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Original Article

Meta-analysis of Circulating Adiponectin, Visfatin, and Ghrelin Levels in Patients with Systemic Lupus Erythematosus

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Objective. To evaluate the association between circulating adiponectin, visfatin, and ghrelin levels and systemic lupus erythematosus (SLE). **Methods.** We conducted a meta-analysis to compare serum/plasma adiponectin, visfatin, and ghrelin levels in patients with SLE to those of healthy controls. **Results.** Eleven articles (822 patients with SLE and 676 controls) were included in the meta-analysis. The meta-analysis showed that the adiponectin level was significantly higher in the SLE group than in the control group (standardized mean difference [SMD] = 0.360, 95% confidence interval [CI] = 0.025 ~ 0.695, p = 0.035). Stratification according to region showed that high adiponectin levels were associated with SLE in the Western population (SMD = 0.225, 95% CI = 0.024 ~ 0.426, p = 0.028), but not in the South American population. A subgroup analysis that adiponectin level is significantly higher in the SLE group than in the control after adjustment for age, sex, body mass index, large sample size (n > 100); and mean age > 40 years (SMD = 0.492, 95% CI = 0.065 ~ 0.920, p = 0.024; SMD = 0.492, 95% CI = 0.065 ~ 0.920, p = 0.024; SMD = 0.429, 95% CI = 0.124 ~ 0.733, p = 0.006, respectively). Stratification by region showed significantly increased visfatin and ghrelin levels in the SLE group in Western and South American populations. **Conclusion.** Our meta-analysis demonstrated that circulating adiponectin, visfatin, and ghrelin levels are significantly higher in SLE. **(J Rheum Dis 2017;24: 99-107)**

Key Words. Adiponectin, Visfatin, Ghrelin, Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by B cell hyperactivity, a high level of autoantibody production, immune-complex deposition, and multiple organ damage [1]. The accumulation of self-antigens due to impaired clearance facilitates autoimmune responses and subsequent inflammation with high levels of inflammatory cytokines in SLE [2].

Adipose tissues form an endocrine organ that regulates immune processes and inflammation by secreting bioactive mediators called adipokines [3]. Adipokines, including adiponectin and visfatin, have been reported to play important roles in the pathogenesis of autoimmune and inflammatory diseases [3]. Adiponectin is a 30-kDa plasma protein produced mainly by adipocytes/macrophages; it is structurally similar to complement component C1q and function as an anti-inflammatory and pro-inflammatory factor [4]. Adiponectin inhibits pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, and adhesion molecules, and it is involved in the modulation of inflammatory responses. However, adiponectin also has pro-inflammatory effects on various cells in the immune system [5]. Adiponectin can increase the production of IL-6 and metalloproteinases (MMPs) from endothelial cells and monocytic cells [6]. Adiponectin may play a role as an enhancer of the inflammatory response in the process of immune response and inflammation [7]. Visfatin is an adipokine secreted by visceral adipose tissue as well as macrophages and neutrophils, and it was initially known as a pre-B-cell colony-enhancing factor that enhances the differentiation of

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B-cell precursors [8]. Visfatin is a pro-inflammatory cytokine, which induces the production of TNF-α, IL-1, IL-6, IL-8, and MMPs [9]. Ghrelin is a growth hormone-releasing peptide secreted from the stomach, and it induces the release of the growth hormone [10]. Ghrelin is not a adipokine, but has a regulatory effect within the immune system, as it is mutually expressed with leptin. Ghrelin exerts multiple immunoregulatory effects by antagonizing leptin [11].

