*ERJ Express*. Published on April 25, 2007 as doi: 10.1183/09031936.00115006

**Title page**

# Hyperleptinemia, respiratory drive and hypercapnic response in obese patients.

Arantza Campo[a], Gema Frühbeck[b], Javier J Zulueta[a], Jorge Iriarte[c], Luis M Seijo[a], Ana B Alcaide[a], Juan B Galdiz[d], Javier Salvador[b].

Departments of Pulmonary Medicine[a], Endocrinology[b], Neurophysiology[b], Clínica Universitaria; Universidad de Navarra, Pamplona, Spain.

Department of Pulmonary Medicine[d]. Hospital de Cruces, Vizcaya, Spain

Correspondence should be addressed to Arantza Campo, M.D., Pulmonary Medicine, Clínica Universitaria, Avda. Pío XII, 36, 31008 Pamplona, Spain.

E-mail: acampoe@unav.es

Fax 34 948296500

Phone number 34 948296632

Sources of support: None

Short title: Leptin, obesity and respiratory center

Word count of manuscript: 2777

This article has not an online data supplement.

**Copyright 2007 by the European Respiratory Society.**

**Abstract**

Leptin is a powerful stimulant of ventilation in rodents. In humans, resistance to leptin has been consistently associated with obesity. Raised leptin levels have been reported in subjects with sleep apnea or obesity-hypoventilation syndrome.

Objective: To assess by multivariate analysis the possible association between respiratory center impairment and levels of serum leptin.

Methods: Three hundred and sixty four obese subjects (BMI $\geq$30 kg/m$^2$) had the following tests: sleep studies, respiratory function tests, baseline and hypercapnic response (P0.1, minute ventilation), fasting leptin levels, body composition and anthropometric measures. Subjects with airways obstruction by spirometry were excluded.

Results: Two hundred and forty-five subjects were included in the analysis. Lung volumes, age, log leptin levels, PetCO2, % body fat and minimal nocturnal saturation were predictors for baseline P0.1 ($R^2$ = 0.222; $p < 0.001$). One hundred and eighty six subjects performed hypercapnic response test; log leptin levels were predictors for hypercapnic response in men ($R^2$ =0.051; p=0.027 for P0.1), but not in women.

Conclusions: Hyperleptinemia is associated with a reduction in respiratory drive and hypercapnic response, irrespective of the amount of body fat. These data suggest the extension of leptin resistance to the respiratory center.

Word count of abstract: 199

Keywords: control of breathing, hypoventilation, leptin, obesity, respiratory center, respiratory function tests

## Introduction

Obese subjects have respiratory impairment[1] due to the increment of total body fat, which produces diminished compliance, and increased resistance and work of breathing. In addition, a significant proportion suffers from obstructive sleep apnea. A small subgroup, most of whom have the sleep apnea syndrome, have diurnal hypoventilation with hypoxemia and hypercapnia[2]. Standard pulmonary function tests show a mild decrease in forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) and a more evident reduction in expiratory reserve volume (ERV). Most of these subjects have an increased respiratory drive[3] and a diminished hypercapnic response. The latter is especially true in subjects with the obesity-hypoventilation syndrome[4] [3]. These alterations are explained mainly by mechanical factors, as the imposed extra fat load provokes a higher work of breathing and obstruction of the upper airways during sleep.

However, some authors have proposed the involvement of several adipose-derived factors. In this context, leptin has emerged as a relevant adipokine playing a role as a stimulant of ventilation[5] and it being raised in subjects with sleep apnea syndrome or obesity-hypoventilation syndrome[6]. The reason for that elevation is attributed either to stimulation by hypoxia or leptin insensitivity in obese subjects. In general, subjects with hypoventilation seem to exhibit higher levels of leptin for a given amount of body fat.

The aim of our study was to assess the relationship between hyperleptinemia and respiratory center parameters after adjusting for respiratory impairment and severity of obesity (sleep apnea, nocturnal desaturation, restrictive pattern, percentage of body fat and fat distribution, age and sex,), taking into account menopausal status in women. Serum leptin levels correlate mainly with body fat percentage and the logarithmic transformation improves linear correlation. Thus, log serum leptin was chosen as an independent variable.

## Methods

*Subjects*

Obese adult subjects referred for obesity treatment were included (≥ 17 years old and BMI ≥ 30 kg/ $m^2$). Those with a diagnosis of restrictive pulmonary disease, neuromuscular disease, or a previous pulmonary resection were excluded. Subjects with an obstructive spirometric pattern defined by an FEV1/FVC < 70% were also excluded.

*Body composition*

Body fat percentage was assessed by air displacement plethysmography (Bod-Pod®, Life Measurements, Concord, CA, USA, which is a bicompartimental method previously validated [7]. Waist and hip circumference were measured in all patients in cm with the standard method.

*Serum leptin levels*

Fasting leptin levels were measured by a double antibody RIA technique (Linco Research Inc. St Charles, MO, USA). Intra- and inter-assay coefficients of variation were 5.0% and 4.5 % respectively.

*Polysomnographic study*

Those patients not previously tested underwent a polysomnographic study. Nocturnal sleep was recorded with Harmonie 5.2 (Stellate, Montreal, Canada) using Lamont 32-Sleep amplifiers (Lamont Medical, Wisconsin, USA). The recordings included 7 channels of EEG referenced to both balanced mastoids, right and left electroculogram, oxygen saturation, airflow thoraco-abdominal bands, body position sensor and electrocardiogram (ECG). Apnea was defined as cessation of nasal or oral airflow for at least 10 s. Hypopnoea was defined as a 50% decrease in the airflow channel for 10 s. The apnea-hypopnoea index (AHI) was calculated as the mean number of apnoeic and hypopnoeic events per hour of sleep. The

hypnogram was visually analysed off-line following standard criteria, while the program automatically calculated the AHI and the frequency and severity of oxygen desaturations.

*Lung function tests*

Spirometry was performed with a calibrated dry rolling seal spirometer (SensorMedics 2130 System; Yorba Linda, CA) according to current guidelines. Static lung volumes were measured by body plethysmography (SensorMedics V6200 Autobox). The predicted values for spirometric and thoracic gas volumes were those of the European Update 1993[8].

