Adiponectin and Leptin Synovial Fluid Concentration as a Marker for the Severity of Knee Osteoarthritis in Obese Patients

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Obez Hastalarda Diz Osteoartrit Şiddetinin Göstergesi Olarak Sinoviyal Sıvıda Adinopektin ve Leptin Konsantrasyonu

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ABSTRACT

Purpose: Osteoarthritis (OA) is a chronic degenerative joint disorder of the synovial joint characterized by loss of articular cartilage, osteophyte formation, and alterations of subchondral bone. An increase of weight bearing affect on knee joint biomechanically and alter concentration of adipokines, such as adiponectin and leptin. Herein we reported a correlation between adiponectin and leptin synovial fluid concentration with the severity of knee OA in obese patients.

Material and Methods: Totally 45 patients were included in this research. ELISA was used to determine adiponectin and leptin concentrations of synovial fluid. The severity of knee OA was classified by Kellgren-Lawrence grading scale. Data analysis was conducted using SPSS for windows.

Results: Based on the leptin measurement, it was shown that leptin concentrations were correlated positively with the severity of knee OA. Vice versa, adiponectin concentrations were correlated negative.

Conclusion: Our study was support the biomarker function of adiponectin and leptin concentration on synovial fluids, in which those concentrations were related with the severity of OA. Those results also suggested the function of leptin and adiponectin on OA.

Key words: Adiponectin; Knee osteoarthritis; Kellgren-Lawrence; Leptin; Obese.

ÖZET

Amaç: Osteoartrit (OA), eklem kıkırdak kaybı,osteofit oluşumu ve kıkırdak altındaki kemikte meydana gelen değişimlerle karakterize edilen, oynar eklemin kronik dejeneratif eklem hastalığıdır. Vücut ağırlığının artması, diz eklemlerini biyokimyasal olarak etkiler, adiponektin ve leptin gibi adipokinlerin konsantrasyonunu değiştirir. Bu çalışmada obez hastalarda, adiponektin ve leptin sinoviyal sıvı konsantrasyonu ile diz osteoartrit şiddeti arasında korelasyon saptanmıştır.

Materyal ve Metod: Çalışmaya 45 hasta dahil edilmiştir. Sinoviyal sıvıda adiponektin ve leptin konsantrasyonlarının saptanmasında ELISA kullanılmıştır. Diz OA'sının şiddeti Kellgren-Lawrence derecelendirmesi ile yapılmıştır. Data analizleri SPSS ile yapılmıştır.

Bulgular: Leptin ölçümlerine göre, leptin konsantrasyonları diz OA'sının şiddeti ile pozitif korelasyon göstermektedir. Bunun aksine adiponektin konsantrasyonları negatif korelasyon göstermektedir.

Sonuç: Bu çalışma, OA'nın şiddeti ile sinovial sıvıdaki adiponektin ve leptin konsantrasyonları arasında bir ilişki olduğundan, adiponektin ve leptinin biomarker fonksiyonuna sahip olduğunu desteklemektedir. Sonuçlar aynı zamanda leptin ve adiponektinin OA üzerinde fonksiyonu olduğunu göstermektedir.
Anahtar Kelimeler: Adiponektin; diz osteoartriti; Kellgren-Lawrence; Leptin; Obez.

INTRODUCTION

Osteoarthritis (OA) is an arthropathy with chronic, degenerative and inflammatory characteristics that influence in all joints structure (hyaline cartilage, subchondral bone, and synovial membrane). Each synovial joints could developed become OA with one of the most cases is knee joint. There are two OA group, primary and secondary OA. Primary OA has an idiopathic characteristics, whereas secondary OA characterized by the presence of varying metabolic aberration, immunologic-inflammatory event, and mechanical factors including obesity[1,2].

One of the main cause for pain and disablement especially elderly around the world is OA. In USA, OA was experienced by more than 20 million people and 10% adults over 50 years old. Almost 10% of Europe population with aged 65 years old or more showed an evidence of OA radiographic and half of those numbers are symptomatic3-8. In Indonesia, prevalence of knee OA which is diagnose with radiographic were 15.5% on male and 12.7% on female aged between 40-60 years old. In addition, several researches conducted at different places in Indonesia showed the higher percentage of OA was happened in female and most of patients have body mass index (BMI) ≥ 23[9].

