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Anthropometric Markers, Visceral Adipocyte Index, Inflammation Markers and Bone Density in Reproductive Obese Women

Meita Hendrianingtyas[1,2*], Lisyani B.Suromo[1], Tri Indah Winarni[3]

ABSTRACT

Background: Obesity has been associated with the risk of various diseases. The correlation between anthropometry and bone health is complex. Visceral adipocyte index (VAI) is one of the compositions of body fat compositions that mostly associated with proinflammatory cytokine, which can stimulate C- reactive protein (CRP) that affects bone density.
Objectives: This study aimed to prove the correlation between VAI, CRP and BMD in Asian reproductive obese women
Materials and Methods: A cross sectional study was conducted in November 2020 - February 2021 and a total of 134 women of reproductive age with obesity participated in this study. Weight, height, body mass index (BMI) and rate of visceral fat were measured by body composition analyzer. Waist (WC) and hip circumferences (HC) measured by using tape; lipid profile and CRP level were examined using a clinical chemistry automatic analyzer, and the examination of bone mineral density (BMD) using dual-energy x-ray absorptiometry. Waist to hip ratio (WHR)and VAI calculated manually. Pearson and Spearman test were used for statistical analysis.
Results: There were positive weak correlations between weight, height, BMI, WC, HC, rate of visceral fat, WHR and VAI. There were weak positive correlations between HC, WHR and CRP. There were positive moderate correlations between weight, height, BMI, waist, visceral fat, WHR and CRP.
Conclusion: Although there were correlations between anthropometric parameters and VAI and also CRP, but we did not found correlation between VAI and CRP to all BMD parameters.

Keywords : VAI, CRP, BMD, anthropometry, obesity, women

BACKGROUND

Obesity is often associated with the risk of various diseases and encountered in the world as well as in Indonesia. The prevalence of obese women in Indonesia is 29.3% higher than in men, and 14.3% of most cases are at the age of 35-49 years.(1) The relationship between body composition and bone health is complex.(2) Cytokines and adipokines produced by fat mass can affect bone density. The C-Reactive Protein (CRP) is one of the acute phase proteins secreted by the liver in the presence of interleukin-6 stimulation(3, 4), and also with bone density.(5)

Previous study has shown that there is an anthropometric relationship including body mass index (BMI) and visceral fat with the risk of bone damage in obesity.(6) The bone mineral density is said to be positively correlated to subcutaneous fat, but negatively related to visceral fat. (7) (8, 9) Adipocyte produces adipokines which can stimulating bone growth. In the other hand, adipocytes can also produce proinflammatory cytokines that will affect bone density.(10) Another parameter of body fat composition is the visceral adipocyte index (VAI). Previous studies linking bone density with body anthropometry are still contradicting each other. This study wanted to use VAI parameters involving several lipid profile parameters to find out more about the relationship between VAI and markers of inflammation with bone density. The parameters used in the VAI calculation can be modified and involve the blood lipid profile, so that if detected early, treatment or intervention can be carried out so that the situation does not become worse. This parameter indicates distribution and function of fat tissue, also, is widely associated with metabolic syndrome and cardiometabolic risk

[1] Doctoral Program of Medical and Health Science, Faculty of Medicine, Universitas Diponegoro
Jl. Prof. Soedarto SH, Tembalang, Semarang, Jawa Tengah 50275, Indonesia
[2] Department of Clinical Pathology, Faculty of Medicine, Universitas Diponegoro
Jl. Prof. Soedarto SH, Tembalang, Semarang, Jawa Tengah 50275, Indonesia
[3] Department of Anatomy, Faculty of Medicine, Universitas Diponegoro
Jl. Prof. Soedarto SH, Tembalang, Semarang, Jawa Tengah 50275, Indonesia
[*]**Correspondence** : E-mail: meitanote2015@gmail.com, Phone +62812-2543265

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There are still few studies on women of reproductive age with obesity regarding the relationship between anthropometric parameters, VAI and CRP to BMD. This study aims to prove the correlation between VAI, CRP and BMD in Asian reproductive obese women.

