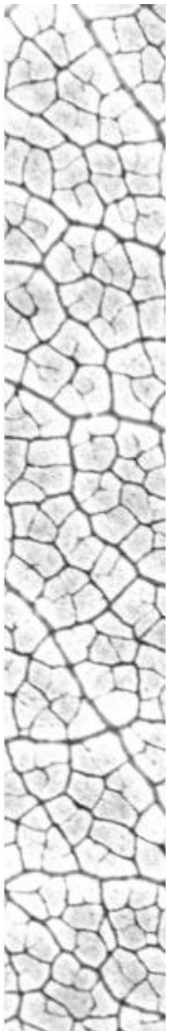

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Leptin serum and disease activity in spondyloarthritis

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Abstract

Background: Spondyloarthritis (SpA) is an active chronic inflammatory disease involving pro-inflammatory cytokines; one of which is leptin. This study aimed to determine correlation between leptin serum level and disease activity in SpA patients.

Method: A cross-sectional study involving patients diagnosed with SpA was conducted according to the 2009 ASAS criteria. Leptin serum level is measured by using ELISA whilst disease activity in SpA by ASDAS-CRP. The correlation was analyzed using Spearman correlation test.

Results: Fifty subjects with SpA aged 54.3±9.32 years old showed mean body mass index of 23.63±3.05 kg/m^2, CRP level of 0.76±0.91 mg/dL, ESR of 40.88±16.92 mm/hour, Schober test of 12.97±1.18 cm, and chest expansion test of 1.39±0.67 cm. Median leptin level and ASDAS-CRP score were 9.6 (0.92-51.57) ng/dL and 2.2 (1.3-3.86), respectively. No correlation was found between leptin level and disease activity (p = 0.174).

Conclusion: Leptin serum level cannot be used as a modality to assess disease activity in SpA.

Keywords: leptin, spondyloarthritis, ASDAS, disease activity, adipokines

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INTRODUCTION

Spondyloarthritis (SpA) is a chronic progressive low-grade inflammation disease which is often accompanied by metabolic syndrome consisting of obesity, dyslipidemia, and hypertension due to interference with adipokines regulation (Dougados et al. 2011, Genre et al. 2014). SpA may also cause the occurrence of secondary osteoarthritis (Ahmad et al. 2018). Furthermore, other studies presented that chronic arthritis is associated with other diseases including Lyme disease and risk factors for TB (Dharmajaya 2018, Kusmiati et al. 2016, Massi et al. 2017, Rotan et al. 2018).

Some researchers report that leptin is closely related to the activity of SpA disease (Elolemy et al. 2013, Kim et al. 2012, ParkMin-Chan et al. 2009). Leptin is an adipokines (proinflammatory cytokine) which is the main component underlying immunopathology that connects rheumatoid arthritis and obesity. This process is assumed to also have a role in the pathogenesis of SpA and obesity (Daïen et al. 2015). In addition, when immune system dysregulation occurs, especially in genetically susceptible individuals, bacterial dysbiosis can trigger autoimmune reactions, including spondyloarthritis (SpA) (Ciccia et al. 2015, 2016, Uotani et al. 2015).

Inflammation is a response to eliminate various pathogens and preserve host integrity (Putra et al. 2018, Umit et al., 2019). Some studies report an association between leptin level, inflammatory markers, and disease activity (ParkMin-Chan et al. 2009). An in vitro study on peripheral blood mononuclear cell (PBMC) culture shows that the leptin level in SpA patients are higher than controls and often formed in organs with active inflammation (Kim et al. 2012). In contrast, other studies found no difference or lower leptin level in SpA patients compared to control group (Derdemezis et al. 2010, Toussirot et al. 2013). Further studies show that the differences in the results of these studies may be due to differences in the population of patients studied, study designs (in vitro or in vivo), and duration of illness (Derdemezis et al. 2010, Kim et al. 2012, ParkMin-Chan et al. 2009).

In SpA, cytokines and acute phase proteins systemically increase by 2-3 times normal level (Dougados et al. 2011). Low-grade inflammation increases the production of leptin and triggers an inflammatory process that occurs continuously. Hyperleptinemia further triggers insulin resistance and

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obesity. Pro-inflammatory action increases when there is infection (Simanjuntak et al. 2018). Leptin acts as proinflammatory cytokines that activates endothelial cells and increases the accumulation of macrophages in adipose tissue which ultimately releases proinflammatory cytokines and aggravates inflammatory process (Castro et al. 2017).

