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Original Article

Association between Circulating Adiponectin Levels and Osteoarthritis: A Meta-analysis

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Objective. The aim of this study was to analyze the relationship between the circulating adiponectin levels and osteoarthritis (OA). **Methods.** Meta-analysis was conducted on the serum/plasma adiponectin levels in patients with OA and controls, and subgroup analysis was performed based on ethnicity, sex, OA site, and adjustment for age, sex, and/or body mass index (BMI). **Results.** Seven studies with eleven comparisons including 538 patients with OA and 366 controls were selected, which showed that the adiponectin levels were significantly higher in the OA group than in controls (standardized mean difference [SMD] = 0.745, 95% confidence interval [CI] = 0.316 ~ 1.174, p = 0.001). Stratification according to ethnicity showed significantly elevated adiponectin levels in Caucasian individuals with OA (SMD = 0.769, 95% CI = 0.218 ~ 1.319, p = 0.006). Stratification according to sex revealed significantly higher adiponectin levels in women with OA, but not in men (SMD = 0.861, 95% CI = 0.099 ~ 1.623, p = 0.027; SMD = 1.177, 95% CI = −0.911 ~ 3.316, p = 0.281). Stratification by an adjustment for age, sex, or BMI showed significantly higher adiponectin levels in the OA group (SMD = 0.837, 95% CI = 0.326 ~ 1.349, p = 0.001). Stratification according to the OA site showed significantly higher adiponectin levels in patients with knee OA (SMD = 0.938, 95% CI = 0.456 ~ 1.419, p < 0.001). **Conclusion.** The significantly higher levels of circulating adiponectin in patients with OA than in healthy controls indicates that adiponectin likely plays a role in the pathogenesis of OA. **(J Rheum Dis 2018;25:231-238)**

Key Words. Osteoarthritis, Adiponectin

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, and it primarily affects the knees, hips, hands, and spine [1]. OA is characterized by progressive degeneration of articular cartilage, along with joint pain, deformity, and disability. Although the etiology of OA remains unknown, it has been established that OA is a multifactorial process, and that environmental factors such as obesity, sex, age, mechanical stress, and joint trauma contribute to its pathogenesis [1].

It has been known that there is a correlation between OA and inflammatory mediators, and inflammation plays a key role in the pathogenesis of OA [2]. Adipose tissues form an endocrine organ that helps regulate immune processes and inflammation by secreting bioactive mediators called adipokines [3]. Adipokines including adiponectin are synthesized in the adipose tissue and have been reported to play important roles in the pathogenesis of inflammatory or metabolic diseases [3]. Adiponectin, the most abundant adipokine, is a 30-kDa plasma protein that is produced mainly by adipocytes/macrophages, and functions as an inflammatory and anti-inflammatory agent [4]. Adiponectin has catabolic and anabolic effects, as well as proinflammatory effects on various cells of the immune system [5]. It can increase the production of interleukin (IL)-6 and metalloproteinases (MMPs) from endothelial cells, monocytic cells, and synovial fibroblasts [6]. On one hand, adiponectin may disrupt cartilage homeostasis through inducing joint structural degra-

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dation or controlling inflammatory processes. On the other hand, it is also involved in the modulation of inflammatory responses [7].