MATERIALS AND METHODS

A cross-sectional observational study was carried out at Diponegoro University academic community Semarang from November 2020 to February 2021. The subjects were 134 women at Diponegoro University aged 25-50 years and BMI >24 kg/m^2. Participants had regular menstruation in the last 6 months, normal body temperature, normal liver and kidney functions, history of bone disorder/fractures during the past 6 months, breastfeeding, taking vitamin D, contraseptions or long-term corticosteroid were excluded from this study. Measurements of WC, hip circumference (HC), height and weight were carried out 2 times and the average results were obtained by 2 nutritionists and tested using the kappa test. Measurements of WC, hip circumference (HC), height and weight were carried out by 2 nutritionists and had been tested using kappa test. The index is calculated based on BMI, waist circumference (WC) and lipid profile in blood including triglyceride levels and high-density lipoprotein cholesterol (HDL) with the formula of {[WC/36.58 + (1.89 × BMI)] × (triglycerides/0.81) × (1.52/HDL-cholesterol)}.[11, 12] The examination of triglycerides was done using the principle of glycerol phosphate oxidase (GPO) while HDL was done by direct method and CRP by immunoturbidimetry using Indiko Thermo Fisher Scientific automatic clinical chemistry analyzer. The bone mineral density (BMD) examination was done using dual energy X-ray absorptiometry (GE-Lundar Prodigy-iDXA instrument) and interpretation was performed by a radiologist. Statistical correlation test with Pearson and Spearman Test. The value of significance if $p < 0.05$.

The study was conducted after obtaining permission from the Health Research Ethics Commission, Faculty of Medicine, Diponegoro University/Dr.Kariadi Semarang with number 242/EC/KPK/FK-UNDIP/X/2020. All subjects signed an informed consent prior to study.

RESULTS

Total of 134 women were participated in the study The subject characteristics could be seen in table 1.

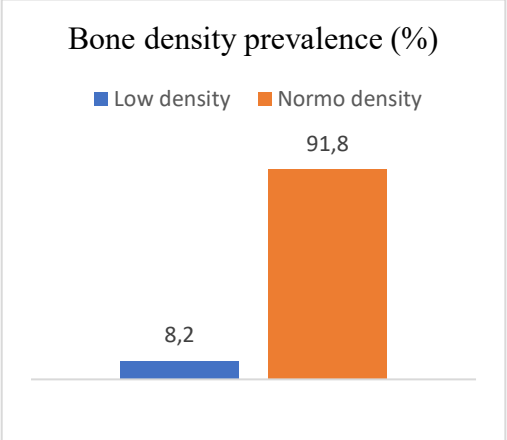
Table 1. Subject Characteristics

PARAMETER	Mean ± SD	Median (Min, max)
Age (years)	35.04 ± 6.12	34 (25 – 50)
Systole (mmHg)	115.15 ± 12.49	110 (90 – 170)
Diastole (mmHg)	73.43 ± 9.97	70 (60 – 110)
Height (cm)	155.18 ± 5.09	155.5 (145 – 169.5)
Weight (kg)	76.40 ± 13.99	72.6 (58.40 – 137.60)
BMI (kg/m2)	31.71 ± 5.05	30.50 (25.30 – 53.10)
Rate of visceral fat	9.62 ± 2.48	9 (6 – 19)
Waist circumference (cm)	93.39 ± 10.00	91(77 – 138)
Hip circumference (cm)	110.16 ± 9.86	110 (90 – 150)
WHR	0.86 ± 0.68	0.85 (0.68 – 1.04)
Total cholesterol (mg/dL)	186.49 ± 32.87	184 (98 – 257)
HDL cholesterol (mg/dL)	51.39 ± 12.05	51 (26 – 102)
LDL cholesterol(mg/dL)	113.49 ± 30.47	111 (56 – 188)
Triglyceride (mg/dL)	115.19 ± 54.26	101 (31 – 300)
VAI	4.57 ± 2.92	3.47 (0.81 – 12.53)
CRP (mg/L)	5.78 ± 5.05	4.25 (0.20 – 25)
SGOT (mg/dL)	24.57 ± 9.55	22 (14 – 78)
SGPT (mg/dL)	25.15 ± 14.37	21 (6 – 82)
Ureum (mg/dL)	23.34 ± 10.09	21 (5 – 81)
Creatinine (mg/dL)	0.78 ± 0.15	0.77 (0.49 – 1.28)
BMD lumbar	0.74 ± 1.34	0.7 (-7.2 – 3.60)
BMD femur neck	0.62 ± 0.97	0.50 (-1.70 – 4.60)
BMD femur total	0.76 ± 1.02	0.55 (-1.70 – 4.80)

Note : BMI = Body Mass Index; WHR = waist to hip ratio; VAI = Visceral Adipocyte Index; HDL = high-density lipoprotein; L low-density lipoprotein; CRP = C reactive protein; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic p transaminase; BMD = bone mineral density

Twenty out of 134 subjects (14.9%) had higher CRP levels (CRP levels > 10 mg/dL). A total of 10 out of 134 subjects (7.5%) had blood fasting glucose levels > 126 mg/dL, while the rest were within normal limits. None of the subjects were taking oral glucose and fat-lowering drugs. Bone mineral density examination

on all subjects is shown in picture 1. A total of 11 (8,2%) subjects had decreased bone density and the remaining 123 (91.8%) subjects were in normo density condition.



