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Review

Serum levels of leptin, adiponectin and resistin in patients with ankylosing spondylitis: A systematic review and meta-analysis

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ABSTRACT

Objectives: Various studies have researched the serum levels of leptin, adiponectin and resistin in patients with ankylosing spondylitis (AS), but the results were inconclusive. The purpose of this study was to systematically evaluate the correlations between serum levels of these adipokines and AS.

Methods: Electronic databases were retrieved to search relevant publications. Pooled standard mean difference (SMD) with 95% confidence interval (CI) was calculated by the random-effect model. Cochrane Q test and I^2 statistic were used to test heterogeneity. Subgroup analysis and meta-regression were applied to assess possible sources of heterogeneity.

Results: A total of sixteen articles were included. Meta-analysis results indicated no statistical differences between AS patients and normal controls in serum leptin and adiponectin levels (leptin, SMD = 0.829, 95% CI = −0.116 to 1.774, $p = 0.085$; adiponectin, SMD = 0.460, 95% CI = −0.004 to 0.924, $p = 0.052$). However, AS patients had higher serum resistin levels than controls (SMD = 1.413, 95% CI = 0.294 to 2.531, $p = 0.013$). Subgroup analyses suggested that Asian and African AS patients as well as patients aged < 40 years had higher serum leptin and resistin levels when compared to controls. Serum adiponectin levels were higher in AS patients compared to controls in subgroup of age ≥ 40, and serum resistin levels in subgroup of BMI ≥ 25. Measurement method was a source of heterogeneity for resistin. Publication bias was not observed and the robustness of study results was confirmed by sensitivity analysis.

Conclusion: Serum resistin, but not leptin or adiponectin levels may be closely associated with the development of AS.

1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that could cause lesions of sacroiliac joint and spinal column, and the incidence of AS is higher in males [1,2]. Previous studies have indicated that various inherited genetic factors and environmental aspects play an important role in the complicated pathogenesis of AS [3,4]. Tumor necrosis factor-α (TNF-α) [5] and interleukin (IL) [6,7] are two cytokines which have been demonstrated to be associated with the underlying mechanisms of AS, recent studies suggested that other cytokines, including leptin [8], adiponectin [9] and resistin [10], may also be involved in AS pathogenesis.

Leptin, adiponectin and resistin belong to adipokines which are secreted by adipose tissue. These adipokines are associated with several physiological processes such as energy expenditure, appetite control and glucose homeostasis, and they are also involved in the processes of immune regulation [11]. Leptin is a secretory protein encoded by obesity-associated gene with a length of 167 amino acids [12]. Previous studies have reported that leptin could activate the JAK-STAT-NF-κB downstream signaling pathway by combining with its transmembrane functional receptors, indicating that leptin is involved in immune and autoimmune responses [13,14]. Furthermore, leptin has been related to various autoimmune diseases, including osteoarthritis (OA), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple

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sclerosis (MS) and AS [15–20]. Adiponectin is a 244-residue protein mainly synthesized by adipose tissue [21]. While adiponectin plays an anti-inflammatory role in cardiovascular diseases (CVDs), type II diabetes and obesity [24–26], this adipokine, however, plays a pro-inflammatory role in spondyloarthritis [27]. Adiponectin could stimulate the producing of pro-inflammatory mediators, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), IL-6 and IL-8 [22,23,28]. Besides, adiponectin has been associated with the pathogenesis of multiple rheumatic diseases, such as AS, RA, OA, SLE and systemic sclerosis (SSc) [9,29–33]. Resistin is a 12.5 kDa protein which descends from the family of resistin-like molecules [21]. The concentrations of resistin are low in human adipocytes, but are high in mononuclear leukocytes, macrophages, spleen, and bone marrow cells [34–36]. Resistin can increase the producing of multiple pro-inflammatory factors, such as TNF-α, IL-6 and IL-1β [37,38]. Thus, serum resistin levels may be highly related to inflammatory responses [37]. In addition, resistin is correlated with a number of diseases, such as psoriasis, Sjögren's syndrome, relapsing–remitting MS, inflammatory bowel disease and AS [19,39–42].

The associations between adipokines and AS were inconsistent. Serum leptin levels have been reported to be higher in AS patients than that in normal controls [43–45], but Toussirot et al. in their studies showed opposite results [17,46], and Kim et al. [47] and Derdemezis et al. [9] suggested that serum leptin levels were not significantly different between AS patients and controls. In terms of serum adiponectin levels, no statistical differences were observed between AS group and control group in most studies [10,17,48,49], though, Derdemezis et al. [9] found that serum adiponectin in AS group were higher than that in control group. For serum resistin concentrations, Toussirot et al. [46] reported similar serum levels of resistin between AS cases and controls in 2013. However, Syrbe et al. [10], Elolemy et al. [48] and Kocabas et al. [41] indicated that AS patients had higher serum resistin levels compared to normal controls. Therefore, the aim of this study was to systematically evaluate the relationships of serum leptin, adiponectin and resistin levels with AS.

