sleep time. The BMI of all 21 subjects was over 25 kg/m^2, which is defined as obese in Japan. The total sleep time, AHI, lowest arterial O_2 saturation, and % time of arterial O_2 saturation<90% during sleep were calculated in each patient. Patients with an AHI of more than 20 events per hour were candidates for nasal CPAP therapy. The patients underwent CPAP titration manually and received CPAP treatment with adequate pressure (9.56 ± 2.01 cmH_2O) on the first night. Thereafter, they received CPAP therapy nightly for 1 month at home before revisiting our outpatient clinic. **We calculated the average daily time of usage of the CPAP machine which was based on a reading of the time counter in each nasal CPAP machine. The average time of usage of the CPAP machine in the 21 OSA patients was 5.5 ± 1.3 (range 3.8 – 8.9) hours per day.**

OSA Untreated group

Fourteen other OSA patients (age, 53.2 ± 9.1 years; AHI 43.7 ± 19.1 events/hour; BMI 27.9 ± 3.0 kg/m^2) were placed in the OSA Untreated group, and were matched in age, BMI and AHI with the OSA Treatment group. The patients in the OSA Untreated group underwent polysomnography more than one month after their first visit to the outpatient clinic. Blood samples were taken in the morning twice at a 1-month interval. **CPAP therapy was started in these patients after the two blood samples were obtained.**

Non-OSA healthy volunteer group

The Non-OSA group was comprised of 13 volunteers (mean age, 48.1 ± 12.0; BMI 24.5 ± 2.99 kg/m^2) who were matched in age with the two OSA groups (Table 1). However, their BMI was significantly lower than that of the two OSA groups. They were not heavy snorers, and it was confirmed that they did not have sleep disordered breathing by oximetry. A blood sample was obtained from the subjects in the Non-OSA group.

In all of the volunteers, the arterial oxygen saturation was continuously monitored during sleep with a pulse oximeter (Pulsox-24; Minolta, Osaka, Japan)

over two consecutive nights. The severity of sleep apnea in the volunteers was quantified by the 3% oxygen desaturation index (3%ODI), which was the number of oxygen desaturations of 3% or more below the baseline level per hour during sleep. Subjects who had a 3%ODI of less than 5 were diagnosed as not having OSA. The 3%ODI of the 13 volunteers was 3.26 ± 1.02 (range, 1.43 – 4.89) and 12 of the 13 subjects showed no desaturations below 90%. One subject showed a lowest SpO_2 value of 88% and % time of 0.5% of desaturation below 90% during sleep.

The rates of co-morbidities (hypertension, diabetes mellitus, hyperlipidemia) and current smoking habit were not significantly different between the Non-OSA group and each of the two OSA groups (Table 1). All OSA and Non-OSA subjects in this study received the same medical regimen beginning 1 month before the start of this study and throughout the study period. Because only the BMI was significantly lower in the Non-OSA group than in the OSA groups, multiple linear regression analysis was performed.

The respiratory disturbance index (RDI)[20] was defined as (a) AHI in the OSA patients and (b) 3%ODI in the Non-OSA group.

Blood samples

Blood samples were drawn at 8:00 am after a fast beginning at 8:00 pm the previous night. Blood samples were immediately centrifuged at 3000 **rpm** at 4°C for 10 minutes and the plasma was separated. Then, 1N HCl (10% volume of plasma volume) was immediately added to the plasma sample. All samples were stored at -80°C until assay. The levels of the acylated and desacyl forms of ghrelin and GH were measured by the previously reported method.[7] **Leptin levels were measured by radioimmunoassay.**

Data analysis

The unpaired *t*-test was used to compare the OSA groups with the Non-OSA group. Differences between the measurements made at the two time points were compared with the paired *t*-test. Because obesity would be expected to affect the plasma ghrelin levels, multiple linear regression analysis was performed for BMI to look for independent associations with OSA. These calculations were performed using StatView software for Windows (Version 5.0; Abacus Concepts, Berkeley, CA). A p value of <0.05 was considered significant.

