

Leptin

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The Relationships Among Leptin, Resistin, Visfatin, Transforming Growth Factor (TGF)- β Level and The Severity Grade of Osteoarthritis in Osteoarthritis Patients with Obesity

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ABSTRACT

Obesity is risk factor for osteoarthritis (OA), that increased production of adipokine from adipocyte, such as leptin, adiponectin, resistin and visfatin. Some studies showed there was a relationship between adipokine level in sinovial fluid and incidence of OA. To determine the relationships among leptin, resistin, visfatin, TGF- β level and the severity grade of osteoarthritis in osteoarthritis patients with obesity. Observational case-series study. The ethical clearance of this study had been approved by bioethics and humaniora unit Faculty of Medicine Sriwijaya University, Indonesia. Osteoarthritis patients with obesity in Internal Medicine Outpatient Dr. Mohammad Hoesin General Hospital, Palembang, South Sumatera, Indonesia were selected as subjects in this study, from April 2013 – February 2014. Level of TGF- β , leptin, resistin and visfatin were assayed by ELISA. The relationships was analysis by correlation-spearman rho test, $p < 0,05$. There was moderate correlation among leptin, resistin, TGF- β level and the severity grade of OA in male and female patients. It was strong correlation among leptin, resistin, TGF- β level in sinovial and the severity grade of OA Kellgren-Lawrence in female patients. There was relationships among leptin, resistin, TGF- β level and the severity grade of OA.

Keyword : Osteoarthritis-leptin-resistin-visfatin-TGF β

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INTRODUCTION

Osteoarthritis (OA) is a chronic, degenerative, inflammatory atrophy that affects all joint structures (hialine cartilage, subcondral bone and synovial membrane) [1,2,3]. In Indonesia, the prevalence of knee OA reaches 15.5% in men and 12.7% in women aged between 40-60 years old. Study in Bandung, Indonesia showed that OA is 69% of all rheumatic cases in outpatient internal medicine, 69% of whom are women and OA of the knee by 87%.¹ Harefa et al., showed that 50 OA patients, 72% of women and 22% of men, 70 % Of patients had BMI \geq 23 [5,6,7,8,9]. Obesity is a risk factor in OA, where there is increased biomechanical joint burden and increased adipokines produced by adipocyte cells such as leptin, adiponectin,

resistin and visfatin. Several studies have shown an increased association of adipokine fluid content of the joints and increased incidence of OA. Along with the evidence of the linkage of the inflammatory process to the synovium, the pathology of OA is not only based on degenerative and biomechanical processes alone, but in combination with inflammatory processes [6,7,10-15].

The increasing of adipokine levels in sinovial fluid, it will increase the induction of the chondrocytes cells resulting in stimulation of proteoglycan synthesis, insulin growth factor-1 (IGF-1) and transforming growth factor- β 1 (TGF- β 1) in the cartilage in response to repair of matrix damage extra cellular by forming cell groups and increasing anabolic activity, this is an indicator of the anabolic role of leptin, adiponectin, resistin and visfatin in cartilago [14,16].

The increasing of adipokines will also induce chondrocytes releasing proinflammatory cytokines such as nitric oxide (NO), interleukin 6 (IL-6), interleukin 8 (IL-8) and degradative cartilage factors such as matrix metalloproteinases (MMPs) and aggrecanases a disintegrin and metalloprotease with thrombospondin motifs (ADAMTS-4, ADAMTS-5) that will damage joint cartilage resulting in osteoarthritis [10-16].

Aim and objective

To determine the relationships among leptin, resistin, visfatin, TGF- β level and the severity grade of osteoarthritis in osteoarthritis patients with obesity.

MATERIALS AND METHODS

Study Design : Observational case-series study.

Ethical Consideration : The ethical clearance of this study had been approved by bioethics and humaniora unit Faculty of Medicine Sriwijaya University, Indonesia.

