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Submission date: 28-Jan-2021 02:35AM (UTC+0700)

Submission ID: 1495476830

File name: 9__fr-ictmhs-s14_saphira.pdf (425.09K)

Word count: 6330

Character count: 33476

Food Research 4 (Suppl. 3) : 54 - 62

Journal homepage: http://www.myfoodresearch.com





Relationship between body type (somatotype) and bone density in perimenopause women

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15 icle history:

Received: 29 December 2019 Received in revised form: 14 February 2020 Accepted: 16 February 2020 Available Online: 30 May

Keywords:

2020

Somatotype, Bone density, Adult women

DOI:

https://doi.org/10.26656/fr.2017.4(S3).S14

Abstract

png with increasing age in women, there will be a decrease of estrogen levels and changes the size, structure, and composition of the body, so those will affect bone density. This study aimed to analyze the regionship between body type (somatotype) and bone density in perimenopause women. This study was a cross-sectional study held in Ngemplak, Simongan, West Semarang with forty-two women subjects aged 31-50 years. Their bone density was estimated using QUS on calcaneal. Somatotype was measured using skinfold caliper, medline and sliding caliper. Bivariate analysis used Pearson Correlation and Rank-Spearman correlation test. Multivariate analysis used multiple regression test. All body types were grouped as endomorph, mesomorph, and ectomorph. Most subjects have mesomorph type were 71.4% (n = 30). Subjects with osteopenia were 4.8% (n = 2). There was a positive correlation between endomorph values, mesomorph values and body fat percentage with bone density scores in bian iate analysis. There was correlation between mesomorph values, body fat percentage and body mass index with bone density scores in subjects (SC = 0.533; p = 0.037, SC = 0.590; p = 0.011, SC = -0.643; p = 0.037) in multivariate analysis. In conclusion, there were significant correlations between mesomorph values with bone density scores.

1. Introduction

The adult period is the period when a person reaches physical maturity, usually occurring from the age of 20 years. Women age 30 years and over, physiologically will experience a decrease in estrogen levels called perimenopause. Decreasing estrogen levels during perimenopause can increase the risk of bone fragility, resulting in a high potential for fractures (McGuire and grerman, 2013). Osteoporosis is a disease characterized by a decrease in bone mass due to the inability of the body to regulate mineral content in the bone, resulting in decreased bone strength. Fractures caused by osteoporosis can lead to death (Dieny and Fitranti, 2017). The prevalence of osteoporosis and fractures caused by osteoporosis keep increasing from years to years and become one of the main health problems in Asian countries (Mithal and Kaur, 2012; Kementrian Kesehatan RI, 2015). Based on a study by Tirtarahardja et al. (2006), the prevalence of osteoporosis in Indonesian women (aged 50-80 years) was 22.5% and 32% on aged 60-80 years. In 2007, the Osteoporosis Association in Indonesia showed that there was an

increase in the prevalence of osteoporosis, especially in women over 50 years by 32% (Kementrian Kesehatan RI, 2015). In addition, data from the Health Profile in Semarang showed that prevalence of osteoporosis increased from 2016 to 2017 was 1.03% (Badan Pusat Statistik Kota Semarang, 2018).

Risk factors that can cause osteoporosis are divided into two namely changeable and unchangeable risk factors. Risk factors that can be changed are nutrient intake, especially vitamin D and calcium intake, alcohol consumption, smoking, use of glucocorticoid drugs and physical activity. Meanwhile, unchangeable risk factors are age, sex and genetic factor related to bone density (Vijayakumar and Busselberg, 2016). Low body mass index (BMI) is often found in studies as a risk factor of osteoporosis (Sözen et al., 2017). However, high body mass index (BMI) in some studies is positively correlated with bone density. Obese women based on BMI are found to have protective factors against bone density. However, obesity as a protective factor for bone mass is still debated. Changes in the body both in terms of size, structure, proportion and body composition can

affect body type (Mazocco and Chagas, 2016). Human body types have been described as endomorph, mesomorph, and ectomorph commonly called somatotype (Carter, 2002).

