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Association between osteopontin expression and asthma: a meta-analysis

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Abstract

Objective: Osteopontin (OPN) plays an important role in chronic airway remodeling and bronchial hyperresponsiveness. The association between OPN protein expression and asthma has been investigated extensively, but the results of these studies are inconsistent. The aim of this meta-analysis was to determine the relationship between OPN protein expression and asthma.
Methods: A systematic search was performed to identify published studies regarding the association between OPN protein expression and asthma. Studies with quantitative data were analyzed, and standardized mean differences were determined with 95% confidence intervals.
Results: Nine studies were included in this analysis, involving 706 patients with asthma and 332 healthy controls. The pooled data from these studies demonstrated that OPN protein expression was significantly higher in patients with asthma than in controls. There was no significant difference in OPN protein between allergic asthma and nonallergic asthma. Moreover, there was no obvious relationship between OPN protein expression and the severity of asthma.
Conclusion: The results of this meta-analysis suggested that OPN protein expression is significantly upregulated in patients with asthma, but that it does not correlate with the type or severity of asthma.

Keywords

Osteopontin, asthma, meta-analysis, airway remodeling, bronchial hyperreactivity, immunomodulation, allergic reaction

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Introduction

Asthma is a chronic inflammatory disorder of the conducting airways that results in variable airflow obstruction due to various stimuli and is associated with structural alterations of airway components, a process known as airway remodeling.[1] The pathogenesis of asthma is typically associated with Th1/Th2 response imbalances and IgE-mediated type I allergies.[1,2] Osteopontin (OPN) is a phosphorylated acidic glycoprotein that was originally regarded as a structural component of the extracellular matrix; it can bind proteins and most types of collagen.[3] OPN can act as both an extracellular matrix molecule and a cytokine. Notably, OPN is produced by a variety of immune cells and structural cells, such as macrophages, T-cells, natural killer cells, B cells, fibroblasts, smooth muscle cells, and epithelial cells. In addition, OPN can promote the proliferation and migration of fibroblasts and smooth muscle cells in mice; it can also stimulate collagen production, leading to tissue remodeling.[4] OPN protein expression is increased in many Th1-mediated lung diseases, such as granulomatous diseases, asthma, and pulmonary fibrosis.[5–8] OPN is significantly upregulated in bronchial epithelial cells and dendritic cell subsets. Moreover, it is overexpressed in peripheral blood eosinophils and is involved in the migration of eosinophils into the airways.[9] Finally, OPN plays an important role in chronic airway remodeling, such that OPN knockout mice are protected against airway remodeling and bronchial hyperresponsiveness.[10,11] However, there are conflicting reports regarding the association between OPN protein expression and asthma.[12–20]

Several studies have indicated that OPN protein expression is significantly higher in patients with asthma, whereas other studies have shown no change. Moreover, reports regarding the association between OPN expression and asthma severity have shown inconsistent results.[12–14] Therefore, we performed a meta-analysis to more comprehensively investigate the relationship between OPN protein expression and asthma.

Materials and methods

Search strategy

Our meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. To identify all articles potentially associated with OPN protein expression and asthma, we searched PubMed, the Web of Science, and the Chinese Medical Database for articles published on or before 31 September 2018. For all three databases, the search terms were asthma and osteopontin (or OPN), and the search strategy was as follows: ("osteopontin" [MeSH Terms] OR "osteopontin"[All Fields] OR "OPN"[All Fields]) AND (asthma [All Fields] OR "asthma" [MeSH Terms]). Referenced original articles and reviews published before 31 September 2018 were also manually retrieved if they were cited by studies found using the main search strategy. This meta-analysis only included articles for which the full text was available in English or Chinese.

Inclusion and exclusion criteria

The included studies met the following criteria: (1) patients with asthma were studied; (2) OPN protein expression was measured in groups of patients; (3) a case–control or cohort study design was used; (4) data were sufficient to estimate standardized mean differences (SMDs). Exclusion criteria were as follows: (1) when data overlapped or were duplicated in multiple studies, only the study with the largest sample size or with the most recent publication date was included in the meta-analysis; (2) all

reviews, editorial letters, abstracts, case reports, and commentaries were excluded.

