management of osteoporosis. Eur J Rheumatol. 2017; 4(1): 46-56.
4. Cheung EYN, Tan KCB, Cheung CL, Kung AWC. Osteoporosis in East Asia: Current issues in assessment and management. Osteoporos Sarcopenia. 2016; 2(3): 118-33.
5. Tan WLB, Low SL, Shen L, De SD. Osteoporotic hip fractures: 10-year review in a Singaporean hospital. J Orthop Surg (Hong Kong). 2015; 23(2): 150-4.
6. Thambiah SC, Yeap SS. Osteoporosis in South-East Asian Countries. Clin Biochem Rev. 2020; 41(1): 29-40.
7. Kementrian Kesehatan RI. Riset Kesehatan Dasar. Jakarta: Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI; 2018.
8. Liu CT, Broe KE, Zhou Y, Boyd SK, Cupples LA, Hannan MT, *et al.* Visceral adipose tissue is associated with bone microarchitecture in the framingham oteoporosis sudy. J Bone Miner Res. 2017; 32(1): 143-50.
9. Liu YH, Xu Y, Wen YB, Guan K, Ling WH, He LP, *et al.* Association of weight-adjusted body fat and fat distribution with bone mineral density in middle-aged Chinese adults: a cross-sectional study. PLoS ONE. 2013; 8(5): e63339.10.1371/journal.pone.0063339.
10. Baioumi AYAA. Comparing measures of obesity: waist circumference, waist-hip, and waist-height ratios. In: Nutrition in the Prevention and Treatment of Abdominal Obesity. Cambridge: Elsevier Inc; 2019. p.29-40.
11. Ashwell M, Gibson S. Waist-to-height ratio as an indicator of 'early health risk': simpler and more predictive than using a 'matrix' based on BMI and waist circumference. BMJ Open. 2016: 14; 6(3): e010159. doi: 10.1136/bmjopen-2015-010159.
12. Yang H, Xin Z, Feng JP, Yang JK. Waist-to-height ratio is better than body mass index and waist circumference as a screening criterion for metabolic syndrome in Han Chinese adults. Medicine (Baltimore). 2017; 96(39): e8192. doi: 10.1097/MD.0000000000008192.
13. Jin J, Wang Y, Jiang H, Kourkoumelis N, Renaudineau Y, Deng Z. The impact of obesity through fat depots and adipokines on bone homeostasis. AME Med J. 2018; 3(10): 1-9.
14. Devlin M, Rosen CJ. The bone fat interface: basic and clinical implications of marrow adiposity. Lancet Diabetes Endocrinol. 2015; 3(2): 141-7.
15. Sumiyati Y, Bakri S, Arif M. Correlation between inflammation and fibrinolysis in hipertensive centrally obese subjects : a study on c-reactive protein, plasminogen activator inhibitor-1 and thrombin activatable fibrinolysis inhibitor. Indones Biomed J. 2012; 4(3): 151-6.
16. Thaha M, Empitu MA, Kadariswantiningsih IN, Nugroho CW, Hasanatuludhhiyah N, Rasyid H, *et al.* Anthropometry-based body fat percentage predicts high hs-CRP in chronic kidney disease patients. Indones Biomed J. 2018; 10(2): 184-91.

17. Hill TR, Aspray TJ. The role of vitamin D in maintaining bone health in older people. Ther Adv Musculoskel Dis. 2017; 9(4): 89-95.
18. Wu J, Zhao F, Ma F, Guan T, Liu P. Relationship analysis of 25-Hydroxy-vitamin-D and parathyroid hormone in bone mineral density from senile osteoporotic fracture patients. Int J Clin Exp Med. 2017; 10(9): 13571-6.
19. Thiering E, Brüske I, Kratzsch J, Hofbauer LC, Berdel D, von Berg A, *et al.* Associations between serum 25-hydroxyvitamin D and bone turnover markers in a population based sample of German children. Sci Rep. 2015; 5: 18138. doi: 10.1038/srep18138.
20. Alkhenizan A, Mahmoud A, Hussain A, Gabr A, Alsoghayer S, Eldali A. The relationship between 25 (OH) D levels (vitamin D) and bone mineral density (BMD) in a Saudi population in a community-based setting. Plos One. 2017; 12(1): e0169122. doi: 10.1371/journal.pone.0169122.
