Metabolic Syndrome and Bone Density in Obese Adolescents

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ABSTRACT

The purpose of this study was to analyse the correlations of metabolic syndrome components (central obesity, triglyceride levels, and hypertension) and related factors including nutrient intake and bone physical activity with bone density in obese adolescents. A cross-sectional study was conducted involving 47 obese adolescents (15-18 years) from three high schools in Semarang city, Central Java, selected by consecutive sampling. Bone density was measured by the Quantitative Ultrasound method. Metabolic syndrome and osteopenia were detected in 28% and 11% subjects, respectively. Positive correlations were found between triglyceride levels, calcium intake, vitamin D intake, current bone-physical activity (cBPA) and bone density (p<0.05). Conversely, central obesity, blood pressure, protein intake, animal protein, plant protein, phosphorus, potassium, sodium, past bone-physical activity (pBPA), and total bone-physical activity (tBPA) were not correlated with bone density. It was found that calcium intake, cBPA, and triglyceride levels were the two strongest factors related to bone density (adjusted R^2=52.5%). This study showed that obese adolescents are at risk of having metabolic syndrome and higher triglyceride levels imply lower bone density.

Keywords: adolescent, bone density, metabolic syndrome, obesity

INTRODUCTION

Obesity is one of the nutritional problems in adolescents and the number is increasing. Increasing prevalence of obesity is in line with increasing prevalence of metabolic syndrome. The increasing prevalence of obesity in chilhood will increase the risk of metabolic syndrome in adolescents and it is feared to be the beginning of the emergence of degenerative disease, such as cardiovascular disease (Liu *et al*. 2010). According to Indonesia Basic Health Research (*Riskesdas*) (2013), the prevalence of obesity in adolescents aged 13-15 years is 2.5% and adolescents aged 16-18 years is 1.6%. The national prevalence of obesity was lower when compared with some studies in Semarang. Research conducted by Fitriyanti & Sulchan (2015) in 2 Senior High Schools in Semarang stated that 15.2% of obese adolescents had metabolic syndrome. Research in 15 Senior High Schools also in Semarang with subject of 66 obese teenagers, finds 47.5% obese teenager had metabolic syndrome (Muhammad & Dieny 2016). The study mentions 31.6% of obese adolescents had a pre-metabolic syndrome and 68.4% of obese adolescents had metabolic syndrome (Dieny 2016).

The Indonesian Pediatric Association has presented the metabolic syndrome criteria for children and adolescents that can be used for the population of children and adolescents in Indonesia. This criteria states that children and adolescents are classified as having metabolic syndrome if they have waist circumference ≥80th percentile and two other criteria are added, i.e. triglyceride levels ≥110 mg/dl, HDL ≤40 mg/dl, fasting blood glucose ≥100 mg/dl, and blood pressure ≥95th percentile (Pulungan *et al*. 2014)

Research has shown that the five components of the metabolic syndrome, high triglyceride levels (hypertriglyceridemia), hypertension and waist circumference are the most components commonly found in adolescents (Dieny *et al*. 2015, da Silva *et al*. 2014; Guadalupe *et al*. 2012). Previous studies conducted in Semarang shows 91.2% of obese adolescents were suffering from central obesity, 71.2% of obese adolescents had high triglyceride levels and 61.4% of obese adolescents had high blood pressure (Dieny *et al*. 2015).

Studies has shown strong correlations between metabolic syndrome and bone density where each component of the metabolic syndrome has an independent effect on bone density (Sok *et al*. 2016). Research with adolescent subjects shows that 14% of adolescents with metabolic syndrome have lower bone density compared to adolescents without metabolic syndrome (da Silva *et al*. 2014). In fact, low bone density (osteopenia) is an early predictor of the occur-

rence of osteoporosis in the future. Central obesity, measured by circumference, is the strongest negative component affecting bone density (da Silva *et al.* 2014). This occurs because visceral fat is an endocrine organ that can release adipokines and cytokines including pro-inflammatory factors i.e. interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-α that can cause bone resorption by accelerating osteoclast division (Kini & Nandeesh 2012).