Although adiponectin exerts inflammatory and anti-inflammatory functions, its role in the pathogenesis of OA still remains unclear. Studies on the status of circulating adiponectin in patients with OA compared to that in healthy controls have shown mixed results [8-14]. These disparities are probably caused by small sample sizes, low statistical power, and/or clinical heterogeneity; therefore, to overcome the limitations of individual studies and resolve inconsistencies, we conducted a meta-analysis. The present study aimed to determine serum/plasma adiponectin levels in patients with OA compared to those in healthy controls by using a meta-analytic approach.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a literature search for studies that examined adiponectin levels in patients with OA, and controls. MEDLINE, Embase, and Cochrane library databases were searched to identify all available past articles (up to August 2017). The following keywords and subject terms were used in the search: "adiponectin" and "osteoarthritis." All references cited were also reviewed to identify additional studies that were not covered by the above-mentioned electronic databases. Studies were considered eligible if they (1) were case-control, cross-sectional, or cohort studies and (2) provided data on serum/plasma adiponectin levels in OA and control groups. No language or race restrictions were applied. Studies were excluded if they (1) contained overlapping or insufficient data or (2) were reviews or case reports. The following information was extracted from each study: primary author, year of publication, country, ethnicity, number of participants, OA site, sample type, and the mean and standard deviation (SD) of adiponectin levels. Data on methods and results were extracted from original studies by two independent reviewers. Any discrepancies between reviewers were resolved by consensus, and the meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Systematic reviews and Meta-Analyses (PRISMA) guidelines [15]. When the data given were medians, interquartile ranges, or ranges, the mean and SD values were computed [16]. The quality of each study included in the meta-analysis was scored according to the Newcastle–Ottawa Scale [17]. Scores ranging from 6 to 9, with 9 being the highest score possible, indicated high methodological quality.

Evaluation of statistical associations

We performed a meta-analysis examining the relationship between adiponectin levels and OA. For continuity of data, results were presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). SMDs were calculated by dividing the mean difference between two groups by the pooled SD, and were used when different scales were integrated to measure the same concept. This measure compares case and control arms in terms of standardized scores. The magnitude of SMD was considered as follows: 0.2∼0.5, small effect; 0.5∼0.8, medium effect; and ≥0.8, large effect [18]. Within-study and between-study variations and heterogeneities were assessed using Cochran's Q-statistics [19]. The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When the significant Q-statistic ($p<0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis [20]. In case of no heterogeneity, the fixed effects model was used, which assumed that all studies estimated the same underlying effect and considered within-study variation only [19]. We quantified the effect of heterogeneity using $I^2=100\%\times(Q\text{-}df)/Q$ [21], where I^2 measured the degree of inconsistency between studies and determined whether the percentage total variation across studies was due to heterogeneity rather than chance. I^2 ranged between 0% and 100%; I^2 values of 25%, 50%, and 75% were referred to as low, moderate, and high estimates, respectively [21]. Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biostat Inc., Englewood, NJ, USA).

Evaluation of heterogeneity, sensitivity test, and publication bias

To examine the potential sources of heterogeneity observed in the meta-analysis, subgroup analyses were performed using the following variables: ethnicity, matched variables, sample size, and sample type. A sensitivity test was performed to assess the influence of each study on the pooled odds ratio by individually omitting each study. Although funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and their interpretation involves subjective judgment. Therefore, publication bias was evaluated using Egger's linear regression test [22], which measured

Table 1. Characteristics of individual studies included in the meta-analysis

Author	Country	Ethnicity	Patient		Age (yr)		Sex (female/male)		BMI		OA site	Matched	Quality score
			OA	Control	OA	Control	OA	Control	OA	Control			
Toussirot-1, 2017 [8]	France	European	23	22	64.5±0.2*	59.7±0.1*	23/0	22/0	29.9±0.9*	24.9±0.7*	Knee	Sex	7
Toussirot-2, 2017 [8]	France	European	27	28	64.5±0.2*	59.7±0.1*	0/27	0/28	29.9±0.9*	24.9±0.7*	Knee	Sex	7
Tootsi, 2016 [9]	Estonia	European	70	70	62.0±7.0	60.0±7.0	35/35	34/36	28.0±3.0	26.0±3.0	Knee, hip	Age, sex	7
Cuzdan-1, 2015 [11]	Turkey	Turkish	30	25	67.03±12.71	43.08±14.60	27/3	13/12	23.39±1.77	27.45±5.55	Knee	NA	6
Cuzdan-2, 2015 [11]	Turkey	Turkish	30	25	64.56±10.60	43.08±14.60	30/0	98/34	33.11±3.42	27.45±5.55	Knee	NA	6
de Boer, 2012 [14]	Netherlands	European	172	132	67.4±8.4	56.5±4.5	119/53	19/5	29.5±5.3	28.1±3.8	Knee	Sex	7
Honsawek, 2010 [10]	Thailand	Asian	76	24	69.8±1.1*	71.2±1.5*	62/14	26/0	26.1±0.6*	25.5±0.6*	Knee, hip	Age, sex, BMI	8
Laurberg-1, 2009 [12]	Denmark	European	22	26	63.0±10.3	46.0±14.4	22/0	0/19	29.9±5.2	NA	Knee	Sex	7
Laurberg-2, 2009 [12]	Denmark	European	13	19	65.0±7.8	54.0±7.4	0/13	20/0	27.1±4.0	NA	Knee	Sex	7
Filkova-1, 2009 [13]	Czech	European	27	20	NA	NA	27/0	20/0	NA	NA	Knee, hip	Sex	6
Filkova-2, 2009 [13]	Czech	European	48	20	NA	NA	48/0	20/0	NA	NA	Knee, hip	Sex	6