2. Materials and methods

2.1. Publication search

The present meta-analysis was conducted according to a standard guideline [50]. We performed a comprehensive literature search to locate relevant articles published on electronic databases including PubMed, Embase, Medline, Web of Science, Cochrane Library, WANFANG (Chinese Database), VIP (Chinese Database) and China National Knowledge Infrastructure (CNKI) before July 2017. Keywords and search strategy were as follows: “Leptin” or “LEP” or “Adiponectin” or “ADPN” or “APN” or “Resistin” or “RETN” or “RELM” or “FIZZ” or “adipose tissue-specific secretory factor” or “C/EBP-epsilon-regulated myeloid-specific secreted cysteine-rich protein” combined with “Ankylosing spondylitis” or “AS”. The corresponding Chinese terms were used for Chinese libraries. In addition, the references cited in these articles were reviewed to identify additional publications.

2.2. Inclusion criteria and exclusion criteria

Inclusion criteria were as follows: a) study used a case-control, clinical cohort or cross-sectional design; b) study provided detailed data concerning serum or plasma leptin, adiponectin or resistin levels in AS cases and healthy controls; c) study published in English or Chinese. As for duplicate publications, the one with the largest sample size and/or the most recent publication date was included.

Exclusion points were a) conference abstracts, case reports and review articles, b) studies without sufficient data for serum leptin, adiponectin or resistin concentrations in AS patients and healthy controls, and c) in vitro, ex vivo or animal study.

2.3. Quality assessment and data extraction

Two investigators (JY and XZ) assessed and scored the quality of all included studies according to the Newcastle–Ottawa quality assessment scale (NOS) [51]. A higher score indicates better quality in methodology. The following characteristics of all eligible articles were collected: first author's name, publication year, study population, study design, participants characteristics (age and sex), body mass index (BMI), source of controls, and assay approaches for serum adipokines levels. If any significant data of the above characteristics were not provided in the original articles, we tried to send an e-mail to the authors for available information.

2.4. Statistical analysis

Statistical analyses were conducted using Stata 11.0 (StataCorp, College Station, TX, USA) software. Standardized mean difference (SMD) and 95% confidence interval (CI) were calculated for each study. Mean and standard deviation were available for most studies, but in a few studies, only the median and range were provided. In this case, raw data were transformed and computed to speculate the mean and standard deviation [52]. Cochrane Q test (chi-square test, χ^2) was used to estimate statistical heterogeneity across studies, and I^2 test was applied to further evaluate the extent of heterogeneity ($I^2 = [(Q\text{-}df) / Q] \times 100\%$). The fixed-effect models were used when there was no significant heterogeneity ($p > 0.05$ for the Q test or $I^2 < 50\%$), otherwise the random-effect models were used. To determine the sources of heterogeneity, subgroup analyses stratified by region, age, BMI and measurement type were performed. Random-effect meta-regression analysis was implemented to evaluate other potential confounders, including publication year and sex ratio. Begg's and Egger's test were adopted to assess the potential publication bias amongst the incorporated studies. Sensitivity analysis was performed to detect the impact of single study on the overall result if there was a high heterogeneity. A two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Literature research and study characteristics

Of the initially retrieved 401 articles, 287 duplicate records were excluded. After title and abstract screening, 41 articles were retrieved for full-text identifications. Finally, 16 articles met the inclusion criteria [8–10,16,41,43–49,53–56] (Fig. 1). Among them, 15 studies from 14 articles have researched the serum leptin levels in 619 AS patients and 481 controls [8,9,16,43–49,53–56], six articles including 273 cases and 202 controls have studied the serum adiponectin levels [9,10,46,48,49,53], and four articles consisting of 172 AS patients and 126 controls have studied the serum resistin levels [10,41,46,48]. The study populations were from Europe or America (five studies), Asia (11 studies) and Africa (one study), and these studies were published from 2007 to 2017. AS patients in 13 papers were diagnosed based on the modified New York classification criteria in 1984, and two studies applied the diagnose criteria established by Chinese Rheumatology Association (CRA) in 2014, whereas the diagnosis criteria of two researches were unknown. Adipokines serum levels were gauged by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA). The overall methodological quality was satisfactory, with 16 studies scored 5 to 8. Characteristics of the included studies are detailed in Table 1.

3.2. Results of meta-analysis

3.2.1. Heterogeneity test results

Heterogeneity was significant across these studies (all $p < 0.001$,

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