Patients underwent ventilatory drive assessment, including minute ventilation(VE), tidal volume(Vt), inspiratory time(Ti), mouth occlusion pressure at 0.1 s of inspiration(P0.1) and end-tidal carbon dioxide(Pet-CO2). Mouth occlusion pressure (P0.1) was measured using the method described by Whitelaw [9]. The occlusion pressure valve was occluded automatically at random every two to six respiratory cycles, using software provided by SensorMedics. Hypercapnic response was assessed by the method described by Read [10] and the slope of P0.1/PetCO2 and VE/ PetCO2 was calculated by the minimal square regression method.

*Statistical analysis*

Statistical analysis was performed using SPSS software version 11.0. Variables are shown as mean(SD). The effect of sex, menopausal status and obstructive sleep apnoea syndrome (OSAS) on the descriptive variables was initially analysed by U Mann-Whitney test and Chi Squared test. Bivariate correlations were studied by Spearman Rho.

P0.1 analysis. Multivariate analysis was performed as a lineal stepwise regression model with baseline P0.1 as the dependent variable and age, sex, height, waist circumference, % body fat, %TLC predicted, baseline PetCO2, serum log leptin level, AHI, minimal and mean nocturnal O2 saturation as independent variables. Male and female subjects were analysed together and as different groups. Menopausal status as an independent variable was included in the analysis of the group of women. The inclusion criteria for the analysis by steps were p in (0.05), p out

(0.10) and tolerance (0.01).A listwise exclusion for multivariate analysis was performed. Hypercapnic response. The analysis of hypercapnic response was performed with the same independent variables and the slope of response (P0.1 /PetCO2) as the dependent variable. A similar regression analysis was performed using VE/PetCO2 as the dependent variable.

Protocol study was approved by the local Ethical Committee.

**Results**

*Descriptive data*

Three hundred and sixty-four subjects were included in the study. Descriptive variables and differences between genders and between pre and postmenopausal women are shown in table 1. The number of subjects undergoing the different tests is shown in table 2. Excluding lost values in the multivariate analysis, we included 245 subjects in analysis of baseline respiratory center assessment and 186 in the hypercapnic response assessment.

Sleep studies were performed in 194 women and 104 men. The AHI was between 5 and 30 /hour in 29.7% and 23.3% of women and men respectively and higher than 30 / hour in 15.1% and 44.7% of women and men respectively ($p<0.001$)

Respiratory drive measurements were not different between subjects with or without OSAS (AHI > or <15 /hour) after stratifying by sex, as it is shown in table 3. Subjects with OSAS had a greater BMI, a larger waist circumference and a higher respiratory impairment.

The relationship between the percentage of body fat and leptin improved with logarithmic transformation ). The lineal correlation between leptin and percentage of body fat was stronger using log leptin (R=0.629) rather than leptin (R=0.565). The correlation of body fat and log leptin was 0.342 for women and 0.513 for men.

*Bivariate correlations*

Bivariate correlations are shown in tables 4, 5 and 6 for P0.1, hypercapnic response by P0.1 and hypercapnic response by minute ventilation respectively. Each table provide data for the whole sample, men and women.

*Multivariate analysis models*

The multivariate analysis included the following variables: age, obesity parameters (% body fat and fat distribution), log leptin levels, pulmonary function (total lung capacity% predicted) and sleep study parameters (apnoea-hypopnoea index, minimal and mean nocturnal saturation). The analysis of the whole group includes gender as a variable. The analysis of women includes menopausal status. After bivariate analysis we decided to use waist to hip ratio in men and waist circumference in women as a measurement of fat distribution.

The results of the multiple linear regression analyses are summarised in table 7. Figure 1 shows significant adjusted partial correlation between log leptin levels and P0.1 in men and premenopausal women and log leptin levels and hypercapnic response in men, after the multivariate analysis.

A) *Baseline P0.1*.

The variables associated with P0.1 in the whole sample were age, % body fat, log leptin levels, %total lung capacity, baseline PetCO2 and minimal nocturnal saturation. In men the associated variables were% body fat, log leptin levels, %total lung capacity, baseline PetCO2, minimal nocturnal saturation and waist to hip ratio. In this group log leptin levels accounted for a change in $r^2$ of 0.029, with a p value for the change in F of 0.050. The analysis in women showed a significant association with log leptin levels in premenopausal but not in postmenopausal women, which accounted for a change in $r^2$ of 0.05 (p=0.017) The other explanatory variables in this group were age, %body fat and PetCO2.*B)Hypercapnic response*

The multivariate analysis for hypercapnic response showed that the explained variability of the slope of P0.1/PetCO2 was 5.6% (p=0.002), with height and leptin levels as the only explanatory variables. The separate analyses showed that log leptin level was the only explanatory variable in men ($r^2$=0.051; p=0.027), but not in women.

The regression analysis for VE/PetCO2 showed an explained variability of 26.1% (p<0.001), with height and log leptin levels as the independent variables. The separate analyses showed that height was the only explanatory variable in men. In premenopausal women height and waist were explanatory variables. In postmenopausal women %total lung capacity was the only independent variable.

**Discussion**

This study demonstrates that in obese patients higher concentrations of serum leptin are associated with a reduced respiratory drive and a reduced hypercapnic response. As leptin is a stimulant of ventilation, these results suggest an extension of leptin resistance to the respiratory center. Clinical studies of obesity-hypoventilation syndrome suggest the association between respiratory drive and leptin but this has not been demonstrated before.

Leptin, the product of *Ob* gene, is a protein secreted by adipocytes that regulates body weight[12] [13] [14] by increasing satiety and reducing food intake. Serum leptin levels correlate with body fat percentage[15]. It has been shown in mice that leptin deficiency induced by an *Ob* gene mutation is associated with morbid obesity, hyperphagia, insulin resistance and hypoventilation. Seminal studies in animals describe the characteristic hypoventilation of mice associated with *Ob* mutation and the subsequent improvement with exogenous leptin administration, even before the consequent reduction in body weight[5]. Prolonged treatment (6 weeks) with leptin in leptin-deficient mice modifies the animal's ventilatory pattern, increases lung compliance and restores the abnormal adaptation of the

diaphragm muscle[16]. While most obese subjects have markedly increased levels of plasma leptin, only a few cases of human genetic abnormalities of leptin have been reported. Obesity has been postulated to be a state of leptin resistance. Two distinct mechanisms of resistance have been proposed in human obesity: an impaired transport of leptin across the blood-brain barrier[17] [18], and altered signalling pathways or receptors. Leptin resistance can also be induced by feeding animals a high-fat diet[19].