Somatotype is a quantitative description of a person's physique type introduced by Heath and Carter which consisted of three components: endomorph, mesomorph, and ectomorph (Galic et al., 2016). Endomorph has a fat body build; mesomorplotas strong bones and ectomorph has a very thin build. Endomorph is characterized by a round body, big and round head, short bones, short neck, narrow shoulders, wide legs, and waist. Mesomorph type is characterized by a solid body, hard, muscular, large bones, relatively have a small waist, and broad shoulders, usually this type is found in athletes. The ectomorph type is characterized by a thin or slender body, small bones, uniform lumbar abdomen and arches, narrow shoulders and invisible muscles. In this type of muscle ness and fat is lower than the other two types (Saitoglu et al., 2007; Galić et al., 2016).

Research related to the relationship between somatotype ambone density is still limited. Previous studies have shown a correlation between somatotype and bone density in mid-adult male subjects that the endomorph and mesomorph types are prositively and significantly correlated with high levels of bone density, from measurements of the proximal hip bone and femur density using DXA. Subjects with endomorph and mesomorph type are related to bone density (Saitoglu et al., 2007). However, it is not explained how somatotype relates directly to bone density. However, it is explained indirectly through the existence of a significant relationship between body mass index with the somatotype component. Body mass index with normal, overweight, and obese categories was found to be more dominant than the underweight category. Therefore, the dominant types of somatotype found in this study are mesomorph and endomorph. The results of this study stated that the higher BMI, the better bone density. However, the weakness of BMI cannot describe 16 dy composition (fat mass and muscle mass) (Galić et al., 2016). Research about association between somatotype and bone density has never been done in Indonesia. Based on this background, the researchers wanted to conduct research on the relationship between body shape (somatotype) and bone density in adult women aged 31-50 years.

19

2. Materials and methods

This study was an observational study with a crosssectional study design in which each variable was measured once at a time. This study was conducted in Ngemplak Region, Simongan, West Semarang. The variables were components of body type (endomorph, mesomorph, and ectomorph), bone density, age, physical activity, nutrient intake (carbohydrate, fat, protein, caffeine, vitamin D, calcium intake), BMI and body fat percentage. Criteria for inclusion of the sample included women aged 31-50 years, not menopause yet, not pregnant or breastfeeding, not suffering from chronic diseases, not taking drugs such as glucocorticoids, steroids, and hormone drugs, not smoking, not consuming alcohol and willing to be the subject of research by filling out the Informed Consent. Exclusion criteria in this study included not being present during data collection, resigning before the study was completed, and passing away. The selection of research subjects was done by purposive sampling method.

Screening was done through the interview to the subjects, adjusting the inclusion criteria. Ninety-three subjects from screening process, obtained 50 person who met the inclusion criteria. Fifty subjects become 42 people due there were subjects who were absent during data collection and were excluded during data processing. The significance of the study (Za) was 95%, while the research power (ZB) was 80%, and the correlation coefficient (r) was 0.48 (Saitoglu et al., 2007). The result of calculating the sample size by considering the drop out was 37 subjects. Data of anthropometric measurements were body weight, height, skinfolds (triceps, calf, subscapular and supraspinal), bone width measurement (humerus and femur), girth (bicep girth and calf girth). In addition, bone density a, food intake and physical activity. This study was approved by The Ethical Committee of Medical Research of Faculty of Medicine, Universitas Diponegoro (No.143/EC/KEPK/FK/UNDIP/V/2019).

Anthropometry data of bod 11 ype was done by direct measurements, such as body weight, height, skinfolds (triceps, calf, subscapular and supraspinal), width (hume 3 and femur), and girth (bicep girth and calf girth). Body weight was measured up a digital weight scale (OMRON) with an accuracy of 0.1 kg. Height was measured using microtoise with an accuracy of 0.1 cm. Jamar type skinfold caliper, to measure the body skinfolds with an accuracy of 1 mm. Girth measurement using medline and body width using sliding caliper with an accuracy of 0.02 mm. Measurement of body fat percentage using the Bioimpedance Analysis (BIA) (OMRON). Anthropometry measurements were done twice for each variable.

Measurement of bone density using bone densitometry OsteoSys SONOST 2000 and categorized by T-score. Bone density measurements were carried out

by experts from the KALBE Company. We used QUS because it was inexpensive, easy to parry, easily available, and easily accessible as an alternative to measuring Dual-X absorptiometry energy (DXA) measurements of bone mineral density (BMD) to assess fracture risks n many studies (Hans and Baim, 2017). Among the quantitative ultrasound measurements of the heel is considered or of the best alternative methods at present because it is available for assessment of fracture risk. The advantage of this technique is the possibility of detecting structural bone characteristics (elastic properties, trabecular orientation) thus enabling better quantification of bone quality (Quiros-Roldan al., 2017). Normal bone density if it has T-score ≥ -1.0 SD and has low bone density if T-score <-1.0 SD. Food intake data was done by interview using the Semi-Quantitative FFQ method and food photographic instruments. Food intake data were analyzed using the Nutrisurvey 2004 program. Physical activity data was measured using the short-form International Physical Activity Query (IPAQ) form.