Disease activity in SpA can be measured by the Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP) score, in order to determine the presence of active inflammation in SpA. In 2009 The Assessment of Spondyloarthritis International Society (ASAS) introduced the ASDAS score system which can be used to measure disease activity categories more objectively (Markov Alexander 2019). In Indonesia, there has been no study linking between leptin and ASDAS-CRP scores. The results of this study are expected to shed a light about the controversy that arises between the roles of leptin in SpA. This study aimed to determine correlation between leptin serum level and disease activity in SpA patients (Shahsavar et al, 2013).

METHODS

Subjects

This cross-sectional study involved 50 subjects who were consecutively sampled. All subjects were outpatients in Dr. Soetomo General Hospital, Surabaya, diagnosed with SpA according to the 2009 Assessment of Spondyloarthritis International Society (ASAS) criteria. Patients with BMI >30kg/m^2, diabetes mellitus, liver cirrhosis, asthma, tuberculosis, and history of smoking were all excluded. Every patient who was enrolled in this study had voluntarily signed a consent form stating their willingness without force nor coercion to participate as study subjects. All study subjects were aware that they were involved in this cross-sectional study and their rights and confidentiality as patients were preserved with utmost respect. This study was conducted strictly according to the 2016 ICH-GCP and the Declaration of Helsinki and had been approved by Ethics Committee of Dr. Soetomo General Hospital, Surabaya.

Leptin Serum

Leptin serum level was measured by *Enzyme Linked Immunosorbent Assay* (ELISA), using *Human Leptin (Quantikine® ELISA Human Leptin Immunoassay, R&D System, IncCatalog* D1700, USA) as reagent. The minimum detectable level was 7.8 pg/ml. Blood sample was drawn in a serum separator tube for 30 minutes, then centrifuged for 15 minutes and stored in < -20 C fridge. 100 µL of each standard, control, and sample were added into tubes containing 100 µL of *Assay Diluent* RD1-19. Tubes were sealed with adhesives and incubated in room temperature for 2 hours before aspirated and washed 4 times. Aspiration and washing were repeated after adding 200 µL of *Leptin Conjugate* and one-hour incubation period. Furthermore, 200 µL of *substrate solution* was added, and tubes were stored in light-proof storage for 30-minute incubation period. After that, 50 µL of *stop solution* was added, and finally sample was run through microplate reader with 450 nm wavelength for 30 minutes.

Table 1. Subjects' characteristics

Characteristics	Results
Sex	
Male	13 (26%)
Female	37 (74%)
Age (year old)	54.3±9.32[a]
Body Mass Index (kg/m^2)	23.6±3.05[a]
CRP (mg/dL)	0.76±0.91[a]
ESR (mm/hour)	40.88±16.92a[a]
Schober Test (cm)	12.97±1.18a [a]
Chest Expansion Test (cm)	1.39±0.67a [a]
ASDAS-LED (score)	3.38±0.81a [a]
ASDAS-CRP (score)	2.2(1.3-3.86)[b]

[a] Mean±SD; [b] Median(min-max)

Table 2. Leptin Serum According to SpA type and BMI grade

Variable	Category	Leptin serum (ng/dL)
Type of SpA	Axial SpA	10.10 (0.92-51.57)[b]
	Peripheral SpA	16.72±1.38 [a]
BMI	Normal	6.03(0.92-48.21)[b]
	Overweight	10.2 (1.33-51.57)[b]
	Obese I	19.84±3.39[a]

[a] Mean±SD; [b] Median (min-max)

Disease Activity

Severity of SpA is evaluated by Ankylosing Spondylitis Disease Activity Score (ASDAS). This scoring system evaluates back pain, duration of morning stiffness, peripheral joint pain or swelling, and global assessment of disease activity. The score is often combined with C-reactive protein (CRP) level or erythrocyte sedimentation rate (ESR). ASDAS-CRP is more recommended to evaluate SpA than its alternative, ASDAS-LED (Zochling 2011).

Statistical Analysis

Data collected from this study was analyzed in SPSS 17 (IBM Corp., Armonk, NY, USA). Subjects' demographics and characteristics were shown as descriptive data. Correlation of leptin serum level and ASDAS were analyzed by Spearman's correlation test, with significance level of 0.05.