Data extraction and statistical analyses

Two investigators (WL and HX) independently extracted the relevant data from the retrieved articles. Disagreements were resolved by consensus with a third reviewer (FF). The Newcastle–Ottawa quality assessment scale (NOS) was used to assess the methodological quality of the included studies.[21] The SMD and corresponding 95% confidence interval (CI) were used for quantitative data analysis. When a clinical trial provided only the median, range, and size of the trial, we used formulas provided by Hozo et al.[22] to calculate the mean and standard deviation. STATA software (version 10.0, STATA Corporation, College Station, TX, USA) was used to perform quantitative meta-analysis. The heterogeneity of the pooled data was estimated using Cochrane's Q test and the I^2 measurement. Heterogeneity was regarded as significant when $P < 0.10$ or $I^2 > 50\%$, which indicated that a fixed effects model should be used; otherwise, a random effects model was used. To evaluate the validity and reliability of the meta-analysis, a sensitivity analysis was conducted. The risk of publication bias was estimated using Begg's funnel plot and Egger's test, where $P \leq 0.10$ was indicative of publication bias. A subgroup analysis was performed based on ethnicity and types of specimens.

Results

Characteristics of the included studies

In total, 197 studies were found using the initial literature search strategy. A flowchart depicting the screening process used in this meta-analysis is shown in Figure 1.

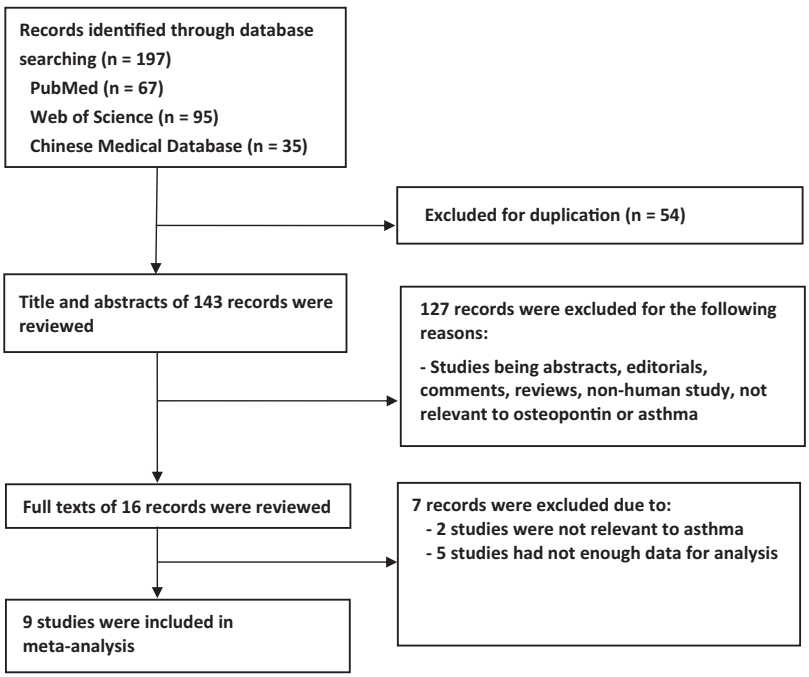

Figure 1. Flow chart of the study selection protocol.

Fifty-four articles were eliminated because they included duplicate data. Sixteen articles were retained after careful review of their titles and abstracts. After the full texts had been read, seven papers were excluded because of insufficient data. Ultimately, our meta-analysis included nine studies that involved 706 asthma patients and 332 healthy controls. The main characteristics of the nine studies are described in Table 1.