Body types are categorized into three: endomorph, mesomorph and ectomorph. Endomorph can be categorized if the first number is greater than the other two numbers (mesomorph and ectomorph). Classified as mesomorph if the second number is greater than the other two numbers (endomorph and ectomorph). Ectomorph can be categorized if the third number is greater than the other two numbers (mesomorph and and omorph) (Carter, 2002). Physical activity is divided into three categories: low (<600 MET/minute/week), moderate (600-2999 MET/minute/week) and high (≥3000 MET/minute/week) (IPAQ Guideline). Body mass index is divided into three categories: underweight $(<18.5 \text{ kg/m}^2)$, normal $(18.5 - 22.9 \text{ kg/m}^2)$, and overweight (>22.9 kg/m²) (Anjani and Kartini, 2013; Pisunyer et al., 2014). Body fat percentage consist of three categories: normal (18-32%), overweight (33-35%), and obesity (>35%) (Pi-sunyer et al., 2014). Adequate intake of nutrients, such as carbohydrate, fat, protein, vitamin D and calcium intake are divided into three categories: low (<90% of RDA), normal (90-119% of RDA), and excessive (≥120% of RDA) (Rochmah 24 al., 2017). Caffeine intake is categorized into three: low (<200 mg/ day), moderate (200-400 mg/day), and high (>400 mg/ day) (Devi et al., 2016).

Somatotype was done by anthropometric measurements such as body weight, height, skinfold to eps, calf, subscapular and supraspinal, width (humerus and femur, and girth (biceps girth and calf girth. The results of anthropometric data measurements are then entered into the somatotype for 22 a equation. The endomorph component formula is -0.7182 + 0.1451

(X) – 0.00068 (X²) + 0.0000014 (X³) where X is 170,18 x (trisep skinfold + subscapula skinfold + suprasiaca skinfold). The mesomorph component formula is [(0.858 x humerus width) + (0.601 x femur width) + (0.188 x CAG) + (0.161 x CCG) – (height x 0.131) + 4.5. CAG (corrected arm girth) is bicep girth – triceps skinfold/10, meanwhile CCG (corrected calf girth) is calf girth – calf skinfold/10 (Carter, 2002).

Somatotype has three numbers, where the first number is an indication of endomorph, the second number is mesomorph and the third number is ectomorph. The three numbers then categorized into 13 somatotype categories by Heath-Carter, namely central, endomorph, mesomorphic balanced endomorph, mesomorph-endomorph, endomorphic mesomorph, balanced mesomorph, ectomorphic mesomorphic, mesomorph-ectomorph, mesomorphic ectomorph, balanced ectomorph, endomorphic ectomorph, endomorph-ectomorph, ectomorphic endomorph. The 13 categories can be simplified into four categories are central, endomorph, mesomorph dan ectomorph (Carter, 2002).

Univariate analysis was performed to describe the characteristics of the subject, the variables studied included independent (somatotype measurement), dependent variable (measurement of bone density) and nfounding variables (age, carbohydrate intake, fat intake, caffeine intake, calcium intake, vitamin D intake, BMI, percentage body fat, and physical activity) by entering data in the frequency distribution table. Normality test used Saphiro-Wilk because the number of samples 5 less than 50. Bivariate analysis was done to analyze the relationship between somatotype and bone density in dult women aged 31-50 years. Moreover, bivariate analysis was also conducted to determine the relationship of each confounding variable with bone density scores. Bivariate analysis was performed using the Spearman Rank test on which data were abnormally distributed and the Pearson Correlation test on normally distributed data. Multivariate analysis using the Multiple Linear Regression test.

36

3. Results

3.1 Subject characteristics

The means age of the study subjects was 40 years old as seen in Table 1. The minimum value of the subject's bone density score was -1.3, which indicated that there were subjects who had osteopenia. Body type categories can be divided into two, namely based on 13 categories (category 1) and 4 categories (category 2).