Picture 1. BMD result

Table 2 shows the statistical analysis of the correlation between VAI, CRP and the anthropometry.

Table 2. The correlation between anthropometry marker, VAI, and CRP

Parameter	VAI		CRP	
	r	*p*	r	*p*
Weight (kg)	0.250	0.004	0.448	0.0001
Height (cm)	-0.11[illegible]	0.172*	-0.01[illegible]	0.874*
BMI (kg/m2)	0.314	0.0001	0.491	0.0001
Waist circumference (cm)	0.334	0.0001	0.447	0.0001
Hip circumference (cm)	0.183	0.034	0.368	0.0001
Rate of visceral fat	0.312	0.0001	0.455	0.0001
WHR	0.234	0.006*	0.175	0.043*

Note : WHR =waist to hip ratio; BMD = bone mass density
*Pearson correlation test

There were positive weak correlations between weight, height, BMI, WC, HC, rate of visceral fat, WHR and VAI. Increase in body weight, height, BMI, WC, HC, rate of visceral fat, there will be an increase in VAI. There were weak positive correlations between HC, WHR and CRP. There were positive moderate correlations between weight, height, BMI, waist, visceral fat, WHR and CRP. Which means, increase HC, WHR, weight, height, BMI, waist, rate of visceral fat and WHR, there will be an increase CRP levels.

Table 3. The correlation between anthropometry parameters, VAI, CRP and BMD

Parameter	BMD *lumbar spine*		BMD *femur neck*		BMD *femur total*	
	r	*p*	r	*p*	r	*p*
Weight (kg)	**0.046**	**0.600**	**0.271**	**0.002**	**0.366**	**0.0001**
Height (cm)	**0.107**	**0.219***	**0.122**	**0.159***	**0.087**	**0.319***
BMI (kg/m2)	**0.001**	**0.992**	**0.246**	**0.004**	**0.357**	**0.0001**
Waist circumference (cm)	**-0.02[illegible]**	**0.749**	**0.212**	**0.014**	**0.319**	**0.0001**
Hip circumference (cm)	**-0.11[illegible]**	**0.207**	**0.087**	**0.319**	**0.160**	**0.065**
Rate of visceral fat	**-0.02[illegible]**	**0.792**	**0.245**	**0.004**	**0.353**	**0.0001**
WHR	**0.108**	**0.213***	**0.204**	**0.018***	**0.259**	**0.003***
VAI	**-0.001**	**0.994**	**0.031**	**0.721**	**0.107**	**0.220**
CRP (mg/L)	**0.009**	**0.916**	**0.016**	**0.856**	**0.111**	**0.202**

Note : BMI = Body Mass Index; WHR = waist to hip ratio; VAI = Visceral Adipocyte Index; CRP = C reactive protein
*Pearson correlation test

Based on table 3, there were weak positive correlations between weight, BMI, waist, visceral fat, WHR and BMD neck and total femur. No correlations were found between VAI, CRP and all BMD parameters. However, in this study, there was positive weak correlation between VAI and CRP (r = 0.306; p = 0.0001; data was not shown).

DISCUSSION

A moderately positive correlations between body anthropometry markers (HC, WHR, weight, height, BMI, waist, rate of visceral fat and WHR) HC, WHR, weight, height, BMI, waist, rate of visceral fat and WHR and CRP is supported by Aguirre's previous study which stated that increased CRP levels was accompanied by increased body fat mass.[6] Furthermore, Mulyamin (2021) concluded that there was a correlation between

BMI, WC, visceral fat and CRP. Meta-analysis studies have shown the same results between BMI, WC, WHR and CRP.[13] The increase in body fat mass examined from anthropometric parameters indicates the presence of chronic inflammation in an individual.[14] In this study, there was no relationship between CRP and BMD. This result is different from previous research by Sinya Ishii (2014) which showed that CRP levels > 3 mg/L increased the risk of fractures.[5] This different result may due to population differences, namely, only obese-reproductive women without drinking-habit were analyzed in this study. However, the previous study was conducted on Caucasians and American-Africans with moderately high drinking-habit without taking BMI into account.

