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

Zeynep Kart Sahin, Recep Ulu Fartan, Muhammad Ratu, Saniullah Muhammad, Hammadah Hameyshan.

Abstract

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

Methods: Totally 45 patients were included in this research. ELSA was used to determine adiponectin and lepton 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 Kellgren-Lawrence grading scale, 3 patients were classified as grade 1, 10 patients were classified as grade 2, 13 patients were classified as grade 3, and 19 patients were classified as grade 4. In the obese patients, adiponectin and lepton synovial fluid concentration was significantly correlated with the severity of knee OA.

Conclusion: Our study was support the biomarker function of adiponectin and lepton concentration on synovial fluid, in which these concentrations were related with the severity of OA. These results also supposed the function of lepton and adiponectin on OA.

Key words: Adiponectin, Knee osteoarthritis, Kellgren-Lawrence, Lepton (Obes)

Obez Hastalarda Diz Osteoartriti Süzetinin Göstergesi Olarak Sinovyal Sıvıda Adiponectin ve Lepton Kontenansını


Anahat Kelimeler: Adiponectin; diz obezı; Kellgren-Lawrence; Lepton; Obez

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

Obez Hastalarda Diz Osteoartrit Şiddetinin Göstergesi Olarak Sinovyal Sıvıda Adiponectin ve Leptin Konsantrasyonu

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¹Dr. Mohammad Hoesin Central General Hospital, Medical Faculty, Division of Rheumatology, Department of Internal Medicine, Sriwijaya University, Palembang, South Sumatera, INDONESIA.


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. Hence 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 kayıbı, osteofit oluşumu ve kıkırdak altındaki kemikte meydana gelen değişikliklerde konsantre edilen, olay eklem Kronik Degeneratif eklem hastalığıdır. Vücut ağırlığının artması, eklemi bükülmesine neden olmaktadır, adipokinerin ve leptin gibi adipokinerin konsantrasyonuna değişimler. Bu çalışmada obez hastalarda, adiponeksin ve leptin sinovial sıvı konsantrasyonu ile diz osteoartrit şiddetinde korrelasyon sağlanmıştır.


Bulgular: Leptin ölçümlerine göre, leptin konsantrasyonları diz OA’sının şiddet ile pozitif korrelasyon göstermektedir. Bunun aksine adiponectinin konsantrasyonları negatif korrelasyon göstermektedir.
Adipokines and Leptin Synovial Fluid

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 joint 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 13.

One of the main cause for pain and disability 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. 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) ≥ 232.

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 plectropy 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 development14,17.

Several researches was showed a relation between leptin and adiponectin on OA. Leptin is a cytokine-like hormone that form from ungycosylated peptides with molecular weight 16kDa and consist of 187 amino acids. Leptin is mainly produce in adipocyte cells of WAT by Ob/Lep gene13. 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-inflammatory2,13,15,16,20 the effect of adiponectin on OA event still unclear, whether it correlated positively21,26 or negatively27,29. Herein we reported a 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 Hoesan Hospital Palembang. The OA criteria based on American College of Rheumatology (ACR) year 2000 inform of knee pain with osteoili 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/m²), 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 arthritic intra injection with steroids or
other injections on knee joint in the last three
months; patients with steroid therapy in the last 14
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°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 21,22. Enzyme-linked immunosorbent
assay (ELISA; Prodiol 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.

Ethnic
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 (26.66%) 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 (905.9±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 (7286.1 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

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Narrowing of joint gap is unclear and osteophytes possibly exist</td>
</tr>
<tr>
<td>2</td>
<td>Osteophytes is clear and also accompanied with narrowing of joint gap</td>
</tr>
<tr>
<td>3</td>
<td>Osteophytes multiple moderate and accompanied with clear narrowing of joint gap; usually sclerosis also found and deformity of bone contour</td>
</tr>
<tr>
<td>4</td>
<td>Large osteophyte and marked with narrowing of joint gap; severe sclerosis and also clearly found deformity of bone contour</td>
</tr>
</tbody>
</table>