RESULTS

Table 1 shows that the subjects are all middle-aged (54.3±9.32 years old) with female as majority (74%). Median ASDAS-CRP score was 2.2. In **Table 2**, out of 50 subjects, median serum leptin level was 9.6(0.92-51.57) ng/dL, with higher leptin level found in the peripheral SpA group of 16.72±1.38 ng/dL. Based on BMI grade, subjects in Obese I category had the highest mean leptin level (19.84±3.39 ng/dL). According to ASDAS-CRP as seen in **Table 3**, this study has no case categorized as inactive disease whilst the majority of the

Table 3. Leptin level and other various parameters to disease activity in SpA

Parameters	Moderate Disease n=17 (34%)	High Disease n=27 (54%)	Very High disease n=6 (12%)
ESR	33.5±13.5 [a]	43.22±16.31 [a]	51.67±21.97 [a]
Schober Test	12.76±0.79 [a]	13.12±1.19 [a]	12.5±1.48 [a]
Chest Expansion	1.32±0.53 [a]	1.37±0.76 [a]	1.66±0.6 [a]
CRP	0.3(0.1-2.3) [b]	0.5 (0.1-5.7) [b]	0.95 (0.5-1.3) [b]
Leptin	7.57 (1.33-36.7) [b]	9.04 (0.92-45.73) [b]	33.05(7.17-51.57) [b]

[a] Mean±SD; [b] Median(min-max)

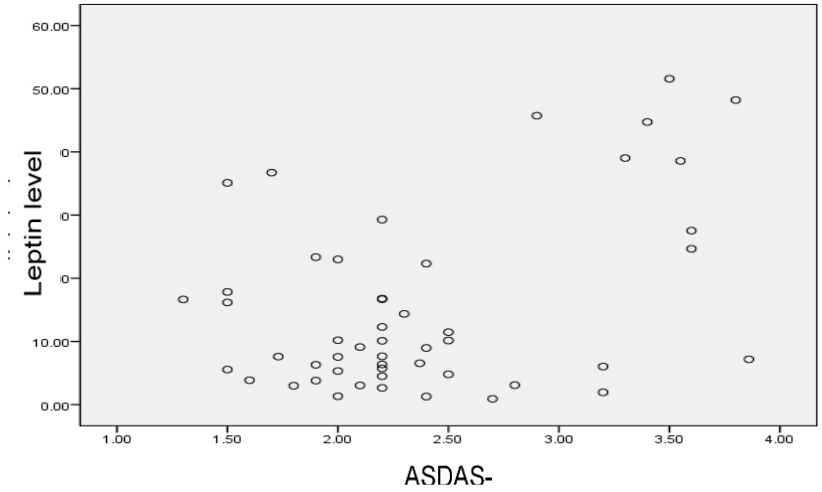

Fig. 1. Scatterplot for Leptin level and Disease activity

subjects fell into high disease category (54%). Leptin level appears to be the highest in subjects with very high disease.

Based on Kolmogorov-Smirnov analysis of disease activity to leptin level, the study appears to be having abnormal data distribution with p-value of 0.000. Furthermore, this study obtained insignificant p-value of 0.174 through Spearman test, hence no correlation between leptin level and disease activity in SpA (ASDAS-CRP score) as seen in **Fig. 1**. Statistically, the scatterplot showed that leptin level among all three categories of disease activity overlaps. Correlation test was performed for each category of disease activity to leptin level. The results showed no correlation between serum leptin level and ASDAS-CRP scores in patients with either moderate, high, or very high disease activity (p-value of 0.217, 0.278, and 0.178). Correlation coefficient (r-value) was not analyzed as there was no significant value found in the first place (Shahsavar et al, 2013).

DISCUSSION

There was no association between leptin serum level and disease activity using ASDAS-CRP score. Leptin may play a role at local sites of inflammation rather than systemically. This adipokine does not show any effect on the disease activity in SpA (Mei et al. 2016).

The role of leptin in the pathogenesis of SpA is still unclear. Past studies have shown contradictory results about this matter. Leptin is produced by adipocytes. Adipose tissue synthesizes hormones, cytokines and immune factors, such as TNF-α, IL-1 and IL-6. Chronic inflammation triggers white adipose tissue (WAT) to secrete adipokines, which are inflammatory cytokines consisting of leptin, adiponectin, resistin, vistatin, etc. (Moon et al. 2013). Chronic inflammation can reduce the amount of body fat and reducing the production of leptin by adipocytes which are the main source of leptin (Sari et al. 2007). The reduction of adipose tissue mass leads to low production of leptin (Toussirot et al. 2013). A study compared serum leptin level in SpA patients to a control group (Sari et al. 2007). The study reported that leptin level in SpA patients was significantly lower than that of controls. Furthermore, previous studies reported no difference of leptin levels between SpA patients and control group and no correlation between serum leptin levels and disease activity (Derdemezis et al. 2010, Toussirot et al. 2013). A systematic review and a meta-analysis mentioned that serum leptin level was not associated with other inflammatory markers, such as ESR, CRP, TNF-α and also BASDAI (Mei et al. 2016).