Studies on circulating adiponectin, visfatin, and ghrelin levels in patients with SLE compared to healthy controls have shown mixed results [12-22]. The reasons for such disparity may be the small sample size, low statistical power, and/or clinical heterogeneity [23-25]. To overcome the limitations of individual studies and resolve these inconsistencies, we performed a meta-analysis. The present study aimed to compare the serum/plasma adiponectin, visfatin, and ghrelin levels in patients with SLE compared to those in healthy controls.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a literature search for studies that examined serum/plasma adiponectin, visfatin, and ghrelin levels in patients with SLE and healthy controls. We searched the PubMed, EMBASE, and Cochrane databases to identify all available and relevant past articles (until May 2016). The following keywords and subject terms were used in the search: "adiponectin level," "visfatin," "ghrelin," "systemic lupus erythematosus," and "SLE." All references cited in the articles were reviewed to identify additional studies not found in the aforementioned electronic databases. Studies were considered eligible if (1) they were case-control studies; and (2) they provided data on adiponectin, visfatin, or ghrelin levels in healthy controls and patients diagnosed as having SLE according to the American College of Rheumatology classification criteria [26]. No language restriction was applied. Studies were excluded if (1) they contained overlapping or insufficient data or (2) they were reviews. Data on methods and results were extracted from original studies by two independent reviewers. Discrepancies between the reviewers were resolved by consensus. The meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. The following information was extracted from each study article: primary author; year of publication; country; study region; number of subjects; age; patients' disease duration; patients' body mass index (BMI); adjustment for age, sex or BMI; and mean and standard deviation (SD) of adiponectin, visfatin, and ghrelin levels. When the data were presented as medians, interquartile ranges, or ranges, we computed the mean and SD using previously described formulae [28,29]. We scored the quality of each study included in the meta-analysis based on the Newcastle-Ottawa Scale [30]. Scores ranging from 6～9, with 9 being the highest score possible, indicated high methodological quality.

Evaluation of statistical associations

We performed a meta-analysis to examine the association between adiponectin, visfatin, and ghrelin levels and SLE. Results are presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). SMDs were calculated by dividing the mean difference between the two groups using the pooled SD, and they 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 magnitudes of the SMD were as follows: 0.2～0.5, small effect; 0.5～0.8, medium effect; and ≥0.8, large effect [31]. We assessed within-study and between-study variations and heterogeneities using the Cochran Q statistic [32]. The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When a significant Q statistic ($p<0.10$) indicated heterogeneity across the studies, the random effects model was used in the meta-analysis [33]. When no heterogeneity was found, the fixed effects model was used. The fixed effects model assumed that all studies estimated the same underlying effect, and it only considered within-study variation [32]. We quantified the effect of heterogeneity using the following equation: $I^2=100\%\times(Q-df)\div Q$ [34], where I^2 measured the degree of inconsistency between studies and Q indicated whether the percentage total variation across the studies was due to heterogeneity rather than chance. I^2 ranged between 0% and 100%; I^2 values of 25%, 50%, and 75% were considered low, moderate, and high estimates, respectively [34]. Statistical manipulations were performed using the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ, USA).

Evaluation of heterogeneity and publication bias

To examine potential sources of heterogeneity observed

in the meta-analysis, meta-regression analysis was performed using the following variables: study region; adjustment for age, sex, or BMI; mean age; sample size; and type of data. Funnel plots are often used to detect publication bias. However, because of the limitations of funnel plotting, which requires studies with a range of sizes that involve subjective judgments, publication bias was evaluated using the Egger linear regression test [35], which measures funnel plot asymmetry using a natural logarithm scale of odds ratios.

RESULTS

Studies included in the meta-analysis

We identified 117 relevant studies using electronic and manual search methods. Sixteen studies were selected for full-text review based on the title and abstract, but five of these were excluded because they were a review or had no data on the adipokine levels. Finally, 11 articles met the inclusion criteria for this meta-analysis (Figure 1) [12-22]. Three of the eligible studies included data on two different groups [13,18,20] that were treated independently. Therefore, 14 comparison studies were considered in the meta-analysis, which included 822 patients with SLE and 676 controls (Table 1). Twelve studies examined the adiponectin levels, three assessed the visfatin levels, and four examined the ghrelin levels in SLE and control groups (Table 1). The quality assessment score of each study ranged between 6 and 9, and all the studies had a quality score ≥6 (Table 1). Table 1 shows the character-