Table 2. General characteristics of all patients based on sex

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n=45)</th>
<th>Sex Male(n=16)</th>
<th>Sex Female (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.76 ± 8.42</td>
<td>56.94 ± 9.99a</td>
<td>56.52 ± 7.61a</td>
</tr>
<tr>
<td>Grouping based on age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 – 49</td>
<td>19 (42.2%)</td>
<td>5 (11.1%)</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>50 – 69</td>
<td>13 (28.9%)</td>
<td>2 (4.4%)</td>
<td>11 (24.5%)</td>
</tr>
<tr>
<td>60 – 69</td>
<td>19 (42.2%)</td>
<td>7 (15.6%)</td>
<td>12 (26.6%)</td>
</tr>
<tr>
<td>≥ 70</td>
<td>3 (6.7%)</td>
<td>2 (4.4%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Grouping based on education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary School</td>
<td>12 (26.7%)</td>
<td>4 (8.9%)</td>
<td>8 (17.6%)</td>
</tr>
<tr>
<td>Junior High School</td>
<td>4 (8.9%)</td>
<td>1 (2.2%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Senior High School</td>
<td>22 (48.9%)</td>
<td>0 (13.3%)</td>
<td>16 (35.0%)</td>
</tr>
</tbody>
</table>
Table 3. Distribution of all patients based on severity degree of knee OA (Kellgren-Lawrence)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Severity degree of knee OA (Kellgren-Lawrence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=45)</td>
<td>Level 1</td>
</tr>
<tr>
<td></td>
<td>(n=2)</td>
<td>(n=10)</td>
</tr>
<tr>
<td>* Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Male</td>
<td>10(35.6%)</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>29(94.4%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>* Aged (years)</td>
<td>55.76 ± 8.42a</td>
<td>45.00 ± 4.68a</td>
</tr>
<tr>
<td>* Grouping based on age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* 40 - 49</td>
<td>10 (22.2%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>* 50 - 59</td>
<td>13 (28.9%)</td>
<td>0</td>
</tr>
<tr>
<td>* 60 - 69</td>
<td>19 (42.2%)</td>
<td>0</td>
</tr>
<tr>
<td>* ≥ 70</td>
<td>3 (6.7%)</td>
<td>0</td>
</tr>
<tr>
<td>* Grouping based on jobs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Housewife</td>
<td>19 (42.2%)</td>
<td>0</td>
</tr>
<tr>
<td>* Public servant</td>
<td>9 (20.0%)</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>* Private sectors</td>
<td>10 (22.2%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>* Labor</td>
<td>2 (4.4%)</td>
<td>0</td>
</tr>
<tr>
<td>* Farmer</td>
<td>5 (11.1%)</td>
<td>0</td>
</tr>
<tr>
<td>BMI (Kg/m2)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male**</td>
<td>29.99 (25.07-29.90)b</td>
<td>25.95 (25.52-27.46)b</td>
</tr>
<tr>
<td>Female***</td>
<td>25.50 (25.15-26.76)b</td>
<td>26.70 (25.95-27.46)b</td>
</tr>
<tr>
<td>VAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (2.2%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (6.7%)</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (2.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Average ± SD; **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

<table>
<thead>
<tr>
<th>Sex</th>
<th>N</th>
<th>Adiponectin Concentration (ng/mL)</th>
<th>(\bar{p})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>16</td>
<td>(605.90 \pm 47.86)</td>
<td>0.000</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>(1420.50 \pm 853.00)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>(1243.40 \pm 777.80)</td>
<td></td>
</tr>
</tbody>
</table>
* Unpaired t test (significantly different if \(p < 0.05\)