21. Kharroubi A, Saba E, Smoom R, Bader K, Darwish H. Serum 25-hydroxyvitamin D and bone turnover markers in Palestinian postmenopausal osteoporosis and normal women. Arch Osteoporos. 2017; 12(1): 13. doi: 10.1007/s11657-017-0306-7.
22. Risteli J, Winter WE, Kleerekoper M, Risteli L. Disorders of bone and mineral metabolism. In: Burtis CA, Brun DE, Sawyer BG, editors. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics. St. Louis: Elsevier/Saunders; 2015. p.741-70.
23. Stanley T, Bredella MA, Pierce L, Misra M. The ratio of parathyroid hormone to vitamin D is a determinant of cardiovascular risk and insulin sensitivity in adolescent girls. Metab Syndr Relat Disord. 2013; 11(1): 56-62.
24. Shakoor S, Ilyas F, Abbas N, Mirza MA, Arif S. Prevalence of osteoporosis in relation to serum calcium and phosphorus in aging women. J Glob Innov Agric Soc Sci. 2014; 2(2): 70-5.
25. Campos-Obando N, Koek WNH, Hooker ER, Eerden BCvd, Pols HA, Hofman A, *et al.* Serum phosphate is associated with fracture risk: The Rotterdam Study and MrOS. J Bone Miner Res. 2017; 32(6): 1182-93.
26. Madeo B, Kara E, Cioni K, Vezzani S, Trenti T, Santi D, *et al.* Serum calcium to phosphorous (Ca/P) ratio is a simple, inexpensive, and accurate tool in the diagnosis of primary hyperparathyroidism. JBMR. 2018; 2(2): 109-17.
27. Lee KJ, Kim KS, Kim HN, Seo JA, Song SW. Association between dietary calcium and phosphorus intakes, dietary calcium/phosphorus ratio and bone mass in the Korean population. Nutr J. 2014; 13(114): 2-8.
28. Adatorwovor R, Roggenkamp K, Anderson JJB. Intakes of calcium and phosphorus and calculated calcium-to-phosphorus ratios of older adults: NHANES 2005–2006 data. Nutrients. 2015; 7(11): 9633-9.
29. Greendale GA, Jackson NJ, Han W, Huang M, Cauley JA, Karvonen-Gutierrez C, *et al.* Increase in C-reactive protein predicts increase in rate of bone mineral density loss: the study of women's health across the nation. JBMR Plus. 2021; 5(4): e10480. doi: 10.1002/jbm4.10480.
30. Meiliana A, Dewi NM, Wijaya A. Adipose tissue, inflammation (meta-inlammation) and obesity management. Indones Biomed J. 2015; 7(3): 129-46.
31. Qu Z, Yang F, Hong J, Wang W, Yan S. Parathyroid hormone and bone mineral density: a Mendelian randomization study. J Clin Endocrinol Metab. 2020; 105(11): e4038-45.
32. Gao C, Qiao J, Li SS, Yu WJ, He JW, Fu WZ, *et al.* The levels of bone turnover markers 25(OH)D and PTH and their relationship with bone mineral density in postmenopausal women in a suburban district in China. Osteoporos Int. 2017; 28(1): 211-8.
33. Cipriani C, Pepe J, Piemonte S, Colangelo L, Cilli M, Minisola S. Vitamin D and its relationship with obesity and muscle. Int J Endocrinol. 2014; 2014: 841248. doi: 10.1155/2014/841248.
34. Dalemo S, Eggertsena R, Hjerpeb P, Almqvistd EG, Bostrom KB. Bone mineral density in primary care patients related to serum calcium concentrations: a longitudinal cohort study from Sweden. Scand J Prim Health Care. 2018; 36(2): 198-206.
35. Khatake PD, Jadhav SS, Afroz S. Relation between serum calcium level, bone mineral density and blood pressure in postmenopausal women. Int J Recent Trends Sci Technol. 2013; 7(3): 86-9.
36. Lee AW, Cho SS. Association between phosphorus intake and bone health in the NHANES population. Nutr J. 2015; 14: 28. doi: 10.1186/s12937-015-0017-0.
37. Marwaha RK, Garg MK, Mahalle N, Bhadra K, Tandon N. Role of parathyroid hormone in determination of fat mass in patients with vitamin D deficiency. Indian J Endocr Metab. 2017; 21(6): 848-53.