OPN protein expression and asthma

Nine studies contained sufficient data for analysis of OPN protein expression in asthma patients and healthy controls. Figure 2 shows that OPN protein expression was significantly higher in patients with asthma than in healthy controls (SMD = 0.66, 95% CI: 0.24–1.07, $P = 0.002$), but significant heterogeneity was detected among the studies ($I^2 = 87.6\%$, $P < 0.001$). Egger's test did not identify any significant publication bias in this meta-analysis. A sensitivity analysis was performed by excluding single studies in a sequential manner, and no significant effects were observed in analyses of the remaining studies. Three studies reported an association between OPN protein expression and the severity of asthma. As shown in Figure 3a, analysis of the pooled data showed no significant correlation between OPN protein expression and severity of asthma (SMD = 0.28, 95% CI: −0.23–0.79), but significant heterogeneity was detected among these three studies ($I^2 = 65.8\%$, $P = 0.054$). There were two studies regarding the relationship between OPN protein expression and the type of asthma. Analysis of the pooled data showed no significant difference in OPN protein expression between allergic asthma and non-allergic asthma (SMD = −0.10, 95% CI: −0.45–0.25); moreover,

Table 1. Main characteristics of included studies regarding the association between OPN protein expression and asthma.

Author	Year	Patients (total = 706)	Controls (total = 332)	Country	Severity of asthma (Severe/ mild-to-moderate)	Type of asthma	Detection method	Examined specimens	NOS
Delimpoura V et al.[12]	2010	83	20	Greece	33/50	Adult-onset	ELISA	Sputum	8
Samitas K et al.[13]	2011	54	17	Greece	19/35	Adult-onset	ELISA	Serum	6
Zhao JJ et al.[14]	2011	130	41	China	39/91	Adult-onset	ELISA	Serum	7
Akelma AZ et al.[15]	2013	51	42	Japan	NR	Pediatric	ELISA	Serum	6
Hillas G et al.[16]	2013	103	40	Greece	NR	Adult-onset	ELISA	Sputum	8
Yang AM et al.[17]	2016	98	30	China	NR	Pediatric	ELISA	Serum	7
Makowska JS et al.[18]	2016	96	30	Poland	NR	Adult-onset	ELISA	Serum	7
Nacaroglu HT et al.[19]	2017	43	75	Japan	NR	Pediatric	ELISA	Plasma	6
Dombai B et al.[20]	2017	48	37	Hungary	NR	Adult-onset	ELISA	Plasma	8

OPN, osteopontin; ELISA, enzyme-linked immunosorbent assay; NOS, Newcastle-Ottawa quality assessment scale; NR, not reported.

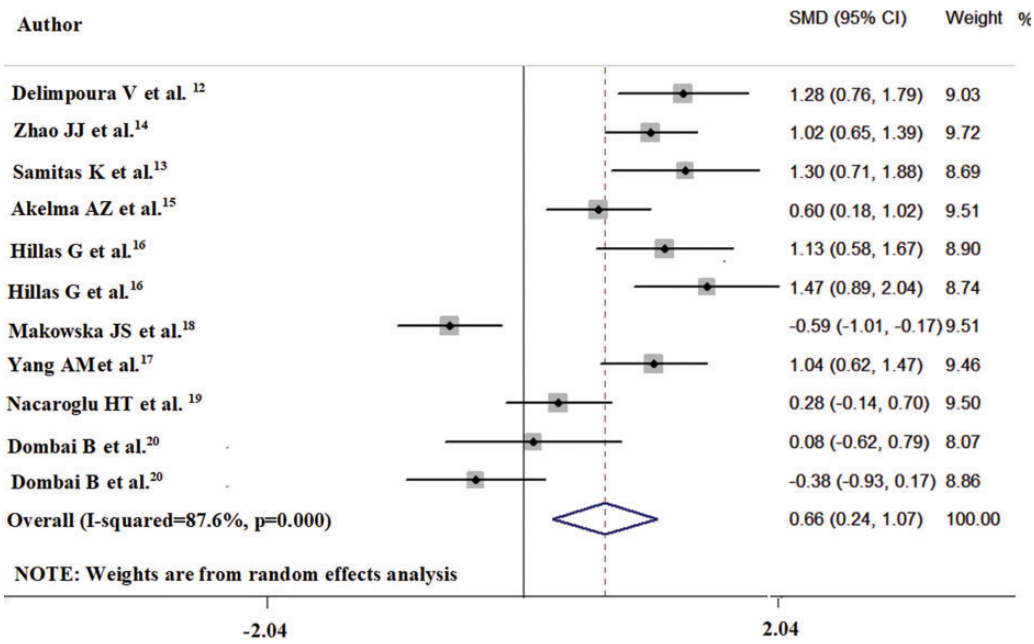

Figure 2. Forest plot describing relationships between osteopontin (OPN) protein expression and asthma.

no heterogeneity was detected between these two studies ($I^2 = 0.0\%$) (Figure 3b).

