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

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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 concentration in serum also shows no variation after 12 weeks of CPAP treatment [10]. Besides, a study that aimed to investigate 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 subjected 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.ncbi.nlm.nih.gov/), Springerlink (www.link.springer.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) (<http://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

case and control group with variations about baseline characteristics; (3) repeatedly published researches and (4) unclear criteria to diagnose subjects.

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, ethnicity, 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 important factors were under control; (NOS6) whether other confounding 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 examined by Cochran *Q*-statistic ($P < 0.05$ indicated heterogeneity) [12] and I^2 test was applied to assess the degree of heterogeneity. I^2 value ranged 0–100%, and the heterogeneity became more remarkable with higher I^2 value [13]. Collectively, $P < 0.05$ or $I^2 > 50\%$ 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.

PRISMA Flow Diagram

Figure 1: Flow chart of the study screening process and exclusion reasons.

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.

Table 1: Baseline characteristics of the included studies

First author	Year	Country	Ethnicity	Language	Disease	Number			Gender (M/F)		Age (years)		Interventions		NOS
						Total	OSAS	Control	OSAS	Control	OSAS	Control	OSAS	Control	
Li W	2013	China	Asians	Chinese	OSAS	74	39	35	30/9	28/7	45.74 ± 9.19	46.13 ± 9.07	PSG	PSG	7
Li YM	2012	China	Asians	Chinese	OSAS	60	30	30	18/12	17/13	46.67 ± 8.79	47.13 ± 8.30	—	—	7
Caragnano G	2010	Italy	Caucasians	English	OSAS	20	12	8	8/4	4/16	47.3 ± 13.2	42 ± 4	PSG	PSG	8
Kim J	2010	Korea	Asians	English	OSAS	50	28	22	NR	NR	42 ± 10.77	26 ± 6.91	PSG	PSG	7
Li AM	2008	HK	Asians	English	OSAS	142	47	95	33/14	64/31	11.1 (8.8–13.2)	10.7 (8.2–12.8)	nCPAP	nCPAP	7
Devouassoux G	2007	France	Caucasians	English	OSAS	70	57	13	43/14	7/6	54 ± 11	45 ± 7	CPAP	CPAP	8
Dou XH	2007	China	Asians	Chinese	OSAS	82	60	22	NR	NR	NR	NR	UPPP	UPPP	8
Tam CS	2006	Australia	Caucasians	English	OSAS	113	44	69	30/14	44/25	7.3 ± 3.7	7.6 ± 4	nCPAP	nCPAP	7
Ryan S	2006	Ireland	Caucasians	English	OSAS	61	30	31	30/0	31/0	41 ± 8	43 ± 9	CPAP	CPAP	7
Ohga E	2003	Japan	Asians	English	OSAS	30	20	10	20/0	10/0	NR	NR	nCPAP	nCPAP	7

Note: OSAS, obstructive sleep apnea syndrome; NOS, Newcastle–Ottawa scale; PSG, polysomnography; nCPAP, nasal continuous positive airway pressure; UPPP, uvulopalatopharyngoplasty; NR: Not reported.

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

Figure 2: Quality evaluation for each of the included case-control studies according to 10 items of Newcastle–Ottawa scale (NOS). The quality of all included studies was above moderate standard (NOS score ≥ 7).

Figure 3: Forest plot presenting the comparison of the serum level of IL-8 between OSAS patients and healthy controls.

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

Figure 4: Forest plot presenting subgroup analyses of the serum level of IL-8 between OSAS patients and healthy controls based on ethnicity and age. (a) The levels of serum IL-8 between adults and children with OSAS and their corresponding healthy controls. (b) Comparison of serum IL-8 levels between Asian, European and American OSAS patients and their corresponding healthy controls.

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

Figure 5: Results of sensitivity analysis demonstrating no single study significantly affected the overall results.

Figure 6: Funnel plot showing the risk of publication bias.

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 $\text{TNF-}\alpha$, 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

- [1] Banno K, Kryger MH. Sleep apnea: Clinical investigations in humans. *Sleep Med.* 2007;8:400–26.
- [2] Leger D, Bayon V, Laaban JP, Philip P. Impact of sleep apnea on economics. *Sleep Med Rev.* 2012;16:455–62.
- [3] Kasai T. Sleep apnea and heart failure. *J Cardiol.* 2012;60:78–85.
- [4] Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc.* 2008;5:136–43.
- [5] Mannarino MR, Di Filippo F, Pirro M. Obstructive sleep apnea syndrome. *Eur J Intern Med.* 2012;23:586–93.
- [6] Hedges JC, Singer CA, Gerthoffer WT. Mitogen-activated protein kinases regulate cytokine gene expression in human airway myocytes. *Am J Respir Cell Mol Biol.* 2000;23:86–94.
- [7] Hirani N, Antonicelli F, Strieter RM, Wiesener MS, Ratcliffe PJ, Haslett C, *et al.* The regulation of interleukin-8 by hypoxia in human macrophages — A potential role in the pathogenesis of the acute respiratory distress syndrome (ARDS). *Mol Med.* 2001;7:685–97.
- [8] Oyama J, Yamamoto H, Maeda T, Ito A, Node K, Makino N. Continuous positive airway pressure therapy improves vascular dysfunction and decreases oxidative stress in patients with the metabolic syndrome and obstructive sleep apnea syndrome. *Clin Cardiol.* 2012;35:231–6.
- [9] Ohga E, Tomita T, Wada H, Yamamoto H, Nagase T, Ouchi Y. Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. *J Appl Physiol.* 1985;2003(94):179–84.
- [10] Guasti L, Marino F, Cosentino M, Maroni L, Maresca AM, Colombo F, *et al.* Cytokine production from peripheral blood mononuclear cells and polymorphonuclear leukocytes in patients studied for suspected obstructive sleep apnea. *Sleep Breath.* 2011;15:3–11.
- [11] Tamisier R, Pepin JL, Remy J, Baguet JP, Taylor JA, Weiss JW, *et al.* 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. *Eur Respir J.* 2011;37:119–28.
- [12] Hoaglin DC. Misunderstandings about Q and 'Cochran's Q test' in meta-analysis. *Stat Med.* 2016;35:485–95.