The possible interaction between leptin and ventilatory parameters in humans is not as clear as that seen in animal models. Most of the studies in this regard have investigated the relationship between leptin levels, sleep apnea syndrome and obesity-hypoventilation syndrome. However, there are no studies assessing the relationship between the respiratory center and leptin in humans.

Compared with BMI-matched controls, higher plasma levels of leptin are described in hypercapnic obese subjects and those with obstructive sleep apnea syndrome (OSAS)[20] [21]. Furthermore, treatment of the latter with continuous positive airway pressure (CPAP) reduces plasma leptin levels[22] [23] [24] [25] [26]. The possible explanations for the reduction in leptin levels after treatment are a change in fat distribution [24], an improvement in sympathetic function[27] or an improvement in leptin sensitivity. However, the existence of an independent association between leptin and OSAS is controversial between the different studies. Some studies have failed in demonstrating the existence of this relationship, independent of adiposity[25] [28].

Another hypothesis is that hypoxemia, as has been shown in experimental studies, causes leptin secretion[29]. In this hypothesis, leptin resistance and hyperleptinemia might not cause hypoventilation but be caused by it. Tatsumi *et al*[30] studied 96 male non obese patients with OSAS and 52 male patients without OSAS matched for BMI. They found that average SaO2 and lowest SaO2 were explanatory variables for serum leptin values, but AHI, BMI, visceral

fat, or subcutaneous fat were not. These results suggest that the elevation of leptin levels was a consequence of hypoxia and not of fat accumulation.

We analysed a larger size sample (245 subjects) than previously reported series, and in addition to body composition also took into account fat distribution, nocturnal saturation, apnoea-hypopnoea index, pulmonary function and sex. Leptin levels were an independent factor of respiratory drive, independent of apnoea events, nocturnal saturation, restrictive impairment, or fat distribution. There are no previous studies in humans that analyse correlate respiratory drive measurements with leptin, although the relationship between hypercapnia and circulating leptin levels has been reported. However, as this is a cross sectional study, the results cannot imply causality. These results are significant in the whole sample and in the group of men, but the association in women could not be demonstrated. The association is weak, and log leptin levels account only for a 2.9% and 6.3% of the variance of baseline P0.1 and Delta P0.1/PetCO2 in men, so the size of the sample and the differences in the behaviour of leptin in women might explain the lack of significance in women.

Phipps *et al* [6] found higher leptin serum levels in subjects with the obesity-hypoventilation syndrome than in subjects with the same amount of fat but without hypoventilation. OSAS severity had no effect. Shimura et al[31] studied 185 male patients with OSAS (106 eucapnic and 79 hypercapnic) in which visceral and subcutaneous fat distribution was assessed by computerized tomography (CT). They found that leptin was the only predictor of hypercapnia, and not fat distribution. No association was found between circulating leptin levels and AHI, nocturnal mean and nadir oxygen saturation, %FVC, FEV1/FVC, or fat content. They suggest that hypoventilation in OSAS is partly due to depressed sensitivity to leptin in the CNS.

One limitation of our study is that we did not perform arterial blood gas analysis, so we cannot be certain of how many of our subjects had an established hypoventilation-obesity syndrome.

In our study, respiratory drive measured as baseline P0.1 was increased with respect to other reports [32] [33], although we did not performed a control group assessment. There was a significant and independent correlation between the presence of a restrictive impairment and the increment in respiratory drive, as has been seen in obese subjects. This suggests a stimulation of the respiratory center by the increased work of breathing. Respiratory drive also correlated positively with the severity of obesity defined as % body fat, and inversely with baseline PetCO2, age and minimal nocturnal saturation. The nadir SpO2 was an independent variable for baseline P0.1 in men and postmenopausal women. The respiratory center parameters were not different between subjects with and without OSAS.

Bivariate analysis did not demonstrate significant correlations between apnoea-hypopnoea index and ventilatory control parameters, although there were significant correlations with nocturnal saturation indices. However the effect of respiratory disorders during sleep was assessed also by including apnoea-hypopnoea index and minimal and mean nocturnal saturation in the multivariate analysis.

We did not find any association between the apnoea-hypopnoea index or the saturation parameters with hypercapnic response. Studies have found that the hypercapnic response is increased in obese women irrespective of the presence of sleep apnoea syndrome, whereas the hypoxic response is significantly increased in obese women with OSAS compared with obese women without OSAS [34].

The hypercapnic response in men measured by the increase in minute ventilation had a strong correlation with height, as it correlates with absolute total lung capacity and baseline minute ventilation. In women it correlated with height but also with the presence of a restrictive pattern and waist circumference, probably reflecting mechanical limitations for ventilation.

Differences in variables between genders were analysed. Several obesity and respiratory variables, but not BMI were significantly different between men and women. Women had a

different fat distribution, higher circulating leptin levels and a greater percentage of body fat, but fewer alterations in lung volumes and less and milder respiratory disorders during sleep. Sexual dimorphism in the leptin levels has been repeatedly reported[36]. This finding may be attributed to the different distribution of fat in both genders, as visceral fat produces less leptin and is found in higher proportion in men. However, we did not find an effect of female gender or menopausal status on the respiratory center measurements.

In conclusion, in obese subjects a lower respiratory drive is associated with higher serum leptin levels, adjusted by ventilatory parameters, age, severity of obesity, apnoea-hypopnoea index and nocturnal saturation. In men higher leptin levels are also associated with a lower hypercapnic response. These results suggest an extension of leptin resistance to the respiratory center in obese subjects.

**Acknowledgements**

The authors thank Ms Teresa Jimenez and Ms Elena de Miguel for their invaluable technical assistance.