RESULTS

Effect of OSA on ghrelin levels

It was reported that the blood ghrelin level was higher in lean individuals than in obese individuals.[7,8] While the Non-OSA group had leaner body than the OSA Treatment group in this study as demonstrated by the significantly lower BMI in the former group, we found that the acylated ghrelin level was significantly higher in the OSA Treatment group before CPAP therapy than in the Non-OSA group (11.4 ± 5.86 vs. 7.19 ± 3.80 fmol/mL, $p = 0.03$). The desacyl ghrelin level was also significantly higher in the OSA Treatment group than in the Non-OSA group (84.2 ± 50.6 vs. 48.3 ± 23.2 fmol/mL, $p = 0.02$). There was no significant difference in the ratio of acylated to unacylated ghrelin levels between the two groups (0.17 vs. 0.15, $p = 0.67$). After adjustment for BMI, the differences in the acylated ($p = 0.007$) and desacyl ($p = 0.01$) ghrelin levels between the OSA Treatment group and the Non-OSA group became more significant (Figure 1). Moreover, even after adjustment for all variables including age, BMI, rate of current smoking and co-morbidities, the acylated ($p = 0.003$) and desacyl ($p = 0.03$) ghrelin levels were significantly higher in the OSA Treatment group than in the Non-OSA group.

In our previous study,[7] the acylated and desacyl ghrelin levels of 16 males (age 34.7 ± 7.1 years, mean BMI 23.4 ± 3.0 kg/m^2) were 10.9 ± 6.1 and 49.1 ±

23.5 fmol/mL, respectively. The BMI of the group in the previous report was similar to that of the non-OSA group in the present study (p= 0.29) and the ghrelin levels of the group in the previous report[7] were also similar to those of the non-OSA group in this study (acylated: p=0.10, desacyl: p=0.99). The desacyl and total ghrelin levels of the OSA patients in the present study were significantly higher than those of the normal subjects in the previous study (p=0.01, p=0.01, respectively), although there was no significant difference in the acylated ghrelin level (p=0.83).

Relationships between various parameters before nasal CPAP treatment and ghrelin levels

The relationships between various parameters such as BMI, RDI, or the percentage of time with SaO_2<90% and ghrelin levels were analyzed among the 48 subjects (OSA Treatment, n = 21; OSA Untreated, n = 14; Non-OSA, n = 13). The total ghrelin level (acylated plus desacyl) and desacyl ghrelin level were positively correlated with RDI (total: p = 0.002 and desacyl: p= 0.003), although the acylated ghrelin level was not (p = 0.14). Lowest arterial O_2 saturation was not significantly correlated with the total ghrelin level (p = 0.27), acylated ghrelin level (p = 0.25), nor the desacyl ghrelin level (p= 0.31). The % time of arterial O_2 saturation<90% was not correlated with the total ghrelin level (p = 0.33), the acylated ghrelin level (p = 0.86) nor the desacyl ghrelin level (p= 0.29).

Effect of nasal CPAP treatment on ghrelin levels

The BMI did not significantly change after 1 month of nasal CPAP treatment (28.8 ± 3.75 vs. 28.8 ± 3.66 kg/m^2, p = 0.58). There were no significant changes in the acylated (p = 0.25) and desacyl (p = 0.24) ghrelin levels after 3 or 4 days of nasal CPAP treatment. The acylated ghrelin level significantly decreased after 1 month of nasal CPAP usage (11.4 ± 5.86 to 9.08 ± 4.79 fmol/mL, p = 0.02), while the desacyl ghrelin

level tended to decrease (84.2 ± 50.6 to 65.1 ± 41.3 fmol/mL, $p = 0.09$) (Figure 2). After one month of nasal CPAP treatment, the differences in the acylated and desacyl ghrelin levels between the OSA patients and Non-OSA subjects were not significant.

Growth Hormone level in OSA patients and effect of nasal CPAP treatment

There was no significant change in the GH level ($p = 0.33$) after 3 or 4 days of nasal CPAP treatment. The GH level in the OSA Treatment group was significantly lower than that in the Non-OSA subjects, but it increased significantly after 1 month of nasal CPAP therapy (Figures 1,2). Among the 14 untreated OSA patients, no significant changes in the acylated ghrelin level, desacyl ghrelin level, and GH level (acylated ghrelin: $p = 0.97$, desacyl ghrelin: $p = 0.59$, GH: $p = 0.51$) were noted at a 1-month interval.