Another possible cause is the population in this study were productive-age women with regular menstrual cycles for the last 6 months. This condition allowed for the protection of the hormone estrogen. The estrogen plays an important role in bone homeostasis in longitudinal bone growth. During the early stages of puberty in women, low levels of estrogen stimulates the secretion of growth hormone/ insulin-like growth factor-1 which plays a significant role in bone growth at puberty. Towards the end of puberty, high estrogen levels cause the closure of bone growth.[15, 16]

Sex hormone receptors were detected in osteoblasts, osteoclasts, osteoblast progenitor cells and mesenchymal stromal cells. Estrogen and androgen hormones in bone tissue will work through estrogen and androgen receptors (Era, ERb, AR) which are mostly found in the cytoplasm and cell membranes.[17]

Achieving peak bone mass is crucial for bone health, and plays a key role in preventing osteoporosis and bone fracture risk. The risk of hip fracture can be reduced up to 30% with a 10% increase in peak bone mass. Estrogen deficiency during menopause will affect the normal bone turnover cycle due to the presence of estrogen receptors in osteoclasts, thus, osteoclast resorption activity is increased and osteoblastic activity is decreased. Enhanced overall bone resorption may weakened the inhibitory effect on osteoclastogenesis and osteoclast activity due to the decreased of estrogen levels.[18, 19]

An increase in CRP level without a decrease in BMD could be due to the role of adipokines (such as adiponectin) which have bone-protective properties but did not analyze in this study. The state of obesity with increased number of adipocytes stimulates the production of adipokines, including adiponectin and leptin which are protective against the bone. Adiponectin is secreted by adipocytes and plays role in osteogenesis, specifically the differentiation of mesenchymal stem cells into pro-osteoblasts and the proliferation and maturation of osteoblasts. Leptin is produced by white fat mass and has protective effect on bone by stimulating osteoblastic proliferation and differentiation.[20, 21]

Decrease of bone mineral content from BMD examination appears if there has been real damage to the bone. Osteoporosis is characterized by bone fragility which can be seen from the quality of micro-architecture, micro-damage and the level of bone remodeling that will affect the bone fracture. The reading of two-dimensional DXA technique still has intrinsic limitations to determine the changes of bone geometry. While measuring BMD with DXA is not sufficient enough to determine a diagnose, so bone biomarker examinations are needed for bone damage early screening.[22]

A meta-analysis study mentions several bone biomarkers such as osteocalcin (OC), procollagen type 1 propeptide and urine N-terminal crosslinking telopepeptide of type 1 collagen (U-NTX) might have a role in evaluating long-term changes in BMD and predict future fracture risk. [23] There is weak positive correlation between VAI and CRP, in accordance with the study of Carbone (2019) which showed that there was a significant relationship between visceral fat and CRP.[24] Previous study stated that higher VAI was followed by increase CRP levels. [25] This study showed positive results between BMI, WC, rate of visceral fat with BMD of the femur and neck. This result is different from research by Zhang (2015) which shows the opposite relationship between visceral adiposity and bone density. This could be due to the population in this study was female subjects of reproductive age with obesity. The BMI of the subjects in this study was above the normal average, so there was an increase in subcutaneous and/or visceral fat that could affect the production of adipokines that are protective to bone.[9]

Visceral adipose tissue secretes inflammatory mediators, which stimulate liver and endothelial-cell acute-phase proteins. Adipocytes express and secrete TNF-α, which enhances the secretion of CRP by hepatocyte. This statement explains how body fat mass correlates with the inflammation. Increased abdominal fat mass which associated with increased CRP levels, and independent of BMI, is measurable for general adiposity detection. CRP levels were higher in individuals with abdominal adiposity than control group even though they had a similar BMI. [26]

In this study, VAI measurements based on WC, triglycerides and HDL were associated with CRP examination. The fat accumulation is identified by the balance of triglyceride synthesis and breakdown in the intestine or liver. Adipose tissue is the main source of pro-inflammatory cytokines, one of which is IL-6. This cytokine will induce liver lipogenesis and trigger systemic acute phase responses. [27] This study did not examine adipokines or proinflammatory cytokines levels produced by adipocytes. Further investigation is needed by measuring subcutaneous fat thickness, adipokines and proinflammatory cytokines levels to find out more about the relationship between anthropometric parameters and BMD especially in women of reproductive age with obesity.

CONCLUSION

There were weak positive correlations between VAI and anthropometric parameters but CRP had moderate positive correlations with other anthropometric parameters. However, VAI and CRP had no correlation to all BMD parameters but weak correlations were found between some anthropometrics parameters and BMD neck and total femur

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