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Body mass index as the most influential factor of high-sensitivity C-reactive protein in non-diabetic adults

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ABSTRACT

BACKGROUND
High-sensitivity C-reactive protein (hsCRP) has been widely accepted as a predictor of future cardiovascular risk that reflects a microinflammatory state. Obesity linked to microinflammation increases the prevalence of metabolic disorders and cardiovascular diseases. This study aimed to determine the association between several obesity indices namely body mass index (BMI), waist circumference (WC), body fat percentage (fat), and visceral fat (VF) with hsCRP in non-diabetic adults.

METHODS
This was a cross-sectional study performed on 80 non-diabetic adults with ages ranging from 20-40 years. The obesity indices BMI, WC, body fat percentage, and VF were measured. We then measured the hsCRP levels using an immunoturbidimetric method. Simple and multiple linear regression tests were used to analyze the association between obesity indices and hsCRP levels.

RESULTS
Mean of log BMI, log WC, and log VF was 1.41 ± 0.08 kg/m^2, 1.93 ± 0.06 cm, and 0.95 ± 0.27 units, respectively. Simple linear regression tests showed that log BMI (β=3.506; p<0.001), log WC (β=3.672; p<0.001), log VF (β=0.833; p<0.001), and log systolic blood pressure (β=3.739; p=0.024) had a significant positive correlation with log hsCRP levels. Further multiple linear regression test showed that log BMI (β=3.772; Beta=0.674; p<0.001) had the greater effect on log hsCRP levels compared to other indices.

CONCLUSIONS

BMI had a greater influence on hsCRP levels compared to other obesity indices in non-diabetic adults. Body mass index can be used as a better index in predicting hsCRP levels compared to other indices.

Keywords: Body mass index, waist circumference, visceral fat, body fat, hsCRP, non-diabetic adults

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INTRODUCTION

C-reactive protein (CRP) is commonly associated with inflammatory reactions, particularly during infection. High-sensitivity CRP (hsCRP), which can be detected at levels of <1 mg/L, has been linked to several chronic low-grade inflammatory processes leading to cardiovascular disease (CVD).[1] High-sensitivity CRP has been used to predict future CVD risk worldwide in both developed and developing countries in Asia, Africa, Europe, and North/ Central/South America.[2] Persons with hsCRP levels of >3mg/L are considered to have high hsCRP levels because they are at high risk of developing CVD in the future.[3]

Obesity marked by excess of body fat is associated with insulin resistance and systemic low-grade inflammation leading to CVD.[4] Obesity is commonly measured by body mass index (BMI) and waist circumference (WC). Visceral obesity is linked to higher CVD risk compared to other types of fat deposition.[5] High-sensitivity CRP levels are reported to have a significant correlation with obesity indices. In the Indian adult population, hsCRP showed a significant correlation with BMI and WC.[6,7] In the Swiss Caucasian population, several obesity indices including BMI, body fat percentage, and WC also had a significant correlation with hsCRP levels.[8] A significant correlation of hsCRP with BMI, WC, hip circumference, and waist-hip ratio was also reported in the young Saudi population.[9] The body adiposity index is correlated with hsCRP in hypertensive and normotensive obese adult subjects.[10] On the other hand, it was reported that waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) had a significant association with hsCRP, but that BMI and WC showed no significant association with hsCRP.[11]

The present study was focused on the association of several obesity indices with hsCRP levels in the Indonesian non-diabetic population, especially young adults (age range 20-40 years). A previous study reported that hsCRP had a better association with BMI compared to WC, but its association with other newly proposed obesity indices including body fat percentage (fat), and visceral fat (VF) had not been revealed.[12] The present study aimed to determine the relationship between traditional obesity indices, such as BMI, WC, and the newly proposed obesity indices including body fat percentage, and visceral VF with hsCRP levels, and to determine which index had the best value in predicting high hsCRP levels as the novelty of this study.

METHODS

Study design

This was an analytical cross-sectional study, conducted from August to September 2020 among non-diabetic Indonesian adults at Hasanuddin University Hospital, Makassar, Indonesia.

Study subjects

The study subjects were non-diabetic adults in the age range of 20-40 years who voluntarily joined this research by signing informed consent according to the Declaration of Helsinki. The inclusion criteria were male and female adults aged ≥18 years who had no history of cerebrovascular disease (CVD) and diabetes and had never experienced other cardiovascular symptoms including cardiac chest pain and dyspnea. The exclusion criteria were subjects with fasting plasma glucose levels of ≥126 mg/ dL, smokers, and those suffering from infectious disease in the last month. The sample size was determined based on the correlation coefficient of 0.359 between BMI and hsCRP levels as reported in previous research.[8] By using α=0.05, β=0.20, and drop-out rate of 20%, the minimal sample size required was 59. A total of 80 adults joined the study, consisting of 39 male and 41 female subjects.