Values are presented as number only or mean±standard deviation. OA: osteoarthritis, BMI: body mass index, NA: not available. *Standard error.

funnel plot asymmetry using a natural logarithm scale of SMDs. When asymmetry was indicated, the "trim and fill" method was used to adjust summary estimates for the observed bias [23].

RESULTS

Studies included in the meta-analysis

A total of 507 studies were identified using electronic and manual search methods, 16 of which were selected for full-text review based on the title and abstract, and 9 were excluded because they had no data on adiponectin or on control group. Thus, seven articles met the inclusion criteria [8-14] (Figure 1). Four reports contained data on two different groups; these studies were independently analyzed. Therefore, in total, 11 separate studies were considered in the meta-analysis, consisting of 538 patients with OA and 366 controls (Table 1). The quality assessment score of each study ranged between 6 and 8, and all of studies having a high or moderate quality score >6. Selected characteristics of these studies related to the association between the adiponectin and OA are summarized in Table 1.

Meta-analysis of adiponectin levels in patients with OA compared to those in controls

Adiponectin level was significantly higher in the OA group than in the control group (SMD=0.745, 95% CI=0.316～1.174, p=0.001) (Table 2, Figure 2). In addition, stratification by ethnicity showed a significantly elevated adiponectin level in the OA group among Caucasian individuals (SMD=0.769, 95% CI=0.218～1.319, p=0.006) (Table 2). And the single Asian study showed a significantly increased adiponectin level in the OA group (SMD=1.377, 95% CI=0.880～1.874, p<0.001) (Table 2).

Meta-analysis of adiponectin levels in patients with OA compared to those in controls in each subgroup

Stratification by sex revealed that the adiponectin level was significantly higher among women in the OA group, but not in men (SMD=0.861, 95% CI=0.099～1.623, p=0.027; SMD=1.177, 95% CI=−0.911～3.316, p=0.281) (Table 2). Stratification by adjustment for age, sex, and body mass index (BMI) indicated that the adiponectin level was significantly higher in the OA group by adjustment, but not by non-adjustment (SMD=0.837, 95% CI=0.326～1.349, p=0.001; SMD=0.362, 95% CI=

Table 2. Meta-analysis of adiponectin levels in patients with OA compared to that in controls

Group	Population	Study (n)	Number		Test of association			Test of heterogeneity		
			OA	Control	SMD*	95% CI	p-value	Model	p-value	I^2
All	Overall	11	538	366	0.745	0.316～1.174	0.001	R	<0.001	88.4
Ethnicity	European	8	402	337	0.769	0.218～1.319	0.006	R	<0.001	90.6
	Turkish	2	60	25	0.362	−0.017～0.741	0061	F	0.274	16.2
	Asian	1	76	24	1.377	0.880～1.874	<0.001	NA	NA	NA
Sex	Female	4	20	68	0.861	0.099～1.623	0.027	R	<0.001	84.4
	Male	2	40	47	1.177	−0.911～3.316	0.281	R	<0.001	94.0
Age-, sex-, or BMI-matched	Matched	9	478	341	0.837	0.326～1.349	0.001	R	<0.001	90.3
	Not-matched	2	60	25	0.362	−0.017～0.741	0.061	F	0.274	16.2
OA site	Knee	7	317	252	0.938	0.456～1.419	<0.001	R	<0.001	83.3
	Knee, hip	4	221	114	0.409	−0.377～1.194	0.308	R	< 0.001	90.9

