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Plasma ghrelin and pro-inflammatory markers in patients with obstructive sleep apnea and stable coronary heart disease

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Background: Inflammation is associated with obstructive sleep apnea (OSA) and coronary heart disease (CHD). Ghrelin, a multifunctional hormone, may play a key role in patients with OSA and/or CHD. The aim of this study was to investigate plasma ghrelin and pro-inflammatory cytokines in patients with OSA and /or CHD and assess the association of these cytokines with ghrelin.

Material/Methods: Plasma ghrelin, interleukin-6(IL-6) and tumor necrosis factor alpha (TNF-α) were measured in 75 patients and in 25 age-, sex-, and BMI-matched healthy control subjects. These patients were further classified into 3 groups (25 with OSA, 25with OSA and CHD, and 25 with CHD), matched for age, sex, body mass index, and the severity of OSA or CHD.

Results: Plasma ghrelin levels were increased, and TNF-α and IL-6 were decreased in OSA patients with and without CHD, when compared with controls with similar CHD clinical characteristics (both $P<0.05$). Further, OSA patients with CHD tended to have higher plasma levels of TNF-α and IL-6, and lower plasma levels of ghrelin than OSA controls ($P>0.05$). Notably, plasma ghrelin levels were independently negatively correlated with plasma TNF-α and IL-6 ($P<0.05$).

Conclusions: Increased plasma ghrelin levels might constitute an independent determinant of decreased TNF-α and IL-6, suggesting that higher ghrelin level may in part represent a compensatory mechanism to overcome the pro-inflammatory effects of OSA. Further large-scale and prospective studies are needed to confirm these effects.

Key words: OSA • CHD • TNF-α • IL-6 • ghrelin

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Background

Obstructive sleep apnea (OSA) is a major public health problem, affecting an estimated 9% of adult women and 24% of adult men [1]. A growing body of evidence shows that OSA is independently associated with cardiovascular diseases [2–4]. The mechanisms underlying this association remain obscure. The presence of chronic systemic inflammation is proven to be linked with OSA and coronary heart disease (CHD) [5,6].

Ghrelin, an orexigenic hormone, has been proposed as a cause of increased appetite and obesity [7]. Administration of ghrelin increases adiposity, food intake, and body weight [8]. It also regulates or influences a number of other biological actions, including effects on sleep and cardiovascular function. Previous studies [9] reported that plasma ghrelin levels were significantly higher in OSA patients than in BMI-matched controls. On the contrary, findings from Kotani et al. [10] suggested that ghrelin levels were lower in patients with carotid atherosclerosis and were inversely correlated with carotid intima-media thickness. Recent studies have also demonstrated that ghrelin acts as an anti-inflammatory factor via inhibiting the expression of pro-inflammatory cytokines such as TNF-α and IL-6 in humans and animals [11–15]. However, there are few published studies on ghrelin and its association with TNF-α and IL-6 in patients with OSA and/or CHD.

The aim of this study was to investigate plasma ghrelin and pro-inflammatory cytokines in patients with OSA and/or CHD and assess the association of these cytokines with ghrelin.

Material and Methods

Patients

The study population consisted of patients recruited from the 19th ward at Fuwai Hospital, who were referred for a clinical suspicion of stable CHD accompanied by OSA. On the admission night before coronary angiography, polysomnography (PSG) testing was performed to exclude OSA. This study was approved by the Human Ethics Committee of Fuwai Hospital and all participants provided their written informed consent.

Exclusion criteria were: prior percutaneous coronary intervention, previous myocardial infarction or coronary artery bypass graft surgery, acute coronary syndrome or other chronic inflammatory processes, gastric disease or prior gastric surgery, malignant tumors, thyroid dysfunction, chronic obstructive pulmonary disease, central sleep apnea or Cheyne-Stokes respiration, chronic renal or hepatic failure, or who were receiving sleep apnea treatment with continuous positive airway pressure.

Clinical assessment

Medical history and sleep questionnaires were recorded. Anthropometric data, such as body weight (in kilograms), height (in meters), waist circumference (WC), and neck circumference (NC) (in centimeters) were measured, with the patient lightly clothed and shoeless. Body mass index (BMI) was calculated as weight divided by height squared. Subjective sleepiness was evaluated by use of the Epworth Sleepiness Scale (ESS) [16]. The Gensini score [17]was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance. Subjects with a Gensini score >4 were included in the CHD group.