Measurement of obesity indices and blood pressure

Obesity indices were measured right before blood sampling. Body weight and height of the

subjects were measured and BMI was calculated using the formula: body weight (kilograms)/height^2 (meters, squared). Waist circumference was then measured by using tape at midway between the lower border of the 12th rib and the iliac crest. The bioelectrical impedance analysis (BIA) method was used to measure body fat and VF using a Tanita BC-541 body composition monitor (Tokyo, Japan). Blood pressure was measured using a Riester sphygmomanometer (Germany) after the subject had rested for 15 minutes in the seated position. Systolic and diastolic blood pressures were measured on the subject's right arm. All measurements were taken twice, and the average was calculated.

Laboratory analysis

Blood sampling was performed after 8-12 hours of overnight fasting. A 3 mL venous blood sample was taken from each subject, separated to obtain the serum, and directly tested for fasting plasma glucose levels by the hexokinase method (Abx Pentra 400, Horiba, USA) for excluding those with diabetes. The remaining serum was kept in 200 µL aliquots and kept refrigerated at -20^o Celcius until the time for the hsCRP test (immunoturbidimetry, Cobas c 311 analyzer, Roche Diagnostics, Mannheim).

Statistical analysis

The normality of data was tested with the Kolmogorov-Smirnov test. All parameters including hsCRP, BW, height, BMI, WC, VF, systolic and diastolic blood pressures which were not normally distributed, were transformed into logarithmic (log) format to normalize them. Simple and multiple linear regression were performed to determine which obesity index had the largest effect on log hsCRP levels. Statistical analyses were performed by using the IBM Statistical Package for the Social Sciences Statistics program (IBM, USA), version 21.0. Statistical analysis was considered significant if p-value <0.05.

Ethical Clearance

This study was approved by the *Komite Etik Penelitian Kesehatan* (Committee of Health Research Ethics), Medical Faculty, Hasanuddin University, Makassar, Indonesia, under number 395/UN4.6.4.5.31/PP36/2020, and protocol number UH20060245.

Table 1 Distribution of age, anthropometrics, blood pressure and hsCRP of subjects (n=80)

Variable	Mean ± SD/ Median (Min-Max)
Age, years	29.96 ± 5.00
BW, kg	64.55 (48.70-137.60)
Log BW, kg	1.82 ± 0.09
Height, m	1.60 (1.49-1.84)
Log height, m	0.21 ± 0.02
BMI, kg/m^2	24.43 (19.73-47.61)
Log BMI, kg/m^2	1.41 ± 0.08
WC, cm	83 (68-136,50)
Log WC, cm	1.93 ± 0.06
Fat, %	31.35 ± 7.39
VF, unit	9 (3-30)
Log VF, unit	0.95 ± 0.27
Systolic blood pressure, mmHg	120 (90-140)
Log systolic blood pressure, mmHg	2.06 ± 0.03
Diastolic blood pressure, mmHg	80 (60-80)
Log diastolic blood pressure, mmHg	1.88 ± 0.04
hsCRP, mg/L	1.65 (0.20-11.0)
Log hsCRP, mg/L	0.15 ± 0.45

Notes: Normally distributed parameters are expressed as mean ± standard deviation, Non-normally distributed parameters are expressed as median (minimum-maximum). BW: body weight, BMI: body mass index, WC: waist circumference, VF: visceral fat, hsCRP: high sensitivity C-reactive protein

Table 2. Simple linear regression of obesity indices and other parameters with log hsCRP

Variables	β	p-value
Log BMI	3.506	<0.001
Log WC	3.672	<0.001
Fat	0.013	0.067
Log VF	0.833	<0.001
Age	0.013	0.215
Log systolic blood pressure	3,739	0.024
Log diastolic blood pressure	1.693	0.218

Notes: β: regression coefficient; BMI: body mass index; WC: waist circumference; VF: visceral fat

RESULTS

The characteristics of the research subjects are shown in Table 1. Mean of age was 29.96 ± 5.00 years, while mean of log BMI, log WC, and log VF were 1.41 ± 0.08 kg/m^2, 1.93 ± 0.06 cm, and 0.95 ± 0.27 units, respectively. Mean of body fat percentage was 31.35 ± 7.39%, while the mean of log hsCRP was 0.15 ± 0.45 mg/L.

Simple linear regression analysis results are shown in Table 2. Log BMI (β=3.506; p<0.001), log WC (β=3.672; p<0.001), log VF (β=0.833; p<0.001), and log systolic blood pressure (β=3.739; p=0.024) correlated with log hsCRP, but body fat (β=0.013; p=0.067), age (β=0.013; p=0.215), and log diastolic blood pressure (β=1.693; p=0.218) had no significant correlation with log hsCRP. All variables with p-value <0.200 were subsequently entered for analysis into a multiple linear regression model.

As presented in Table 3, multiple linear regression analysis showed that log BMI was the most effective marker for increased levels of log hsCRP (Beta=0.674, p<0.001) compared to other obesity indices.