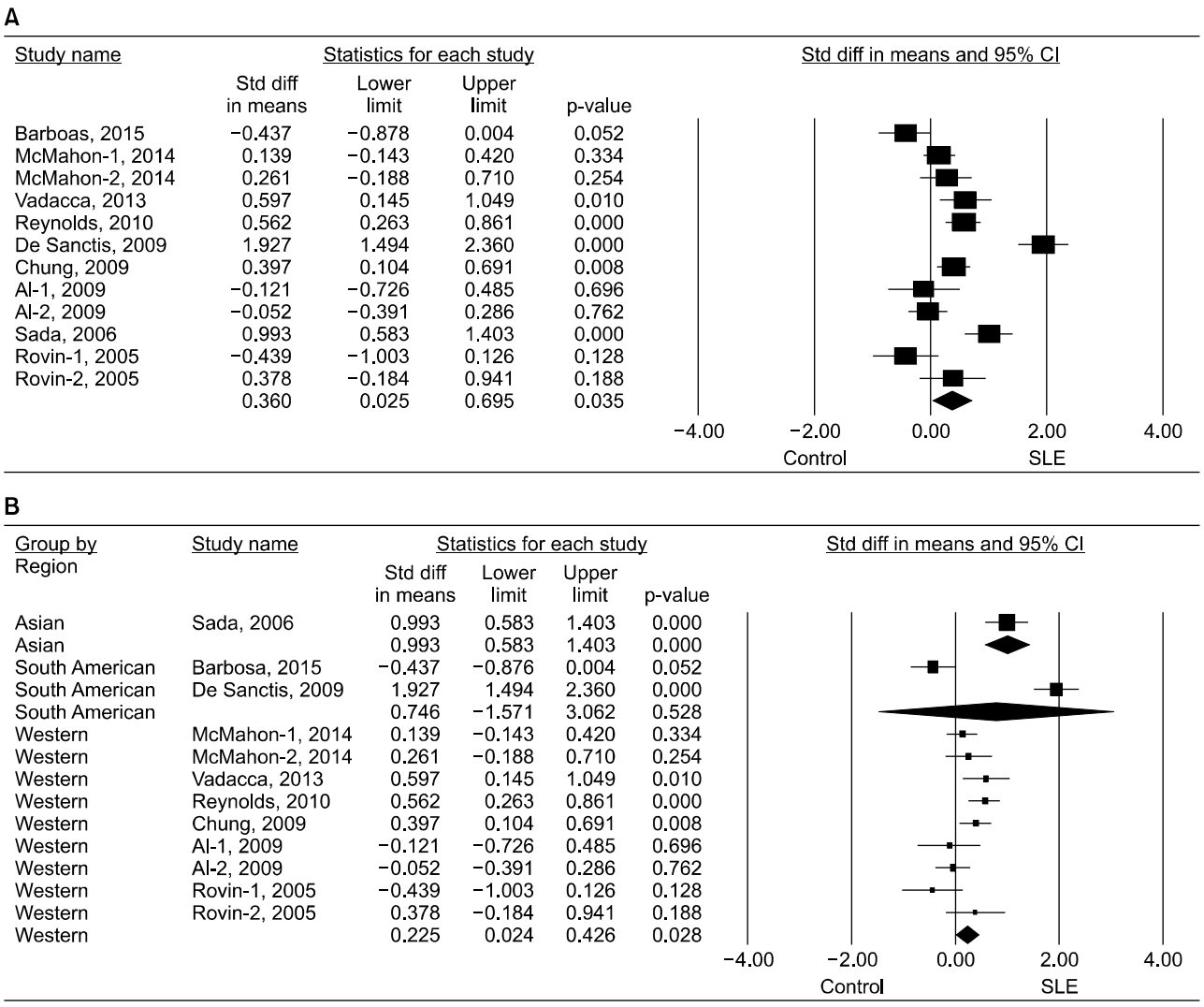

Figure 1. Meta-analysis of the relationship between adiponectin and systemic lupus erythematosus (SLE) in all study subjects (A) and each study region (B). Std diff: standardized difference, CI: confidence interval.