Sleep study

After baseline assessment, patients underwent overnight PSG testing (Embletta 9, Medcare Flaga, Reykjavik, Iceland) at the 19th ward. The following variables were included: nasal airflow (thermistor), peripheral oxygen saturation (pulse oximetry), thoracic and abdominal movements (plethysmography), body position, and snoring (microphone). PSG data were manually scored according to established criteria [18]. Respiratory events needed a minimum duration of 10 s for analysis. Apnea was considered obstructive when nasal flow was absent in the presence of thoracic movements, and central when movements were absent as well. Hypopnea was defined as a 50% reduction in airflow, together with a drop in oxygen saturation of ≥4%. Apnea-hypopnea index (AHI) was calculated as the mean number of apneas and hypopneas per hour of sleep. Subjects with AHI ≥5 were considered to have OSA after excluding central sleep apnea. Central sleep apnea was diagnosed when at least 50% of sleep events were of central origin.

Blood collection and biochemical measurements

After overnight fasting, blood samples were collected into ethylenediamine tetra acetic acid (EDTA)-coated polypropylene tubes. The clear plasma supernatants were frozen in aliquots at –80°C immediately after centrifugation (5000r/m for 10 min at 4°C). Plasma ghrelin levels were measured by radioimmunoassay (RIA) kit (LINCO Research, St. Charles, MO, USA). Intra- and interassay coefficients of variation (CV) were 10.0% and 14.7%, respectively, for ghrelin. Ultrasensitive ELISAs were used for TNF-α and IL-6 determination (Quantikine HS; R&D Systems, Inc., Minneapolis, MN, USA). Intra- and interassay CV were 3.1 and 7.4% for TNF-α and 7.8% and 7.2% for IL-6, respectively.

Statistical analysis

Normally distributed data are expressed as means ± standard deviation (SD), skewed data as median (ranges), and

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Table 1. General and sleep characteristics of study groups.

Variables	OSA (n=25)	OSA and CHD (n=25)	CHD (n=25)	Control group (n=25)
Age, years	54 (7)	53 (7)	54 (8)	53 (7)
Sex, male (%)	23 (92%)	23 (92%)	23 (92%)	23 (92%)
BMI, kg/m2	27.39 (2.91)	27.5 (2.98)	26.22 (2.15)	26.27 (1.9)
WC, cm	97.72 (8.29)§	99.8 (8.07)*,§§	90.74 (8.01)†,‡‡	94.98 (8.02)‡
NC, cm	41 (3.19)§	41.12 (2.33)§	38.1 (2.07)*,††,‡‡	39.78 (2.27)§
Current smoker, n (%)	12 (48)	11 (44)	10 (40)	12 (48)
HT, n (%)	16 (64)	18 (72)	14 (56)	–
DM, n (%)	5 (20)	6 (25)	4 (16)	–
Dislipidemia, n (%)	19 (76)	19 (76)	17 (68)	– Metabolic co-medications
Statins, n (%)	9 (36)	10 (40)	8 (32)	–
ACEI/ARB, n (%)	6 (24)	9 (36)	4 (16)	–
CCB, n (%)	4 (16)	7 (28)	6 (24)	–
Beta-blockers, n (%)	6 (24)	4 (16)	3 (12)	–
Lowing glucose, n (%)	4 (16)	6 (24)	3 (12)	–
Gensini	1.22 (1)§§,‡‡	55.6 (47.12)**,††	53.18 (32.03)**,††	–§§,‡‡
AHI, events/h	24 (17)**,§§	25 (15)**,§§	3 (1)††,‡‡	3 (1)††,‡‡
ODI, events/h	24 (17)**,§§	23 (15)**,§§	3 (2)††,‡‡	3 (1)††,‡‡
Minimum SpO2,%	79.76 (9.76)*	79.6 (10.93)*	84.96 (17.36)	89.32 (2.53)†,‡
t<90, %TST	2.2 (52.3)*,§	4 (68.2)*,§	0 (2)†,‡	0 (0.5)†,‡
ESS	8 (5)**,§	7 (3)**	5 (1)†	3 (1)††,‡

Data are expressed by mean (SD) or median (ranges) or *n* (%). OSA – obstructive sleep apnea; CHD – coronary heart disease; BMI – body mass index; WC – waist circumference; NC – neck circumference; HT – hypertension; DM – diabetes mellitus; ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CCB – calcium channel blockers; AHI – apnea-hypopnea index; ODI – oxyhemoglobin desaturation index; SpO_2 – pulse oximetric saturation; TST – total sleep time; ESS – Epworth Sleepiness Scale. * P<0.05, ** P<0.001 *vs.* healthy controls; § P<0.05, §§ P<0.001 *vs.* CHD; † P<0.05, †† P<0.001 *vs.* OSA; ‡ P<0.05, ‡‡ P<0.001 *vs.* CHD with OSA.