**Figure legends**

Figure 1. Partial correlations between log leptin levels and respiratory control parameters which were significant in the multivariate analysis.

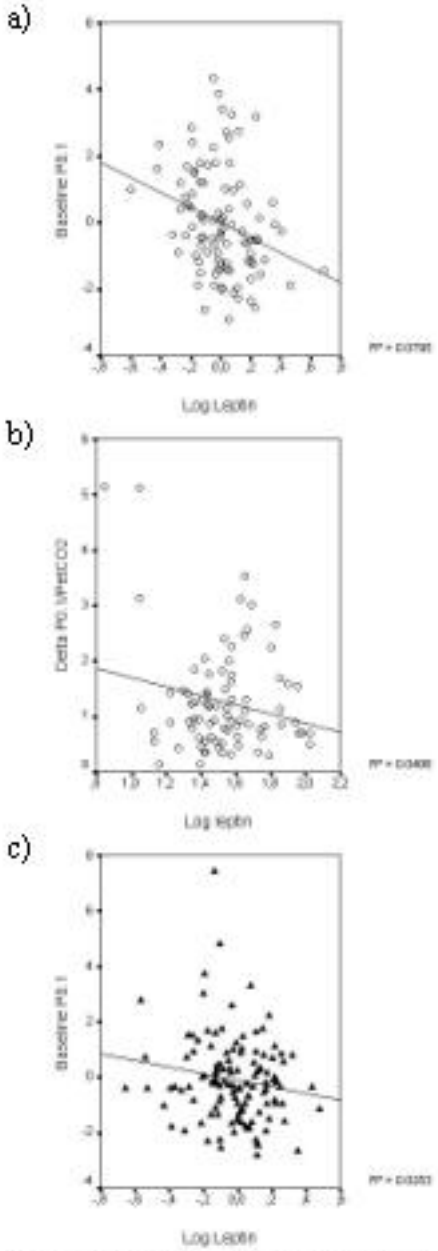


Figure 1. Significant relationships between log leptin levels and respiratory control parameters. a) Partial correlationship between log leptin levels and baseline P0.1 in men after adjusting by multivariate analysis. b) Correlationship between log leptin levels and Delta P0.1/PetCO2 in men. c) Partial correlationship between log leptin levels and baseline P0.1 in women after adjusting by multivariate analysis.

## Tables

Table 1. Characteristic of subjects and comparison by gender and menopausal status. Variables shown as mean (SD) and categorical variables as absolute count (percentage)

| | | Comparison by gender | | | Comparison by menopausal status in women | | |
|---|---|---|---|---|---|---|---|
| | Total | Women | Men | p value | Non menopausal | Menopausal | p value |
| Age (y) | 43.1 (12.9) | 43.7 (13.1) | 42.1 (12.4) | 0.256 | 35.53 (9,71) | 57.18 (6.25) | <0.001 |
| Smoking: | | | | 0.044 | | | 0.043 |
| Current | 94 (26%) | 59 (25.8%) | 35 (26.5%) | | 43 (33.1%) | 12 (16.7%) | |
| Former | 103 (28.5%) | 56 (24.5%) | 47 (35.6%) | | 29 (22.3%) | 20 (27.8%) | |
| Never | 164 (45.4%) | 114 (49.8%) | 50 (37.9%) | | 58 (44.6%) | 40 (55.6%) | |
| BMI ($kg/m^2$) | 43.0 (6.86) | 43.0 (7.0) | 42.91 (6.6) | 0.890 | 43.33 (6.83) | 42.43 (7.52) | 0.276 |
| Waist/hip ratio | 0.94 (0.09) | 0.904 (0.08) | 1.002 (0.08) | <0.001 | 0.88 (0.07) | 0.94 (0.07) | <0.001 |
| Waist (cm) | 122 (14) | 117 (13) | 129 (13) | <0.001 | 116.8 (13) | 119.72 (12) | 0.093 |
| Body fat % | 48.9 (7.2) | 52.2 (4.9) | 42.9 (6.8) | <0.001 | 52.18 (4.93) | 52.64 (4.29) | 0.638 |
| Leptin (mcg/L) | 54.5 (30.2) | 65.4 (29.3) | 36.0 (21.4) | <0.001 | 64.91 (30.13) | 64.64 (28.96) | 0.993 |
| Log leptin (mcg/L) | 1.666 (0.259) | 1.769 (0.212) | 1.491 (0.238) | <0.001 | 1.76 (0.22) | 1.76 (0.21) | 0.993 |
| Log leptin / fat% | 3.487 (0.490) | 3.408 (0.434) | 3.506 (0.553) | 0.159 | 3.39 (0.44) | 3.39 (0.39) | 0.926 |
| TLC % predicted | 88.93 (11.66) | 92.19 (10.56) | 83.32 (11.39) | <0.001 | 92.50 (10.71) | 91.56 (10.54) | 0.578 |
| Baseline P0.1 (cm H2O) | 4.51 (1.87) | 4.385 (1.833) | 4.738 (1.921) | 0.084 | 4.49 (1.68) | 3.82 (1.35) | <0.001 |
| Baseline PetCO2 (mm Hg) | 33.32 (5.75) | 32.97 (5.743) | 33.93 (5.72) | 0.126 | 32.51 (5.34) | 34.27 (5.77) | 0.025 |
| P0.1/(Vt/Ti) (cmH2O/L/s) | 7.735 (3.020) | 7.850 (2.885) | 7.536 (3.242) | 0.086 | 8.00 (2.68) | 7.05 (2.53) | 0.007 |
| P0.1/PetCO2 (cmH2O/mmHg) | 1.01 (0.90) | 0.87 (0.84) | 1.27 (0.94) | <0.001 | 0.90 (0.88) | 0.82 (0.75) | 0.776 |
| VE/PetCO2 (L/min/mmHg) | 2.61 (1.87) | 2.07 (1.27) | 3.60 (2.34) | <0.001 | 2.15 (1.28) | 1.92 (1.29) | 0.251 |
| AHI (/h) | 22.05 (25.35) | 15.53 (18.21) | 34.21 (31.64) | <0.001 | 13.79 (18.54) | 20.05 (18.76) | 0.002 |
| Min SpO2% | 80.55 (11.17) | 82.13 (10.64) | 77.63 (11.56) | 0.001 | 84.4 (10.31) | 78.63 (10.78) | <0.001 |
| Mean SpO2% | 94.50 (2.83) | 94.83 (2.61) | 93.92 (3.12) | 0.016 | 95.46 (2.45) | 93.69 (2.81) | <0.001 |