Procedure of Study : Osteoarthritis patients with obesity in Internal Medicine Outpatient Dr. Mohammad Hoesin General Hospital, Palembang, South Sumatera, Indonesia were selected as subjects in this study, from April 2013 – February 2014. Inclusion criteria of this study : had OA diagnostic based on American College of Rheumatology (ACR), had the severity grade 1-3 of OA based on Kellgren-Lawrence, obesity grade I with BMI 25-29,9 kg/m², and age \geq 40 years old. Exclusion criteria of this study : had an intraarticular injection with steroid on last three months. Forty-five samples were

included in this study by nonprobability consecutive sampling.

Laboratory Assay : Patient's blood sample was collected from a median cubital vein for 3 mL and stored in *ethylene diamine tetraacetic acid* (EDTA) coated tube for leptin, resistin, visfatin and TGF- β assay. Blood samples were centrifuged 10.000 rpm for 10 minutes. Supernatant was collected. Solid phase sandwich ELISA (Human leptin, resistin, visfatin, TGF- β ELISA kit, Elabscience) were used to analysis concentration of SDH. Add samples and standards and incubate the plate at 37°C for 90 minutes, do not wash. Add biotinylated antibodies and incubate the plate at 37°C for 60 minutes, wash plate 3 times with PBS 0,01 M. Add ABC working solution and incubate the plate at 37°C for 30 minutes. Wash plate 5 times with PBS 0,01 M. Add TMB colour developing agent and incubate the plate at 37°C in dark for 20 minutes. Add TMB stop solution and read the OD absorbance at 450nm in a microplate reader. The standard curve was plotted as the OD 450 of each standard solution vs the concentration of standard solution. The human leptin, resistin, visfatin and TGF- β level of the samples were interpolated from the standard curve.

Statistical Analysis : The data was analyzed using SPSS 23. The relationship among leptin, resistin, visfatin, TGF- β level and the severity grade of OA were analyzed by spearman correlation, with 95% confidence interval. The data was shown descriptively in narration, table, and percentage.

Tabel 1. Baseline Characteristics of Samples

Characteristics	Total Samples (n=45)	The Severity Grade of OA : Kellgren-Lawrence		
		Grade 1 (n=3)	Grade 2 (n=10)	Grade 3 (n=32)
Sex				
Male	16(35,6%)	2 (4,4%)	2 (4,4%)	12 (26,7%)
Female	29(64,4%)	1 (2,2%)	8 (17,8%)	20 (44,4%)
Age (year)	56,76 \pm 8,42 ^a	45,00 \pm 4,58 ^a	50,00 \pm 3,43 ^a	59,84 \pm 7,62 ^a
Age (year)				
40 – 49	10 (22,2%)	3 (6,7%)	4 (8,9%)	3 (6,7%)
50 – 59	13 (28,9%)	0	6 (13,3%)	7 (15,6%)
60 – 69	19 (42,2%)	0	0	19 (42,2%)
\geq 70	3 (6,7%)	0	0	3 (6,7%)
BMI (Kg/m ²)*	26,99 (25,07-29,90) ^b	25,95 (25,80-27,46) ^b	27,04 (25,46-29,90) ^b	27,05 (25,07-29,76) ^b
Male**	26,50 (25,15-29,76) ^b	26,70 (25,95-27,46) ^b	25,97 (25,59-26,35) ^b	26,89 (25,15-29,76) ^b
Female***	27,11 (25,07-29,90) ^b	25,80 (25,80-25,80) ^b	27,20 (25,46-29,90) ^b	27,05 (25,07-29,59) ^b

^a Mean \pm SD, ^bMedian (min – max), * Kruskal-Wallis test $p=0,916$; ** Kruskal-Wallis test $p=0,438$; *** Kruskal-Wallis test $p=0,539$ (significancy $p < 0,05$).