categorical data as percentages. Data were analyzed using one-way ANOVA with least significant difference tests for post hoc comparisons, or Kruskal-Wallis H test, as appropriate. Categorical variables were compared using chi-square test. Correlations between variables were explored using Pearson coefficient. To assess the relative strength of the association, multiple linear regression analysis was performed to examine the possible factors that impact TNF-α and IL-6. A P value of <0.05 was considered statistically significant. Statistical analysis was carried out by use of SPSS statistical software version 16.0 (Chicago, Illinois, USA).

Results

Clinical Characteristics

We enrolled 75 patients with a recently confirmed diagnosis of CHD and/or OSA. According to the OSA status (determined by AHI) and the severity of CHD (defined by Gensini score), patients were classified into 3 groups (25 with OSA, 25 with OSA and CHD, and 25 with CHD), matched for age, sex, BMI, and the severity of OSA or CHD. As a control group, we also studied 25 healthy volunteers in whom OSA and CHD were excluded by PSG and coronary

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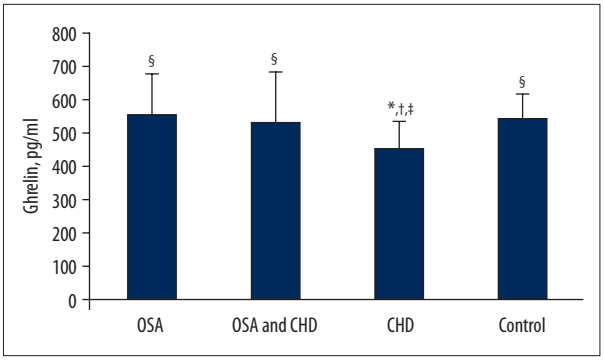

Figure 1. Mean ±SD of ghrelin level in the four groups studied. Abbreviations: OSA, obstructive sleep apnea; CHD, coronary heart disease; SD-standard deviation. * P<0.05 *vs.* control group; § P<0.05 *vs.* CHD; † P<0.05 *vs.* OSA; ‡ P<0.05 *vs.* CHD with OSA.

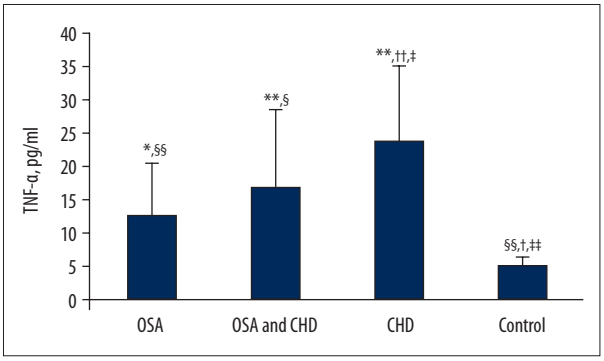

Figure 2. Mean ±SD of TNF-α level in the four groups studied. TNF-α – tumor necrosis factor alpha; OSA – obstructive sleep apnea; CHD – coronary heart disease; SD – standard deviation. * P<0.05, ** P<0.001 *vs.* control group; § P<0.05, §§ P<0.001 *vs.* CHD; † P<0.05, †† P<0.001 *vs.* OSA; ‡ P<0.05, ‡‡ P<0.001 *vs.* CHD with OSA.

angiography. The control group was matched with patients for age, sex, and BMI. Table 1 shows the general and sleep characteristics of the subjects studied. Age, sex, and BMI were similar in all study groups, as well as AHI between OSA groups and Gensini score between CHD groups. Interestingly, despite similar BMI, WC and NC were significantly higher in the OSA with or without CHD group compared to the CHD alone group. No significant differences were found between OSA groups in nocturnal oxygenation indices, such as oxygen desaturation index, minimum oxygen saturation, and % of time spent at SpO_2 <90%. The prevalence of hypertension, diabetes, dyslipidemia and the use of cardio-metabolic medications (e.g., statins, ACE inhibitors or angiotensin receptor blockers and beta-blockers) were similar between groups.