Leptin level in OSA patients and effect of nasal CPAP treatment

Leptin levels were measured in 14 of the 21 OSA patients in the OSA Treatment group. Among the 14 patients, only the acylated ghrelin level tended to decrease after 1 month of nasal CPAP usage (p=0.08) but not significantly. The leptin level in the 14 OSA subjects was not significantly different from that in the Non-OSA subjects and did not change after one month of CPAP treatment (Table 2).

DISCUSSION

In this study, we found that both the plasma acylated and desacyl ghrelin levels were significantly higher in the OSA patients than in the non-OSA subjects. In addition, among the 48 subjects (OSA Treatment, n = 21; OSA Untreated, n = 14; Non-OSA, n = 13), the RDI before nCPAP treatment was significantly correlated with both the total ghrelin level and desacyl ghrelin level. After one month of nCPAP treatment, the acylated ghrelin level significantly decreased. The elevated acylated ghrelin level in

OSA patients may be one factor that explains the recent body weight gain in OSA patients who are newly diagnosed with OSA. It was reported that the BMI of OSA patients did not change after nCPAP treatment.[4] Therefore, the reduction in acylated ghrelin level with nCPAP therapy in the OSA patients may explain the constancy of the BMI in OSA patients after nCPAP treatment.

The mechanism through which the ghrelin level becomes elevated in OSA patients was not fully investigated in this study. **In this study, the RDI (acylated ghrelin: $p = 0.14$, desacyl ghrelin: $p = 0.003$, total ghrelin: $p = 0.002$), but not desaturation (arterial O2 saturation<90%:% of time) (acylated ghrelin: $p = 0.86$, desacyl ghrelin: $p = 0.29$, total ghrelin: $p = 0.33$), before nasal CPAP treatment was significantly associated with the ghrelin level. It was reported that ghrelin has anti-inflammatory and anti-oxidant effects.[21,22,23] OSA has been associated with inflammation, endothelial dysfunction and increased oxidative stress,[24,25] which are generated by the repetitive episodes of nocturnal hypoxaemia and reoxygenation.[26] Intermittent hypoxemia in OSA patients may increase ghrelin levels. It was also reported that the neural branch of the sympathetic nervous system could directly stimulate ghrelin secretion.[27] Studies on patients with OSA have shown that these patients have a high level of sympathetic nerve activity.[28,29,30] The elevated sympathetic nerve activity in OSA patients may increase ghrelin secretion. The acylated ($p = 0.14$, $R = -0.30$), desacyl ($p = 0.51$, $R = 0.14$) and total ($p = 0.72$, $R = 0.074$) ghrelin levels were not correlated with the arousal index. Although we did not evaluate the sympathetic nerve activity in OSA patients in this study, the intermittent hypoxia (RDI) might have more significant effects on the ghrelin levels than sympathetic nerve activity (arousal index). Recently, it was reported that ghrelin stimulates GH release and that its secretion is stimulated by a reduced GH level.[31] The GH level was decreased in the untreated OSA patients, and it increased after CPAP therapy in this study as well as in a previously-reported study.[32] The**

reduced GH level may stimulate ghrelin secretion in OSA patients. GH secretion is closely related to slow wave sleep (SWS) and the reduced GH level in OSA patients is probably due to loss of SWS.[32] CPAP therapy may improve sleep quality and increase GH secretion in OSA patients, which in turn may decrease ghrelin levels.

After one month of nasal CPAP treatment, the acylated ghrelin level in the OSA patients in this study significantly decreased and the ghrelin levels were similar to those in the Non-OSA subjects. These results may suggest the presence of "ghrelin resistance" in OSA patients. The high ghrelin levels before nasal CPAP treatment may indicate the presence of "ghrelin resistance" and one month of nasal CPAP treatment may not have been sufficient to improve "ghrelin resistance" completely whereas it was sufficient to reduce acylated ghrelin secretion.