Table 2. The Relationships Between Leptin Level in Sinovial Fluid and The Severity Grade of OA Kellgren-Lawrence

Characteristics	Total Samples (n=45)	The Severity Grade of OA : Kellgren-Lawrence			r*	p*
		Grade 1 (n=3)	Grade 2 (n=10)	Grade 3 (n=32)		
Leptin (ng/ml)	18.831,1 (4.314,5-31.861,9)	4.595,2 (4.553,6-6.477,7)	10.010 (4.314,5-31.861,9)	22.921 (4.491,1-31.324,0)	0,37	0,012
Sex						
Male	7.286,1 (4.314,5-31.324,0)	5.515,6 (4.553,6-6.477,7)	4.533,1 (4.314,5-4.751,7)	7.774,0 (5.244,2-31.324,0)	0,25	0,33
Female	24.189 (4.491,1-31.861,9)	4.595,2 (4.595,2-4.595,2)	15.681 (4.803,9-31.861,9)	24.650 (4.491,1-31.270,5)	0,54	0,003

* Spearman rho test (significance $p < 0,05$); If $r = 0$: no correlation; $r > 0-0,25$: weak correlation; $r > 0,25-0,5$: moderate correlation, $r > 0,5-0,75$: strong correlation, $> 0,75-0,99$: very strong correlation.

Table 3. The Relationships Between Resistin Level in Sinovial Fluid and The Severity Grade of OA Kellgren-Lawrence

Characteristics	Total Samples (n=45)	The Severity Grade of OA : Kellgren-Lawrence			r*	p*
		Grade 1 (n=3)	Grade 2 (n=10)	Grade 3 (n=32)		
Resistin (ng/ml)	2.959 (574-12.806)	1.689 (574-9.398)	2.383 (1.357-12.806)	3.649,5 (687-12.492)	0,31	0,038
Sex						
Male	1.354,1 (574-2.324,0)	619,6 (574-1.398)	1.533,1 (1.357-2.721,7)	2.764,6 (687-7.324,0)	0,21	0,36
Female	4.189,6 (603,7-7.661,9)	1.095,2 (1.095,2-1.095,2)	3.681,5 (1.503,7-12.806)	4.689,7 (4.491,1-12.492)	0,53	0,002

* Spearman rho test (significance $p < 0,05$); If $r = 0$: no correlation; $r > 0-0,25$: weak correlation; $r > 0,25-0,5$: moderate correlation, $r > 0,5-0,75$: strong correlation, $> 0,75-0,99$: very strong correlation.

Table 4. The Relationships Between Visfatin Level in Sinovial Fluid and The Severity Grade of OA Kellgren-Lawrence

Characteristics	Total Samples (n=45)	The Severity Grade of OA : Kellgren-Lawrence			r*	p*
		Grade 1 (n=3)	Grade 2 (n=10)	Grade 3 (n=32)		
Visfatin (ng/ml)	8,19 (2,64-24,41)	10,97 (3,11-22,28)	6,57 (2,64-23,34)	8,36 (2,68-24,41)	-0,07	0,30
Sex						
Male	8,54 (2,79-22,28)	12,69 (3,11-22,28)	4,91 (3,83-6,00)	9,02 (2,79-18,66)	-0,10	0,35
Female	8,12 (2,64-24,41)	10,97 (10,97-10,97)	7,92 (2,84-23,34)	6,49 (2,68-24,41)	-0,17	0,17

* Spearman rho test (significance $p < 0,05$); If $r = 0$: no correlation; $r > 0-0,25$: weak correlation; $r > 0,25-0,5$: moderate correlation, $r > 0,5-0,75$: strong correlation, $> 0,75-0,99$: very strong correlation.

Table 5. The Relationships Between TGF- β Level in Sinovial Fluid and The Severity Grade of OA Kellgren-Lawrence

Characteristics	Total Samples (n=45)	The Severity Grade of OA : Kellgren-Lawrence			r*	p*
		Grade 1 (n=3)	Grade 2 (n=10)	Grade 3 (n=32)		
TGF- β (pg/ml)	458,5 (17-945,4)	28,25 (17-39,5)	409,3 (271,3-520,0)	468,80 (304,1-945,4)	0,528	0,001
Sex						
Male	219,92 (17-398,56)	18,33 (17-19,65)	259,43 (271,3-320,56)	331,65 (304,1-398,56)	0,53	0,002
Female	555,63 (39,5-945,4)	39,5 (39,5-39,5)	498,65 (432,56-520,0)	632,56 (453,54-945,4)	0,623	0,001

* Spearman rho test (significance $p < 0,05$); If $r = 0$: no correlation; $r > 0-0,25$: weak correlation; $r > 0,25-0,5$: moderate correlation, $r > 0,5-0,75$: strong correlation, $> 0,75-0,99$: very strong correlation.