Hypertriglyceridemia is one of the most common metabolic syndrome components found in adolescents and is associated with decreasing bone density (da Silva *et al.* 2014). Hypertriglyceridemia is a sign of lipid metabolism abnormalities. Impaired lipid metabolism can lead to increasing lipid oxidation. Lipid oxidation stimulates adipocyte secretion that will inhibit osteoblast differentiation through increasing production of Peroxisome Proliferation Activation Receptor (PPAR-g) (Czernik *et al.* 2002). Hypertension is one of the metabolic syndromes component that affects bone density. A study suggests that adolescents with a history of hypertension or pre-hypertension are at higher risk for fractures (Pluwdoski *et al.* 2007). Decreasing bone density is also associated with the increasing of calcium metabolism from bone, parathyroid activation of the gland, and the increasing of calcium loss from the kidneys (Kini & Nandeesh 2012).

Based on Indonesia Basic Health Research, the prevalence of obesity among population >15 years old is increasing in Indonesia, that is 18.8% in 2007, to 26.6% in 2013, and become 31% in 2018 (MoH 2018). The prevalence of metabolic syndrome at age >15 years old in Indonesia is 17.5% (Bantas 2012). Therefore there is a need to conduct a study about metabolic syndrome and its relationship with bone mass density in obese adolescent.

METHODS

Design, location, and time

This study was a cross sectional study, conducted in SMA 2, SMA 11 and SMA 15 Semarang. Data collection was conducted from July to August 2017.

Sampling

Subjects obtained in the calculation of observational research formula were 45 subjects. Based on anthropometric measurements performed on 324 adolescents, as many as 99 obese teenagers were found in this study and those who were willing to be the subject were 52 students, but 5 resigned during data collection. The research inclusion criteria were adolescents aged

15-18 years old, had BMI for age >2 SD, lived in Semarang City and willing to be the subject of research. The exclusion criteria applied in this research were sick and cannot follow the rules of research. This research has obtained the ethical clearance from Health Research Ethic Commission, Faculty of Medicine, Diponegoro University Number 524/FK-RSDK/VIII/2017.

Data collection

Independent variables were waist circumference, triglyceride level, and blood pressure. The waist circumference was measured using a 0.1 cm metline performed by trained students. The waist circumference data were categorized as normal (<80th) and central obesity (>80th) (Pulungan *et al.* 2014). Blood sampling for triglyceride level measurements was performed by trained personnel and tested using the enzymatic enzyme method (GPO-PAP). Data on triglyceride level were categorized to be normal (<110 mg/dl) and hypertriglyceridemia (≥110 mg/dl) (Pulungan *et al.* 2014). Blood pressure measurements were performed by a trained health worker, using a sphygmomanometer and performed twice on the subject then categorized to normal (<90th), pre-hypertension (90th≤SD≤95th), and hypertension (>95th) (Pulungan *et al.* 2014).

The dependent variable was bone density measured by trained personnel using quantitative ultrasound method. Bone density variables were categorized into normal (-1≤SD<2.5) and osteopenia (-2.5≤SD<-1) (Lee 2007). Confounding variables were the intake of vitamin D, calcium, sodium, phosphorus, potassium, and physical activity. Subject intake was measured using semi-quantitative food frequency (FFQ-SQ) method which was then converted by using nutrisurvey 2005. Animal and vegetable protein requirement were obtained from 30% and 70% of total protein requirement per individual (MoH 2014). Total intake of protein, vegetable, and animal were categorized into 3, they were excess (>120%), enough (90-119%), and less (<90%) (Kusharto & Supariasa 2014). Micro nutrient data were categorized into 3, those were less (<80%), enough (80-100%), and more (>100%) (Widajanti 2009), while the physical activity used the instrument Bone-Specific Activity Questionnaire (BPAQ). This instrument presented 3 types of data, those were current Bone-Physical Activity (cBPA), past Bone-Physical Activity (pBPA), and total Bone-Physical Activity (tBPA). Data of cBPA was the subject's physical activity data for the past 12 months, pBPA was the subject's physical activity data from the age of 1 year, and tBPA was a combination of cBPA and pBPA scores (Weeks & Beck 2008) .