Harsch et al.[13] and Ulukavak et al.[14] previously reported ghrelin levels in patients with OSA. In the former study, the ghrelin levels were measured by RIA, and in the latter study the ghrelin levels were measured by ELISA as in the present study. Harsch et al.[13] reported that the baseline plasma ghrelin level was significantly higher in OSA patients. The unit of measurement in Harsch's study differed from that in our study as well as from that in Ulukavak's study. RIA measurement can not distinguish acylated ghrelin from desacyl ghrelin and inactive fragments of ghrelin. Ulukavak et al.[14] reported that there was no significant difference in ghrelin levels between OSA patients and normal controls. After 2 days of nasal CPAP treatment, the total ghrelin level significantly decreased in Harsch's study. In the present study, a significant decrease in acylated ghrelin level was found not after 3 or 4 days, but after one month of nasal CPAP treatment. Neither of the two previous studies measured the levels of the two forms of ghrelin. The present study is the first to measure the levels of the two forms of ghrelin; in addition, we believe that our results are reliable because we used a new direct ELISA assay[7] in this study. However, since there are several differences in the results

among the three studies including this study, additional studies are needed.

Leptin is a circulating hormone produced by adipocytes whose plasma level is increased in obese individuals. Leptin induces a complex response involving control of body weight and energy expenditure.[15] The ghrelin levels tended to decrease after 1 month of nasal CPAP usage but not significantly (p=0.08). However, the leptin level did not change after one month of CPAP treatment (p=0.80). The reported leptin levels before and after nasal CPAP treatment were controversial.[14,16] In the present study, the number of patients in whom the blood leptin levels were measured, was small (n=14). Therefore, the difference in blood leptin level before and after nasal CPAP treatment might not be significant. This study suggests that the acylated ghrelin level may be a more sensitive marker in OSA patients than the leptin level, and would be one of the markers that show the effectiveness of nasal CPAP therapy. However, further studies are needed to investigate whether the acylated ghrelin level might become a sensitive marker of CPAP.

One major limitation of this study was that there was a significant difference in BMI between the OSA patients and non-OSA subjects. **However, ghrelin levels are ordinarily lower in obese individuals than in lean individuals.[8] Therefore, if we had a BMI-matched control group, the differences in ghrelin levels between the OSA patients and the controls would be more significant. Indeed, in addition to a significant decrease in acylated ghrelin level after one month of nasal CPAP treatment without significant body weight change, the differences in the acylated ghrelin and desacyl ghrelin levels between the OSA Treatment group and Non-OSA group became more significant after adjustment for BMI: the p-value of the difference in acylated ghrelin level between the OSA Treatment group and Non-OSA group changed from 0.03 to 0.007 and that of the difference in desacyl ghrelin level changed from 0.02 to 0.01 after adjustment for BMI.** Secondly, we

should have measured the amount of physical daytime activity in the OSA patients because ghrelin exhibits a variety of biological activities. In the future, a study that investigates the ghrelin levels, BMI and biological activities of OSA patients is warranted.

Significant OSA is present in 40% of obese individuals, and 70% of OSA patients are obese.[33,34] Therefore, studies on the relationship between OSA, obesity and the management of body weight in OSA patients are necessary. The results of our study suggest that the plasma level of ghrelin may have significant effects on the body weight of OSA patients before and after treatment.

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Conflict of Interest Statement

We declare that none of the authors have a conflict of interest in relation to this work.

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FIGURE LEGENDS

Figure 1: Comparison of adjusted plasma acylated ghrelin, desacyl ghrelin and growth hormone levels in OSA patients and non-OSA subjects. Data were adjusted for BMI. GH: growth hormone, Bars: standard deviation.

Figure 2: Figure 2: Change in plasma acylated ghrelin, desacyl ghrelin and growth hormone levels before and after 1 month nasal CPAP therapy. GH: growth hormone, nCPAP: nasal continuous positive airway pressure, Bars: standard deviation.