Table 2. Number of subjects (%) who underwent each test.

| | Women (%) | Men (%) | Total |
|---|---|---|---|
| Spirometry | 231 (100%) | 133 (100%) | 364 (100%) |
| Baseline P0.1/ respiratory pattern | 229 (99.1%) | 132 (99.25%) | 361 (99.2%) |
| Hypercapnic response | 159 (68.8%) | 86 (64.7%) | 245 (67.3%) |
| Polysomnographic study | 194 (84%) | 104 (78.2%) | 298 (81.87%) |
| Apnoea hypopnoea index | 192 (83.1%) | 103 (77.4%) | 295 (81.0%) |
| Minimal SpO2% | 195 (84.4%) | 106 (79.7%) | 301 (82.69%) |
| Mean SpO2% | 174 (75.3%) | 96 (72.2%) | 270 (74.2%) |
| Body composition | 220 (95.2%) | 125 (94.0%) | 345 (94.8%) |
| Leptin | 224 (97%) | 131 (98.5%) | 355 (97.5%) |
| Waist | 223 (96.5%) | 131 (98.5%) | 354 (97.3%) |

Table 3. Differences between subjects with and without OSAS stratified by gender.

| | Men–OSAS n= 42 Mean (SD) | Men+OSAS n= 61 Mean (SD) | p-value | Women–OSAS n= 125 Mean (SD) | Women+OSAS n= 67 Mean (SD) | p-value |
|---|---|---|---|---|---|---|
| Age (yrs) | 35.8 (11.) | 44.4 (10.9) | <0.001 | 41.2 (12.8) | 47.7 (12.3) | <0.001 |
| Height (cm) | 1.76 (0.6) | 1.75 (0.1) | 0.382 | 1.61 (0.1) | 1.61 (0.1) | 0.490 |
| BMI | 40.5 (6.9) | 44.8 (6.2) | <0.001 | 42.6 (5.6) | 44.3 (7.7) | 0.227 |
| Waist | 124.7 (13.5) | 132.6 (12.6) | 0.001 | 115.8 (11.9) | 122.45 (13.7) | 0.002 |
| Waist-hip ratio | 0.99 (0.07) | 1.01 (0.07) | 0.234 | 0.89 (0.07) | 0.93 (0.07) | 0.001 |
| % body fat | 40.9 (6.9) | 44.4 (6.4) | 0.017 | 52.2 (4.6) | 52.5 (5.0) | 0.500 |
| AHI (n/h) | 5.96 (3.9) | 53.7 (27.4) | <0.001 | 5.32 (4.0) | 34.6 (19.1) | <0.001 |
| Spmin | 86.3 (4.6) | 71.8 (11.4) | <0.001 | 85.1 (8.2) | 76.7 (12.6) | <0.001 |
| Spmed | 95.5 (1.8) | 92.8 (3.4) | <0.001 | 95.4 (1.9) | 93.6 (3.38) | <0.001 |
| %Time SpO2<90% | 1.07 (1.93) | 18.58 (21.1) | <0.001 | 3.46 (10.6) | 11.42 (19.3) | <0.001 |
| %TLC | 84.6 (10.1) | 82.3 (12.2) | 0.292 | 92.1 (10.4) | 92.7 (10.7) | 0.807 |
| %FVC | 98.2 (13.2) | 92.0 (14.5) | 0.022 | 104.7 (12.1) | 103.2 (17.0) | 0.398 |
| %ERV | 54.4 (21.6) | 44.2 (24.5) | 0.010 | 61.4 (27.2) | 46.5 (21.2) | <0.001 |
| PetCO2 | 32.5 (5.4) | 34.8 (5.3) | 0.047 | 32.4 (5.7) | 34.3 (5.8) | 0.016 |
| BaselineP0.1 | 4.57 (1.8) | 4.77 (1.9) | 0.582 | 4.52 (2.1) | 4.25 (1.5) | 0.853 |
| Delta P0.1/PetCO2 | 1.15 (0.73) | 1.37 (0.99) | 0.396 | 0.95 (0.90) | 0.73 (0.78) | 0.174 |
| Delta VE/PetCO2 | 3.33 (1.96) | 4.12 (2.4) | 0.152 | 2.18 (1.3) | 1.85 (1.09) | 0.272 |
| Log leptin | 1.47 (0.25) | 1.51 (0.23) | 0.295 | 1.78 (0.21) | 1.77 (0.22) | 0.422 |
| Log leptin/%body fat | 3.64 (0.48) | 3.43 (0.61) | 0.025 | 3.43 (0.42) | 3.40 (0.48) | 0.357 |

Table 4. Bivariate correlations for baseline P0.1 (Spearman Rho)