Subgroup analysis

The included studies used either blood or sputum samples; therefore, a subgroup analysis was performed based on the types of specimens to evaluate the relationship between OPN protein expression and asthma. As shown in Figure 4, high OPN protein expression was associated with asthma in studies that used sputum samples (SMD = 1.28, 95% CI: 0.97–1.60, $P < 0.01$). However, OPN protein expression was not significantly associated with asthma in studies that used blood samples (SMD = 0.39, 95% CI: −0.09–0.87). An ethnicity-based subgroup analysis showed that OPN protein expression was associated with asthma in Asians (SMD = 0.74, 95% CI: 0.39–1.10, $P < 0.01$), but not in non-Asian populations (SMD = 0.56, 95% CI: −0.14–1.26) (Figure 5).

Discussion

OPN is a promising biomarker for inflammation because it plays a variety of roles in many inflammatory processes. OPN is an extracellular matrix protein and an immunomodulator that is expressed in many types of cells, such as eosinophils, bronchial epithelial cells, T cells, and dendritic cells.[20,23] Importantly, OPN plays a role in many inflammatory diseases, especially in the context of immune responses associated with CD4+ T helper cells.[23] The present meta-analysis included nine studies that involved 706 asthma patients and 332 healthy controls. Among these studies, the expression levels of OPN protein varied greatly, and we therefore calculated SMDs to facilitate comparisons among the studies. Our results demonstrated that OPN protein expression was significantly higher in asthma patients than in healthy controls; however, the I^2 value was 87.6%, which indicated significant heterogeneity.

