The Effect of Surgical Treatment of Obstructive Sleep Apnea Syndrome on the Plasma TNF-α Levels

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KATAOKA, T., ENOMOTO, F., KIM, R., YOKOI, H., FUJIMORI, M., SAKAI, Y., ANDO, I., ICHIKAWA, G. and IKEDA, K. The Effect of Surgical Treatment of Obstructive Sleep Apnea Syndrome on the Plasma TNF-α Levels. Tohoku J. Exp. Med., 2004, 204 (4), 267-272 —— Obstructive sleep apnea syndrome (OSAS) is defined as intermittent complete or partial upper airway obstruction during sleep, causing mental and physical effects. Both the local and systemic inflammation observed in OSAS induce certain potent pro-inflammatory mediators, which may contribute to the development of cardiovascular consequences. The present study was designed to evaluate the plasma levels of TNF-α, which is one of the known pro-inflammatory cytokines, in patients with OSAS and to assess the effect of surgical treatment on the levels of TNF-α levels. Twenty seven patients diagnosed to have OSAS, 7 non-apneic patients with chronic tonsillitis (non-OSAS patients), and 4 healthy subjects were enrolled in this study. Blood samples were collected one week preoperatively and postoperatively, and the plasma TNF-α levels were measured using high-sensitivity ELISA. The plasma TNF-α levels in patients with OSAS were significantly elevated in comparison to normal healthy subjects. In contrast, there was no difference between the patients with non-OSAS and healthy subjects. Moreover, the surgical treatment to enlarge the upper airway in patients with OSAS significantly decreased the levels of TNF-α levels. Surgical treatment of patients with OSAS reduces the plasma TNF-α levels, thereby ameliorating the systemic inflammation and preventing the development of cardiovascular consequences. —— obstructive sleep apnea syndrome; TNF-α; surgical modality; inflammation; cardiovascular consequences

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Obstructive sleep apnea syndrome (OSAS) is defined as intermittent complete or partial upper airway obstruction during sleep, causing mental and physical effects. OSAS consists of snoring, sleep disruption, nocturnal hypoxemia and cardiovascular complications, which may lead to sudden death during sleep (Hung et al. 1990). Although the etiology of OSAS is uncertain, intense local and systemic inflammation tends to present in these patients (Saul et al. 1988; Woodson et al. 1991; Sekosan et al. 1996). In the upper airway, this process may promote oropharyngeal inspiratory muscle dysfunction and amplify both upper airway narrowing and collapsibility thereby worsening the frequency and duration of apneas during sleep. The presence of systemic inflammation, characterized by an elevation of certain potent pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF)-α, may predispose patients with OSAS to develop cardiovascular complications observed in patients with OSAS. Recent studies (Vgontzas et al. 1997; Shamsuzzaman et al. 2002; Yokoe et al. 2003) indicate that the concentration of IL-6 and TNF-α were higher in obese men with OSAS than in non-apneic obese men. The treatment of OSAS with nasal continuous positive pressure (nCPAP) was proven to reduce the level of IL-6 levels, thus suggesting that nCPAP is useful for decreasing cardiovascular morbidity and mortality (Yokoe et al. 2003). However, many patients refuse to undergo nCPAP and prefer surgery to enlarge the upper airway because of its potential as a long-term essential cure. Therefore, another treatment options for treatment include several kinds of upper airway surgery such as a tonsillectomy, an adenoidectomy, uvulopalatopharyngoplasty (UPPP), and a midline glossectomy.

The present study was designed to evaluate the plasma level of TNF-α in patients with OSAS and determine the effect of surgical treatment on the TNF-α levels.

**Patients and Methods**

Twenty seven patients consisting of 23 males and 4 females diagnosed to have OSAS, 7 non-apneic patients consisting of 5 males and 2 females with chronic tonsillitis (non-OSAS patients), and 4 healthy subjects (2 males and 2 females) ranging in age from 3 to 69 years with an average of 28.5 years, were enrolled in this study. A diagnosis of OSAS was made in patients with an apnea index (AI), oxygen desaturation associated with respiratory events, and/or such symptoms such as excessive daytime sleepiness and morning headache. An AI > 5 was considered to be diagnostic for OSAS. An AI of ʾ 5 to < 20 indicated mild OSAS, and ʾ 20 indicated severe OSAS. Before enrollment, all subjects gave their written informed consent and underwent a complete sleep history and a sleep evaluation using portable monitor (Apnomonitor, Chest Corporation, Tokyo). The surgical modalities included UPPP, tonsillectomy, and adenoidectomy. Flomoxef or fosfomycin as antibiotics and loxoprofen or acetaminophen as anti-inflammatory drugs were administered during and after the operation. A second apnomonitor evaluation was also carried out one week after the operation.

Samples of peripheral venous blood in all subjects were collected at 8 AM one week preoperatively and postoperatively. All samples were stored at −80°C until assay. The plasma levels of TNF-α were measured by a high-sensitivity ELISA which could detect concentrations as low as 0.06 pg/mL. ELISA kits to determine the TNF-α levels were obtained from the R&D system Co., Ltd. (Minneapolis, MI, USA)

The significance of differences between the 2 groups was analyzed using the Wilcoxon-t-test. In addition, the TNF-α levels among the 3 groups classified based on their severity of apnea were evaluated by the Kruskal-Wallis-H-test. All data are expressed as the mean ± s.d., and a probability of less than 0.05 was considered to indicate significance.
RESULTS

Fig. 1 shows the preoperative and postoperative values of AI, which indicated a significant reduction in the AI in all patients. However, only 11 out of 27 patients eventually demonstrated normal sleep conditions. The TNF-α levels were significantly higher in the patients with OSAS than in the healthy subjects ($p < 0.05$) whereas no significant difference was observed between the patients with non-OSAS and healthy subjects (Fig. 2). OSAS patients tended to show higher plasma TNF-α levels than those in non-OSAS patients, but the difference was not significant.

