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Correlation of radiographic damage and central obesity in ankylosing spondylitis: A cross sectional study

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ABSTRACT

Background: Cardiovascular complications remain the leading of many long-term complications in Ankylosing Spondylitis (AS), accounting for 40% of all-cause mortalities. Previous studies reported the high prevalence of metabolic syndrome in AS with its prevalence ranging from 27% to 54.5%. Among its components, central obesity was the most prevalent component seen in AS with its prevalence ranging from 45.8 to 90.9%. However, lack of study, differences of disease activity index used, and inability to exclude confounding risk factors, might have contributed with previous studies report's conflicting results. Thus, the correlation between severity of AS and central obesity remains controversy.

Aim: To investigate the correlation of AS's severity measured with radiographic damage and central obesity measured with Indonesian's Waist circumference and Body Mass Index (BMI) criteria with Indonesian's cut-off.

Methods: This is a cross-sectional study with consecutive sampling involving 28 AS patients aged 18–60 years old receiving csDMARDs. Exclusion criteria of this study were recent infections, recent anti-TNFα, history of end state renal disease, history of metabolic syndrome before Ankylosing Spondylitis diagnosis, current smokers, and current alcohol consumption. Radiographic damage was scored using modified Stokes Ankylosing Spondylitis Spinal Score (mSASSS) score. Statistical analysis was computed with SPSS v21.0 for mac OSX.

Results: There were 7 males and 21 females with average age 45.07 ± 10.46 years old. Average anthropometric measures of the subjects were: waist circumference 87.37 ± 11.91 cm, height 157.05 ± 8.57 cm, weight 62,28 ± 11,50 kg, and BMI 25.42 ± 5.23 kg/m^2. The average mSASSS score was 22.39 ± 5.85 (κ:0.92, p = 0.00). Analysis with Pearson's correlation revealed positive correlation between mSASSS score and waist circumference (ρ:0.49, p = 0.02) and particulary female subjects (ρ:0.52, p = 0.01). Furthermore, revealed positive correlation between mSASSS score and BMI (ρ:0.389, p = 0.04).

Conclusion: Positive correlation between severity of AS measured with mSASSS score with central obesity measured with waist circumference and BMI was observed in Indonesian AS patients receiving csDMARDS. Further studies are needed to investigate the nature of the relationships regarding chronic inflammation's pathway of AS and central obesity.

1. Background

It is widely known that people with Ankylosing Spondylitis (AS) have a higher risk of cardiovascular complications. Previous studies reported that cardiovascular complications is one of the leading long-term complications in AS, accounting for 40% in all-cause mortalities (Bakland et al., 2011; Mathieu et al., 2011). One of the risk factors of cardiovascular complications, in which had been investigated associated with the disease activity parameter measured with BASDAI or BASFI (Alonso Blanco-Morales et al., 2015; Papadakis et al., 2009). However, the results of previous studies remained inconsistent, partly due to the differences of anti-TNFα duration, as well as the inability to eliminates smoking and alcoholic, both of which had a well-known role in the pathogenesis of metabolic syndrome (Malesci et al., 2007; Arnson et al., 2010; Jones et al., 2017; Van De Wiel, 2011).

Papadakis et al., reported that among the metabolic syndrome, central obesity was one of the most prevalent component seen in AS patients (Papadakis et al., 2009; Malesci et al., 2007). Central obesity

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are often associated with proinflammatory state due to dysfunctional adipose tissue. Several proinflammatory cytokines such as TNF-α, IL-6, CRP, PAI-1, angiotensinogen, and adipocytokines (leptin, resistin, visfatin) are increased combined with decreased anti-inflammatory cytokines (IL-10, adiponectin) are often seen in central obesity (Jung and Choi, 2014; Nigro et al., 2014; Patel and Shahane, 2014; Pradhan et al., 2001).

The pathogenesis of AS mainly involves HLA-B27. Current hypothesis supports the misfolding of HLA-B27 which promotes the activation the IL-23/IL-17 pathway and increased TNF-α via TNFR2 which contributes to the structural damage in AS by activating RANKL reflected as a Radiographic damage in clinical setting (Mai et al., 2016; Raychaudhuri and Raychaudhuri, 2016; Smith and Colbert, 2014). Besides its role in AS, the increased IL-17 can inhibit the expression of several adipocytokines such as *CCAAT/enhancer-binding protein alpha* (C/EBP-α), *Peroxisome Proliferator-activated receptor* γ (PPAR-γ), adiponectin, GLUT-4, as well as promote the mRNA expression of IL-6 which have direct impacts on insulin resistance (Jung and Choi, 2014; Nedergaard et al., 2005; Zuniga et al., 2010).