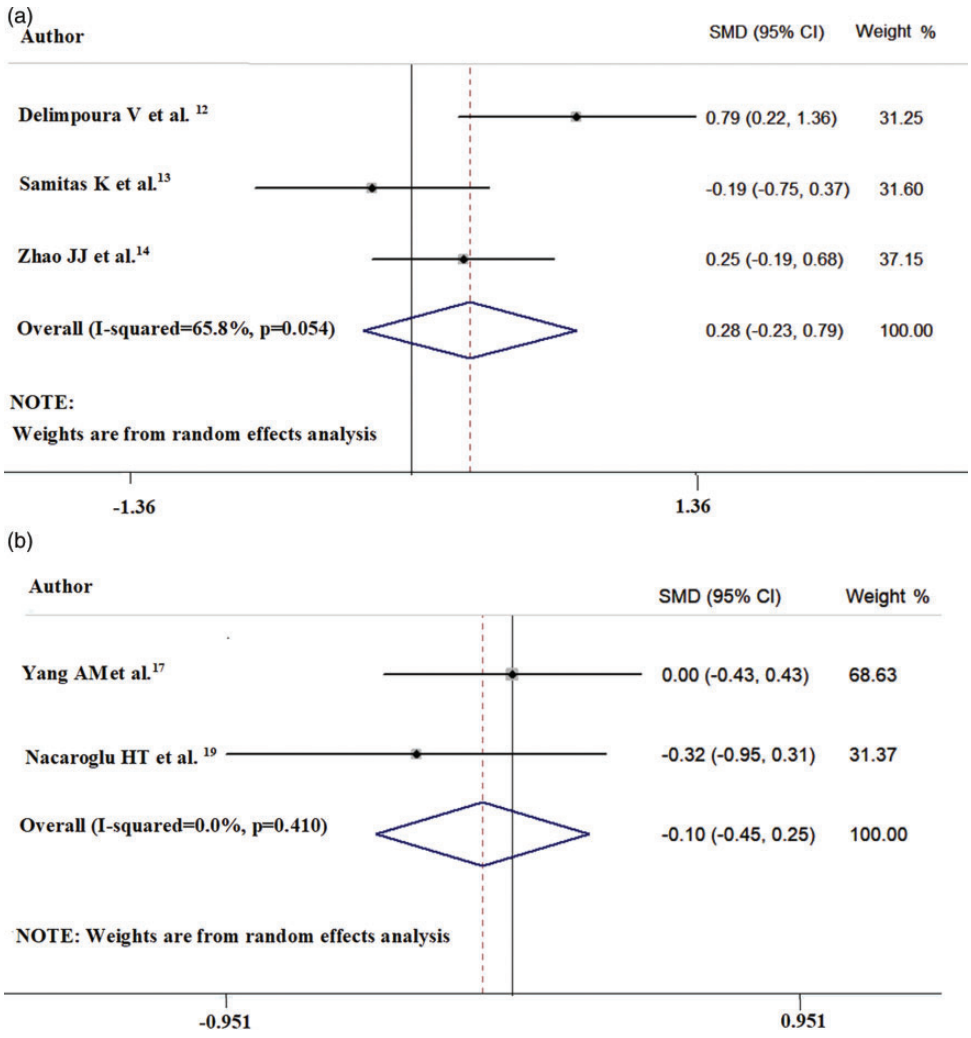

Figure 3. Forest plot of the association between osteopontin (OPN) protein expression and severity or type of asthma. (a) Association between OPN protein expression and severity of asthma and (b) Association between OPN protein expression and type of asthma.

Therefore, a random effects model was used for analysis. The heterogeneity among these studies may have resulted from differences in the types of the specimens, severities of asthma, ages of onset, and ethnicities of included patients. Funnel plot analysis showed no publication bias. Sensitivity analysis was performed and no significant effect was observed when any single study was omitted, indicating that the results of the meta-analysis were statistically stable.[24] Moreover, the association between OPN protein expression and severity of asthma was analyzed. Although no statistically significant difference was found, OPN tended to be highly expressed in patients with severe asthma. Subgroup analysis demonstrated that OPN protein expression was

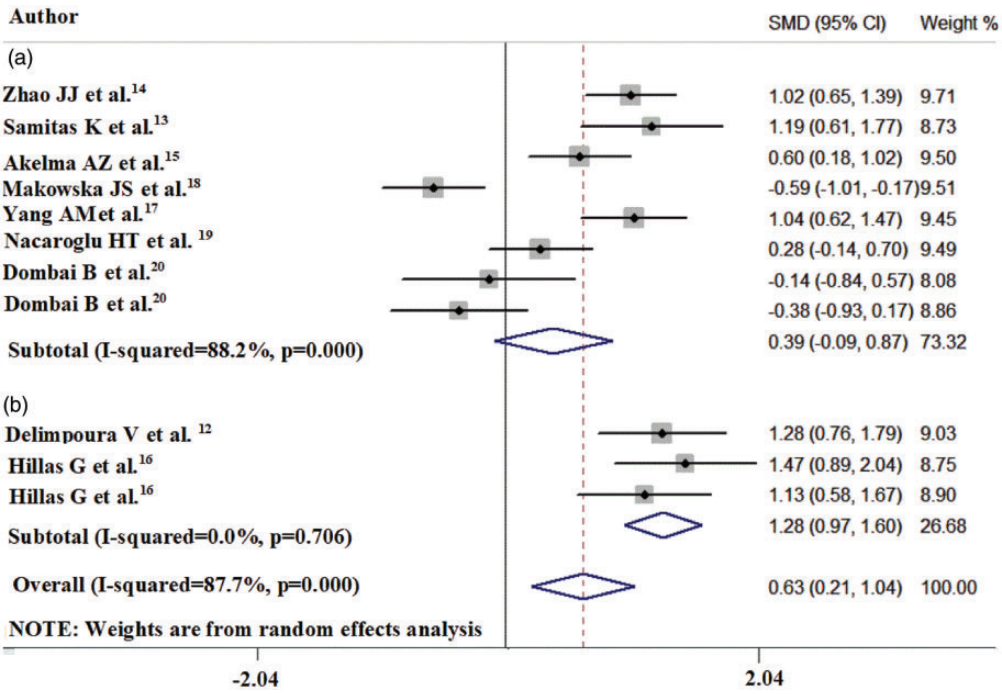

Figure 4. Forest plot of subgroup analysis based on types of specimens. (a) Blood and (b) Sputum.

