ORIGINAL ARTICLE

Correlation of Plasma and Synovial Fluid Adiponectin with Knee Osteoarthritis Severity

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Background and Aims. 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. The purposes of this study were to measure adiponectin concentrations in plasma and synovial fluid of patients with knee OA and to analyze the correlation of adiponectin levels with disease severity.

Methods. Seventy six OA patients (mean age 69.8 ± 1.1 years) and 24 healthy controls (mean age 71.2 ± 1.5 years) were enrolled in this study. OA grading was performed using the Kellgren-Lawrence (KL) criteria by evaluating x-ray changes observed in anteroposterior knee radiography. Adiponectin levels in plasma and synovial fluid were determined by commercial enzyme-linked immunosorbent assay.

Results. Plasma levels of adiponectin were higher in OA patients compared to healthy individuals, but the difference did not reach statistical significance (2428.0 ± 245.1 vs. 2030.3 ± 399.4 ng/mL, $p = 0.4$). Adiponectin levels in plasma were remarkably higher with regard to paired synovial fluid (2428.0 ± 245.1 vs. 301.3 ± 44.9 ng/mL, $p < 0.001$). Additionally, adiponectin concentrations in plasma and synovial fluid showed significant inverse correlation with disease severity evaluated by KL grading criteria ($r = -0.68$, $p < 0.001$ and $r = -0.47$, $p < 0.001$, respectively). Further analysis showed that plasma adiponectin levels positively correlated with synovial fluid adiponectin levels ($r = 0.71$, $p < 0.001$).

Conclusions. Adiponectin levels in both plasma and synovial fluid decreased significantly as the severity of OA increased. These findings suggested that adiponectin may play a protective role in OA. More studies are warranted to gain insight into the potential utility of adiponectin as a biochemical determinant of disease progression and prognosis.   © 2010 IMSS. Published by Elsevier Inc.

Key Words: Adiponectin, Body mass index, Disease severity, Osteoarthritis, Plasma, Synovial fluid.

Introduction

Osteoarthritis (OA) is a heterogeneous and multifactorial process of chronic degenerative joint disease with prominent features of articular cartilage destruction along with bone, muscle, ligament, and synovial involvement (1). It is epitomized pathologically by the loss of cartilage, subchondral bone sclerosis or cyst, and osteophyte formation. The develop-

ment of preventive or therapeutic strategies for OA seemingly depends on identification of pathophysiological mechanisms and biochemical markers that underlie progressive joint deterioration. To date, etiopathogenesis of OA is still unclear. Nevertheless, many potential factors have been apparently demonstrated the abilities to increase the risk of OA. Among these circumstances, obesity is undoubtedly of great importance.

Obesity is believed to play a deleterious role in osteoarthritis by the increment in mechanical stresses on joint tissues. According to recent studies (2,3), the effect of obesity on joint destruction in OA may be more complex than expected. After receiving pressure load, mechanoreceptors located on chondrocyte surface and osteoblasts stimulate

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intracellular signaling cascades (2). These activated pathways lead to the increased production of cytokines, prostaglandins, nitric oxide, and matrix metalloproteinases. Consequently, extracellular matrix synthesis is inhibited while cartilage destruction is promoted (3). However, the aforementioned mechanism cannot entirely explain the link between obesity and hand OA, which was evidently connected with body mass index (BMI) (4). Additionally, it was recently shown that the loss of body fat provided more beneficial effect than the loss of body weight, in terms of symptomatic relief (5). These findings implied that the correlation of obesity and OA may be the effect of substances released systemically by adipose tissues, such as adipokines.