Table 1
Baseline characteristics of the OSA Treatment group and Non-OSA group

Variable	OSA Treatment	Non OSA	*p*
Number	21	13	
Age (year)	52.5 ± 8.66	48.1 ± 12.0	0.22
Body mass index (kg/m^2)	28.8 ± 3.75	24.5 ± 2.99	**0.001**
Respiratory disturbance index (events/hour)	46.2 ± 14.7	3.26 ± 1.02	**<0.0001**
Lowest arterial O_2 saturation (%)	68.2 ± 9.86	94.5 ± 3.41	**<0.0001**
Arterial O_2 saturation<90% (% of time)	24.6 ± 18.8	0.36 ± 0.67	**<0.0001**
Arousal index (events/hour)	37.4 ± 16.2		
Hypertension (number)	13	6	0.38
Diabetes mellitus (number)	5	2	0.57
Hyperlipidemia (number)	8	2	0.17
Current smoking (number)	3	3	0.53

"Hypertension" was defined as a diastolic pressure greater than 90 mm Hg, a systolic pressure greater than 140 mm Hg or the use of antihypertensive medication.
"Diabetes mellitus" was defined as a fasting blood glucose level greater than 126 mg/dL, increased blood glucose level greater than 200 mg/dL 2 hour after a 75-g oral glucose load or the use of antidiabetic medication.
"Hyperlipidemia" was defined as a total cholesterol level greater than 220 mg/dL, triglyceride level greater than 150 mg/dL or the use of lipid-lowering medication.

OSA: obstructive sleep apnoea

Table 2

Characteristics of 14 of the 21 OSA patients in the OSA Treatment group in whom leptin levels were measured.

Variable	OSA	OSA after one month of CPAP	*P*
Number	14		
Age (year)	53.2 ± 8.81		
Body mass index (kg/m^2)	28.5 ± 3.68	28.5 ± 3.53	0.86
Respiratory disturbance index (events/hour)	47.7 ± 14.1	2.5 ± 3.24	**0.001**
Lowest arterial O_2 saturation (%)	67.5 ± 9.46	87.1 ± 5.88	**0.001**
Arterial O_2 saturation<90% (% of time)	22.7 ± 18.6	0.30 ± 0.34	**0.001**
Arousal index (events/hour)	39.4 ± 15.5	16.1 ± 6.72	**0.002**
Acylated ghrelin (fmol/mL)	12.1 ± 6.50	9.64 ± 4.81	0.08
Desacyl ghrelin (fmol/mL)	102.6 ± 56.2	74.0 ± 47.8	0.18
Leptin (ng/mL)	4.99 ± 3.18	5.10 ± 2.97	0.80