significantly higher in patients with asthma in Asian populations than in European populations. Although there was no significant correlation between high expression of OPN protein and the presence of asthma in patients in European populations, the expression of OPN protein tended to be higher in patients with asthma than in healthy controls. Furthermore, a subgroup analysis was performed based on the types of specimens used. There was a significant association between OPN protein expression and asthma in studies that used sputum samples; however, the association between OPN protein expression and asthma was not significant in studies that used blood samples. These results indicated that, compared with OPN protein expression in blood, OPN protein expression in sputum could serve as a more objective indicator of the airway inflammation status in asthma patients. Because the number of included studies was limited in this meta-analysis, additional studies should be conducted in the future to validate our findings.

Although this meta-analysis provides the most comprehensive assessment thus far of the relationship between OPN protein expression and asthma, its limitations should be considered when interpreting the findings. First, the current meta-analysis used a small number of data points, particularly with regard to subgroup analyses. Moreover, this meta-analysis was influenced by heterogeneity and confounding factors, as moderate to high heterogeneity was detected in analyses of the association between OPN protein expression and asthma, as well as in the subgroup analysis based on ethnicity.

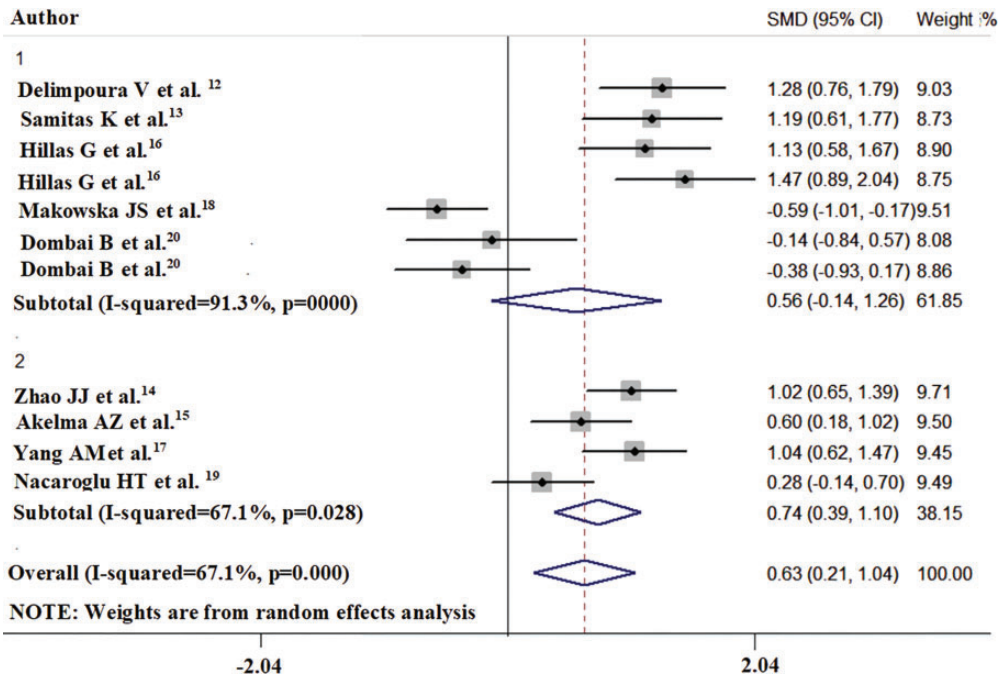

Figure 5. Forest plot of subgroup analysis based on ethnicity. (a) European and (b) Asian.

Conclusion

This meta-analysis provided a systematic evaluation of the relationship between OPN expression and asthma. The results suggested that OPN protein expression may be significantly associated with asthma, particularly when expression levels are determined using sputum specimens. OPN protein expression may be useful as a biomarker for asthma, but this finding should be validated in additional well-designed multicenter studies.

Declaration of conflict of interest

The authors declare that they have no conflicts of interest.

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