OA: osteoarthritis, SMD: standard mean difference, CI: confidence interval, BMI: body mass index, F: fixed effects model, R: random effects model, NA: not available. *Magnitude of Cohen's d effect size (SMD): 0.2～0.5, small effect; 0.5～0.8, medium effect; ≥0.8, large effect.

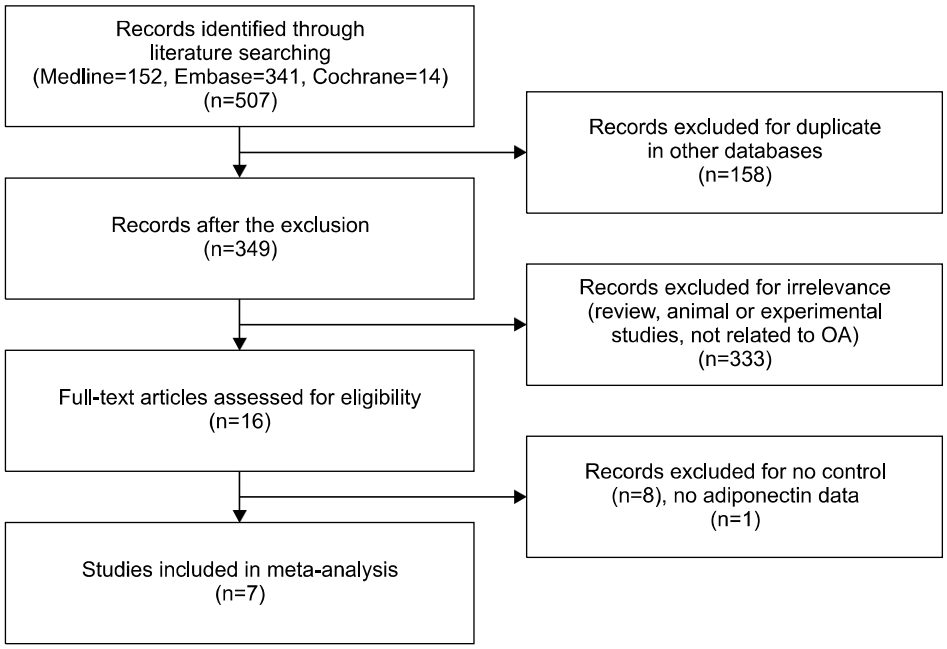

Figure 1. Flow diagram of the study selection process. OA: osteoarthritis.