Adiponectin, a 244 amino acid polypeptide, represents the highest proportion of all adipokines in the circulation. Adiponectin is structurally homologous to complement factor C1q and tumor necrosis factor-α (TNF-α) (6). It has been shown that adiponectin exerts the anti-inflammatory effect by reducing the release of pro-inflammatory cytokines, e.g., TNF-α and IL-6, and inducing the expression of anti-inflammatory cytokines (7–9). Furthermore, several studies have demonstrated that adiponectin possessed abilities to counteract insulin resistance, atherosclerosis, and inflammatory processes (6,7,10–12). However, whether adiponectin plays pro- or anti-inflammatory roles in joint disease pathogenesis is still the subject of debate. Recent data showed that adiponectin could be secreted by synovial fibroblasts, chondrocytes and infrapatellar fat pad in patients with OA and rheumatoid arthritis (RA), which led to the increased production of IL-6, IL-8, matrix metalloproteinase, and nitric oxide (13,14). These mediators promoted inflammation and joint destruction (7,10). In contrast, Chen et al. proposed that adiponectin may play a protective role in OA by inducing tissue inhibitor of metalloproteinase-2 expression and suppressing IL-1β-induced matrix metalloproteinase-13 production (15).

Recent studies demonstrated that various cytokines are related to clinical parameters of disease activity in knee OA and may play important parts in the pathogenesis of OA (16–19). Hence, we hypothesized that adiponectin in plasma and synovial fluid may be associated with disease severity in knee OA patients. In the present study we aimed to determine the correlation between plasma and synovial adiponectin concentrations and the radiographic disease severity in patients with knee OA in order to assess its role in OA pathophysiology.

Materials and Methods

Subjects

Seventy six patients (62 females and 14 males) diagnosed with knee OA according to the criteria of the American College of Rheumatology and 24 healthy volunteers with no clinical and radiological evidence of OA (19 females and 5 males) were enrolled in the present study. The present study was conducted in agreement with the guidelines of the Declaration of Helsinki. Written informed consent was received from every patient and healthy subject before participating in the study. This study was approved by the Institutional Review Board on Human Research of the Faculty of Medicine, Chulalongkorn University.

Knee X-ray was taken when each participant was standing on both legs with fully extended knee and the X-ray beam was centered at the level of the joint. Disease severity assessment was performed using the Kellgren and Lawrence (KL) grading system (20). Depending on changes observed in conventional weight-bearing antero-posterior radiographs of the affected knee in extension, OA was divided into five grades (0–4): grade 0 (normal findings), no X-ray changes; grade 1 (questionable), doubtful narrowing of joint space and possible osteophyte lipping; grade 2 (mild), definite osteophytes and possible joint space narrowing; grade 3 (moderate), multiple moderate osteophytes, definite narrowing of joint space, bone sclerosis and possible deformity of bone contour; grade 4 (severe), large osteophytes, marked joint space narrowing, severe sclerosis, and deformity of bone contour. OA patients were defined as having radiographic knee OA of KL grade ≥ 2 in at least one knee. Controls were defined as having neither radiographic hip OA nor knee OA as indicated by KL grades of 0 for both hips and both knees. The grading of the worst affected knee in each patient was used for data analysis.

Laboratory Methods

Following a 12-h overnight fast, venous blood samples were obtained from all participants, centrifuged, and stored immediately at $-80°C$ for later measurement. Synovial fluid was taken from the most affected knee during a total knee arthroplasty. The specimen was then centrifuged to remove cells and joint debris and stored at $-80°C$ until analysis.

Quantitative determination of adiponectin concentration in plasma and synovial fluid was performed using commercial enzyme-linked immunosorbent assay (ELISA) (Quantikine, R&D Systems, Minneapolis, MN). According to the manufacturer's instructions, 50 µL of recombinant human adiponectin standards, plasma, and synovial fluid samples were pipetted into each well, which was pre-coated with mouse monoclonal antibody specific for adiponectin globular domain. After incubating for 2 h at room temperature, every well was washed thoroughly four times with washing buffer. Then, 200 µL of a horseradish peroxidase-conjugated monoclonal antibody specific for adiponectin was added to each well and incubated for a further 2 h at room temperature. After four washes, substrate solution was pipetted into the wells and then the microplate was incubated for 30 min at room temperature with protection from light. Finally, the reaction was stopped by the stop solution and the color intensity was measured with

an automated microplate reader at 450 nm. Adiponectin concentration was determined by a standard optical density-concentration curve. Twofold serial dilutions of recombinant human adiponectin with a concentration of 3.9–250 ng/mL were used as standards. The manufacturer's reported precision was 2.5–4.7% (intra-assay) and 5.8–6.9% (inter-assay). The sensitivity of this assay was 0.246 ng/mL.