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

Study	Country	Patient		Age, yr		BMI, kg/m^2		Disease duration, yr	Adipokines	Adjustment*	Quality score
		SLE	Control	SLE	Control	SLE	Control				
Barbosa, 2015 [12]	Brazil	52	33	33.4±9.4	32.5±10.5	23.8±3.5	21.8±2.5	7.5	A	Age	8
McMahon-1, 2014 [13]	USA	142	72	39.6±13.5	40.5±11.8	25.7±5.9	23.7±5.1	11.4±8.0	A	Age	7
McMahon-2, 2014 [13]	USA	61	28	51.9±10.2	54.6±10.1	28.0±7.1	25.3±5.8	14.9±11.4	A	Age	7
Vadacca, 2013 [14]	Italy	60	29	42.26±40.54	45.69±11.57	25.2±4	24±4.6	10±5	A	Age, gender, BMI	9
Reynolds, 2010 [15]	USA	119	71	42.6±41.3	41.3±11.9	25.9±6.3	24.8±5.3	NA	A	Age, gender, BMI	8
De Sanctis, 2009 [16]	Venezuela	60	60	36±6	32±12	24±2.7	22±2.0	NA	A, V, G	NA	6
Chung, 2009 [17]	USA	109	78	40.2±11.5	40.5±12.0	29.2±7.5	27.0±6.0	8.2±7.3	A, V	Age, gender	9
Al-1, 2009 [18]	Canada	21	21	14.43±2.20	10.04±3.48	24.07±3.57	NA	NA	A, G	Gender	7
Al-2, 2009 [18]	Canada	84	56	14.32±2.67	10.04±3.48	23.76±5.30	NA	NA	A, G	Gender	7
Sada, 2006 [19]	Japan	37	80	44±15	44±6	22.1±3.5	22.2±3.2	9.4±7.1	A	Age, gender, BMI	8
Rovin-1, 2005 [20]	USA	18	39	47.9±7.21	33.5±10.6	32.6±6.36	25.9±5.09	NA	A	NA	6
Rovin-2, 2005 [20]	USA	18	39	34.6±7.64	33.5±10.6	29.5±10.62	25.9±5.09	NA	A	NA	6
Ozgen, 2011 [21]	Turkey	26	29	34.2±11.0	38.0±10.3	23.2±4.4	25.9±4.7	3.8±3.9	V	BMI	7
Kim, 2010 [22]	Korea	15	80	34.6±6.7	27.4±6.6	NA	NA	47.41±33.66†	G	Gender, BMI	8

Values are presented as number and mean±standard deviation. SLE: systemic lupus erythematosus, BMI: body mass index, NA: not available, A: adiponectin, V: visfatin, G: ghrelin, USA: United States of America.*Matched or similar factors, or no statistical difference in variables between the SLE and control groups, †months.

istic features of each study, including the study population and quality score.

Meta-analysis of circulating adiponectin levels in patients with SLE compared to healthy controls