In contrast, several other studies reported significant correlations between leptin level and disease activity SpA. Research in 2013 reported that serum leptin level increased significantly in SpA patients and was correlated to disease activity parameters (BASDAI, BASFI) (Elolemy et al. 2013). SpA patients with syndesmophytes have higher leptin level than those without (Kim et al. 2012). A prospective research also

studied leptin level and disease activity in SpA patients (ParkM-C et al. 2007). After 31 months, it was found that there was a decrease of the disease activity parameters (BASDAI, ESR, and CRP) and serum leptin level. These contradictory findings are possibly due to differences in the demographics of the study population, duration of disease, and treatment provided.

Leptin level in this study was showing similarity with a study in Egypt that found elevated leptin serum in axial SpA (7.6 ±3.3 ng/dL), peripheral SpA (10.9±1.9 ng/dL), and overall cases (9.1±3.9) ng/dL (Elolemy et al. 2013). Patients with peripheral SpA showed higher leptin level as the disease itself exhibits profound arthritis or Rheumatoid Arthritis (RA)-like manifestations. Another study reported that leptin serum level in RA patients was 19.8±2.7 ng/dL (Toussirot et al. 2013).

The American College of Rheumatology reported that SpA occurred three times higher in men than women whilst other researchers state there was no difference. This study had a majority of female patients with the female to male ratio of 3:1 possibly due to sampling method. Among 80% of SpA patients, the initial symptoms appeared under age of 30 and less than 5% starts older than 45 years old. In this study, the average age of the samples was 53.58±9.28 years old (Braun et al. 2008). The mean age reported in this study was higher than previous studies, possibly due to SpA patients coming to a health facility on later age when the disease had already advanced. From the study report, the average SpA patient was diagnosed after 8-10 years after the initial symptoms due to “insidious” symptoms. A study in Brazil showed that axial SpA was more prevalent than peripheral SpA (Sampaio-Barros et al. 2010). Another report mentioned the prevalence of axial SpA was 60% higher than peripheral SpA cases in America (Strand et al. 2013). In this study, there were 35 axial patients (70%) and 15 peripheral patients (30%). The numbers are in accordance with other studies.

In early stage of SpA, erosion occurs at proximal enthesis and it gradually will heal on later stage and the formation of a spur at the distal attachment site will cause vertebral fusion (McGonagle et al. 2009). Spinal mobility can be assessed, among others, by chest expansion and the Schober test. Abnormal spinal mobility can indicate structural damage as well as the severity of SpA. In this study, the Schober test results showed similarity to previous studies which showed 13.3±1.2 cm and 12.9±1.6 cm, respectively (Rezvani et al. 2012, Tian et al. 2014). It is suspected that the progression of the disease between the races is slower, considering that subjects in this study are older than 40 years old. Furthermore, earlier studies reported mean chest expansion of 3.07±1.66 cm and 3.6±1.3 cm (Grubisić et al. 2014, Rezvani et al. 2012). However, this study reported only 1.39±0.67 cm for chest expansion test, which is similar to previous studies.

Study in the Netherlands reported an average ASDAS-CRP value of 2.4±0.9 in active SpA patients (Rubio Vargas et al. 2016). People’s Republic of China reported higher ASDAS-CRP score in patients with axial SpA (2.05±1.07) than those with peripheral SpA (1.86±1.07) because ASDAS-CRP evaluates axial disease activity better than peripheral one (Xue et al. 2012). This study gave a median value of ASDAS-CRP score of 2.2 (1.3-3.86). The majority SpA patients in this study were in high activity disease category, and none was categorized as having inactive disease. Most of SpA patients did not seek treatment until much later they exhibited major symptoms. Considering the socio-economy conditions, these patients were prescribed with conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs) such as Methotrexate (MTX) and/or Sulfasalazine (SSZ) instead of using targeting therapy. Patient’s compliance in medication might also contribute in the lack of inactive cases in this study.

ASDAS-CRP heavily relies on clinical symptoms which are subject to patients’ perspective and understanding about their disease. To confirm a worsening in disease activity, physicians need to evaluate spinal mobility (Reveille et al. 2012). Any limitations in spinal mobility can be evaluated by performing Schober test, occiput-to-wall test dan chest expansion. A study in Morocco showed an association between spinal mobility as measured by the Schober test, occiput-to-wall test and chest expansion with disease activity using BASDAI, BASMI, BASFI and BASRI (Ibn Yacoub et al. 2012). Assessing SpA activity is not simple and it requires a lot of parameters because SpA is a low-grade inflammation with activity and progression that are clinically difficult to assess.

CONCLUSION

There was no association between leptin serum level and disease activity using ASDAS-CRP score. Leptin serum level cannot be used as a modality to assess disease activity in SpA.

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