Increasing of body weight is related with the higher risk of OA and vice versa. Every one unit increasing of BMI, it will also increase the risk of knee OA around 15%. Obesity is one of risk factor in OA, where there is an enhancement of joint burden biomechanically and enrichment of adipokines that produced by adipocytes cells such as leptin, adiponectin, resistin and visfatin 10,13. Adipokines is triggering the pleiotropy event through several pathways and in a large spectrum activities, in which it also modulated the immune responses and inflammatory. Therefore, it could seen as central point that correlated between obesity, inflammation and arthritis. In recent days, obesity is seen as low level chronic inflammatory condition that closely related with releasing several compound by white adipose tissue (WAT) and in turn plays an important role in OA development[14-17].

Several researches was showed a relation between leptin and adiponectin on OA. Leptin is a cytokine-like hormone that form from unglycosylated peptides with molecular weight 16kDa and consist of 167 amino acids. Leptin is mainly produce in adipocyte cells of WAT by Ob/Lep gene[13]. Whereas, Adiponectin is an adipokines member that have biggest proportion compared to others adipokines in our body. Different from leptin that in several cases shown a positive correlation with the pathogenesis and progressivity of OA and suggested act as pro-inflammatory[12,13,18-20], the effect of adiponectin on OA event still unclear, whether it correlated positively[21-26] or negatively[27-30]. Herein we reported correlation between adiponectin and leptin synovial fluid concentration with the severity of knee OA in obese patients.

MATERIALS and METHODS

Patients

The research was done during April 2013 – February 2014. All patients were obtained from outpatients of Internal Medicine Polyclinic Mohammad Hoesin Hospital Palembang. The OA criteria based on American College of Rheumatology (ACR) year 2000 inform of knee pain with osteofit plus one of three criteria age over 40 years; joint stiffness in the morning less than 30 minutes; and crepitus on active motion. Besides that other additional criteria were used for inclusion criteria such as outpatients aged ≥ 40 years old

with synovial fluid that could be aspirated; patients with knee OA level 1-3 based on Kellgren-Lawrence; patients with obese I based on WHO criteria for Asia regions (BMI 25-29.9 kg/m^2); and willing to follow the study by signing an informed consent form. A criteria for exclusion criteria were used in this research such as patients who have got surgery on the knee joint; patients who have ever got articular intra injection with steroids or other injections on knee joint in the last three months; patients with steroid therapy in the last14 days; patients with chronic diseases like diabetes mellitus and chronic renal disease; and other knee disease. BMI, VAS and demographic information was collected by OA Research Team of Mohammad Hoesin Hospital Palembang. OA was graded from radiology appearance by radiologist from the hospital.

Sample Preparation

Synovial fluids were taken from all patients that included in this research. Aspiration of synovial fluid was done by a rheumatologist. Prior to aspiration, Ultrasonography (USG) of musculoskeletal was performed to determine the point of aspiration and the existence of synovial fluid. Then, septic-aseptic with disinfectant (such as alcohol 70%) was conducted and aspiration was taken using 3cc spuit. Before it used, samples were kept in -70^{0}C. Point of aspiration was covered with sterile gauze and gives some medicine.

Leptin and Adiponectin Measurement

Leptin and adiponectin were measured from synovial fluid of 45 patients after obtaining informed consent. Synovial fluids that used for leptin and adiponectin measurement were prepared based on previous study with some modifications [31,32]. Enzyme-linked immunosorbent assay (ELISA: Prodia Clinical Laboratory) method was conducted for those measurements.

Statistical analysis

Data analysis and processing was done using SPSS for windows. Bivariate analysis was performed to calculate the correlation between leptin or adiponectin concentration of synovial fluids with the severity of OA. Those statistical analyses were Kruskal-Wallis for relation between demographic characteristics and degree of severity; unpaired t-test for relation between adiponectin concentration and sex; Mann Whitney test for relation between leptin concentration and sex; and Spearman's Rho test for relation between adiponectin or leptin with synovial fluid concentration and degree of severity. All test were used significant difference $p<0.05$. All data was shown as an average and median of measurements.

Ethic

This research has been certified by ethic committee of Medical Faculty, Sriwijaya University, Palembang, South Sumatera, Indonesia.

RESULTS

Totally 45 patients (29 female and 16 male patients) were passed the selection criteria and included in this study. Kellgren-Lawrence criteria (Table 1) were performed to determine the severity level of knee OA. Based on those criteria, 32 patients (71.11%) consist of 20 females (44.44%) and 12 males (26.68%) was grouped in level 3 (Figure 1). Based on sex, males and females, the higher percentages of patients were aged between 60-69 years old with number of patients were 7 (15.6%) and 12 (26.6%) respectively (Table 2). Furthermore, the severity level from all of those patients was grouped in level 3 (Table 3). All patients were included in obese type I with median value of BMI 26.99 and based on visual analogue scale (VAS) value almost all patients (33 patients, 73.3%) were experienced moderate pain (Table 3).