- [13] Pelsser LM, Frankena K, Toorman J, Rodrigues Pereira R. Diet and ADHD, reviewing the evidence: A systematic review of meta-analyses of double-blind placebo-controlled trials evaluating the efficacy of diet interventions on the behavior of children with ADHD. *PLoS One*. 2017;12:e0169277.
- [14] Lin L. Graphical augmentations to sample-size-based funnel plot in meta-analysis. *Res Synth Methods*. 2019;10:376–88.
- [15] He XJ, Qin FY, Hu CL, Zhu M, Tian CQ, Li L. Is gestational diabetes mellitus an independent risk factor for macrosomia: A meta-analysis? *Arch Gynecol Obstet*. 2015;291:729–35.
- [16] Tam CS, Wong M, McBain R, Bailey S, Waters KA. Inflammatory measures in children with obstructive sleep apnoea. *J Paediatr Child Health*. 2006;42:277–82.
- [17] Ryan S, Taylor CT, McNicholas WT. Predictors of elevated nuclear factor-kappaB-dependent genes in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 2006;174:824–30.
- [18] Li AM, Lam HS, Chan MH, So HK, Ng SK, Chan IH, et al. Inflammatory cytokines and childhood obstructive sleep apnoea. *Ann Acad Med Singap*. 2008;37:649–54.
- [19] Kim J, Lee CH, Park CS, Kim BG, Kim SW, Cho JH. Plasma levels of MCP-1 and adiponectin in obstructive sleep apnea syndrome. *Arch Otolaryngol Head Neck Surg*. 2010;136:896–9.
- [20] Devouassoux G, Levy P, Rossini E, Pin I, Fior-Gozlan M, Henry M, et al. Sleep apnea is associated with bronchial inflammation and continuous positive airway pressure-induced airway hyperresponsiveness. *J Allergy Clin Immunol*. 2007;119:597–603.
- [21] Carpagnano GE, Spanevello A, Sabato R, Depalo A, Palladino GP, Bergantino L, et al. Systemic and airway inflammation in sleep apnea and obesity: The role of ICAM-1 and IL-8. *Transl Res*. 2010;155:35–43.
- [22] Dou X, Zeng L, Wang Z. Study of inflammatory factors in patients with obstructive sleep apnea-hypopnea syndrome. *Chin Arch Otolaryngology-Head Neck Surg*. 2007;14:303–5.
- [23] Ye-mei Lli X-wY, Wang T. The research on the levels of interleukin-6 and interleukin-8 in patients of obstructive sleep apnea syndrome (OS-AS) and OSAS with hypertension. *J Clin Pulmonary Med*. 2012;17:250–2.
- [24] Li W, Jiang CC. Serum cytokines in patients with obstructive sleep apnea syndrome treated with continuous positive pressure ventilation. *Chin J Gerontol*. 2013;33:1559–61.
- [25] Wali SO, Alkhouli A, Howladar M, Ahmad I, Alshohaib S, Al-Ghamdi S, et al. Risk of obstructive sleep apnea among Saudis with chronic renal failure on hemodialysis. *Ann Thorac Med*. 2015;10:263–8.
- [26] Santos T, Drummond M, Botelho F. Erectile dysfunction in obstructive sleep apnea syndrome—prevalence and determinants. *Rev Port Pneumol*. 2012;18:64–71.
- [27] Waugh DJ, Wilson C. The interleukin-8 pathway in cancer. *Clin Cancer Res*. 2008;14:6735–41.
- [28] Kadria-Vili Y, Canning G, Bachilo SM, Weisman RB. High precision fractionator for use with density gradient ultracentrifugation. *Anal Chem*. 2014;86:11018–23.
- [29] de Lima FF, Mazzotti DR, Tufik S, Bittencourt L. The role inflammatory response genes in obstructive sleep apnea syndrome: A review. *Sleep Breath*. 2015;20:331–8. doi: 10.1007/s11325-015-1226-7.
- [30] Ryan S, McNicholas WT. Inflammatory cardiovascular risk markers in obstructive sleep apnoea syndrome. *Cardiovasc Hematol Agents Med Chem*. 2009;7:76–81.
- [31] Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, et al. Serum inflammatory markers in obstructive sleep apnea: A meta-analysis. *J Clin Sleep Med*. 2013;9:1003–12.