Statistical Analysis

Statistical analysis was performed using the statistical package for social sciences (SPSS) software, v.16.0 for Windows. Tests of normality and test of homogeneity of variances were used to analyze the subject's age, BMI, adiponectin concentration in the plasma and synovial fluid. When the populations from which the samples were normally or approximate normal distribution and the variances of the populations were equal, Student's *t*-test was performed to compare the means of two independent groups, and one-way analysis of variance (ANOVA) was used to compare the means of more than two independent groups. Comparisons between groups were made using Mann-Whitney U test (for two groups) or Kruskal-Wallis test (for more than two groups) when the variances were not equal among the groups. Correlations between plasma and synovial fluid adiponectin and disease severity or BMI were calculated using Pearson's correlation coefficient (*r*). Multinomial logistic regression models were performed to determine the association between plasma/synovial fluid adiponectin and OA severity by taking age, gender, and BMI as the covariates. Data were expressed as mean ± standard error; *p* values <0.05 were considered to be statistically significant for differences and correlations.

Results

Seventy six knee OA patients aged from 51–91 years and 24 healthy individuals aged from 53–83 years were enrolled in the present study. No statistically significant difference of age was observed between the OA patients and healthy controls (69.8 ± 1.1 vs. 71.2 ± 1.5 years, *p* = 0.5). Plasma and synovial fluid adiponectin concentrations of knee OA patients and plasma levels of healthy controls are shown in Figure 1. Adiponectin levels in plasma of OA patients were substantially higher with respect to paired synovial fluid samples (2428.0 ± 245.1 vs. 301.3 ± 44.9 ng/mL, *p* <0.001). Although the mean value of plasma adiponectin in OA patients was higher compared with that of healthy controls, the difference was not statistically significant (2428.0 ± 245.1 vs. 2030.3 ± 399.4 ng/mL, *p* = 0.4).

Table 1 summarizes the comparison of clinical characteristics of the study population. The proportion of females was greater in both OA patients and controls. However, there was no significant difference in BMI between OA patients and
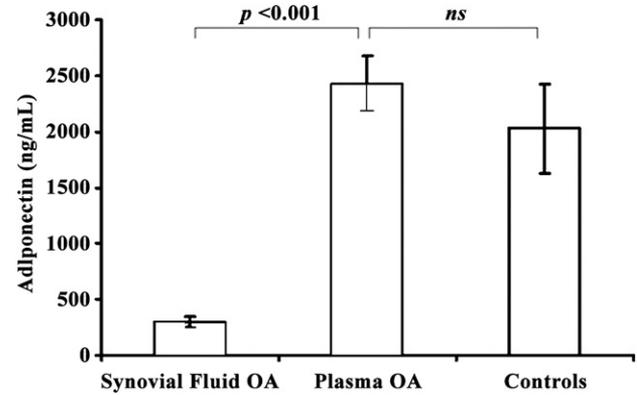
Figure 1. Adiponectin levels in plasma and synovial fluid of patients with osteoarthritis (OA) and healthy controls.

healthy controls (26.1 ± 0.6 vs. 25.5 ± 0.6 kg/m², *p* = 0.4). With regard to the radiological KL classification, patients were classified into three groups in relation to OA grading. Twenty two patients were categorized as grade 2, 27 as grade 3, and 27 as grade 4. The data revealed that knee OA patients with higher radiographic severity had significantly lower adiponectin levels in both plasma and synovial fluid (*p* = 0.001) (Table 2).

