Respiratory Medicine (2009) **103**, 386–392

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

TNF-alpha gene polymorphism and TNF-alpha levels in obese Asian Indians with obstructive sleep apnea☆,☆☆

Bharat Bhushan [a], **Randeep Guleria** [a,*], **Anoop Misra** [c], **Kalpana Luthra** [b], **Naval K. Vikram** [a]

[a] *Department of Medicine, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India*
[b] *Department of Biochemistry, All India Institute of Medical Sciences, New Delhi, India*
[c] *Department of Diabetes and Metabolic Diseases, Fortis Hospital, New Delhi, India*

Received 5 February 2008; accepted 1 October 2008
Available online 20 November 2008

KEYWORDS
Obstructive sleep apnea;
Tumor necrosis factor-α;
Gene polymorphism;
Asian Indians;
Obesity

Summary
Background: Obstructive sleep apnea (OSA) is emerging as a significant disorder in India. Tumor necrosis factor-α (TNFα) is an important marker of inflammation. Recent data indicate that inflammation may be an important correlate of OSA. The relationships of OSA with TNFα levels and *TNFα* gene promoter polymorphism *(−308G/A)* have not been investigated in obese Asian Indians with OSA.
Objective: To look for the correlation if any, between *TNFα gene promoter* polymorphism *(−308G/A)* in obese Asian Indians with and without OSA and correlation of TNFα levels with severity of OSA.
Methods and results: We studied 207 obese (BMI >25 kg/m^2) subjects; 104 with OSA and 103 without OSA. Both groups were matched for age, body mass index (BMI) and percentage body fat (%BF). Measurements included anthropometric and biochemical (fasting blood glucose, lipid profile and serum TNFα levels) parameters and *TNFα gene* promoter polymorphism *(−308G/A)*. The frequency of '*−308A*' *allele* in *TNFα gene* was significantly higher in obese subjects with OSA (28.8%; 60/208), when compared with obese subjects without OSA (12.6%; 26/206, $p = 0.001$). Serum TNFα levels were significantly higher in obese subjects with OSA [(3.6 ± 0.8)pg/ml], when compared with obese subjects without OSA [(3.3 ± 0.6)pg/ml, $p = 0.009$].

☆ Institution where work was performed: All India Institute of Medical Sciences, New Delhi, India
☆☆ Impact of this research on clinical medicine and basic science: This study provides important information regarding *TNFα gene* polymorphism and TNFα levels in Asian Indians with OSA. These data have potential implications for future genotyping of Asian Indians with OSA and in its pathogenesis.

* Corresponding author. Tel.: +91 11 26593676; fax: +91 11 26862663, 26589732.
E-mail addresses: randeepguleria2002@yahoo.com, bharataiims@gmail.com (R. Guleria).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2008.10.001

Conclusions: Frequency of *TNFα (−308A) allele and* serum TNFα level was significantly higher in obese Asian Indians with OSA.

Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by repetitive collapse of upper airway during sleep. It affects about 4–9% of adult population and children.[1] Prevalence of OSA is 7.5% in Asian Indians living in India.[2] OSA is now considered as an independent risk factor for hypertension and cardiovascular mortality.[3,4] There is increasing evidence that OSA is associated with inflammation. *TNFα (−308G/A)* polymorphism is associated with increased TNFα levels.[5,6] Derangements of inflammatory cytokines, such as C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported in OSA.[7,8] Tumor necrosis factor-α (TNFα), a pro-inflammatory cytokine may have a role in regulation of sleep.[9,10] Excessive daytime sleepiness (EDS), a major feature of OSA, is promoted by increase in TNFα levels.[7,9] Ryan et al. have shown that intermittent hypoxia is a strong predictor of serum TNFα levels.[11]

The primary risk factor for OSA is excessive weight gain. Other than male gender, obesity is the strongest risk factor for the development of OSA.[12,13] Various studies indicate that about 66% of patients with OSA are obese. Significant weight loss has been shown to have varying degrees of improvement in OSA.[14] Previous studies on Asian Indians with OSA are limited to assessment of prevalence data, evaluation of relationship of OSA with road traffic accidents and public health awareness of OSA.[2,15,16] Data regarding relationship of sub-clinical inflammation and OSA are limited. Recently, we have shown the association of severity in OSA with increasing levels of CRP in obese Asian Indians.[17] The relationship of TNFα levels and its promoter polymorphism *(−308G/A)* has not been investigated in Asian Indians with OSA. Since high levels of TNFα have been linked to EDS,[11] it is possible that *TNFα (−308G/A)* promoter polymorphism may associate with the development of OSA in obese Asian Indians with OSA.

We conducted this cross-sectional study to determine the frequency of *TNFα (−308A) allele* in obese subjects with and without OSA. Correlation, if any, of serum TNFα levels with OSA severity was also looked at in these obese subjects.

Methods

Subjects

A total of 207 obese subjects were recruited from Medicine out patients department of All India Institute of Medical Sciences, a tertiary care referral hospital. The subjects were North Indians residing in New Delhi or surrounding areas located near New Delhi. 104 obese subjects were newly diagnosed with OSA (84 males and 20 females) and 103 obese subjects were without OSA (65 males and 38 females). To nullify the effect of obesity, subjects were carefully matched for age, body mass index (BMI) and percentage body fat (%BF). Full montage polysomnography (PSG) was performed in all subjects. On the basis of apnea-hypopnea index (AHI), subjects were categorized as with or without OSA (see definitions below). All subjects were free of any acute or apparent chronic inflammatory disorders, chronic obstructive pulmonary disease (COPD) and coronary heart disease (CHD; based on clinical history and ECG). Subjects with other sleep disorders such as upper airway resistance syndrome (UARS), central sleep apnea (CSA), periodic limbs movement (PLMs) or narcolepsy were excluded. All subjects were non-smokers or had quit smoking before three years. No subject was taking any medications at the time of evaluation. Clinical evaluation for all subjects included thyroid profile and an ECG was done on enrollment. The study was approved by institutional ethics committee and written informed consent was obtained from all subjects.

Metabolic parameters

Blood samples were collected after an overnight fast for estimation of fasting blood glucose (FBG) and blood lipoproteins. Levels of FBG, total cholesterol (TC) and serum triglycerides (TG) were estimated using commercial kits (Randox Laboratory, San Francisco, CA, USA) in a semi-automated analyzer (Micro Semi-Autoanalyser 2000, C.L. Micromed, Italy).

Anthropometric measurements

The anthropometric measurements were carried out by a physician according to methods described earlier.[18] Briefly, waist circumference was measured midway between the highest point of superior iliac crest and lowest point of costal margin; hip circumference was measured at the maximum circumference of buttocks. All measurements were taken in standing position with feet placed together. Measurement of % BF was carried out using leg-to-leg (two point contact) bioelectrical impedance method (Tanita TBF 300, TANITA Corp., Tokyo, Japan). For estimation of bioelectrical impedance, subjects were evaluated after an overnight fast. They were instructed to avoid fluid intake and void urine 1 h prior to measurements and just before the test. Gender and height details were manually entered into the system. Subjects were instructed to stand on apparatus so that both feet were in firm contact with the surface of apparatus and hands were not in touch with any surface.

Polysomnography (PSG)

All subjects underwent overnight digital full montage PSG (Medi palm; Braebon Medical Corp., Canada) and classified according to AHI (see definitions). Digital PSG included electrooculogram, electroencephalogram, electromyogram, electrocardiogram, airflow (with an oro-nasal thermistor),