| Variable | Whole sample | | Men | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Premenopausal | | Posmenopausal | |
| | Rho | p-value | Rho | p-value | Rho | p-value | Rho | p-value |
| Height | 0.092 | 0.080 | 0.071 | 0.421 | -0.060 | 0.498 | -0.012 | 0.923 |
| Age | -0.154 | 0.003 | -0.080 | 0.360 | -0.092 | 0.296 | -0.045 | 0.708 |
| % body fat | 0.088 | 0.104 | 0.241 | 0.007 | 0.227 | 0.010 | -0.031 | 0.807 |
| Leptin | -0.048 | 0.371 | 0.010 | 0.908 | -0.024 | 0.787 | -0.035 | 0.775 |
| Log leptin | -0.048 | 0.371 | 0.010 | 0.908 | -0.024 | 0.787 | -0.035 | 0.775 |
| Leptin* | -0.151 | 0.005 | -0.143 | 0.117 | -0.126 | 0.164 | -0.081 | 0.530 |
| Log leptin* | -0.146 | 0.008 | -0.153 | 0.093 | -0.105 | 0.249 | -0.063 | 0.626 |
| Log leptin /% body fat | -0.176 | 0.001 | -0.259 | 0.004 | -0.161 | 0.075 | 0.014 | 0.912 |
| Waist | 0.147 | 0.006 | 0.105 | 0.233 | 0.125 | 0.161 | 0.058 | 0.636 |
| Waist/ hip ratio | -0.053 | 0.319 | -0.256 | 0.003 | 0.015 | 0.864 | 0.104 | 0.397 |
| TLC% predicted | -0.125 | 0.018 | -0.220 | 0.011 | -0.024 | 0.783 | -0.033 | 0.783 |
| PetCO2 | -0.261 | <0.001 | -0.251 | 0.004 | -0.276 | 0.001 | -0.147 | 0.222 |
| AHI | 0.034 | 0.567 | -0.031 | 0.754 | 0.123 | 0.200 | 0.040 | 0.774 |
| Minimal SpO2 | -0.076 | 0.192 | -0.017 | 0.863 | -0.132 | 0.160 | -0.097 | 0.480 |
| Mean SpO2 | -0.065 | 0.289 | -0.084 | 0.414 | -0.170 | 0.084 | -0.063 | 0.659 |
| Gender | 0.092 | 0.080 | | | | | | |

*Bivariate correlations adjusted by % body fat.

Table 5 Bivariate correlations with hypercapnic response (P0.1/PetCO2)

| Variable | Whole sample | | Men | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Premenopausal | | Posmenopausal | |
| | Rho | p-value | Rho | p-value | Rho | p-value | Rho | p-value |
| Height | 0.252 | <0.001 | 0.077 | 0.480 | 0.165 | 0.110 | 0.173 | 0.234 |
| Age | -0.120 | 0.062 | -0.053 | 0.626 | -0.111 | 0.283 | -0.185 | 0.203 |
| % body fat | -0.229 | <0.001 | 0.085 | 0.457 | -0.077 | 0.468 | -0.232 | 0.125 |
| Leptin | -0.151 | 0.019 | 0.010 | 0.931 | -0.002 | 0.988 | 0.036 | 0.809 |
| Log leptin | -0.151 | 0.019 | -0.010 | 0.931 | -0.002 | 0.988 | 0.036 | 0.809 |
| Leptin* | -0.072 | 0.281 | -0.148 | 0.200 | -0.051 | 0.633 | 0.155 | 0.315 |
| Log leptin* | -0.094 | 0.156 | -0.256 | 0.025 | -0.030 | 0.780 | 0.163 | 0.291 |
| Log leptin /% body fat | 0.104 | 0.121 | -0.123 | 0.288 | 0.072 | 0.503 | 0.359 | 0.017 |
| Waist | -0.018 | 0.779 | -0.029 | 0.796 | -0.148 | 0.155 | -0.090 | 0.541 |
| Waist/ hip ratio | 0.084 | 0.193 | -0.158 | 0.152 | -0.102 | 0.328 | 0.101 | 0.493 |
| TLC% predicted | -0.059 | 0.360 | -0.065 | 0.550 | 0.045 | 0.668 | 0.122 | 0.402 |
| PetCO2 | 0.034 | 0.600 | -0.114 | 0.295 | 0.024 | 0.816 | 0.026 | 0.862 |
| AHI | 0.056 | 0.428 | 0.052 | 0.671 | -0.052 | 0.642 | -0.102 | 0.536 |
| Spmin | 0.112 | 0.108 | -0.019 | 0.879 | 0.226 | 0.038 | 0.071 | 0.666 |
| Spmed | 0.080 | 0.258 | -0.141 | 0.260 | 0.222 | 0.042 | 0.167 | 0.309 |
| Gender | 0.256 | <0.001 | | | | | | |

*Bivariate correlations adjusted by % body fat.

Table 6. Bivariate correlations for hypercapnic response (Minute ventilation/PetCO2)

| Variable | Whole sample | | Men | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Premenopausal | | Posmenopausal | |
| | Rho | p-value | Rho | p-value | Rho | p-value | Rho | p-value |
| Height | 0.393 | <0.001 | 0.309 | 0.004 | 0.242 | 0.018 | 0.009 | 0.950 |
| Age | -0.134 | 0.036 | 0.003 | 0.978 | -0.190 | 0.066 | -0.049 | 0.737 |
| % body fat | -0.289 | <0.001 | 0.038 | 0.739 | -0.122 | 0.247 | -0.118 | 0.439 |
| Leptin | -0.191 | 0.003 | 0.026 | 0.813 | 0.025 | 0.810 | 0.002 | 0.987 |
| Log leptin | -0.191 | 0.003 | 0.026 | 0.813 | 0.025 | 0.810 | 0.002 | 0.987 |
| Leptin* | -0.068 | 0.308 | -0.083 | 0.476 | 0.070 | 0.512 | 0.022 | 0.887 |
| Log leptin* | -0.098 | 0.141 | -0.142 | 0.217 | 0.077 | 0.466 | 0.031 | 0.844 |
| Log leptin /% body fat | 0.104 | 0.119 | -0.085 | 0.464 | 0.137 | 0.200 | 0.184 | 0.231 |
| Waist | 0.042 | 0.513 | 0.162 | 0.142 | -0.207 | 0.046 | -0.175 | 0.234 |
| Waist/ hip ratio | 0.168 | 0.009 | 0.041 | 0.709 | -0.089 | 0.394 | 0.063 | 0.669 |
| TLC% predicted | -0.019 | 0.773 | -0.002 | 0.984 | 0.113 | 0.279 | 0.345 | 0.015 |
| PetCO2 | 0.000 | 0.996 | -0.109 | 0.319 | 0.043 | 0.681 | -0.247 | 0.087 |
| AHI | 0.122 | 0.082 | 0.072 | 0.562 | 0.013 | 0.909 | -0.003 | 0.984 |
| Spmin | 0.075 | 0.284 | -0.053 | 0.669 | 0.281 | 0.010 | 0.238 | 0.145 |
| Spmed | 0.034 | 0.634 | -0.159 | 0.202 | 0.250 | 0.022 | 0.222 | 0.175 |
| Gender | 0.364 | <0.001 | | | | | | |

*Bivariate correlations adjusted by % body fat.