Effects of CHD and OSA on plasma ghrelin, TNF-α, and IL-6

Among all groups, the most pronounced decrease in plasma ghrelin (453.69±79.06 pg/ml) was observed in the CHD alone group (*P*<0.05). No significant difference was found in the level of plasma ghrelin between the OSA with or without CHD group and the control group (all *P*>0.05). Plasma TNF-α and IL-6 levels significantly increased across the OSA (12.55±8.09 and1.89±1.29pg/ml, respectively), OSA with CHD (16.87±11.8 and 2.92±2.09 pg/ml, respectively), and CHD (23.95±11.46 and 5.28±3.85 pg/ml, respectively) groups compared with the control group (5.12±1.23 and 1.0±0.12 pg/ml, respectively) (*P*<0.05). Furthermore, we noted that CHD patients with or without OSA had even higher TNF-α and IL-6 levels than patients with OSA alone (*P*<0.05). The ghrelin, TNF-α, and IL-6 plasma levels found in the 4 groups are shown in Figure 1–3, respectively.

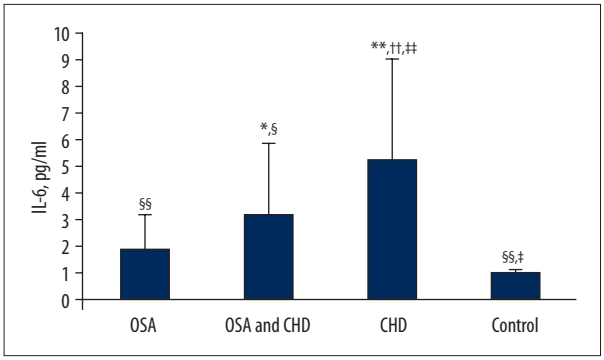

Figure 3. Mean ±SD of IL-6 level in the four groups studied. IL-6 – interleukin-6; OSA – obstructive sleep apnea; CHD – coronary heart disease; SD – standard deviation. * P<0.05, ** P<0.001 *vs.* control group; § P<0.05, §§ P<0.001 *vs.* CHD; † P<0.05, †† P<0.001 *vs.* OSA; ‡ P<0.05, ‡‡ P<0.001 *vs.* CHD with OSA.

To investigate the effects of OSAS, we compared the results obtained in control subjects and patients with OSA alone. The latter showed higher plasma levels of TNF-α (12.55±8.09 *vs.* 5.12±1.23 pg/ml, *P*<0.05) (Figure 2). The BMI, WC, and NC in these 2 groups were not different (Table 1). The effects of CHD were estimated by comparing the plasma levels of ghrelin, TNF-α, and IL-6 in the CHD without OSA group with those in the BMI-matched control group. The former had lower plasma ghrelin levels (453.69±79.06 *vs.* 540.67±75.02 pg/ml, *P*<0.05) (Figure 1), and had higher plasma levels of TNF-α and IL-6 (23.95±11.46 *vs.* 5.12±1.23 pg/ml and 5.28±3.85 *vs.* 1.0±0.12 pg/ml, respectively, *P*<0.001) (Figures 2 and 3). Further, to assess the effects of CHD combined with OSA, plasma ghrelin, TNF-α, and IL-6 of CHD patients combined with OSA were compared with those obtained in control subjects. TNF-α and IL-6 levels were significantly higher in the CHD patients combined with OSA (16.87±11.8 *vs.* 5.12±1.23 pg/ml in TNF-α, *P*<0.001; 2.92±2.09 *vs.* 1.0±0.12 pg/ml, *P*<0.05) (Figures 2 and 3). However, the ghrelin level was similar between the 2 groups (532.51±152.54 *vs.* 540.67±75.02 pg/ml, *P*>0.05) (Figure 1). Despite similar BMI, CHD with OSA showed significantly larger WC and NC (Table 1).

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Table 2. Multiple linear regression analysis.

Variables	B	Std. error	Beta	t value	P value
Constant	–28.747	18.353	–	–1.566	0.124
Ghrelin, pg/ml	–0.023	0.010	–0.299	–2.306	0.026
Age	0.405	0.191	0.273	2.115	0.040
Minimum SpO2,%	0.361	0.140	0.361	2.572	0.013
ESS	0.751	0.345	0.303	2.175	0.035

SpO_2 – pulse oximetric saturation; ESS – Epworth Sleepiness Scale. The dependent variable was tumor necrosis factor-alpha, R was 0.537, R^2 was 0.288; and the estimated standard error was 9.025. One-way ANOVA was used to test the significance of the regression model, F value was 4.547, P=0.004.

Table 3. Multiple linear regression analysis.