The category 1 body type that had the greatest frequency was a balanced mesomorph of twenty

Table 1. Subject characteristics

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Characteristics	n	%	Min	Max	Mean/Median
Age			31	50	40.2 ± 5.41^{a}
31 - 40 years	22	52.4			
41 - 50 years	20	47.6			
Bone Density Score			-1.3	0.9	-0.30 ± 0.54^{a}
Normal (≥ -1 SD)	40	95.2			
Osteopenia (< -1 SD)	2	4.8			
Catergory 1 of body type					
Mesomorphic endomorph	3	7.1			
Endomorphic mesomorph	3	7.1			
Balanced mesomorph	20	47.6			
Ectomorphic endomorph	2	2.4			
Mesomorph-ectomorph	7	11.9			
Mesomorphic ectomorph	1	7.1			
Balanced ectomorph	5	11.9			
Endomorphic ectomorph	1	2.4			
Catergory 2 of body type					
Endomorph	6	14.3	0.1	1	0.35^{b}
Mesomorph	23	71.4	0.1	9	2^{b}
Ectomorph	6	14.3	0.1	5,2	0,1 ^b
Mesomorph-ectomorph	7	11.9			
Nutritional Status			19.6	41,7	27.8 ± 5.24^a
Normal	8	19			
Overweight	34	81			
Physical Activity			360	3297	1524.7±715.1 ^a
Low	4	9.5			
Moderate	37	88.1			
High	1	2.4			
Body Fat Percentage			26.3	43.6	36.5 ± 3.89^a
Normal	4	9.5			
Overweight	10	23.8			
Obesity	28	66.7			

aMean±SD, bMedian

subjects. Based on the four categories, the largest number of body types was mesomorph of 71.4% (n = 30). The dominant nutritional status in the subject was fat with a mean of 27.8 kg/m². Most of the subjects were categorized as obesity according to body fat percentage.

Table 2 shows that adequate levels of carbohydrate, protein, fat, calcium, vitamin D and caffeine intake. Most of the subjects were categorized as low intake. Endomorph body type values (r=0.38; p=0.013) were related to bone density as in Table 3. The higher the endomorph value, the greater the bone density re. The mesomorph type variable (r=0.31; p=0.045) spositively related to bone density. The variable body fat percent (r=0.26; p=0.004) was positively related to bone density. The higher the percentage of body fat, the greater the bone density score.

The body mass index, percent body fat, and mesomorph values had a relationship with bone density after being analyzed using linear regression tests as shown in Table 4. The adjusted R square value was 0.241 = 24.1%. The result showed that bone density was simultaneously influenced by BMI, value mesomorph and body fat percent were 24.1% while the rest were influenced by variables not examined.

4. Discussion

Based on the subject characteristics, there were two subjects with steppenia, while most subjects had normal bone density. The mean age of the subjects was 40 years. This is consistent with the previous study by Dieny and Fitranti (2017) in which subjects in the 40-50 years age range had the lowest frequency in the osteopenia

Table 2. Food intake characteristics

Characteristics	n	%	Min	Max	Mean/Median
Carbohydrate Intake			0.2	1.3	0.48 ^b
Low	39	92.9%			
Normal	2	4.8%			
High	1	2.4%			
Protein Intake			0.27	1.41	0.62 ^b
Low	34	81%			
Normal	5	11.9%			
High	3	7.1%			
Fat Intake			0.19	1.82	0.67 ^b
Low	32	76.2%			
Normal	3	7.1%			
High	7	16.7%			
Calcium Intake			0.08	1.02	0.24 ^b
Low	40	95.2%			
Normal	1	2.4%			
High	1	2.4%			
Vitamin D Intake			0	2.6	0.16^{b}
Low	39	92.9%			
Normal	1	2.4%			
High	2	4.8%			
Caffeine Intake			0	276.8	66.2 ^b
Low	41	97.6%			
Normal	1	2.4%			7

Table 3. Relationship among somatotype components, age, BMI, body fat percentage, and physical activity with bone density

Conformation Maniables	Bone density scores		
Confounding Variables	r	p	
Endomorph	0.38 ^a	0.013 ^a	
Mesomorph	0.31 a	0.045^{a}	
Ectomorph	-0.16 a	0.304^{a}	
Age	0.21 ^b	0.187^{b}	
Body Mass Index (BMI)	0.26^{b}	0.091^{b}	
Body Fat Percentage	$0.44^{\rm b}$	0.004^{b}	
Physical Activity	-0.23 ^b	0.14^{b}	
Food Intake			
Carbohydrate	0.04^{b}	0.785^{b}	
Protein	-0.04^{b}	0.8^{b}	
Fat	-0.42 a	0.792 a	
Calcium	-0.15^{a}	0.342^{a}	
Vitamin D	0.29 a	0.056^{a}	
Caffeine	0.12 a	0.453 a	