Results of the meta-analysis showed that the adiponectin level was significantly higher in the SLE group than in the control group (SMD=0.360, 95% CI=0.025～0.695, p=0.035) (Table 2, Figure 1). Stratification according to region showed that high adiponectin levels were associated with SLE in the Western population (SMD=0.225, 95% CI=0.024～0.426, p=0.028), not in the South American population (SMD=0.746, 95% CI=−1.571～3.062, p=0.528) (Table 2, Figure 1). One study indicated that high adiponectin levels were associated with SLE in the Asian population (SMD=0.993, 95% CI=0.583～1.403, $p=2.1\times10^{-6}$) (Table 2, Figure 1). A meta-analysis was also performed on patients with SLE in each group based on adjustment, sample size, and mean age. Meta-analysis of studies adjusted for age, sex, or BMI showed that the adiponectin level was significantly higher in the SLE group than in the control group (SMD=0.273, 95% CI=0.015～0.531, p=0.008) (Table 2). Results of the group analysis by sample size showed a significantly higher adiponectin level in the SLE group of studies with a large sample size (n＞100) (SMD=0.492, 95% CI=0.065～0.920, p=0.024), not in that with a small sample size (n≤100) (SMD=0.082, 95% CI=−0.386～0.550, p=0.731) (Table 2). Stratification according to mean age showed a significantly higher adiponectin level in the SLE group of studies with mean age ＞40 years, not in that with mean age ≤40 years (Table 2).

Meta-analysis of the circulating visfatin and ghrelin levels in patients with SLE compared to the healthy controls

The visfatin level was marginally higher in the SLE group than in the control group (SMD=0.451, 95% CI=−0.000～0.903, p=0.050) (Table 3). Stratification according to region showed a significantly increased visfatin level in the SLE group that included the Western and South American populations (SMD=0.365, 95% CI=0.072～0.658, p=0.015; SMD=0.892, 95% CI=0.517～1.267, $p=3.2\times10^{-6}$) (Table 3, Figure 2). One study showed no association between the visfatin level and SLE in the Middle Eastern population (Table 3). Results of the meta-analysis showed no association between the ghrelin levels and SLE (SMD=0.611, 95% CI=−0.383～1.605, p=0.228) (Table 3). Further, stratification according to region showed that the ghrelin level was higher in the SLE group than in the control group of Western and South American populations (SMD=0.560, 95% CI=0.258～0.861, $p=2.7\times10^{-4}$; SMD=2.000, 95% CI=1.562～2.438, $p<1.0\times10^{-8}$) (Table 3, Figure 2). However, one study showed no association between the ghrelin levels and SLE in the Asian population (Table 3, Figure 2).

Systematic review of relationship between adipokine levels and cardiovascular disease/renal involvement in SLE

Circulating adiponectin was found to correlate with vascular strain (r=0.28, p=0.039) and negatively correlate

Table 2. Meta-analysis of the adiponectin levels in patients with SLE compared to healthy controls

Group	Population	Number of study	Test of association			Test of heterogeneity		
			SMD*	95% CI	p-value	Model	p-value	I^2
All	Overall	12	0.360	0.025～0.695	0.035	R	0.000	88.1
Region	Western	9	0.225	0.024～0.426	0.028	R	0.018	56.6
	South American	2	0.746	−1.571～3.062	0.528	R	0.000	98.2
	Asian	1	0.993	0.583～1.403	2.1×10^{-6}	NA	NA	NA
Matched variables†	Yes	9	0.273	0.015～0.531	0.008	R	0.000	71.4
	No	3	0.632	−0.808～2.072	0.390	R	0.000	95.6
Sample size, n	＜100	4	0.082	−0.386～0.550	0.731	R	0.010	73.3
	≥100	8	0.492	0.065～0.920	0.024	R	0.000	90.6
Mean age, yr	＜40	6	0.307	−0.336～0.950	0.349	R	0.000	93.0
	≥40	6	0.429	0.124～0.733	0.006	R	0.003	72.1

SLE: systemic lupus erythematosus, SMD: standard mean difference, CI: confidence interval, R: random effects model, NA: not available. *Magnitude of the Cohen's d effect size (SMD) (0.2～0.5, small effect; 0.5～0.8, medium effect; and ≥0.8, large effect), †age, sex, or body mass index.