Adiponectin measurement of synovial fluid showed that the average concentration on females (1429.5±853 ng/mL) were significantly higher compare to male patients (905.99±477.86 ng/mL) (Table 4). Based on the degree of severity (Table 5), the highest concentration of adiponectin was found on OA patients with level 2 severity (1693.4±914.75 ng/mL). Analysis result using Spearman's Rho showed that there was a significantly negative correlation between adiponectin concentrations of synovial fluid with the degree of severity on OA patients. In addition, based on sex, although the negative correlation was not significant on male, but it was significant on female.

Almost similar result was showed in leptin synovial fluids measurement (Table 6), in which median value of leptin concentrations on female patients (24189 ng/mL) were significantly higher than male (7289 ng/mL). Different from adiponectin result, based on the degree of severity (Table 7), the highest concentration of leptin was found on OA patients with level 3 severity (22921 ng/mL). Using the same test, Spearman's Rho, we also analyse the correlation between leptin concentration and the severity degree of OA patients. The result showed that there was a significantly positive correlation between leptin and degree of severity. Furthermore, based on sex, positive correlation was not significant on male, whereas on female, it was significant. Those results were similar with adiponectin correlation test.

Table 1. Severity degree of knee OA based on Kellgren-Lawrence criteria

Level	Criteria
0	Normal
1	Narrowing of joint gap is unclear and osteophytes possibly exist
2	Osteophytes is clear and also accompanied with narrowing of joint gap
3	Osteophytes multiple-moderate and accompanied with clear narrowing of joint gap; usually sclerosis also found and deformity of bone contour
4	Large osteophyte and marked with narrowing of joint gap, severe sclerosis and also clearly found deformity of bone contour

Table 2. General characteristics of all patients based on sex

Characteristics	Total	Sex	
	(n=45)	Male	Female
		(n=16)	(n=29)
Age (years)	56.76 ± 8.42a	56.94 ± 9.99a	56.52 ± 7.61a
Grouping based on age (years)			
40 – 49	10 (22.2%)	5 (11.1%)	5 (11.1%)
50 – 59	13 (28.9%)	2 (4.4%)	11 (24.5%)
60 – 69	19 (42.2%)	7 (15.6%)	12 (26.6%)
≥ 70	3 (6.7%)	2 (4.4%)	1 (2.2%)
Grouping based on education			
Elementary School	12 (26.7%)	4 (8.9%)	8 (17.8%)
Junior High School	4 (8.9%)	1 (2.2%)	3 (6.7%)
Senior High School	22 (48.9%)	6 (13.3%)	16 (35.6%)

College	7 (15.6%)	5 (11.1%)	2 (4.4%)
Grouping based on jobs			
Housewife	19 (42.2%)	0	19 (42.2%)
Public Servant	9 (20.0%)	4 (8.9%)	5 (11.1%)
Private sectors	10 (22.3%)	7 (15.6%)	3 (6.7%)
Labor	2 (4.4%)	2 (4.4%)	0
Farmer	5 (11.1%)	3 (6.7%)	2 (4.4%)

a Average ± SD

Table 3. Distribution of all patients based on severity degree of knee OA

Characteristics	**Total**	**Severity degree of knee OA (Kellgren-Lawrence)**		
	(n=45)	**Level 1**	**Level 2**	**Level 3**
		(n=3)	**(n=10)**	**(n=32)**
• Gender				
• 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%)
Aged (years)	56.76 ± 8.42a	45.00 ± 4.58a	50.00 ± 3.43a	59.84 ± 7.62a
Grouping based on age (years)				
• 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%)
• ≥ 70	3 (6.7%)	0	0	3 (6.7%)
Grouping based on jobs				
• Housewife	19 (42.2%)	0	5 (11.1%)	14(31.1%)
• Public servant	9 (20.0%)	2(4.4%)	1 (2.2%)	6 (13.3%)
• Private sectors	10 (22.2%)	1 (2.2%)	3 (6.7%)	6 (13.3%)
• Labor	2 (4.4%)	0	1 (2.2%)	1 (2.2%)
• Farmer	5 (11.1%)	0	0	5 (11.1%)
BMI (Kg/m2)*	26.9 (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	26.81 (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
VAS				
• Mild	1 (2.2%)	1 (2.2%)	0	0
• Moderate	33(73.3%)	2 (4.4%)	8 (17.8%)	23 (51.1%)
• Severe	11(20.0%)	0	2 (4.4%)	9 (20.0%)

[a] Average ± SD, [b]Median (min – max), *Kruskal-Wallis test p= 0.916; ** Kruskal-Wallis test p=0.438; *** Kruskal-Wallis test p= 0.539 (significantly difference if p < 0.05).