^aRank-Spearman, ^bPearson

Table 4. Multiple linear regression test

		Bone	Density	•
Variables	^a SC	^ь р1	° p2	Adjusted R Square
135 y Mass Index (BMI)	-0.643	0.037	0.004	0.241
Body Fat Percentage	0.59	0.011		
Mesomorph	0.533	0.037		

^a Standardized Coefficient, ^b Significance of T-test,

eISSN: 2550-2166

category compared to subjects in the 51-60 years, 61-70 34 rs and 71-80 years age groups. In addition, previous study showed that there was no change in the mean bone mass at the age of 35-44 years group (Berger et al., 2008). This study showed that most subjects had mesomorph body types. This is in accordance with a study by Kalichman and Kobyliansky (2006) in which mesomorphatody types were more common in subjects with the age group 31-40 years and 41-50 years compared with the age group 18-30 years.18 Based on the results of bivariate analysis test found a correlation between endomorph values, mesomorph and body fat percent with bone density. Variables that have a p value < 0.25 lowed by the analysis of the relationship test using multiple linear regress 23 test. The results of multiple linear regression tests showed that the variables that correlated with bone density were mesomorph values, body fat percent, and Body Mass Index.

4.1 Relationship between body type (somatotype) with bone density

This study showed a 12 relation between mesomorph body type score and bone density. The relationship between the two had a positive correlation, indicating that the greater the value of the mesomorph body type components, the better bone density. Mesomorph type is characterized by a solid body, hard, muscular, large bones, relatively have a small waist, and broad shoulders, usually this type is found in athletes.

^c Significant of F-test (ANOVA)

Mesomorph type is usually dominated by muscle mass. The positive correlation between mesomorph and bone density in this study, in accordance by Patel et al. (2018) that lean mass can improve bone size and strength. Muscles and bone are related to each other from the beginning of embryonic development to adulthood, thus affecting bone function and structure. Muscles and bones will get bigger and stronger due to the growth process, physical activity and adequate intake of nutrient that support bone health, especially vitamin D and calcium (Patel et al., 2018). Lean mass can improve bone density through the body's mechanical load. Bone strength can be affected by mechanical muscle movements and hormonal factors. Bone strength is affected by the amount of lean mass in body composition. Lean mass in human body can be obtained through physical activity. Most of the subjects had moderate physical activity, thus it is possible to have a large mechanical burden as well. This has resulted in the bone density score ip most subjects belonging to the normal category. Muscle strength and physical activity have a more significant impact on bone health compared to harmonal factors, especially in premenopausal women (Ho-Pham et al., 2014). Moreover, lean mass has more significant effect on increasing bone density than body fat mass.

4.2 Relationship between body fat percentage with bone density

The result of this study 10 as similar with study by Moayyeri et al. (2012) that there is correlation between body fat percentage and bone density in subjects (bone density was measured by Quantitative Ultrasound on calcaneal). Women with body fat percentage <20%, have 3.5 times the risk of bone fracture on the waist and 2.2 times increase bone fracture risk on the other areas compared to women with body fat percentage of about 40%.

Fat mass and lean mass in the body have a role to maintain bone density through the mechanism of mechanical load on the bone. Abdominal fat consists of subcutaneous fat and intraabdominal fat. Intraabdominal fat consists of visceral fat which composes fat mass in small intestine and kidney (Wajchenberg, 2000). There are two types of fat associated with bone, namely visceral fat and subcutaneous fat. Both have different effects on bones. Some studies explained that visceral fat has negative ingoct on bones through increased proinflammatory cytokines, such as TNF-α and IL-6. Increasing the amount of visceral fat in the body can cause the risk of arteriosclerosis, insulin resistance, and type 2 das etes mellitus so that it can reduce bone density (Gilsanz et al., 2009; Campos et al., 2012). Subcutaneous fat has protective effect on bones.

However, the mechanism of the protective effect of subcutaneous fat on bone still remain unclear.