Table 7. Regression models for ventilatory control parameters separate by gender and menopausal status.

| | **Dependent variable** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline P0.1 | | | | | Delta P0.1 /PetCO2 | | | | | Delta VE/PetCO2 | | | | |
| Total population | $r^2$= 0.222 n= 245; p<0.001 | | | | | $r^2$ =0.056 n=187; p=0.002 | | | | | $r^2$=0.261 n=187; p<0.001 | | | | |
| | B | CI | Change in $r^2$ | Change in F | p value* | B | CI | Change in $r^2$ | Change in F | p value* | B | CI | Change in $r^2$ | Change in F | p value* |
| Height | | | | | | 1.540 | 0.074 to 3.007 | 0.043 | 10.656 | 0.001 | 8.900 | 6.212 to 11.588 | 0.236 | 57.117 | <0.001 |
| Age | -0.035 | -0.053 to -0.018 | 0.021 | 5.836 | 0.016 | | | | | | | | | | |
| %body fat | 0.072 | 0.033 to 0.110 | 0.013 | 3.598 | 0.048 | | | | | | | | | | |
| Log leptin | -1.777 | -2.834 to -0.720 | 0.036 | 11.178 | 0.001 | -0.594 | -1.119 to -0.070 | 0.029 | 7.452 | 0.007 | -1.416 | -2.378 to -0.455 | 0.034 | 8.445 | 0.004 |
| %TLC | -0.025 | -0.043 to -0.006 | 0.015 | 4.549 | 0.034 | | | | | | | | | | |
| PetCO2 | -0.142 | -0.185 to -0.099 | 0.090 | 23.923 | <0.001 | | | | | | | | | | |
| Spmin | -0.040 | -0.061 to -0.020 | 0.034 | 10.047 | 0.002 | | | | | | | | | | |
| Men | $r^2$= 0.298 n=88; p<0.001 | | | | | $r^2$=0.051 n=61; p=0.027 | | | | | $r^2$=0.127 n=61; p=0.003 | | | | |
| | B | CI | Change in $r^2$ | Change in F | p value* | B | CI | Change in $r^2$ | Change in F | p value* | B | CI | Change in $r^2$ | Change in F | p value* |
| Height | | | | | | | | | | | 12.314 | 4.427 to 20.201 | 0.142 | 9.761 | 0.003 |
| %body fat | 0.064 | 0.006 to 0.123 | 0.034 | 4.737 | 0.032 | | | | | | | | | | |
| Log leptin | -2.262 | -3.855 to -0.668 | 0.029 | 3.946 | 0.050 | -0.990 | -1.866 to -0.114 | 0.063 | 5.069 | 0.027 | | | | | |
| WHR | -7.590 | -11.958 to -3.221 | 0.063 | 7.805 | 0.006 | | | | | | | | | | |
| %TLC | -0.063 | -0.093 to -0.034 | 0.068 | 7.092 | 0.009 | | | | | | | | | | |
| PetCO2 | -0.135 | -0.200 to -0.071 | 0.105 | 12.170 | 0.001 | | | | | | | | | | |
| Spmin | -0.030 | -0.059 to 0.001 | 0.042 | 5.495 | 0.021 | | | | | | | | | | |
| Pre-Menopausal women | $r^2$=0.215 n=93; p<0.001 | | | | | $r^2$=0.075 n=78; p=0.009 | | | | | $r^2$=0.100 n=78; p=0.007 | | | | |
| | B | CI | Change in $r^2$ | Change in F | p value* | B | CI | Change in $r^2$ | Change in F | p value* | B | CI | Change in $r^2$ | Change in F | p value* |
| Height | | | | | | | | | | | 5.074 | 0.862 to 9.285 | 0.070 | 5.719 | 0.019 |
| Age | -0.057 | -0.093 to -0.022 | 0.056 | 5.902 | 0.017 | | | | | | | | | | |
| %body fat | 0.114 | 0.039 to 0.190 | 0.047 | 5.219 | 0.025 | -0.061 | -0.105 to -0.016 | 0.087 | 7.244 | 0.009 | | | | | |
| Log leptin | -2.023 | -3.683 | 0.050 | 5.870 | 0.017 | | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | to -0.364 | | | | | | | | | | | | | |
| Waist | | | | | | | | | | | -0.023 | -0.043 to -0.002 | 0.054 | 4.607 | 0.035 |
| PetCO2 | -0.105 | -0.167 to -0.042 | 0.097 | 9.732 | 0.002 | | | | | | | | | | |
| Pos-Menopausal women | $r^2$=0.270 n=46; p<0.001 | | | | | $r^2$=0.150 n=35; p=0.013 | | | | | $r^2$=0.155 n=35; p=0.011 | | | | |
| | B | CI | Change in $r^2$ | Change in F | p value* | B | CI | Change in $r^2$ | Change in F | p value* | B | CI | Change in $r^2$ | Change in F | p value* |
| Age | | | | | | -0.047 | -0.083 to -0.011 | 0.175 | 6.978 | 0.013 | | | | | |
| %TLC | | | | | | | | | | | 0.047 | 0.011 to 0.083 | 0.180 | 7.226 | 0.011 |
| PetCO2 | -0.095 | -0.176 to -0.013 | 0.089 | 5.471 | 0.024 | | | | | | | | | | |
| SpminO2 | -0.073 | -0.108 to -0.038 | 0.214 | 11.958 | 0.001 | | | | | | | | | | |

*p value for the change in F of each variable.
The $r^2$ of each model is adjusted for the number of variables.

**References**


1 Rochester DF, Enson Y. Current concepts in the pathogenesis of the obesity-hypoventilation syndrome. Mechanical and circulatory factors. Am J Med 1974; 57: 402-420.

2 Kessler R, Chaouat A, Schinkewitch P, Faller M, Casel S, Krieger J, Weitzenblum E. The obesity-hypoventilation syndrome revisited. A prospective study of 34 consecutive cases. Chest 2001; 120: 369-376.