Data analysis

The univariate analysis was used to describe the characteristics of subject, independent variable, bound, and confounder. The normality test data used was the Saphiro-Wilk test. Linear regression test was used to analyse the relation of each variable with adolescent bone density. If the results of the linear regression test had a p-value <0.05 then the variables were included in the multivariate test using multiple linear regression with backward selection method to determine the most influential variable to bone density.

RESULTS AND DISCUSSION

Subject characteristics

Table 1 shows that the average subject age was 15 years. The maximum value of z-score BMI for age was 4.93. Mean diastole blood pressure percentile was higher than mean systolic blood pressure, 92.06±10.42 and 71.67-21.63 for systolic blood pressure. T-Score bone density of the subjects had a low mean of -0.06 ± 0.89. The minimum value of vitamin D and low calcium intake was 0.30 µg and 36 mg. Total protein intake, animal, and vegetable protein also had a high maximum value of 222 g, 116 g, and 128 g. Minimum and maximum values for physical ac-

tivity score had a considerable range. The minimum and maximum scores of pBPA scores were 0.4 and 217.5.

Nutrient intake

Table 2 illustrates that most subjects (72%) had poor calcium intake, 91.5% subjects had less vitamin D intake, and 64% subjects had less sodium intake. On the other hand, 32% of the subjects had excessive a total protein intake, 60% had excessive animal protein, and 42.5% had over phosphor intake.

Metabolic syndrome and bone density

Table 3 describes 91% of subjects had central obesity, 57% of subjects had hypertriglycerides, and 53% of subjects had hypertension. However, the number of subjects with diastolic hypertension (53%) were more than subjects with systolic hypertension (21%), and as many as 15% of subjects had both systolic and diastolic hypertension.

Table 4 shows that all subjects had at least one risk factor for metabolic syndrome. This suggests that obesity is always followed by risk factors for metabolic syndrome (Liu *et al*. 2010). A total of 28% of subjects had metabolic syndrome and as many as 72% had 1-2 risk factors for me-

Table 1. Subject characteristics

Variable	Min	Max	Mean±SD
Age (year)	15	18	15.51±0.71
Weight (kg)	67	141	88.6±15.89
Height (cm)	151	180	165.47±7.01
Z-score BMI-for-age	2.00	4.93	2.63±0.65
Triglyserida levels (mg/dl)	100	136	114.13±10.13
Waist circumference (cm)	79	124	96.28±20.72
Blood pressure (percentile)			
Sistole	30	99.9	71.67±21.63
Diastole	63	99.9	92.06±10.42
Bone density T-core	-2.1	1.7	-0.066±0.89
Intake			
Total protein (g)	39	222	95.11±42.69
Vegetable protein (g)	21	128	49.95±23.61
Animal protein (g)	4	116	45.61±27.24
Vitamin D (µg)	0.3	17.6	5.81±4.25
Calsium (mg)	136	1535	642.7±423.99
Phospor (mg)	284	2,700	1,166.55±890.66
Calium (mg)	274	6,181	2,102.57±1407.06
Natrium (mg)	114	3,480	1,120.06±596.8
tBPA*	0.7	109	19.93±20.08
cBPA**	0.2	41.40	8.18±7.75

*total Bone-Phisycal Activity, **current Bone-Phisycal Activity

Tabel 2. Description of protein, vitamin D, calsium, phospor, natrium, and calium intake

Intake	n	%
Total protein (g)		
Less	20	42.5
Adequate	12	25.5
Excessive	15	32.0
Vegetable protein (g)		
Less	30	64.0
Adequate	9	19.0
Excessive	8	17.0
Animal protein (g)		
Less	9	19.0
Adequate	10	21.0
Excessive	28	60.0
Vitamin D (µg)		
Less	43	91.5
Adequate	2	4.25
Excessive	2	4.25
Calsium (mg)		
Less	34	72.0
Adequate	5	11.0
Excessive	8	17.0
Phospor (mg)		
Less	19	40.5
Adequate	8	17.0
Excessive	20	42.5
Natrium (mg)		
Less	30	64.0
Adequate	4	8.5
Excessive	13	27.5
Kalium (mg)		
Less	41	87.2
Adequate	3	6.4
Excessive	3	6.4