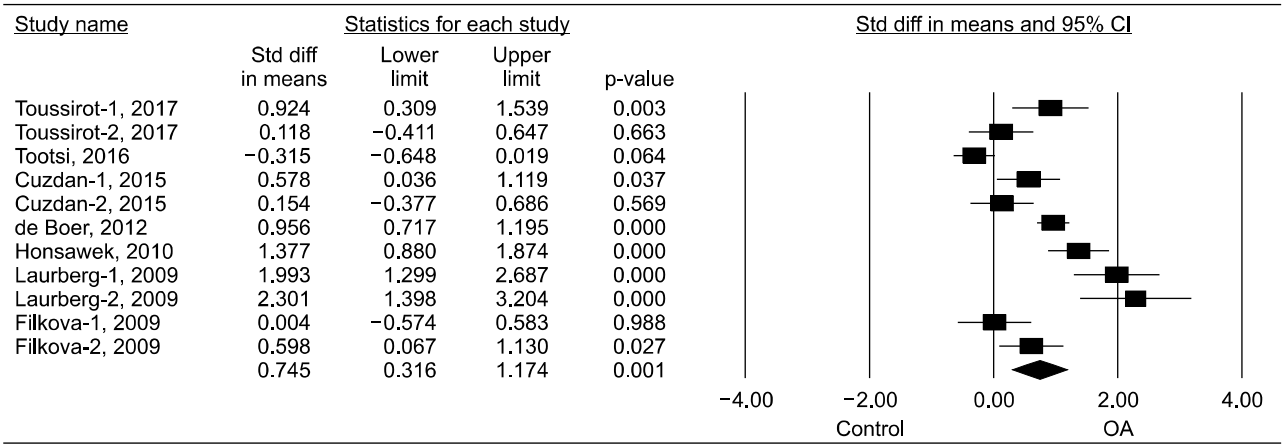

Figure 2. Meta-analysis of the relationship between adiponectin levels and osteoarthritis (OA). Std diff: standard difference, CI: confidence interval.

−0.017∼0.741, p=0.061) (Table 2). Stratification by OA site showed that the adiponectin level was significantly higher in the knee OA group (SMD=0.938, 95% CI=0.456∼1.419, p<0.001) (Table 2). A similar trend was observed in the knee and hip OA group, although it did not reach statistical significance (SMD=0.409, 95% CI=−0.377∼1.194, p=0.308) (Table 2).

Heterogeneity, sensitivity test, and publication bias

Between-study heterogeneity was identified during the meta-analyses of adiponectin levels in patients with OA (Table 2). Subgroup analysis showed decreased heterogeneity in women and in patients with knee OA (Table 2). The main cause of heterogeneity was the difference in the magnitude of effect size. Meta-analytic SMDs remained significant after using a half number of controls to avoid duplicate data in two studies (SMD=0.730, 95% CI=0.328∼1.212, p=0.001) [11,13]. Sensitivity analysis showed that excluding individual study or two studies using a half number of controls did not significantly affect the pooled SMDs, indicating that the results of this meta-analysis were robust. Although Egger's regression test showed no evidence of publication bias (Egger's regression test p-value=0.559), the funnel plot showed asymmetry suggesting publication bias, Therefore, the "trim and fill" method was used to adjust for publication

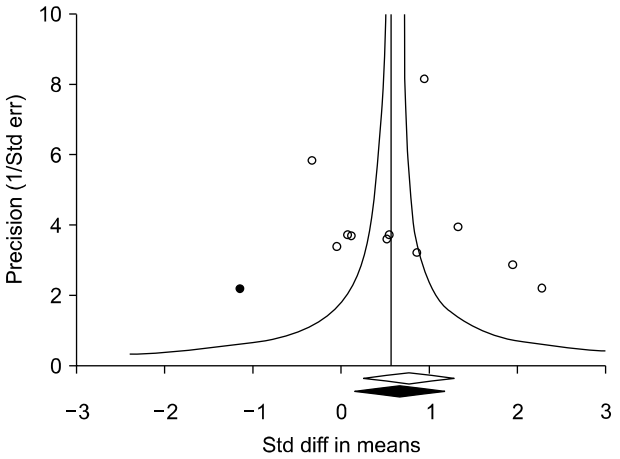

Figure 3. Funnel plot of studies that examined the association between adiponectin levels and osteoarthritis (Egger's regression p-value=0.559). The filled circles represent studies that showed publication bias. The diamonds at the bottom of the figure show summary effect estimates before (open) and after (filled) publication bias adjustment. Std diff: standard difference, Std err: standard error.

bias (Figure 3). However, SMD that had been significant before this adjustment remained significant after the adjustment (SMD=0.621, 95% CI=0.184∼1.058), indicating publication bas did not significantly affect this meta-analysis results.

DISCUSSION

In this meta-analysis, we combined the evidence of circulating adiponectin status in OA. This meta-analysis showed that circulating adiponectin levels were significantly higher in the OA group than in the control group. High adiponectin levels associated with OA were found after adjustment for age, sex, and/or BMI. The meta-analysis data suggested that circulating adiponectin plays a role in the pathogenesis of OA. It suggests the notion that adiponectin plays a role in the proinflammatory state in OA.