Despite the current understandings of both AS and central obesity pathophysiology, the results of previous studies which investigated the correlation of inflammatory state in AS and central obesity were conflicting (Papadakis et al., 2009; Vargas et al., 2016). Based on previous studies, the conflicting results might be due to inability to exclude several risk factors (smoking, alcohol consumption), the usage of disease activity such as BASDAI or ASDAS which were greatly affected by patient's perception of their current state, or inflammatory marker (CRP, ESR) which greatly fluctuated in short amount of time (Papadakis et al., 2009; Vargas et al., 2016; Harrison, 2015; Sbong and Feldman, 2015; Braun et al., 2014; Garrett et al., 1994; Rudwaleit et al., 2011). Furthermore, previous studies used anti-TNFα medication which have positive effect on metabolic syndrome but are not available in The Indonesian National Health Insurance System's formularies and different cut-off for obesity which might not applicable in Asian populations especially Indonesians (Papadakis et al., 2009; Vargas et al., 2016; Kesehatan, 2017; Tan et al., 2004; Tjokroprawiro et al., 2014). Based on these findings, our aim was to investigate the correlation of severity of AS from radiographic damage and central obesity in Indonesian AS populations which are different from western populations.

2. Methods

This study is a cross sectional study conducted from July 2018 to September 2018 in Rheumatology outpatient installation Dr. Soetomo General Hospital Surabaya, a tertiary hospital with consecutive sampling technique to recruit the subject. This study is a part of a study "Prevalence of metabolic syndrome in Spondyloarthritis patients" which had been approved by the Ethics Committee of Dr. Soetomo General Hospital on July 10th, 2018 with reference number: 0385/KEPK/VII/2018.

2.1. Study population

Consecutive patients (n = 28; 7 males and 21 females; mean age 45.07 ± 10.26 yrs) attending the Rheumatology outpatient department of Dr. Soetomo General Hospital Surabaya between July 2018 and September 2018, were enrolled in the study. All patients fulfilled the ASAS 2010 criteria for ankylosing spondylitis (Rudwaleit et al., 2011). The exclusion criteria in this study are current or history of smoking, current or history of alcohol consumption, chronic kidney disease, previous medications (glucocorticoid, anti-TNFα), history of malignancy, infection (HIV, hepatitis), and other autoimmune diseases.

2.2. mSASSS score

Radiographic damage was measured using mSASSS score. There are two components which are evaluated in mSASSS score, the anterior vertebrae which consist of lower border of C2 to upper border of Th1 and the lumbar vertebrae which consist of lower border of Th12 to upper border of S1 combined to 24 vertebrae segments at a lateral view. The vertebrae segments were evaluated for the presence of erosion and/or sclerosis and/or squaring (1 point), syndesmophytes (2 points), and bridging syndesmophytes (3 points). The total score ranges from 0 to 72 (Creemers et al., 2005). The radiology assessment was performed by 2 rheumatologists (AW and LDR) who were blinded to demographic and patients' clinical manifestations. Both readers scored the radiography assessment at the same time and registered the changes of vertebrae segments separately, therefore both scores could be computed.

2.3. Central obesity

Central obesity was measured with waist circumference. Waist circumference was measured with modified criteria of central obesity based on Asian Population cut-off waist circumference > 90 cm for male and > 80 cm for female (Tan et al., 2004). Body Mass Index was measured with Indonesian populations cut-off which defines underweight at < 18,5 kg/m^2, normal at 18,5–22,9 kg/m^2, overweight at 23,0–24,9 kg/m^2, obese I at 25,0–29,9 kg/m^2 and obese II at ≥ 30 kg/m^2 (Tjokroprawiro et al., 2014). Both were examined during patient's visit in Rheumatology outpatient department.

2.4. Statistical analysis

The statistical analysis was made by SPSS v21.0 software for MacOSX. Interobserver analysis of mSASSS score to validate the mSASSS score was performed with Cohen-Kappa analysis. Pearson correlation was used for correlation analysis between mSASSS score and central obesity.