Table 3. Meta-analysis of visfatin and ghrelin levels in patients with SLE compared to healthy controls

Group	Population	Number of study	Test of association			Test of heterogeneity		
			SMD*	95% CI	p-value	Model	p-value	I^2
Visfatin	Overall	3	0.451	−0.000∼0.903	0.050	R	0.018	75.2
	Western	1	0.365	0.072∼0.658	0.015	NA	NA	NA
	South American	1	0.892	0.517∼1.267	3.2×10^{-6}	NA	NA	NA
	Middle Eastern	1	0.025	−0.505∼0.554	0.927	NA	NA	NA
Ghrelin	Overall	4	0.611	−0.383∼1.605	0.228	R	0.000	94.3
	Western	2	0.560	0.258∼0.861	2.7×10^{-4}	F	0.170	46.9
	South American	1	2.000	1.562∼2.438	$<1.0\times10^{-8}$	NA	NA	NA
	Asian	1	−0.478	−1.034∼0.077	0.091	NA	NA	NA

SLE: systemic lupus erythematosus, SMD: standard mean difference, CI: confidence interval, R: random effects model, F: fixed effects model, NA: not available. *Magnitude of the Cohen's d effect size (SMD) (0.2∼0.5, small effect; 0.5∼0.8, medium effect; and ≥0.8, large effect).