Table 3. Description of metabolic syndrome components

Metabolic syndrome components	n	(%)
Waist circumferences		
Normal	4	9
Obesity	43	91
Triglyseride levels		
Normal	20	43
Hypertrigliserida	27	57
Blood pressure		
Normal	9	19
Prehypertension	13	28
Hypertension	25	53

Table 4. Description of metabolic syndrome and bone density in subject

Category	n	(%)
Metabolic syndrome		
Pre-metabolic syndrome (1-2 FR)	34	72
Metabolic syndrome	12	28
Bone density		
Normal	42	89.4
Osteopenia	5	10.6

FR Risk Factor

tabolic syndrome. There were 21% of subjects with 1 risk factor of metabolic syndrome, and 51% of subjects had 2 risk factors for metabolic syndrome.

A total of 42 subjects (89%) had normal bone density and 5 subjects (11%) had low bone density (osteopenia). Although the subject with osteopenia were only 5 students (11%), subjects who had positive bone density T-score were only 19 students (40%), and the remaining 23 (49%) had a negative bone density T-score, with 8 subjects having a density T-score bone <-0.5.

Correlation between metabolic syndrome components, confounding variables, and bone density

The results show a significant relationship between triglyceride levels, calcium intake, vitamin D, current physical activity, with adolescent bone density and obesity. On the other hand, there was no significant relationship between central obesity, systolic blood pressure, diastolic blood pressure, total protein intake, animal protein, vegetable protein, phosphorus, potassium, sodium, past physical activity, total physical activity and bone density of obese adolescents.

Based on the result of linear regression of variables having significant relationship ($p<0.05$) with bone density (triglyceride level, calcium intake, vitamin D, and cBPA intake), multivariate analysis was conducted to obtain factors with strongest correlation. The result of double linear regression analysis showed that calcium intake ($p=0.000$), cBPA ($p=0.001$), and triglyceride value ($p=0.002$) had the strongest correlation with bone density, while vitamin D did not show significant relationship ($p=0.248$). Final result using backward selection method resulting equation is bone density=2.589+0.001 calcium intake+0.041 cBPA-0.032 triglyceride level. The coefficient of determination (adjusted R^2)=52.5%, so that bone density variation can be explained 52.5% by calcium intake, cBPA, and triglyceride value. While 47.5% is explained by other variables.

The research on the association of metabolic syndrome components with bone density still shows different results. In this study, it is found a significant relationship between hypertriglyceridemia and bone density. The results of this study are in line with research conducted by da Silva *et al.* (2014) in Brazil, suggesting adolescents with hypertriglyceridemia have lower bone density than teenagers who have normal trigly-ceride levels. This can occur because lipid metabolic abnormalities can increase lipid oxidation levels. Some studies have also shown similar result that hypertriglyceridemia had negatively correlated with bone mass density in adolescents (da Silva 2017; Debbie 2012, Hwang & Choi

2010). Lipid oxidation can stimulate adipocyte differentiation that will suppress osteoblast differentiation by activation of peroxisome proliferation-activated receptor-γ (PPAR-γ). PPAR-γ is a special receptor used to detect signals from fatty acids and convey to fatty acids to control fat metabolism and inflammation. PPAR-γ activation will inhibits osteoblast differentiation in mesenchymal cells (Czernik *et al*. 2002).