Adipose tissue may play an important role in the development of OA, and the pro- or anti-inflammatory effects of adipokines may contribute to the pathogenesis of OA [4]. Adiponectin may disturb cartilage homeostasis through directly inducing joint structural degradation. Adiponectin enhances the proliferation and mineralization of human osteoblasts, and destroys chondrocytes and synovial fibroblasts by increasing the production of the inflammatory mediators including IL-6, IL-8, and monocyte chemo-attractant protein-1, MMP-3, and MMP-9 [6]. A positive correlation has been shown between serum levels of cartilage oligomeric matrix protein MMP-3 and adiponectin. Increased production of intracellular adhesion molecule-1 by adiponectin results in adhesion of monocytes in the synovial fluid in OA. It also has been reported that circulating adiponectin levels were higher in patients with advanced OA compared to those in patients with less severe disease [24].

In contrast, adiponectin may play a role in modulating the inflammatory response by inhibiting the expression of adhesion molecules, and suppressing macrophage and nuclear factor-kappaB signaling [4]. Adiponectin may have a protective role on cartilage by increasing the level of tissue inhibitor of metalloproteinases-2 and down-regulating IL-1β-induced MMP-13 production [25]. It can stimulate the release of anti-inflammatory molecules such as IL-10 and IL-1 receptor antagonist, suggesting its protective role against cartilage damage [26]. This discrepancy may be explained partially by the fact that the proinflammatory activities are related only to high-molecular-weight adiponectin, whereas low-molecular-weight adiponectin has anti-inflammatory effects [27]. Analysis of specific adiponectin isoforms in further studies may help further clarify whether adiponectin has pro- or anti-inflammatory effects in the pathogenesis of OA. Our results are in line with the notion that adiponectin exerts pro-inflammatory activity. However, our results could also rule out the possibility of a beneficial counter-regulatory function of adiponectin through counteracting the pro-inflammatory effects of inflammatory cytokines.

This meta-analysis has some shortcomings that should be considered. First, most of the studies had a small sample size, and only a small number of studies were included in subgroup analysis. Thus, the meta-analysis may be underpowered. Second, the studies included in the meta-analysis were heterogeneous in demographic characteristics and clinical features. The heterogeneity and confounding factors such as disease severity and limited clinical information provided by the study population may have affected the results. This limited data did not allow further analysis. Third, it is known that serum adiponectin is correlated with OA severity [8]. Thus, the whole study results could have been confounded by OA severity. For example, if OA severity had been more severe in females than males, the significant result on the association in only females would have been due to severity difference rather than gender difference. However, we could

not check if OA severity was more severe in females than males due to limited data in the studies.

Nevertheless, this meta-analysis also has its strengths. To the best of our knowledge, our meta-analysis is the first study that provides combined evidence for adiponectin status in patients with OA. Previous individual studies included a population size ranging from 13 to 172 only; however, our pooled analysis consisted of 538 patients. Compared to individual studies, our study was able to provide more accurate data on the relationship between adiponectin level and OA by increasing the statistical power and resolution through pooling of the results of independent analyses. Meta-analysis determines the magnitude of adiponectin levels in OA compared to controls and summarizes the overall results. Thus, meta-analysis is significant in this case, although adiponectin level was high in OA patients in six articles and low in only one article.

CONCLUSION

In conclusion, our meta-analysis demonstrated that circulating adiponectin levels were significantly higher in patients with OA than in controls. The levels were especially elevated in European patients with OA, women, and in patients with knee OA, and after adjustment for age, sex, and/or BMI. This analysis indicates that adiponectin likely plays an important role in the pathogenesis of OA. Further studies are warranted to determine whether increased adiponectin levels are correlated with the severity of OA and whether adiponectin directly contributes to the pathogenesis of OA.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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