DISCUSSION

In this study, we found that the obesity indices had a significant correlation with hsCRP levels in non-diabetic adults, with BMI as the most effective on hsCRP levels compared to the other obesity indices. Several other reports have supported our findings. Sadanand et al.[6] reported that BMI (r=0.51), WC (r=0.42), and waist-to-hip ratio (WHR) (r=0.32) had a significant correlation with hsCRP levels in the Indian population. The same finding was reported by Lavanya et al.[7] who performed a study on the Indian adult population aged 20-70 years and by Farooq et al.[9] in the Saudi population. Marques-Vidal et al.[8] reported that BMI, WC, and percent body fat had a significant correlation with hsCRP levels both in the male and female Caucasian Swiss population. Kawamoto et al.[13] reported that the overweight Japanese population (BMI ≥25 kg/m^2) aged<75 years had a higher prevalence of elevated hsCRP concentration compared to those with BMI <22 kg/m^2, but that the association did not occur in persons aged ≥75 years. A significant correlation between BMI and hsCRP levels was also found in obese children and adolescents.[14] On the other hand, Mahwati et al.,[11] after performing logistic regression, reported a significant association of WHR and WHtR with hsCRP, but no association was observed of BMI and WC with hsCRP. The different results compared with those of the present study might be caused by different research models. Mahwati et al.[11] adjusted the effect of social variables including marital status, education, and residence in the analysis while the present study measured the effect of several

Table 3. Multiple linear regression of obesity indices and systolic blood pressure with log hsCRP

Variables	β	Beta	p-value
Log BMI	3.772	0.674	<0.001
Log WC	-1.382	-0.172	0.329
Fat	-0.010	-0.161	0.179
Log VF	0.278	0.165	0.417
Log systolic blood pressure	1.506	0.102	0.295

Notes: β: regression coefficient; Beta: standardized regression coefficient; BMI: body mass index, WC: waist circumference, VF: visceral fat

obesity indices, age, and blood pressure on hsCRP levels. In our study, age and diastolic blood pressure showed no significant association with hsCRP levels, and after multiple linear regression analysis, BMI was a consistent indicator associated with hsCRP.

Obesity is a condition marked by an excess of body-fat mass that may impair health by generating a low-grade inflammatory state.[15,16] Obesity occurs when energy intake exceeds energy expenditure.[17] Several indices have been used to measure obesity including BMI, WC, and body adiposity index.[18] Obesity induces chronic inflammatory conditions through the role of adipose tissue. The adipocytes secrete pro-inflammatory adipokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) while the secretion of adiponectin which has an anti-inflammatory role is decreased.[19,20] This results in the development of endothelial dysfunction and a hypercoagulability state, therefore triggering the atherosclerotic process.[21]

High -sensitive CRP is a protein produced mainly in the liver in response to inflammation and has been identified as a CVD risk predictor marker. C-reactive protein is synthesized in response to cytokine expression including IL-6 and has an important role in the atherogenic process. It acts by binding oxidized low-density lipoprotein (oxLDL) which has a high atherogenic property. C-reactive protein might induce the adhesion and movement of monocytes to the arterial wall as the early step of the atherosclerotic process. Monomeric CRP also has prothrombogenic and inflammatory properties which increase its atherogenic role.[1,22]

Our findings reveal that obesity indices particularly BMI, WC, and VF may be used to predict the high hsCRP levels which reflect the high CVD risk in the Indonesian non-diabetic adult population, while body fat percentage has no significant correlation with hsCRP. This may be explained by the fact that body fat percentage not only measures white fat which has an adverse inflammatory function but also brown fat which has a beneficial catabolic function. Multiple linear regression analysis reveals that BMI has the largest effect on hsCRP levels compared to other obesity indices. Therefore, we propose that BMI might be used as the chosen obesity index to predict CVD risk, particularly in the Indonesian population. This study to our knowledge is among the few studies that compare and evaluate the ability of several obese indices in predicting hsCRP levels and stratify the ability of each index as a predictor in the Indonesian adult population.

There are several limitations to this study. First, the cross-sectional design cannot explain a causal association between obesity indices and hsCRP levels. Second, we did not use magnetic resonance imaging (MRI) or computed tomography (CT) as the gold standard method in measuring obesity especially the body fat percentage and VF. Third, our findings can only be applied to adult subjects with ages ranging from 20-40 years.

The clinical implication of this study is that BMI can be used as a simple traditional obesity index to better predict hsCRP levels than do WC and other non-traditional obesity indices including body fat and VF. Further research must be done using a better design like cohort study to explain the causal association between obesity indices and hsCRP levels in the elderly.

CONCLUSION

This study demonstrated that BMI had the most consistent effect on hsCRP levels compared to other obesity indices. BMI may be used to predict hsCRP levels as a CVD risk factor for early intervention.

CONFLICT OF INTEREST STATEMENT

The authors state that they have no conflicts of interest associated with this manuscript.

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CONTRIBUTORS

WM contributed to designing the study, collecting samples, performing the experiment, and writing the manuscript draft; LBK analyzed and interpreted the data, and also wrote the manuscript draft; EA, YW, II, AS, and IY contributed to the revision and finalization of the manuscript. All authors have read and approved the final manuscript.

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