Table 4. Distribution of adiponectin concentration on synovial fluids based on sex

Sex	N	Adiponectin Concentration (ng/mL)	p*
		Mean ± SD	
Male	16	905.99 ± 477.86	0.000
Female	29	1429.50 ± 853.00	
Total	45	1243.40 ± 777.80	

* Unpaired t test (significantly difference if p < 0,05)

Table 5. Correlation between adiponectin concentration of synovial fluids and severity degree of knee OA

Sex	Total	Severity Degree of Knee OA (Kellgren-Lawrence)				
	(n=45)	Level 1 (n=3)	Level 2 (n=10)	Level 3 (n=32)	r*	p*
Total						
Mean	1243.40 ± 777.80	1445.90 ± 642.73	1692.40 ± 914.75	1084.10 ± 702.91	-0.30	0.04
Median	996.80 (368.40 – 3134.40)	1249.8 (924.00 – 2163.00)	1551.00 (914.75 – 3134.40)	958.00 (368.40 – 2692.00)		
Male						
Mean	905.99 ± 477.87	1543.90 ± 876.67	706.90 ± 420.02	832,86 ± 372,10	-0.14	0.62
Median	955.75 (368.40 – 2163.80)	1543.90 (924.00 – 2163.80)	706.90 (409.90 – 1003.90)	817.00 (368.40 – 1389.30)		
Female						
Mean	1429.50 ± 853.00	1249.80	1938.7 ± 838.94	1243.80 ± 813.75	-0.28	0.14
Median	1249.8 (378.00 – 3134.40)	(n = 1)	1862.00 (950.40 – 3134.40)	958.00 (278.00 – 2692.00)		

*Spearman's Rho test (significantly difference if p < 0.05). r = 0: no correlation; r > 0-0.25: weak correlation; r > 0.25-0.5: moderate correlation, r > 0.5-0.75: strong correlation; r > 0,75-0,99: very strong correlation; r = 1: perfect correlation

Table 6. Distribution of leptin concentration on synovial fluids based on sex

Characteristics	Total	Sex		
	(n=45)	Male	Female	p**
		(n=16)	(n=29)	
Leptin (ng/mL)	18831.1 (4314.5-31861.9)*	7286.1 (4314.5-31324.0)*	24189 (4491.1-31861.9)*	0.011

*Median (min – max),**Mann Whitney test (significantly difference if p < 0.05)

Table 7. Correlation between leptin concentration of synovial fluids and severity degree of knee OA

Characteristic	Total	Severity Degree of Knee OA (Kellgren-Lawrence)				
	(n=45)	Level 1	Level 2	Level 3	r*	p*
		(n=3)	(n=10)	(n=32)		
Leptin (ng/ml)	18831.1 (4314.5-31861.9)	4595.2 (4553.6-6477.7)	10010 (4314.5-31861.9)	22921 (4491.1-31324.0)	0.37	0.012
Sex						
Male	7286.1 (4314.5-31324.0)	5515.6 (4553.6-6477.7)	4533.1 (4314.5-4751.7)	7774.0 (5244.2-31324.0)	0.25	0.33
Female	24189 (4491.1-31861.9)	4595.2 (4595.2-4595.2)	15.681 (4803.9-31861.9)	24650 (4491.1-31270.5)	0.54	0.003

*Spearman's Rho test (significantly difference if p < 0.05). r = 0: no correlation; r > 0-0.25: weak correlation; r > 0.25-0.5: moderate correlation, r > 0.5-0.75: strong correlation; r > 0,75-0,99: very strong correlation; r = 1: perfect correlation

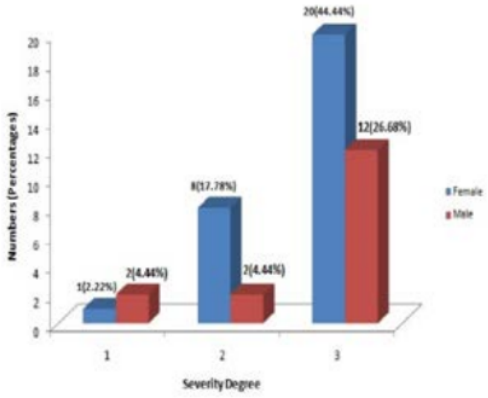

Figure 1. Distribution of severity degree from all patients based on Kellgren-Lawrence criteria. Kellgren-Lawrence criteria were used to determine the degree of severity from all patients. Patients were grouped in level 1-3 of severity degree. Most of patients, male and female, were included in level 3 severity.