3. Results

3.1. Demography

There were 28 ankylosing spondylitis patients who visited rheumatology outpatient department on July to October 2018 consisted of 21 females and 7 males. The average of disease duration was 5.31 ± 4.49 years and 6 patients (21.4%) were diagnosed with AS at the time of the recruitment. Sixteen patients were taking sulfasalazine with average dose 1125.0 ± 387.29 mg/day and six patients were taking methotrexate with average dose 9.58 ± 1.02 mg/weekly. Table 1 shows the basic characteristics of the subjects.

Based on Table 1, we found that female subjects were older than did the male subjects. Furthermore, female with AS′ average waist circumference and BMI were higher than did the male counterpart.

Distribution of Central Obesity in Ankylosing Spondylitis.

Fig. 2 shows the distribution of central obesity according to the sex. Central obesity was observed in 64.28% of the subjects predominantly in female. The average of waist circumference in male was 81.42 ± 12.55 cm, whereas in female was 88.69 ± 13.17 cm. Table 2 shows further characteristics of the subjects according to the presence of central obesity.

According to Table 2, subjects with central obesity were older, had a higher BMI, and had longer duration of disease. However, subjects without central obesity tend to be taller than did subjects with central obesity.

Average score of mSASSS score in this study was 22.39, as shown in Table 1 with interobserver agreement calculated with Cohen-Kappa's method $\kappa = 0.92$, $p = 0.00$. Subjects with central obesity had higher average of mSASSS score than did subjects without central obesity.

Table 1
Basic characteristics of the study.

Parameter	
Age (years)	45.07 ± 10.26
Female	48.67 ± 7.13
Male	34.23 ± 11.90
Waist circumference (cm)	87.37 ± 11.91
Female	88.54 ± 12.26
Male	83.85 ± 10.85
Body Mass Index (kg/m^2)	25.42 ± 5.23
Female	26.13 ± 4.811
Male	23.28 ± 6.21
Blood pressure	
Systolic (mmHg)	127.75 ± 17.67
Diastolic (mmHg)	80.36 ± 7.93
Height (cm)	157.05 ± 8.57
Weight (cm)	62.28 ± 11.50
Hemoglobin (g/dL)	12.7 ± 1.40
Leukocytes (μ/L)	8.381 ± 2.522
Platelets (μ/L)	352.281 ± 81.102
Fasting plasma glucose (mg/dL)	111.32 ± 48.27
Total cholesterol (mg/dL)	194.75 ± 33.75
Triglycerides (mg/dL)	133.57 ± 61.15
HDL-cholesterol (mg/dL)	50.29 ± 15.06
LDL-cholesterol (mg/dL)	114.96 ± 27.89
Duration of disease (years)	5.31 ± 4.49
mSASSS score	22.39 ± 5.85

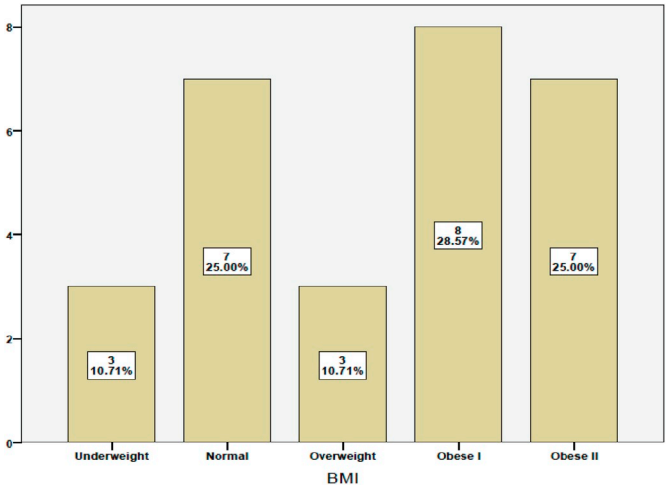

Fig. 1. BMI Distribution in AS patient. As shown in Fig. 1, majority of the subjects had an obese-I BMI category according to the Indonesian cut-off (28.6%), followed with obese-II and normal BMI (25.0% each).

3.2. Correlation of mSASSS score and central obesity

Positive correlation analyzed with Pearson's correlation was observed between mSASSS score and central obesity measured with waist circumference (ρ:0.49, p = 0.02) (Fig. 3) especially with female's waist circumference (ρ:0.53, p = 0.01) and BMI (ρ:0.389, p = 0.04) (Fig. 4).

