Research Article

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Relation between IL-8 level and obstructive sleep apnea syndrome

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Abstract

Objective – This meta-analysis was conducted to explore the relationship between serum level of IL-8 and obstructive sleep apnea syndrome (OSAS).

Methods – Electronic databases were retrieved according to the inclusion and exclusion criteria, relevant studies exploring the relationship between serum level of IL-8 and OSAS were enrolled. Statistical analysis was performed using STATA 12.0.

Results – Totally 199 studies were retrieved, among which 10 were qualified for the inclusion criteria and were finally included in the meta-analysis with 367 cases of OSAS patients and 335 control cases. Serum level of IL-8 was higher in patients than healthy controls (Standard mean difference (SMD) = 2.16, 95% CI = 1.17–3.15, P < 0.001). The subgroup analysis based on ethnicity revealed that average serum level of IL-8 were higher in Asian and Caucasian OSAS patients than healthy controls (Asian: SMD = 2.50, 95% CI = 1.13–3.87, P < 0.001; Caucasian: SMD = 1.59, 95% CI = 0.11–3.06, P = 0.035). Further subgroup analysis based on age indicated a statistical difference in serum level of IL-8 between adult OSAS patients and healthy counterparts (SMD = 2.73, 95% CI = 1.49–3.98, P < 0.001).

Conclusion – The level of IL-8 was related to OSAS in adult patients, and increased serum IL-8 level may increase the risk of OSAS.

Keywords: obstructive sleep apnea syndrome, IL-8, relationship, serum, meta-analysis

1 Introduction

Obstructive sleep apnea syndrome (OSAS) is a prevalent sleep disease resulting from pharyngeal collapse or airway narrowing (hypoxia), which can cause daytime fatigue and sleepiness, metabolic dysfunction, cognitive deficits and cardiovascular disorders [1]. As a significant consequence of medical incidence and mortality, the diagnosis of OSAS has increased sharply during the past few years with a prevalence of 2–10% in adults and an upward trend in the aging population [2]. It is also reported that the occurrence of OSAS in males is 2–3 times higher than in females [3]. Obesity is recognized as one of the major causes for OSAS, and other risk factors including craniofacial abnormalities, macroglossia, adenotonsillar hypertrophy, unhealthy lifestyles (smoking and alcoholism) and family history can also raise the possibility of pharyngeal obstruction [3,4]. OSAS management is multidisciplinary and supposed to be long term. Behavioral, medical and surgical therapies have been implicated in the treatment, in which continuous positive airway pressure (CPAP) is the most common treatment with remarkable efficacy in relieving symptoms and sequel of the OSAS [5]. However, there are accumulating analyses on the adoption of inflammatory serum biomarkers for the assessment of disease prognosis.

Interleukin-8 (IL-8) is a chemokine secreted by macrophages as well as other cells such as epithelial cells, endothelial cells and airway smooth muscle cells [6]. Hypoxia has been announced to induce the expression and generation of IL-8, indicating that OSAS could lead to overexpression of IL-8 [7]. Oyama et al. recruited 32 patients with OSAS and discovered that levels of...
serum IL-8 decreased after 3-month CPAP treatment [8].
Studying in 20 OSAS cases and 10 control individuals, 
Ohga et al. revealed that IL-8 levels of OSAS patients 
with CPAP treatment were significantly higher than the 
control individuals perioperatively [9]. Nevertheless, in 
contrast to 16 OSAS patients with 11 healthy controls, IL-8 
serum levels and its release from neutrophils exhibit no 
difference in both groups. In addition, cytokines concen-
tration in serum also shows no variation after 12 weeks of 
CPAP treatment [10]. Besides, a study that aimed to inves-
tigate the effect of intermittent hypoxia in healthy people 
demonstrated that there was no up-regulation of IL-8 [11]. 
Therefore, the level of serum IL-8 as a predisposing factor 
for OSAS remains controversial. This meta-analysis is sub-
jected to confirm the effect of serum IL-8 on OSAS based on 
former researches.

2 Materials and methods

2.1 Search strategy

To identify relevant papers in English or Chinese, we 
searched electronic databases including PubMed (www.
com/), Wiley (onlinelibrary.wiley.com/), EBSCO (search.
ebscohost.com), Ovid (ovidsp.ovid.com/), Web of Science 
(www.webofknowledge.com/), WANFANF DATA (http://
www.wanfangdata.com.cn/index.html), China National 
Knowledge Infrastructure (CNKI) (https://www.cnki.net/)
and CQVIP (http://www.cqvip.com/) from the inception to 
January 2019. A combination of keywords and free words 
was applied and search terms consisted of obstructive 
sleep apnea, OSA, central sleep apnea, mixed sleep apnea, 
sleep apnea and IL-8.