As demonstrated in Figure 2, plasma adiponectin levels in KL grade 4 were significantly lower than those of KL grade 2 and 3 (*p* <0.001) and controls (*p* = 0.04). Moreover, KL grade 2 had higher plasma adiponectin compared to KL grade 3 and controls (*p* <0.001). Notwithstanding that the mean plasma levels of adiponectin in KL grade 3 were more than those in the controls, the difference was not significant (*p* = 0.3). Furthermore, the synovial fluid adiponectin levels in KL grade 4 were markedly reduced compared with those of KL grade 2 and 3 (*p* <0.001) (Figure 3). The mean synovial fluid levels of adiponectin in KL grade 3 were significantly lower than those in KL grade 2 (*p* = 0.04).

In addition, the relationships between plasma and synovial fluid levels of adiponectin and the disease severity of OA were statistically evaluated. The plasma concentrations of adiponectin negatively correlated with knee OA severity (*r* = −0.68, *p* <0.001). Further analysis demonstrated that synovial fluid adiponectin levels of knee OA patients also inversely correlated with OA grading (*r* = −0.47, *p* <0.001). Adiponectin levels in plasma and synovial fluid

Table 1. Characteristics of knee OA patients and controls

	OA patients	Controls	*p*
n	76	24	
Age (years)	69.8 ± 1.1	71.2 ± 1.5	0.5
Gender (F/M)	62/14	19/5	0.5
BMI (kg/m²)	26.1 ± 0.6	25.5 ± 0.6	0.4

OA, osteoarthritis; BMI, body mass index.
Data expressed as mean ± SEM.

Table 2. Plasma and synovial fluid adiponectin in OA patients

	Total	KL grade 2	KL grade 3	KL grade 4	p
n	76	22	27	27	
SF adiponectin (ng/mL)	301.3 ± 44.9	566.1 ± 128.9	277.6 ± 40.2	109.4 ± 12.4	0.001
Plasma adiponectin (ng/mL)	2428.0 ± 245.1	4638.5 ± 525.0	2078.4 ± 194.1	976.5 ± 172.7	0.001

OA, osteoarthritis; SF, synovial fluid; KL, Kellgren and Lawrence.
Data are expressed as mean and SEM; p values for differences among KL subgroups.

displayed negative correlation with BMI ($r = -0.31$, $p = 0.03$ and $r = -0.48$, $p = 0.001$, respectively). Additionally, there was a significant positive correlation between plasma and synovial fluid adiponectin concentrations ($r = 0.71$, $p < 0.001$) (Figure 4).

As age, gender, and BMI can influence OA severity, we therefore performed multinomial logistic regression analyses to investigate the association between plasma/synovial fluid adiponectin and the severity of OA by taking age, gender, and BMI as the covariates. We observed no significant association between plasma adiponectin and the severity of OA ($p = 0.171$), whereas there was a negative association between synovial fluid adiponectin and OA severity after controlling of the influence of age, gender, and BMI ($p = 0.024$).

Discussion

OA is a common age-related joint disorder leading to pain, stiffness, reduced motion, swelling, crepitus, and disability. It is characterized by articular cartilage breakdown combined with bony outgrowth at joint margin and chronic nonspecific inflammation of synovium (1). Currently, a conventional method to examine the affected joint is radiological investigation, which reflects disease severity by grading the joint degeneration. Additionally, there are two main categories of biochemical markers presently studied as a promising indicator for OA. One includes components of extracellular matrix

of the involved joint; the other includes cytokines that metabolize the molecules of joint tissues (21). In spite of obscured pathogenesis, obesity is considered a major risk factor of OA. Obesity contributes to joint destruction not only by pressure overload, but also by various adipokines secreted from adipose tissues (2,3,7). In the present study we focused mainly on adiponectin.