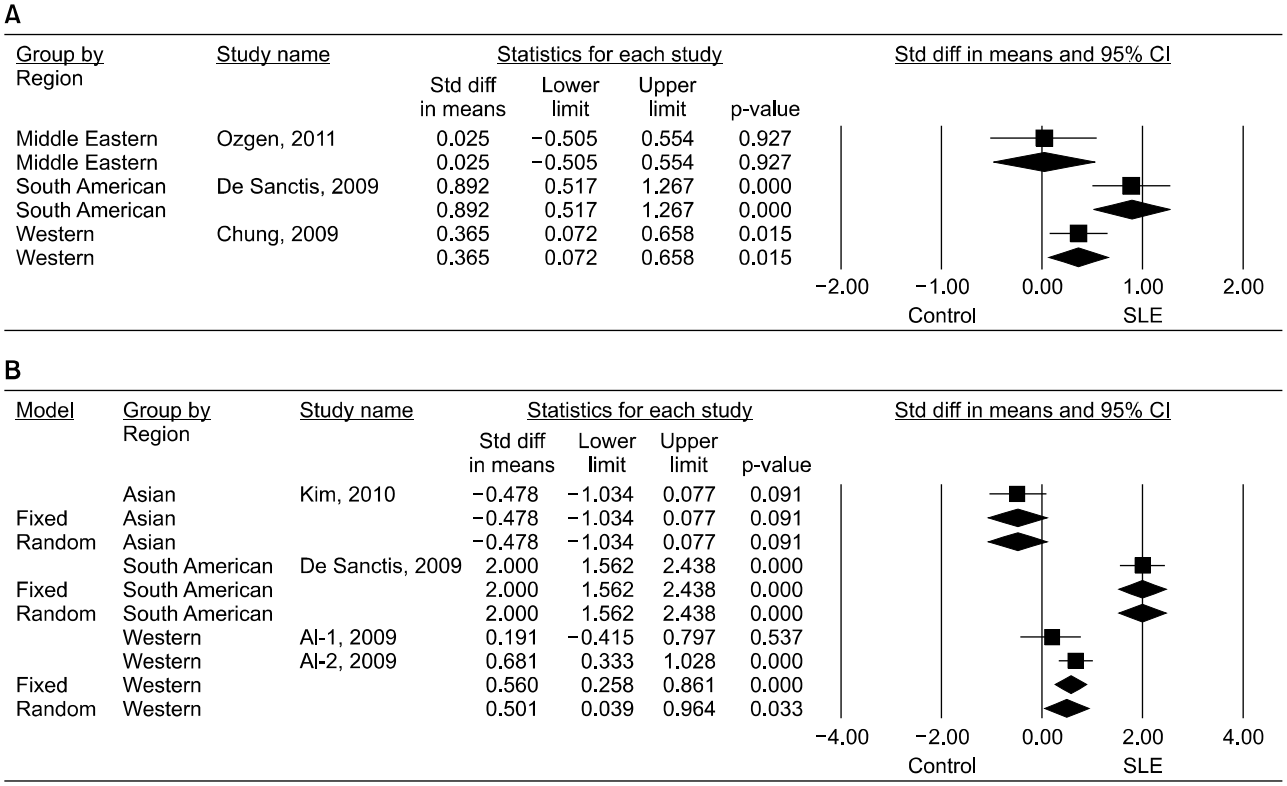

Figure 2. Meta-analysis of the relationship between visfatin (A) or ghrelin (B) levels and systemic lupus erythematosus (SLE) in each study region. Std diff: standardized difference, CI: confidence interval.

with vascular stiffness (r=−0.38, p=0.039) [14]. Adiponectin were significantly higher in the SLE patients with plaque compared to those without plaque in multivariate analysis, indicating that adiponectin may serve as independent predictor of carotid plaque [15]. Adiponectin was negatively associated with BMI, insulin resistance (IR) and C-reactive protein ($\rho=-0.40$, $p<0.001$; $\rho=-0.38$, $p<0.001$; $\rho=-0.22$, $p=0.02$, respectively) [17,18], and ghrelin levels correlate with homocysteine [18]. Authors suggested that adipokines may represent cardiovascular risk and are not just markers for disease activity [18]. SLE patients with IR showed significantly lower adiponectin levels than those without IR (10.9±4.6 vs. 15.4±4.4 μg/mL) and adiponectin levels were correlated inversely with homeostasis model assessment of insulin resistance in SLE patients [19]. Plasma adiponectin levels are increased in patients with renal SLE compared to healthy controls and patients with nonrenal SLE [20].

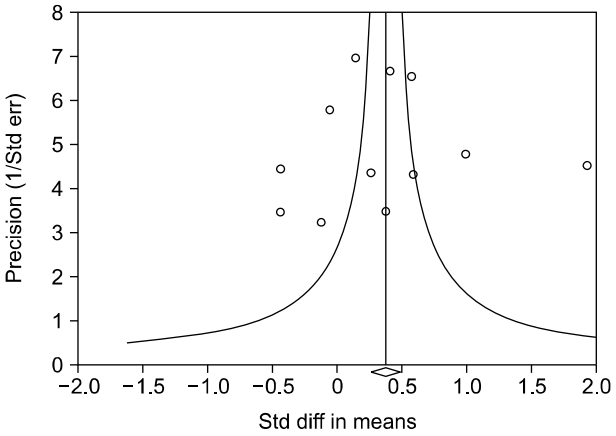

Figure 3. Funnel plot of studies that examined the relationship between adiponectin and systemic lupus erythematosus (Egger regression p-value=0.894). Std diff: standardized difference, Std err: standardized error.

During renal flare, urine adiponectin levels increase significantly. Urine adiponectin may be a biomarker of renal SLE flare [20].

Heterogeneity and publication bias

Between-study heterogeneity was identified in the meta-analyses of adiponectin, visfatin, or ghrelin levels in patients with SLE (Table 2). Results of meta-regression analysis showed that the study region; adjustment for age, sex, or BMI; and sample size ($p<0.001$) had a significant effect on heterogeneity in the meta-analysis of adiponectin levels, not mean age and type of data ($p>0.05$). Publication bias causes a disproportionate number of positive studies, and it poses a problem for meta-analyses. However, we found no evidence of publication bias among all the studies (Egger regression test p-values>0.1) (Figure 3).

DISCUSSION

This analysis of 11 articles showed that circulating adiponectin levels were significantly higher in patients with SLE than in the healthy controls. Stratification according to region showed that high adiponectin levels are associated with SLE in the Western population, not the South American population. Results of the group analysis showed a significantly higher adiponectin level in the SLE group of studies with adjustment for age, sex, or BMI; large sample size ($n>100$), and mean age >40 years. In addition, results of the analysis showed that circulating visfatin and ghrelin levels were significantly higher in patients with SLE of the Western and South American populations.