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

<table>
<thead>
<tr>
<th>Sex</th>
<th>Total</th>
<th>Severity Degree of Knee OA (Kellgren-Lawrence)</th>
<th>Level 1 (n=5)</th>
<th>Level 2 (n=10)</th>
<th>Level 3 (n=20)</th>
<th>(r^*)</th>
<th>(p^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Mean</td>
<td>1243.40 (\pm 777.80)</td>
<td>1445.90 (\pm 642.73)</td>
<td>1692.40 (\pm 914.75)</td>
<td>1044.10 (\pm 702.91)</td>
<td>-</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>905.90 (\pm 477.67)</td>
<td>1543.90 (\pm 876.67)</td>
<td>706.90 (\pm 420.20)</td>
<td>832.80 (\pm 372.10)</td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Female</td>
<td>Mean</td>
<td>1240.50 (\pm 853.00)</td>
<td>1240.80 (\pm 913.84)</td>
<td>1243.80 (\pm 813.75)</td>
<td>958.00 (\pm 292.09)</td>
<td>-</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>949.80 (\pm 550.40)</td>
<td>958.00 (\pm 3134.40)</td>
<td>958.00 (\pm 292.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
*Pearson's Rho test (significantly different if \(p < 0.05\)); \(r = 0\): no correlation; \(r > 0.25\): weak correlation; \(r > 0.50\): moderate correlation; \(r > 0.75\): strong correlation; \(r > 0.95\): very strong correlation; \(r = 1\): perfect correlation

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Sex</th>
<th>(\bar{p})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=45)</td>
<td>(n=15)</td>
<td>(n=29)</td>
<td></td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>1412.1</td>
<td>1412.1</td>
<td>0.011</td>
</tr>
<tr>
<td>(3.141.5-3.1861.9)</td>
<td>(3.141.5-3.132.4)</td>
<td>(3.141.5-3.1861.9)</td>
<td></td>
</tr>
</tbody>
</table>
*Median (min – max), **Mann Whitney test (significantly different if \(p < 0.05\)
### Table 7. Correlation between leptin concentration of synovial fluids and severity degree of knee OA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=45)</th>
<th>Level 1 (n=20)</th>
<th>Level 2 (n=35)</th>
<th>Level 3 (n=33)</th>
<th>( r^* )</th>
<th>( p^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin (ng/ml)</td>
<td>18631.1</td>
<td>4595.2</td>
<td>10010</td>
<td>22921</td>
<td>0.3</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>(4314.6-31861.9)</td>
<td>(4553.6-5477.7)</td>
<td>(4314.6-31861.9)</td>
<td>(4491.1-31324.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7286.1</td>
<td>5515.6</td>
<td>4933.1</td>
<td>7774.0</td>
<td>0.2</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>(4314.6-31324.0)</td>
<td>(4553.6-4751.7)</td>
<td>(4314.6-31861.9)</td>
<td>(4244.2-31324.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24189</td>
<td>4595.2</td>
<td>15681</td>
<td>24009</td>
<td>0.5</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>(4391.1-31861.9)</td>
<td>(4553.6-4751.7)</td>
<td>(4314.6-31861.9)</td>
<td>(4491.1-3170.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Spearmen’s Rho test (significantly difference if \( p < 0.05 \)). \( r = 0 \): no correlation; \( r \approx 0-0.25 \): weak correlation; \( r \approx 0.25-0.5 \): moderate correlation; \( r \approx 0.5-0.75 \): strong correlation; \( r \approx 0.75-0.99 \): 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 synthesis 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^{23,25,27}.

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=220) compare to male OA (n=16), although not significantly difference. Other study by Tsu-Hein et al.^{36} 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 adipose culture media^{37}.

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^{17,42}. During the development of OA, progressive degradation of joint cartilage is causing a joint dysfunctions, disabiement and pain. Erosion of joint cartilage matrix was resulted from local imbalance between protease content and their inhibitors. Major enzyme that involved in matrix catabolism is MMPs, in which most of the activities are inhibited by TIMPs^{27,36,41}. Ryo et al.^{43} reported that adiponectin has an ability to increase the expression of TIMP-1 through IL-10 induction on human macrophages. Other study by Tsu-Hein 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^{23,44,45}.

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^{35} and Schmidt et al.^{46} 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-y, leptin could stimulate iNOS-II to forming NO, a major pro-inflammatovery 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^{47}.

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:
ADAMTS: Aggrecan cleavage by disintegrin and metalloproteinase with thrombospondin type 1 motif
BMI: Body Mass Index
ELISA: Enzyme-Linked Immunosorbent Assay
INOS: inducible Nitric Oxide synthase
MMPs: Matrix Metalloproteinases
NO: Nitric Oxide
UA: Urate Arthritis
TIMPs: Tissue Inhibitor Metalloproteinases
USG: Ultrasonography
VAS: Visual Analogue Scale
WAT: White Adipose Tissue

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