Adiponectin is a polypeptide that assembles into complexes of different sizes, namely, trimers (low molecular weight), hexamers (middle molecular weight), and higher order oligomeric structures (high molecular weight) (22). Adiponectin shows the association with lifestyle and plays a critical aspect in the development of metabolic diseases such as diabetes mellitus and coronary heart disease (23). Although adiponectin may act as an anti-inflammatory mediator in many conditions, its role in joint diseases is still controversial.

Our data showed that plasma adiponectin positively correlated with synovial fluid adiponectin; however, adiponectin concentrations in plasma were remarkably higher than those observed in paired synovial fluid samples. Our result was in accord with previous studies in OA and RA (6,15,24,25). These findings implied that adiponectin was released from extra-articular tissues and peripheral fat stores into a systemic circulation and entered the joint through synovial membrane. The reason for lower levels of adiponectin in synovial fluid may be the limited transport of adiponectin across the synovial membrane barrier due to its molecular weight and complex structure. The major
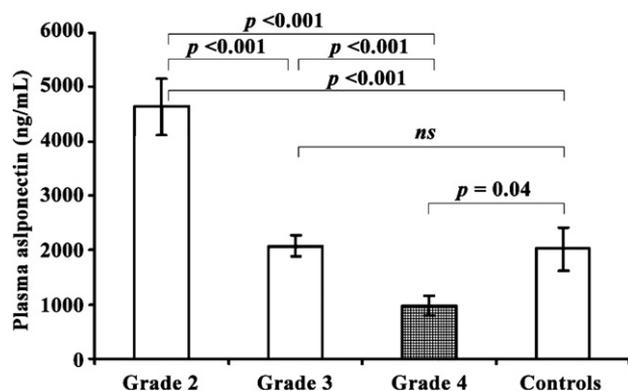
Figure 2. Comparison of plasma adiponectin levels in patients with OA classified according to Kellgren and Lawrence grading scale and healthy controls.
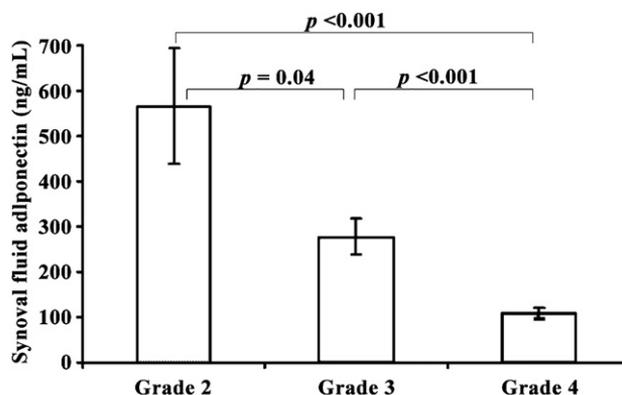
Figure 3. Comparison of synovial fluid adiponectin levels in patients with OA classified according to Kellgren and Lawrence grading scale.
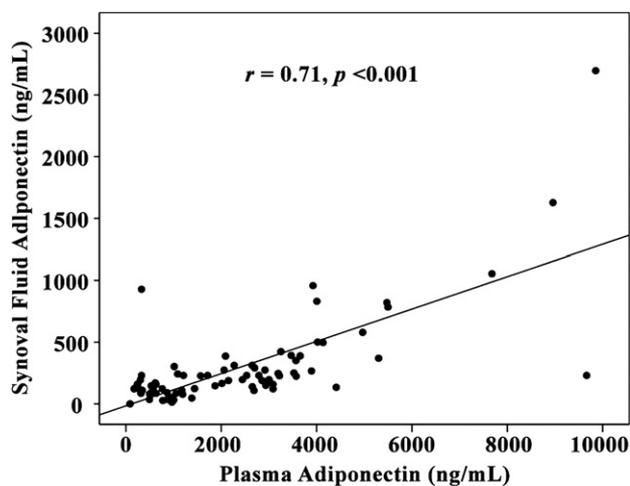
Figure 4. Scattergram showing the positive correlation between plasma and synovial fluid adiponectin concentrations ($r = 0.71$, $p < 0.001$).

source of synovial adiponectin could be derived from the local tissues within the affected joint such as synovium, articular cartilage, and infrapatellar fat pad (7,24). Alternatively, it is possibly attributed to the increased adiponectin destruction, which exceeded its production, in the inflamed joints (24).