OSA: obstructive sleep apnoea

CPAP: continuous positive airway pressure

Figure 1

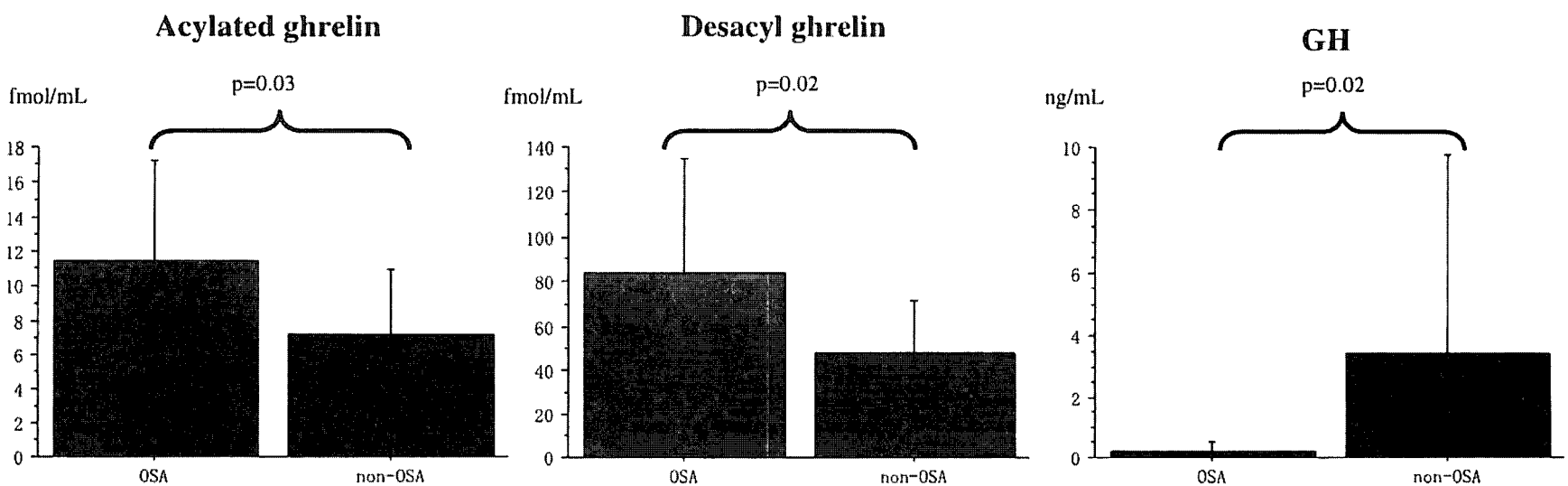
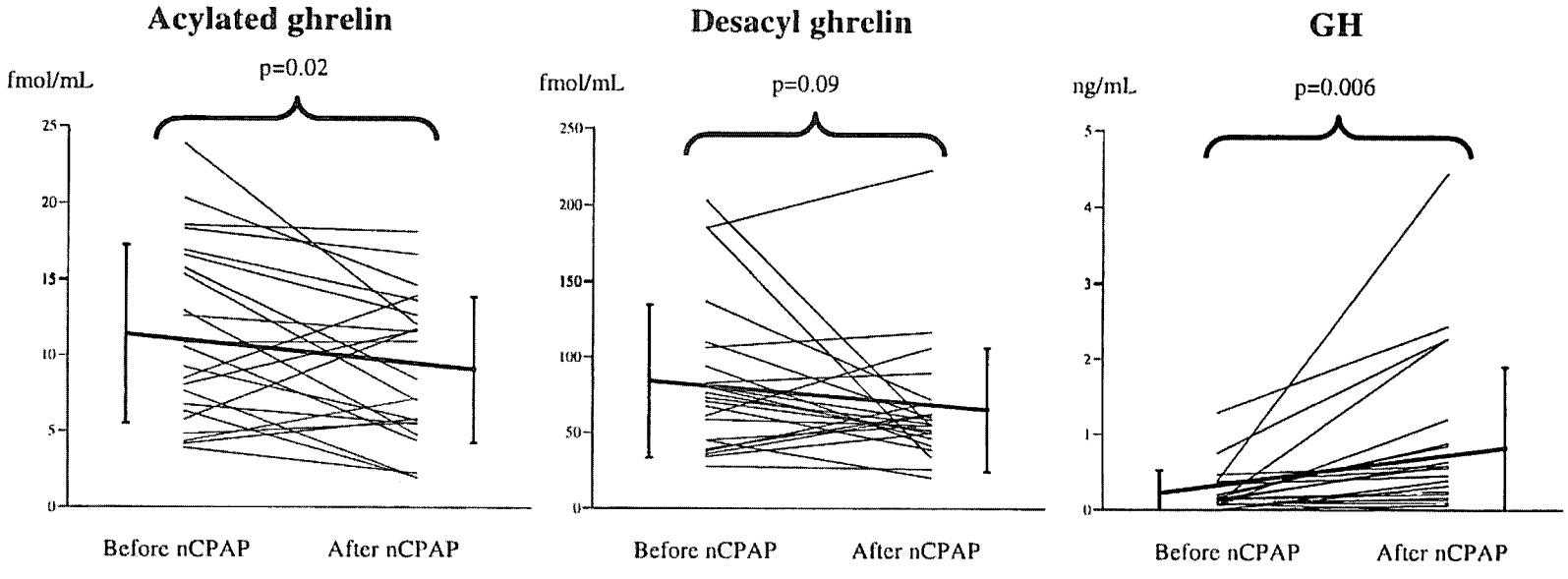

Acylated ghrelin
fmol/mL
p=0.03
18
16
14
12
10
8
6
4
2
0
OSA
non-OSA
Desacyl ghrelin
fmol/mL
p=0.02
140
120
100
80
60
40
20
0
OSA
non-OSA
GH
ng/mL
p=0.02
10
8
6
4
2
0
OSA
non-OSA

Figure 2


Acylated ghrelin
fmol/mL
p=0.02
25
20
15
10
5
0
Before nCPAP
After nCPAP
Desacyl ghrelin
fmol/mL
p=0.09
250
200
150
100
50
0
Before nCPAP
After nCPAP
GH
ng/mL
p=0.006
5
4
3
2
1
0
Before nCPAP
After nCPAP