4. Discussion

Ankylosing Spondylitis is a part of spondyloarthritis, a group seronegative chronic inflammatory rheumatic disease. Ankylosing spondylitis characterized by inflammation primarily affecting the spine (vertebrae and intervertebral discs) as well as sacroiliac joints in various grades ranging from no abnormalities to complete bridging of intervertebral joints or complete ankylosis in sacroiliac joint (Gilgil et al., 2005; Montandon et al., 2007; Haroon et al., 2018). Previous studies reported that AS was a disease occurring predominantly in males, but recent researches revealed that AS also frequently occurred in females

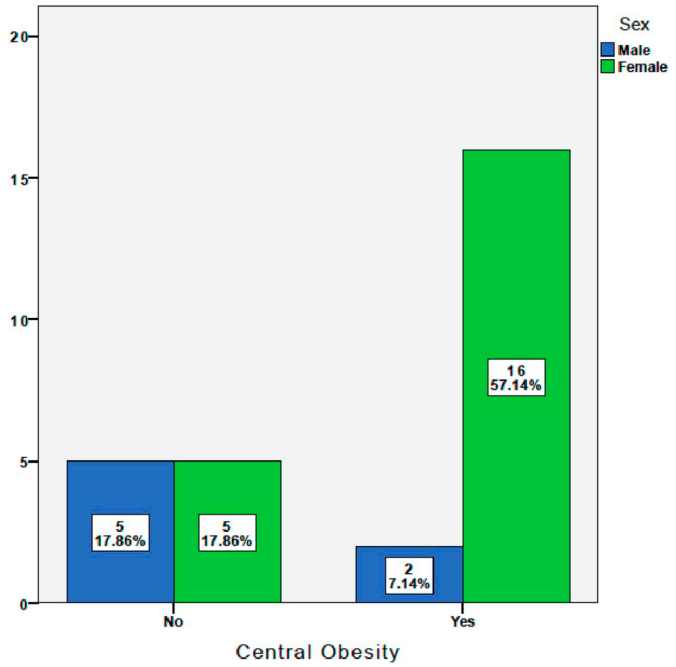

Fig. 2. Central obesity in AS patients.

Table 2
Subject's characteristics according to central obesity.

Parameter	No central obesity (n = 10)	Central obesity (n = 18)	P[a]
Age (years)	37.3 ± 11.71	49.39 ± 6.75	0,01
BMI (kg/m^2)	19.74 ± 1.75	28.57 ± 3.50	0,00
Waist circumference (cm)	74.7 ± 4.79	94.41 ± 8.13	0,00
Height (cm)	161.3 ± 8.19	154.69 ± 8.04	0,05
Weight (kg)	51.5 ± 6.96	68.28 ± 8.83	0,00
Fasting plasma glucose (mg/dL)	91.1 ± 9.02	122.56 ± 57.31	0,03
Total cholesterol (mg/dL)	192.7 ± 29.68	195.89 ± 36.58	0,81
Triglycerides (mg/dL)	120.3 ± 48.78	140.94 ± 67.21	0,41
HDL-cholesterol (mg/dL)	52.0 ± 13.06	49.33 ± 16.35	0,67
LDL-cholesterol (mg/dL)	110.80 ± 25.59	117.28 ± 29.60	0,57
mSASSS score	19.5 ± 5.50	24.0 ± 5.53	0,04
Duration of disease (years)	2.75 ± 1.61	6.74 ± 4.96	0,02

[a] Calculated with independent *t*-test with p value is considered significant if < 0.05 (two-tail hypothesis).

especially in > 45 years old population. The estimated AS male:female ratio nowadays is 2–3:1 (Webers et al., 2016; Lee et al., 2008; Haroon et al., 2014; Skare et al., 2012). In this study, female was more predominant with ratio 3:1 with higher average age compared to the male counterpart (48.67 vs 34.23 years old). This might be due to location of the study, which is a tertiary class hospital. Therefore, all of our patients are referral cases (Flegel, 2015). Besides the location, female aged ≥45 years old is associated with lesser quality of life, atypical manifestations, but lesser radiologic damage compared to the male counterpart. Therefore, this finding might reflect the predominance of female in our study (Webers et al., 2016; Skare et al., 2012).