RESULTS

Table 1 showed the incidence OA was higher in female than male. The incidence OA in female

was 64,4% and the incidence OA in male only 35,6%. The average of age was more older, 59 years old, in grade 3 (severity grade OA: kellgren-lawrence) than grade 1, 45 years old,

and grade 2, 50 years old. There was moderate correlation between leptin level and the severity grade of OA in male and female patients. It was strong correlation between leptin level in sinovial and the severity grade of OA Kellgren-Lawrence in female patients.

Resistin level in sinovial fluid had moderate correlation with the severity grade of OA Kellgren-Lawrence. Resistin level in female sinovial fluid had strong positive correlation with the severity grade of OA Kellgren-Lawrence. Resistin level in sinovial fluid had not correlation with the severity grade of OA Kellgren-Lawrence. There was strong correlation between TGF- β level and the severity grade of OA in male and female patients.

DISCUSSION

Ku JH showed there was a correlation between leptin level in sinovial fluid and the severity degree of OA ($p = 0.0125$). Schmidt J et al showed there was a correlation between leptin level in sinovial fluid and the severity degree of OA, but not statistically significant, in males $r = 0,422$; $P = 0,06$ and in women $r = 0,407$; $P = 0,084$.^{17,18} In this study there was a positive correlation between leptin level of joint fluid in women who was significant and not significant in men. This is very likely to occur because in some studies found leptin levels of joint fluid in women is higher than men who are statistically significant. Schmidt J et al also found a correlation of OA severity with elevated estrogen serum and joint fluid levels. In obese women, BMI has a positive correlation with elevated levels of estrogen in the joint fluid ($r = 0.49$, $p = 0.03$).¹⁸ Gutierrez CAK found that high leptin levels were associated with the radiographic osteofit OA radiographs in women compared with men. In this study found that higher leptin levels were associated with an increased risk of knee OA in women but not the same in men. Differences in sex to leptin may also be related to differences in levels of sex steroid hormone metabolism between men and women. The presence of higher estrogen levels in women (even menopausal women), where estrogen has been shown to induce leptin secretion in women. Further studies, in male rats exposed to exogenous estrogens have increased sensitivity to leptin.¹⁹

Koskinen A et al assessed the levels of resistin in joint fluid and explore the relationships with degree of inflammation in 88 subjects with knee

OA. It showed increasing levels of joint fluid resistin (627.5) % and a positive correlation with levels IL-6 ($r = 0.39$, $p < 0,000$), MMP-1 ($r = 0.31$, $p = 0.004$) and MMP-3 ($r = 0.24$, $p = 0.024$).²⁰ Kaser et al showed that expression of resistin gene was increased in PBMCs cells due to stimulation of proinflammatory cytokines IL-1, IL-6 and TNF- α .

The degree of joint damage according to Kellgren-Lawrence is based on the narrowing of the joint gap, the formation of osteophytes due to growth factor TGF- β (TGF- β 1). Davidson et al mentioned that TGF- β induced the formation of osteophytes. [21]

In the study of Scartuhl et al in OA TMJ, TGF- β levels of TMJ joint fluid increased ($p < 0.000$), also in the study of Yang et al, in animal OA obtained by increasing TGF- β 1 ($p < 0,000$). Yang noted that administration of TGF- β 1 induces pathological effects associated with OA and osteophyte formation.

CONCLUSION

There was moderate correlation among leptin, resistin, TGF- β level and the severity grade of OA in male and female patients. It was strong correlation among leptin, resistin, TGF- β level in sinovial and the severity grade of OA Kellgren-Lawrence in female patients.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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