2.2 Screening criteria

Studies were enlisted into this meta-analysis if they 
met the inclusion criteria: (1) case-control studies about 
serum IL-8 level and obstructive sleep apnea syndrome 
(OSAS); (2) patients clinically diagnosed with OSAS as 
the case group and healthy individuals as the control 
group; (3) studies providing complete data; (4) studies in 
English or Chinese and (5) study with the largest sample 
size or the up-to-date one if the study author published 
several articles with the same case. The exclusion criteria 
were (1) studies without sufficient data; (2) subjects in the 

2.3 Data extraction and quality estimation

Based on a standard sheet, data extraction from eligible 
studies was performed by two researchers separately. The 
data included the first author, publication year, country, 
etnicity, language, detection method, age, gender, and 
case and control numbers. Any disagreement in the 
extracting process was reconciled through the discussion 
of several researchers. Newcastle–Ottawa scale (NOS) 
was applied to assess the quality of each eligible studies 
by more than two researchers, including 10 items: (NOS1) 
whether the case definition was fully and independently 
verified; (NOS2) whether the cases were representative; 
(NOS3) whether the control was the community control; 
(NOS4) whether there was no disease history or no end 
incidences in controls; (NOS5) whether the most im-
portant factors were under control; (NOS6) whether other con-
founding factors were controlled; (NOS7) whether there 
were reliable records of exposure determination; (NOS8) 
whether the blind method was utilized; (NOS9) whether 
the same method was employed to determine the exposure 
of the cases and controls and (NOS10) whether the non-
response rate of the two groups was identical.

2.4 Statistical analysis

Meta-analysis was carried out by employing STATA 12.0 
software (Stata Corp, College Station, TX, USA). Standard 
mean difference (SMD) with 95% confidence intervals 
(95% CI) computed by fixed-effects model or random-
effects model was used to evaluate differences of serum 
IL-8 levels between the case and control group. Then 
Z test was conducted to examine the significance of the 
overall results. Heterogeneity among studies was exam-
ined by Cochrane Q-statistic (P < 0.05 indicated hetero-
genity) [12] and I² test was applied to assess the degree of 
heterogeneity. I² value ranged 0–100%, and the hetero-
genity became more remarkable with higher I² value 
[13]. Collectively, P < 0.05 or I² > 50% revealed significant 
heterogeneity among studies. Sensitivity analyses were 
performed to evaluate the impact of every single study 
on the overall results. Funnel plot [14] and Egger’s linear 
regression analysis [15] were used to confirm whether 
there was publication bias of included studies to ensure 
the reliability of the results.
Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors. Ethical approval is not applicable.

Consent for publication: Not applicable.

3 Results

3.1 Baseline characteristics of included studies

In this study, 199 related literatures were retrieved, and 110 articles were excluded according to their titles and abstracts. After further reading the full text and evaluating the data integrity, 67 articles were excluded. In addition, two studies were excluded due to lack of data integrity. Finally, according to predefined inclusion and exclusion criteria, 10 studies were finally qualified to be included in the meta-analysis with 367 cases of OSAS patients and 335 control cases (Figure 1) [9,16–24]. The included literatures were published between 2006 and 2013, of which six studies were performed in Asian population, while four studies were performed in Caucasians. The quality of all included studies was above moderate standard (NOS score ≥7 points). The baseline characteristics and quality evaluation were listed in Table 1 and Figure 2, respectively.
3.2 Main results of meta-analysis

Ten studies reported the relationship between the serum level of IL-8 and OSAS. Because of the existence of heterogeneity among these studies ($I^2 = 96.2\%$, $P = 0.000$), the random-effects model was thus applied. The meta-analysis revealed that the serum level of IL-8 was significantly higher in the patients than the healthy controls (Figure 3). Additionally, a subgroup analysis concerning ethnicity implied that the IL-8 levels in Asian and Caucasian OSAS patients were both higher than those in the healthy controls (Figure 4). Further subgroup analysis based on age indicated a statistical difference in the serum level of IL-8 between adult OSAS patients and their healthy counterparts, but there was no difference between children OSAS patients and healthy children (Figure 4).

3.3 Sensitivity analysis and publication bias

Included studies were deleted one by one for sensitivity analysis to assess the influence of single study on the overall results, and we found no single studies significantly affected the overall results (Figure 5). Funnel plot showed an asymmetry, and Egger’s test indicated significant publication bias (Figure 6).

4 Discussion

Recently, there is a growing interest in the correlation between the plasma level of IL-8 and OSAS. To decide the connection of these two factors, we conducted a meta-analysis that demonstrated that the plasma level of IL-8 might be related to OSAS. The results revealed that IL-8 levels in patients with OSAS were significantly higher than the healthy controls.