Central obesity was measured with Asian cut-off of waist circumference since a difference in stature between Asian, especially Indonesian and western population was observed (Tan et al., 2004). Using Asian cut-off, we found that central obesity occurred in 64.28% of subjects. This finding supports previous studies which reported the proportion of central obesity ranging from 45.8 to 90.9%. Using Indonesian's BMI cut-off, we found that majority AS patients were in obese-I category (28.57%). To our knowledge, there has been no study

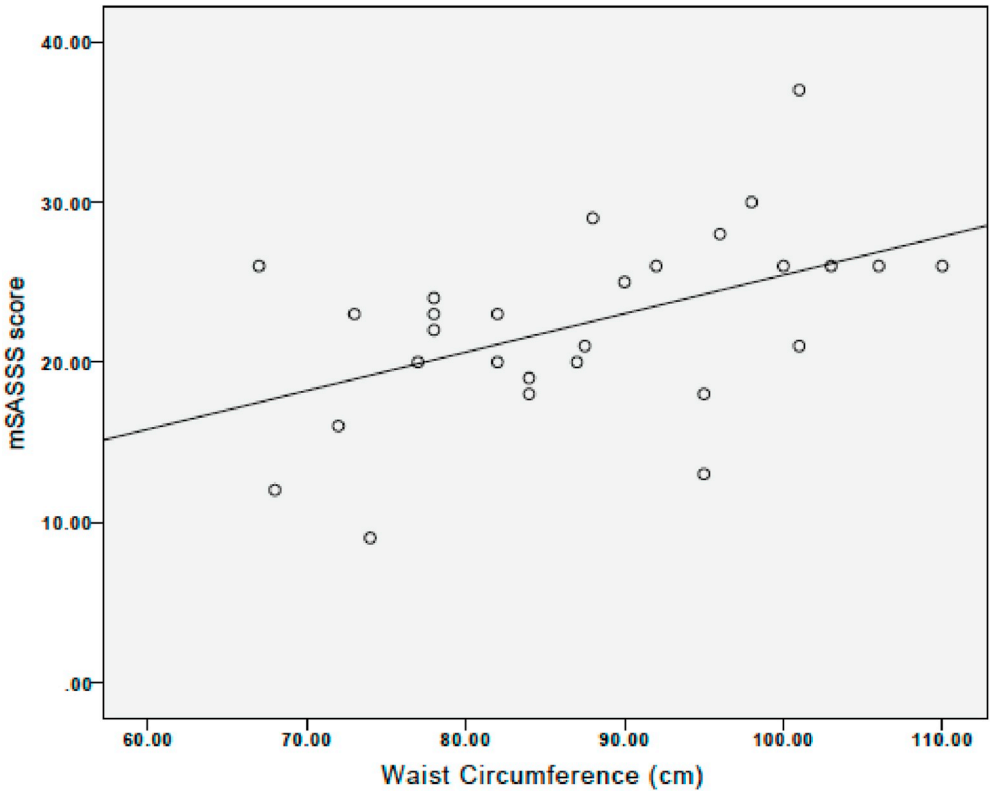

Fig. 3. Correlation of mSASSS and waist circumference.