DISCUSSION

Based on sex, patients that included in our research were dominated by female patients with 29 patients (64.4%) from total 45 patients. The increasing of OA prevalence drastically in female population especially after menopause was related with the hormonal factors. Metabolite compound of estrogen plays an important role on arachidonic acid metabolism, a compound for synthesize of leukotriene pro-inflammatory, that in turn could caused an inflammation and pain at OA.

Furthermore, the higher fat proportion in females also plays a specific role. Adipose tissue produces several kind of adipokines that suggested involve in OA. At certain degree of BMI, in general, females have higher body fat proportion compare to males. In which, those fats are mainly spread in subcutaneous regions[33-37].

In general, our research showed that adiponectin concentration was significantly high in females than in males. This result was in line with previous study by Pottie et al. [35], in which adiponectin concentration of synovial fluids was high in female OA (n=20) compare to male OA (n=15), although not significantly difference. Other study by Tsu-Hsin et al. [38] also reported the same result. The lower concentration of adiponectin in males was caused possibly by the hormonal effect that proved using a in vitro method, wherein testosterone could decreasing adiponectin secretion on adiposite culture media[39].

Correlation test using Spearman's Rho showed a significantly negative correlation between adiponectin concentration of synovial fluids and severity degree of knee OA. Similar result was reported in several previous studies, suggested that adiponectin plays an important role as protective agent of joint cartilage and on pathophysiology of OA[17,40]. During the development of OA, progressive degradation of joint cartilage is causing a joint dysfunctions, disablement and pain. Erosion of joint cartilage matrix was resulted from local imbalance between proteinase content and their inhibitors. Major enzyme that involved in matrix catabolism is MMPs, in which most of the activities are inhibited by TIMPs[21,38,41]. Ryo et al.[42] reported that adiponectin has an ability to increase the expression of TIMP-1 through IL-10 induction on human macrophages. Other study by Tsu-Hsin et al.[38] showed that pre-treatment of primary chondrocytes with adiponectin could elevated regulation of TIMP-2 and partially dismiss the expression of MMP-13. Those result suggested that adiponectin possibly involve in homeostasis maintenance between MMPs and TIMPs. Furthermore, adiponectin also have shown several anti-inflammatory activity [38,39].

Leptin measurement analysis also showed similar result compare with adiponectin measurement. Median value of leptin concentration on females was significantly high compare to the male patients. This result was in line with several other studies related with leptin measurement in OA patients [20,43-45]. Gutierrez [20] suggested that high leptin concentration on females is caused by estrogen that stimulated the elevation of leptin secretion. Besides that, several studies also expect that the difference in leptin concentration was caused by body fat proportion in females higher than in males [20,44,45].

In this study, result of Spearman's Rho test of leptin showed a significantly positive correlation between leptin concentration and the severity degree in knee OA. Previous study by Ku[19] and Schmidt et al.[45] also showed a similar results. Those results suggested that leptin plays an important role as a pro-inflammatory cytokine. Together with IL-1 and IFN-γ, leptin could stimulate iNOS-II to forming NO, a major pro-inflamattory cytokine on joint cartilage. In addition, leptin also related with catabolism event through stimulation of compound that have function in cartilage degradation such as MMPs and ADAMTS (ADAMTS 4-5), thus in turn could damage the cartilage and develop OA[46].

In conclusion our study was support the biomarker function of adiponectin and leptin concentration on synovial fluids, in which those concentrations were related with the severity of OA. Generally, adiponectin was showed a significantly negative correlation with severity of OA, whereas leptin was showed a vice versa result. At least in part, our study also suggested the anti-inflammatory effects of adiponectin and pro-inflammatory effects of leptin in OA development. Further research are still needed to revealed the detail function and molecular mechanism of both adipokines in OA development,

since leptin and adiponectin actually also involved in anabolism and catabolism event of joint cartilage.

Conflict of interest

The authors report no conflicts of interest.

Abbreviations:

ADAMATS: Aggrecan cleavage by disintegrin and metalloproteinase with thrombospodin type 1 motif
BMI: Body Mass Index
ELISA: Enzyme-Linked Immunosorbent Assay
iNOS: inducible Nitric Oxide synthase
MMPs: Matrix Metalloproteinases
NO: Nitric Oxide
OA: Osteoarthritis
TIMPs: Tissue Inhibitor Metalloproteinases
USG: Ultrasonography
VAS: Visual Analogue Scale
WAT: White Adipose Tissue

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