This study reported that the controls had lower plasma adiponectin than patients with mild knee OA (KL grade 2), but exhibited higher plasma adiponectin compared to those with severe knee OA (KL grade 4). The reason why the controls had such a low mean adiponectin level is still not entirely clear. It may be due to lower amounts of peripheral fat stores, which secrete less adiponectin into the blood circulation of the controls. Additionally, hormonal, metabolic, and environmental factors may be associated with decreased adiponectin. Nevertheless, our study did not allow for specific identification of the exact mechanism of this observation.

We also found a significant negative correlation between plasma and synovial fluid adiponectin concentrations and OA grading. A similar finding has been observed in the study by Chen et al. (15). Data in RA research demonstrated that plasma and synovial fluid adiponectin levels tended to be higher in RA compared with OA (6,25). However, the negative correlation between adiponectin levels and disease severity appeared to be the same in some studies (6,26). This trend may be explained by the protective role of adiponectin in OA as an anti-inflammatory mediator. Deficiency of adiponectin either in the joint or in the circulation may promote inflammation and joint destruction. Thus, patients with low adiponectin concentrations may be exposed to a higher risk of more severe disease.

On the contrary, Filkova and co-workers revealed that serum adiponectin was higher in patients with erosive OA compared to non-erosive counterparts (27). This finding was in accordance with that of Olczyk-Wrochna et al.,

which demonstrated a positive correlation between adiponectin levels and disease duration in OA patients (28). Possible speculation of these results may be the attempt of the body to counteract destructive processes in OA by increasing adiponectin production. The explanation for these conflicting data is unclear but may be attributable to differences in disease advancement, populations or assays applied, or incomplete control for confounding variables.

In the present study we found a negative correlation between plasma adiponectin levels and BMI. This result could cast some light on the relationship of adiponectin and obesity in the initiation and progression of osteoarthritis. Nonetheless, there was also a significant inverse correlation between synovial fluid adiponectin concentrations and BMI. These findings suggest that adiponectin may provide a metabolic link with obesity in OA.

It should be mentioned, however, that the current study inevitably has some limitations. First, because this was an association study, it did not establish the causal relationships between adiponectin, obesity, and the presence of OA. Secondly, we did not determine functional impairment and pain in these patients. More studies are needed to examine whether adiponectin correlates with functional impairment (WOMAC or Lequesne score) and/or pain (visual analogue scale). Thirdly, insufficient assessment of potential confounders such as age, gender, medical comorbidities, and body habitus (waist circumference) need to be taken into account. However, our study provides evidence for the role of adiponectin in the development and severity of knee OA. Prospective longitudinal investigations are warranted to demonstrate disease progression and define the precise role of adiponectin in knee OA. Finally, we mainly measured adiponectin levels in plasma and synovial fluid, but not its expression in the intra-articular tissues. Therefore, additional prospective studies on tissue adiponectin expression are essential to elucidate the pathogenic mechanisms of adiponectin in OA.

In conclusion, adiponectin concentrations in plasma were significantly higher than those in synovial fluid. Plasma and synovial fluid adiponectin levels were shown to be inversely associated with disease severity in OA patients. These findings supported the hypothesis that portrayed adiponectin as a protective factor in OA. More longitudinal studies are required to gain insight into the potential utility of adiponectin as a biochemical determinant of disease progression and prognosis. However, different complex of adiponectin may act differently in the pathogenesis of OA. Further investigations with differential function of each isoform of adiponectin may be needed to confirm the exact role of adiponectin in OA.

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