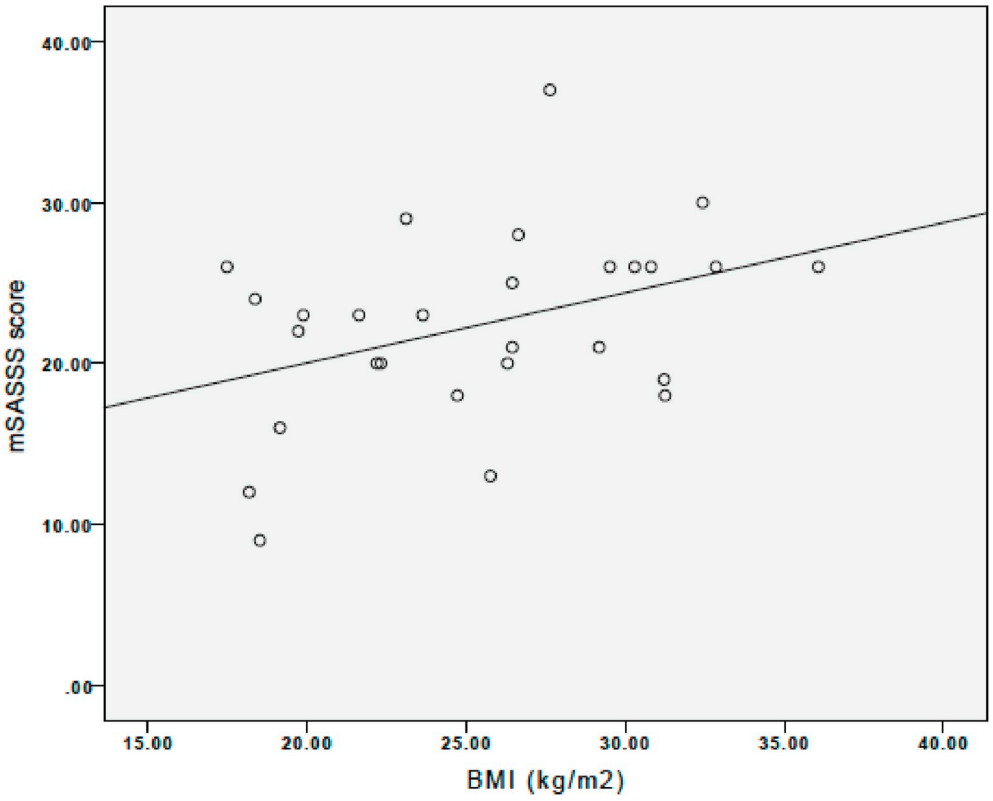

Fig. 4. Correlation of mSASSS and BMI.

which investigates central obesity in Indonesian population using Asian's waist circumference and Indonesian's BMI cut-off (Tan et al., 2004; Tjokroprawiro et al., 2014).

However, since our results showed a difference in male:female ratio in this study compared to the previous study, the possibility of higher central obesity due to hormonal factor and aging could not be ruled out. The average age of female in this study was 48.67 years old with 66.67% already were in menopause period. Menopause is associated with hypoestrogenemia and hyperandrogenemia which increased the deposition of abdominal fat. The hyperandrogenemia in menopause is a compensation to elevate estrogen level in menopause. Estrogen which are produced from androgen do not have cardioprotective level as well as estrogen from ovary (Dominguez and Barbagallo, 2016; Kozakowski et al., 2017).

The average mSASSS score in this study was 22.39. When we classified patients to the presence of central obesity we found higher average mSASSS score in subjects with central obesity compared to those without central obesity in AS patients with csDMARDs therapy. To our knowledge, there has been no study which investigates mSASSS score in AS patients with csDMARDs therapy. However, the average mSASSS score in this study was higher compared to Ramiro et al., which reported the average mSASSS score in their large-scale multicenter cohort (10.8) (Ramiro et al., 2014). The higher mSASSS score in this study might be due to the longer disease duration of the subjects with average 5.31 years. Longer disease duration was associated with increased mSASSS score (Ramiro et al., 2014).

Using Pearson's correlation test, we found that mSASSS score positively correlated with central obesity measured with waist circumference (ρ:0.49, $p = 0.02$) especially with female's waist circumference (ρ:0.53, $p = 0.01$) and BMI (ρ:0.389, $p = 0.04$). This is the first study to investigate the correlation of mSASSS score with central obesity in Indonesian AS patients receiving csDMARDs, as Maas et al., reported that higher BMI associated with poor radiographic outcome in AS patients receiving anti-TNFα therapy (Maas et al., 2017). There were no correlation between csDMARDs used in subject's management in this study (methotrexate, sulfasalazine) with metabolic parameters in AS (Owczarczyk-Saczonek et al., 2018; Vohra et al., 2016). We thought that mSASSS was a better disease severity index to evaluate the long-term complications of AS, since Vargas et al., reported that BMI was not related to disease activity index, eg: ASDAS-CRP in AS from the large-scale cohort (Vargas et al., 2016). However, recent study reported that BMI was associated with greater burden of symptoms and higher level of disease activity, consistent with the result of this study (Zepa et al., 2018; Durcan et al., 2012).

This study has some limitations. First, the average age especially in female subjects was 48.67 years old and 66.7% of the subjects were already in the menopause period, the possibility of menopause's impact on metabolic parameter could not be excluded. Second, it was conducted in small AS populations with some exclusion criteria in such limited time and the cross-sectional study design which might not reflect the cause-effect relationships of AS's severity and central obesity. Last, the role of sedentary lifestyle or physical activity in our subjects were not investigated thoroughly, so it could be assumed as a confounding factor. Therefore, further studies in large-scale Indonesian AS patients are needed to investigate the severity of AS and the long-term outcome.

5. Conclusion

Positive correlation was observed between severity of AS measured as a radiographic damage with mSASSS score and central obesity measured as waist circumference and BMI in Indonesian AS patients receiving csDMARDs. Majority of the subject classified as obese-I according to Indonesian's BMI-cutoff. Further studies in large-scale are needed to investigate the long-term outcome in AS.

Disclosure

The authors declare that there is no conflict of interest regarding the publication of this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.obmed.2019.100091.

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