OSAS has been defined as repeated episodes of upper airway occlusion characterized by cessation or reduction of breathing during sleep, with consequent sleep fragmentation and desaturation of blood oxygen [25]. It is associated with significant cardiovascular disease, daytime somnolence, stroke, neurocognitive defects and even dysfunction of the immune and endocrinology system [26]. IL-8 is a chemokine secreted by macrophages and other cells, such as epithelial cells, endothelial cells and airway smooth muscle cells. IL-8 is an important member of the chemokine family and plays a
critical role in enhancing endothelial cell survival, proliferation, and regulating angiogenesis and matrix metalloproteinases production [27]. Previous studies have shown that hypoxia, including OSAS, can induce the expression and production of IL-8. And the recurrent OSAS induced nighttime hypoxic stress might boost the
adherence of neutrophils to endothelial cells [20]. This promoted adhesion is significantly mediated by pro-inflammatory mediators, which contain intercellular adhesion molecule 1 (ICAM-1) 5 and IL-8, via the activation of nuclear transcription factor-KB [21]. Previous evidence has demonstrated that inflammatory activity was...
significantly increased in patients with sleep disturbances [28]. Carpagnano et al. has found in their experiment that plasma IL-8 concentration was overexpressed in obese OSAS patients and non-obese OSAS patients than in healthy subjects [21]. Oyama et al. recruited 32 patients with OSAS and found that the serum IL-8 level decreased after CPAP treatment for 3 months [8]. In the study of 20 OSAS patients and 10 control subjects, Ohga et al. found that the level of IL-8 in OSAS patients after CPAP treatment was significantly lower than that before treatment [9]. However, a study to investigate the effects of intermittent hypoxia on healthy people showed that IL-8 was not up-regulated [19]. Therefore, the level of serum IL-8 as an inducer of OSAS is still controversial and needs to be further confirmed.

It has been reviewed that several inflammatory factors, such as TNF-α, IL-6 and IL-8, can have high concentrations in individuals with OSAS and might act as biological markers of this disease [29]. There is increasing evidence that inflammatory process of IL-8, IL-6 and C-reactive protein (CPR) also plays an essential role in the cardiovascular progression of OSAS, which is suggested by cell culture as well as animal studies detecting activation of inflammatory pathways through intermittent hypoxia (IH), the marker of OSAS [30]. Also, IL-8 is overexpressed in human bronchial epithelial cells, which has been found in response to a vibratory stimulus caused by snoring [31].

Additionally, our study also conducted subgroup analyses based on ethnicity and age. The subgroup analysis concerning ethnicity implied that the serum level of IL-8 in the Asian and Caucasian OSAS patients, as we detected, were higher than the healthy controls.
Inflammatory markers such as CRP, IL-6 and IL-8 have all been found to increase in adult patients with serious sleep problems [18]. Our further subgroup analysis based on age indicated a significant difference in the serum level of IL-8 between adult OSAS patients and their healthy counterparts, but our study found no difference in young OSAS patients and healthy children concerning the plasma level of IL-8. Consistent with our results, Tam et al. were unable to demonstrate the increased levels of IL-6 and IL-8 in children with OSAS after correction for age, gender as well as body mass index (P = 0.05) [16]. Our study showed that there was no difference in IL-8 levels between children with OSAS and healthy children. This result is different from that observed in adults, which may be related to the difference of immune system between adults and children, and may be related to the immature immune system of children.

However, several limitations should be emphasized in this meta-analysis. First, available literatures are limited in number. We have included only 10 studies for meta-analysis. Second, most associated studies concerning the relationship between OSAS and serum level of IL-8 were cross-sectional, and thus the specific association between the two factors still needs further study. Third, we merely collected data based on Asian and Caucasian populations, which consequently cannot be representative of all ethnicities. Fourth, some other factors, such as hypertension, diabetes and obesity, have been considered as more associated with OSAS, since they are also related to inflammation status in bodies and could account for high serum level of IL-8 in OSAS. While our study focused only on roles of serum level of IL-8, we will extend experiments to other predisposing factors for IL-8 induction in our future studies.

5 Conclusion

Our meta-analysis revealed the association between the serum level of IL-8 and OSAS. IL-8 levels in adult patients with OSAS were significantly higher than the healthy controls, suggesting that high IL-8 levels may promote OSAS progression. Further studies are needed to explore the specific role of serum IL-8 in OSAS patients, thus providing possible associated prognostic and therapeutic target for OSAS.

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Conflict of interest: The authors declare no conflicts of interest.

Availability of data and material: The datasets generated/analyzed during the current study are available from the corresponding author on reasonable request.

References