3 Sampson MG, Grassino A. Neuromechanical properties in obese patients during carbon dioxide rebreathing. Am J Med 1983; 75: 81-90.

4 Zwillich CW, Sutton FD, Pierson DJ, Creagh EM, Weil JV. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. Am J Med 1975; 59: 343-348.

5 O'Donnell CP, Schaub CD, Haines AS, et al. Leptin prevents respiratory depression in obesity. Am J Respir Crit Care Med 1999; 159: 1477-1484.

6 Phipps PR, Sarritt E, Caterson I, Grunstein RR. Association of serum leptin with hypoventilation in human obesity. Thorax 2002; 57: 75-76.

7 Ginde SR, Geliebter A, Rubiano F, Silva AM, Wang J, Heshka S, Heymsfield SB. Air displacement plethysmography: validation in overweight and obese subjects. Obes Res 2005; 13: 1232-1237.

8 European Respiratory Society. Standardization of lung function testing. Lung volumes and forced ventilatory flows. 1993 update. Eur Respir J 1993; 6(suppl 16): 5-40.

9 Whitelaw WA, Derenne J-P, Milic-Emili J. Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol 1975; 23: 181-199.

10 Read DJ. A clinical method for assessing the ventilatory response to carbon dioxide. Australas Ann Med 1967; 16 (1): 20-32.

12 Haalas JL, Gajiwala KS, Maffei M, Cohen SL, Chait B, Rabinovitz D, Lallone RL, Burley SK, Friedman JM. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995; 269: 543-546.

13 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425-432.

14 Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995; 269: 540-43.

15 Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL, Caro JF. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996; 334: 292-295.

16 Tankersley CG, O'Donnell C, Daood MJ, Watchko JF, Mitzner W, Schwartz A, Smith P. Leptin attenuates respiratory complications associated with the obese phenotype. J Appl Physiol 1998; 85(6): 2261-2269.

17 Caro JF, Kolaczynski JW, Nyce MR, Ohannesian JP, Opentanova I, Goldman WH, Lynn RB, Zhang P, Sinha MK, Considine RV. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a posible mechanism for leptin resistance. Lancet 1996; 348: 159-161.

18 Banks WA, DiPalma CR, Farrell CL. Impaired transport of leptin across the blood-brain barrier in obesity. Peptides 1999; 20: 1341-1345.

19 Frederich RC, Hamann A, Anderson S, Löllmann B, Lowell BB, Flier JS. Leptin levels reflect body lipid content in mice: evidence for a diet-induced resistance to leptin action. Nat Med 1995; 1: 1311-1314.

20 Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin H, Kaless A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000; 85: 1151-1158.

21 Öztürk L, Ünal M, Tamer L, Çelikoglu F. The association of the severity of obstructive sleep apnea with plasma leptin levels. Arch Otolaryngol Head Neck Surg 2003; 129: 538-540.

22 Saarelainen S, Lahtela J, Kallonen E. Effect of nasal CPAP treatment on insulin sensitivity and plasma leptin. J Sleep Res 1997; 6: 146-147.

23 Harsch IA, Konturek PC, Koebnick C, Kuehnlein PP, Fuchs FS, Pour Schahin S, Wiest GH, Hahn EG, Lohmann T, Ficker JH. Leptin and ghrelin levels in patients with obstructive sleep apnoea: effect of CPAP treatment. Eur Respir J 2003; 22: 251-257.

24 Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K, Ohi M. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. Circulation 1999; 100: 706-712.

25 Ip MSM, Lam KSL, Ho Ch, Tsang KWT, Lam W. Serum leptin and vascular risk factors in obstructive sleep apnea. Chest 2000; 118: 580- 586.

26 Sanner BM; Kollhosser P, Buechner N, Zidek W, Tepel M. Influence of treatment on leptin levels in patients with obstructive sleep apnoea. Eur Respir J 2004; 23: 601-604.

27 Shimizu K, Chin K, Nakamura T, Masuzaki H, Ogawa Y, Hosokawa R, Niimi A, Hattori N, Nohara R, Sasayama S, Nakao K, Mishima M, Nakamura T, Ohi M. Plasma leptin levels and cardiac sympathetic function in patients with obstructive sleep apnoea-hypopnoea syndrome. Thorax 2002; 47: 429-434.

28 Barceló A, Barbé F, Llompart E, de la Peña M, Durán-Cantolla J, Ladaria A, Bosch M, Guerra L, Agustí AGN. Neuropeptide Y and leptin in patients with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2004; 171: 183-187.

29 Grosfeld A, André J, Hauguel-de Mouzon S, Berra E, Pouysségur J, Guerre-Millo. Hypoxia-inducible factor 1 transactivates the human leptin gene promoter. J Biol Chem 2002; 45: 42953-42957.

30 Tatsumi K, Kasahara Y, Kurosu K, Tanabe N, Takiguchi Y, Kuriyama T. Sleep oxygen desaturation and circulating leptin in obstructive sleep apnea-hypopnea syndrome. Chest 2005; 127: 716-721.

31 Shimura R, Tatsumi K, Nakamura A, Kasahara Y, Tanabe N, Takiguchi Y, Kuriyama T. Fat accumulation, leptin, and hypercapnia in obstructive sleep apnea-hypopnea syndrome. Chest 2005; 127: 543-549.

32 Van Klaveren RJ, Demedts M. Determinants of hypercapnic and hypoxic response in normal man. Respir Physiol 1998; 113:157-165.

33 Montes de Oca M, Celli BR. Mouth occlusion pressure, CO2 response and hypercapnia in severe chronic obstructive pulmonary disease. Eur Respir J 1998; 12: 666-671.

34 Buyse B, Markous N, Cauberghs M, Van Klaveren R, Muls E, Demedts M. Effect of obesity and/or sleep apnea on chemosensitivity: differences between men and women. Respir Physiol Neurobiol 2003; 1334: 13-22.

36 Saad MF, Damani S, Gingerich RL, Riad-Gabriel MG, Khan A, Boyadjian R, Jinagouda SD, El-Tawil K, Rude RK, Kamdar V. Sexual dimorphism in plasma leptin concentration. J Clin Endocrinol Metab 1997; 82: 579-584.