![Fig. 1. Comparison of the preoperative and postoperative apnea index in patients with obstructive sleep apnea syndrome.](image1)

![Fig. 2. Distribution of plasma TNF-α in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS, and healthy volunteers.](image2)

![Fig. 3. Comparison of the preoperative and postoperative levels of plasma TNF-α in patients with obstructive sleep apnea syndrome (OSAS) and non-OSAS. Open circles indicate the average value.](image3)
The TNF-α levels were postoperatively decreased in all OSAS patients except four. In the non-OSAS patients, it levels increased in 2, it decreased in 4, and it was unchanged in one care after surgery. A statistical analysis revealed that surgical therapy caused a significant decrease in the TNF-α levels in the patients with OSAS (p < 0.05) but not in the non-OSAS patients (Fig. 3). In addition, no correlation was observed between the levels of TNF-α and the preoperative AI (r = 0.262, p = 0.186).

The plasma TNF-α levels were analyzed based on the basis of the severity of sleep apnea. Among the three groups consisting of severe OSAS, mild OSAS and non-OSAS, the patients with severe OSAS alone showed a significant reduction in the TNF-α levels after surgery (Fig. 4).

**DISCUSSION**

The present study demonstrated that the plasma TNF-α levels, one of the known pro-inflammatory cytokines, in patients with OSAS increased significantly more than in normal healthy subjects. This finding confirms the data of a previous report by Vgontzas et al. (1997). Other pro-inflammatory cytokines such as IL-1, IL-6 and CRP have also been reported to increase in patients with OSAS in comparison to non-OSAS subjects (Shamsuzzaman et al. 2002; Yokoe et al. 2003). However, we did not find that the levels of TNF-α in the patients with OSAS to differ substantially from those in patients with non-OSAS. This may be explained by the fact that the elevation in the TNF-α levels in patients with non-OSAS is caused by the presence of an inflammation in the tonsils. In addition, the absence of any correlation between the TNF-α levels and the preoperative AI may also be explained by upper airway inflammation in the tonsils and adenoid tissues.

Both the local and systemic inflammations observed in OSAS (Saul et al. 1988; Woodson et al. 1991; Sekosan et al. 1996) induce certain potent pro-inflammatory mediators. Various underlying mechanisms regarding the role that TNF-α plays in the pathogenesis of OSAS have been postulated. First, TNF-α is known to modulate somnolence and fatigue (Entzian et al. 1996). Second, the increased circulating TNF-α levels in OSAS may promote pharyngeal inspiratory muscle dysfunction (Reid et al. 2002), thereby worsening apneic episode during sleep. Third, elevated TNF-α levels are associated with enhanced slow waves during sleep (Darko et al. 1995), thus suggesting that the cardinal symptoms of OSAS may be mediated by TNF-α. Nocturnal hypoxia
in OSAS produces reactive oxygen and nitrogen species, which are considered to be mediators of systemic inflammation. The local production of cytokines in the inflamed upper airway exposed to systemic circulation also contributes to other sources of the mediators for systemic inflammation. It is therefore possible that the cardiovascular consequence of OSAS is mediated by a heightened systemic inflammatory state, which is associated with free radicals and cytokines (Hatipoglu and Rubinstein 2003).

The present study is the first report to show that the treatment with surgery to enlarge the upper airway in patients with OSAS decreases the TNF-α levels. The treatment with nCPAP in patients with OSAS has already been proven to decrease levels of both the IL-6 and CRP levels, which are associated with risk factors for cardiovascular complications in OSAS (Yokoe et al. 2003), thus indicating that nCPAP is considered to be useful for decreasing these risks. The clinical effectiveness of surgical procedures for the treatment of OSAS remains controversial (de Berry Borowiecki and Sassin 1983; Guilleminault et al. 1983; de Berry Borowiecki et al. 1985; Conway et al. 1985; Fujita et al. 1985; Blakley et al. 1986; Gislason et al. 1988; Sanders et al. 1990; Sato et al. 2000). The success rate of surgical procedures has been reported to be range from 50 to 70%. He et al. (1998) demonstrated that the cumulative survival of the group treated with UPPP alone to not be different from that of untreated patients with an apnea index > 20. Patients with severe OSAS may therefore be effectively treated with nCPAP. A recent randomized controlled study of nCPAP provided confirmative evidence of its clinical effectiveness for the treatment of OSAS (Jenkinson et al. 1999). The compliance of nCPAP is reported to be 40–60% (Hoffstein et al. 1992; Kribbs et al. 1993). The alternative to nCPAP is surgery to enlarge the narrowed upper airway. Based on the present findings, surgical procedures are indicated to ameliorate systemic inflammation observed in OSAS by significantly reducing the plasma TNF-α levels, which are related to the development of cardiovascular complications of OSAS. Blood samples to measure the TNF-α levels were collected one week after surgery in order to minimize any influence of the surgical wound on the findings. Three out of 4 patients showing more than a 5 pg/ml of TNF-α levels one week preoperatively continued to show high levels after the operation, and this phenomenon can be explained by the presence of surgical residual stress and/or an insufficient improvement in the apnea symptoms. Better wound healing and a greater improvement in the TNF-α values may thus require a longer time after surgery. Nevertheless, severe OSAS may require additional treatment such as nCPAP. In conclusion, we demonstrate for the first time that surgery successfully reduces the plasma TNF-α levels in OSAS patients, which will ameliorate the systemic inflammation of OSAS and prevent the development of cardiovascular complications.

References