Variables	B	Std. error	Beta	t value	P value
Constant	–4.150	2.269	–	–1.829	0.074
BMI, kg/m^2	0.210	0.082	0.340	2.569	0.013
Ghrelin, pg/ml	–0.003	0.002	–0.245	–1.853	0.070

BMI – body mass index. The dependent variable was interleukin-6, R was 0.455, R^2 was 0.207; and the estimated standard error was 1.634. One-way ANOVA was used to test the significance of the regression model, F value was 6.146, P=0.004.

Linear regression analysis showed that TNF-α was significantly associated with ghrelin (r=–0.310, *P*=0.014), age (r=0.252, *P*=0.039), and minimum SpO_2 (r=0.240, *P*=0.047). Standard multiple regression analysis revealed an independent relationship of ghrelin, age, minimum SpO_2 and ESS with TNF-α (R^2=0.288, *P*=0.077) (Table 2). In the case of IL-6, we found significant correlations with ghrelin, BMI, and WC (*P*>0.05). The former 2 variables were independent determinants of ghrelin in standard multiple regression analysis (R^2=0.207, *P*=0.004) (Table 3).

Discussion

This is the first study to show that plasma ghrelin levels were increased, and TNF-α and IL-6 were decreased, in OSA patients with or without CHD, when compared to CHD controls with similar clinical characteristics. OSA patients with CHD tended to have higher plasma levels of TNF-α and IL-6, and lower plasma levels of ghrelin compared to OSA controls.Notably, low ghrelin levels constituted an independent determinant of elevated plasma TNF-α or IL-6.

Inflammation is proven to be associated with OSA and CHD. Several previous studies [19–21] reported that pro-inflammatory cytokines (such as TNF-α and IL-6) were elevated in patients with OSA. Ridker et al. [22,23] showed that higher levels of TNF-α and IL-6 were associated with increased adverse coronary events. However, to date, there are few published studies on markers of inflammation in OSA patients with CHD. In the present study, on the basis of similar clinical characteristics, we demonstrated that OSA patients with or without CHD had significantly lower plasma levels of both TNF-α and IL-6 compared with CHD controls, suggesting that OSA may partially contribute to the decrease of these 2 cytokines.

Ghrelin, an appetite hormone, is postulated to act as a contributor to OSA-associated obesity. Our study revealed increased plasma ghrelin levels in OSA patients with or without CHD compared with CHD patients. We and others have shown that patients with OSA have even higher ghrelin levels than subjects without OSAS matched for age and BMI [24,25]. The elevated ghrelin levels in OSA patients may explain the relatively increased deposition of fat in the waist and neck. Conversely, lower ghrelin levels were detected in patients with CHD. This is in agreement with the findings from Kadoglou et al. [26], who demonstrated that ghrelin serum levels were lower in patients with CHD compared with healthy controls and an inverse relationship between ghrelin and CHD presence independent of other cardiovascular risk factors. Taken together, these data suggest that increased ghrelin levels may promote the development of atherosclerosis among OSA subjects with CHD. The underlying mechanisms between these effects remain to be explored in future studies.

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Recent studies have also demonstrated that ghrelin acts as an anti-inflammatory factor via inhibiting the expression of pro-inflammatory cytokines in humans and animals [11–15]. In the current study, we found that the concentrations of ghrelin were significantly negatively correlated with plasma TNF-α and IL-6, in accordance with the study by Rodríguez et al. [27]. These relationships remained after adjustment for WC and NC, which were reported to have a positive association with both subcutaneous and visceral fat with circulating markers of inflammation in Framingham Heart Study participants [28]. One possible mechanistic explanation for the negative associations of ghrelin with TNF-α and IL-6 may be explained by a considerable ghrelin-induced inhibition of nuclear factor-B activity – a crucial mediator of chemotactic cytokines and adhesion molecule expression in the endothelium [11].

A limitation of the present study was its cross-sectional design, which prevented us from demonstrating firm cause-effect relationships. The potential clinical applications of these findings await further mechanistic studies.

Conclusions

We found that plasma ghrelin levels were increased, while TNF-α and IL-6 were decreased in OSA patients with or without CHD compared with CHD patients. Among all groups, CHD group had the highest plasma levels of TNF-α and IL-6, and lowest plasma levels of ghrelin. In addition, plasma ghrelin levels were independently negatively correlated with plasma TNF-α and IL-6, suggesting that higher ghrelin levels may in part represent a compensatory mechanism to overcome the pro-inflammatory effects of OSA. Further large-scale and prospective studies are needed to confirm these findings.

Acknowledgments

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