Blood pressure does not show significant association with adolescent bone density. This result can be caused by the value of blood pressure that can change easily according to subject conditions. Further examinations are needed to determine better diagnosis of hypertension in the subjects. In previous study, blood pressure checks were measured three times at three different examination times. In addition, the subject has been confirmed to have hypertension after

Table 5. Correlation between metabolic syndrome components, nutrients intake, and physical activity with bone density

Variable	Bone density
	p*
Metabolic syndrome components	
Triglyserides level (mg/dl)	0.000
Waist circumference (cm)	0.837
Sistole blood pressure (percentile)	0.947
Diastole blood pressure (percentile)	0.766
Nutrien intake	
Total Protein (g)	0.839
Animal Protein (g)	0.814
Vegetable Protein (g)	0.727
Vitamin D (µg)	0.001
Calcium (mg)	0.000
Phospor (mg)	0.494
Calium (mg)	0.592
Natrium (mg)	0.439
tBPA	0.494
cBPA	0.009
pBPA	0.840

*Linear regression test (significant if p-value <0.05)

undergoing examination at the school clinic and further examination at the hospital (Pludowski *et al*. 2007). Although in this study there is no relationship was found between blood pressure and bone density, the direction of correlation is negative. Yazici *et al*. (2011) mentioned that hypertension is a predictor of osteopenia and osteoporosis. Other studies suggest that bone mineral content (BMC) in juvenile hypertension is lower than the non-hypertensive teenagers (Pludowski *et al*. 2007). Systolic blood pressure (Afghani & Ghoran 2007) and diastolic blood pressure (Joen *et al*. 2011) have an inverse relationship with bone density.

Calcium metabolism abnormalities are the connecting factor between hypertension and bone density. Hypertension can cause hypercalciuria due to the competition between calcium and sodium ions in the proximal tubules in the kidneys. Calcium and sodium have the same binding protein that is claudin-2. Thus, the increasing of sodium ions will decrease the permeability of calcium and increase calcium excretion. The decrease of calcium in the body through urine leads to parathyroid hormone activation in order to increase bone resorption (Yu *et al*. 2010).

There is no association between central obesity (measured by waist circumference) with bone density. Studies of obesity in metabolic syndrome showed conflicting results. Research with adolescent subjects shows central obesity to cause low bone density (da Silva *et al*. 2014, Pollock *et al*. 2011). Adipose tissue such as visceral fat may secrete pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor-α. The presence of cytokines can stimulate bone resorption through activation of the RANKL/RANK pathway. The increasing of inflammatory mediators may increase the production of RANKL (Receptor Activator of Nuclear Factor Kappa β Ligand). RANKL will bind to its receptor, RANK (Receptor Activator of Nuclear Factor Kappa β) located on the surface of the hematopoetic cell and will stimulate proosteoclast differentiation into osteoclasts. In contrast, studies in Egypt mentioned no association between central obesity and bone density in the direction of positive correlation (El-Masry *et al*. 2014).

Table 6. The most significantly correlated factors to bone density

Variable	Bone density		
	Adjusted R^2	B (Unstandardized coefficient)	p
Calcium intake		0.001	0.000
cBPA	0.525	0.041	0.001
Triglyserides		-0.032	0.002
Constanta		2.589	

*Multiple linear regression with backward selection method

Adipocyte tissue plays a role in the secretion of bone active hormones from adipocyte cells such as leptin and estrogen. Leptin and estrogen are mediators that can increase osteoblast proliferation and differentiation (Reid 2002). Bone active hormone is required to support intense bone growth during adolescence and achieve optimal peak bone mass (Lopez *et al.* 2010).

The absence of relationship between central obesity and bone density may be affected by the fat distribution in each subject. Previous studies have suggested that the ratio between visceral fat and subcutaneous fat also affects teen bone density. Teenagers who had more visceral fat than their subcutaneous fat had lower bone density when compared with adolescents who had subcutaneous fat more than their visceral fat (Russel *et al.* 2010).