Anthropometry measurement that can describe visceral fat is waist-hip ratio, whereas to desoibe subcutaneous fat can use somatotype. Initially, fat is stored in subcutaneous fat tissue, but if the capacity of subcutaneous fat tissue has been obtained, it will be stored in visceral fat tissue and non-fat tissue such as skeleton muscle. This study slagged that mesomorph was the dominant body type. This is consistent with the study by Galić *et al.* (2016) that the mesomorph value is higher than the endomorph and ectomorph values caused by fat deposits in skeletal muscle so that the width of the femur and humerus is greater. In addition to the mesomoporh value reflecting muscle mass, the mesomorph value also consists of several measurements of peripheral or subcutaneous fat stored under the skin. Women tend to have total fat deposits in the gluteal or femoral area (thigh area) and subcutaneous area of the skin. Body weight and abdominal fat distribution differ in women of childbearing age and women who have gone through menopause. Decreased 470gen levels in menopausal women are followed by a decrease in subcutaneous fat and an increase in abdominal or visceral fat (Lizcano and Guzmán, 2014). Women that included in this research were a perimenopause woman, it was assumed that subcutaneous fat in the body was still in large amounts and had a positive impact on bone density.

4.3 Relationship between BMI, physical activity, age with bone density

In this study, BMI was negatively correlated with bone density. This means that the greater BMI will reduce the bone density. In addition, this is consistent with research according to Silva et al. (2015) that overweight and obese women tend to have low bone density (osteopenia and osteoporosis). The majority of research states that a greater body mass index will increase bone density through the body's mechanical load mechanism. However, Compston et al. (2011) said that obesity does not have a protective factor in postmenopausal women who experience fractures, although they have high BMI value. Some studies said that obesity can increase bone density through hormonal chanisms and mechanical loads. However, abdominal obesity can lead to some diseases such as insulin resistance, diabetes mellitus, metabolic syndrome so that it can disrupt bone metabolism through inflammation (Gürlek et al., 2018). Our research showed that two subjects who had overweight BMI were included in osteopenia category. This means that BMI is negatively correlated with bone density.

Physical activity has a role as a mechanical load to

stimulate bone formation so that it affects bone \$55 shape and strength. The majority of research shows that physical activity is positively correlated with bone msity (Alghadir et al., 2015). However, there is no relationship between physical activity and bone consity in this study. Some studies state that physical activity and bone density were not related because of the intensity and frequency of low physical activity (Tan et al., 2014). Based on interviews on subjects regarding their physical activity, the results obtained that most subjects have a moderate physical activity. However, they did not do a specific physical activity that can improve bone density significantly such as washing, sweeping, drying and so forth. Most of the subjects are textile factory workers that most of the time they work is sitting. The type of physical activity mentioned in several studies that has a significant impact on bone density is regular exercise. The American College of Sports Medicine (ACSM) states that to improve bone density, a person must have an active lifestyle such as aerobic exercise and moderate to high-intensity sports such as jumping, squats, weightlifting and so on (Arazi and Eghbali, 2017; Benedetti et al., 2018).

One factor that affects bone density is age. Women will experience a decrease in bone mass greater than men when entering into menopause phase due to a decrease in the hormone estrogen. Estrogen plays a role in vitamin D regulation where vitamin D will help reabsorption of calcium in the kidneys and affect the process of bone formation (Aminah et al., 2009). Study expland that low bone density occurs with increasing age (Ho-Pham et al., 2014; Mishra et al., 2016). Along with increasing age, the bone will become thin and more porous about 4-10% since the age of 40 years. After the age of 40 years, bone-thinning will decrease to 3% per decade and increase up to 9% pyzdecade in menopause women (Aminah et al., 2009). There was no association between age and bone density in our study both in 31-40 years and 41-50 years groups. This was because the mean age in this study was 40 years and in perimenopause period where it is possible that estrogen levels have not to decrease yet, thus the bone density in subjects is still in good condition.

The limitation of our study is that we used QUS to measure bone mass density, where QUS is not a gold standard tool. The limitation of QUS is a less accurate tool to predict bone mass density because it only measures calcaneal compared to DXA which predicts bone density through several bones located in the human body (lumbar spine, femoral neck).

4. Conclusion

Increased mesomorph component and body fat percentage values can increase bone density. However, high BMI in this study can decrease bone density in perimenopause women. Further research should examine the body type and bones mass density in adult women the inflammatory biomarkers corrections such as cytokines interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and inflammatory marker of C-reactive protein (CRP).

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

With sincere appreciation, the authors gratefully acknowledge official workers in the Health Service (Puskesmas) and our subjects.

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