Stratification by study region indicated that there was a difference in adipokine levels among different regions. For example, meta-analysis by region showed significantly elevated adiponectin levels in the SLE group in the Western population, but not in the South American population. This indicates that region or ethnicity may correlate with adipokine levels in SLE patients. The regional differences may be partly explained by difference in statistical power due to study numbers. Low statistical power due to a small number of studies may explain the differences in the results between regions. The study number was large in the Western population compared to that in the South American population (9 vs. 2). There was a significantly higher adiponectin level in the SLE group of a large number of study, but not in that with a small number of study. However, other potential factors such as different clinical and environmental characteristics may also influence plasma/serum adipokine levels. Previous meta-analysis also showed a regional difference of leptin levels, showing significantly higher leptin levels in the SLE patients from an Asian population, but not from Europe and America population [36].

This meta-analysis showed increased adiponectin levels in patients with SLE. Adiponectin may exert bidirectional effects of pro-inflammatory and anti-inflammatory activities in SLE. Adiponectin plays a role in modulating the inflammatory response by inhibiting the expression of adhesion molecules, and suppressing macrophage and nuclear factor kappa B signaling [4]. Thus, the finding of this study can be partially explained by a beneficial counter-regulatory function of adiponectin through counteracting the pro-inflammatory effects of inflammatory cytokines. However, adiponectin also may play a role as an enhancer of the inflammatory response by inducing inflammatory mediators [7]. The question whether the effects of adiponectin in SLE are pro-inflammatory or anti-inflammatory needs to be studied further. Visfatin is produced by neutrophils and lymphocytes, bone marrow, and adipocytes, and it has pro-inflammatory and immunomodulatory effects [8]. Visfatin acts as a chemotactic factor on monocytes and lymphocytes by activating T cells and enhancing the expression of co-stimulatory molecules on monocytes [37]. Visfatin levels are increased in inflammatory diseases [38]. Ghrelin has an inhibitory effect on the production of pro-inflammatory cytokines [39], and it exerts a counter-regulatory function through counteracting the pro-inflammatory effects of

leptin [39]. It can also play a role in modulating immune responses and inflammatory processes [40]. Our meta-analysis showed increased visfatin and ghrelin levels in patients with SLE of the Western and South American populations, not the Middle Eastern population, suggesting that they play a possible role in the control of the immune and inflammatory process and the region or ethnicity may correlate with ghrelin levels in patients with SLE.

The present study has some limitations that should be considered. First, most of the included studies had small sample sizes; thus, many of the individual studies that constitute this meta-analysis may have been underpowered. Second, the studies included patients with heterogeneous demographic characteristics and clinical features. The heterogeneity and confounding factors such as disease activity and drugs used (e.g., immunosuppressive agents, hydroxychloroquine, and corticosteroids) may have affected our results, which may be compounded by the limited information provided for patients' clinical status and disease activity. These limited data did not allow further analysis, although we performed a subgroup analysis and meta-regression analysis. Nevertheless, this meta-analysis has some strengths. It is the first to compile evidence from multiple studies to indicate an association between adiponectin, visfatin, and ghrelin levels and SLE. Individual studies included population sizes ranging from only 15 to 822 participants, whereas our pooled analysis included 511 patients. Our study was able to increase the statistical power and resolution by pooling the results from many independent analyses.

CONCLUSION

Our meta-analysis demonstrated that circulating adiponectin levels are significantly higher in patients with SLE than in healthy controls, particularly in the Western population and by the adjustment of age, sex, or BMI; a large sample size ($n>100$), and mean age >40 years. In addition, circulating visfatin and ghrelin levels were significantly higher in patients with SLE of Western and South American populations. This analysis indicates that adiponectin, visfatin, and ghrelin likely play an important role in the pathogenesis of SLE. Further studies are needed to determine whether adiponectin, visfatin, and ghrelin directly contribute to the pathogenesis of SLE.

CONFLICT OF INTEREST

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

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