The results of this study show although all subjects had at least 1 risk factor for metabolic syndrome, the majority of subjects still had normal bone density. This can occur because of the influence of confounding variables, i.e vitamin D intake, calcium and current bone-physical activity that have significant association with bone density. This study shows that there is a significant relationship between cBPA and bone density. These results are supported by Kim *et al.* (2013) which mentions that past activity and physical activity in the present, both affect bone density. A research in Australia suggests that all components of BPAQ, both cBPA, pBPA and tBPA have a positive relationship with bone density of male or female subjects and cBPA is the most influential predictor of total Bone Mineral Density or BMD (Weeks & Beck 2008). Types of weight-bearing exercise and resistance exercises will cause the muscles to squeeze the bones (muscle attached to the tendon), thus it can stimulate bone metabolism to strengthen bones in depressed and needed parts (Kini & Nandeesh 2012). On the other hand, the results of this study show that there is no significant relationship between pBPA, tBPA, and bone density, but the direction of the relationship is positive.

The intake of vitamin D and calcium also has a significant relationship with bone density. Vitamin D has a special role in bone health. The results of this study are in line with the research conducted in Sweden which states that vitamin D intake has a positive relationship with bone density, subjects with the highest vitamin D intake had 5% higher total bone density (Michaelsson *et al.* 2006). A high intake of calcium will increase the adolescent bone density (Hardinsyah *et al.* 2008), that accordance with the results of this study. This study shows that subjects with low calcium intake have a negative bone density T-score including 5 osteopenic subjects; all os-

teopenic subjects had low calcium and vitamin D intake. The lack of a calcium intake continuously will lead to a serum imbalance of calcium in the blood. When serum calcium levels drop, the parathyroid gland secretes the parathyroid hormone that will stimulate vitamin D, that will increase bone resorption (Whitney & Rolfes 2011).

The intake of protein, sodium, potassium, and phospor does not have a significant relationship with the bone density of the subjects in this study. A research on protein intake and bone density has also shown inconsistent results. This study showed that total intake of protein, animal and vegetable has no significant relationship with bone density. Research in Urbana stated that total protein intake has a positive effect on lumbar spine BMD and total BMD by suppressing sulfur content. Research by Thorpe *et al.* (2008) separated between the high-sulfur and low-sulfur protein intakes, the results of subjects taking low-sulfur protein intake had higher bone density (3.2%). Other studies suggest that vegetable protein (Promislow *et al* .2002) and animal protein (Sellemeyer *et al.* 2001) have a negative relationship with bone density. This happens because protein catabolism can produce ammonium and sulfur ions derived from acidic amino acids. Then the calcium in the bone will be ruptured to neutralize the acid, so that the calcium content in the urine will increase (Heaney & Layman 2008).

Lee & Cho (2015) mentioned that high phosphorus intake increased bone mineral content by 4.2% and bone mineral density by 2.1%. The difference in the results of this study may be due to the fact that the subjects in the previous study were more (data derived from NHANES 2005-2010) and the age of the subjects was also more various (13-99 years). High intake of sodium may increase calcium excretion, which in turn increases calcium bone cleavage if the calcium intake was inadequate (Gropper *et al.* 2009). In contrast, other studies showed that high intake of sodium may increase total bone mineral density during the three years of research. (Carbone *et al.* 2016). Differences in research results occur because the study period is shorter when compared with the previous research, so that the data intake obtained only cover the last three months. High intake of potassium may decrease urinary calcium excretion (Whitney & Rolfes 2011). Decreasing calcium excretion will cause decreasing bone resorption due to lack of calcium in plasma. Previous studies have suggested that high intake of potassium (vegetables and fruits) may decrease calcium intake through urine and C-telopeptide serum (Carboxy-terminal Collagen Crosslink or CTX is a telopeptide that can be used as a serum biomarker to measure bone turnover rate) (Gunn *et al.* 2015).

CONCLUSION

A total of 28% (n = 13) subjects have metabolic syndrome and 11% (n = 5) subjects have osteopenia. There is a relationship between triglyceride levels and bone density of obese teenagers, where the higher the triglyceride level of the subjects the lower the bone density. Levels of triglycerides, c-BPA, calcium intake are the factors with the strongest association with bone density in obese adolescent. Adolescent with obesity need to improve the quality of their nutrient intake and increase their physical activity in order to control weight since obesity in adolescent increased the risk for metabolic syndrome that negatively affect bone density. In addition to losing weight, good nutritional intake and regular physical activity can also directly maintain bone health in adolescents.

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