

## SHORT PAPER

## Association of serum leptin with hypoventilation in human obesity

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Thorax 2002;57:75-76

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Revised version received  
24 May 2001  
Accepted for publication  
25 June 2001

**Background:** Leptin is a protein hormone produced by fat cells of mammals. It acts within the hypothalamus via a specific receptor to reduce appetite and increase energy expenditure. Plasma leptin levels correlate closely with total body fat mass operating via a central feedback mechanism. In human obesity serum leptin levels are up to four times higher than in lean subjects, indicating a failure of the feedback loop and central leptin resistance. In leptin deficient obese mice (*ob/ob* mice) leptin infusion reverses hypoventilation. It was hypothesised that a relative deficiency in CNS leptin, indicated by high circulating leptin levels, may be implicated in the pathogenesis of obesity hypoventilation syndrome (OHS).

**Methods:** Fasting morning leptin levels were measured in obese and non-obese patients with and without daytime hypercapnia (n=56). Sleep studies, anthropometric data, spirometric parameters, and awake arterial blood gas tensions were measured in each patient.

**Results:** In the whole group serum leptin levels correlated closely with % body fat ( $r=0.77$ ). Obese hypercapnic patients (mean (SD) % body fat 43.8 (6.0)%) had higher fasting serum leptin levels than eucapnic patients (mean % body fat 40.8 (6.2)%), with mean (SD) leptin levels of 39.1 (17.9) and 21.4 (11.4) ng/ml, respectively ( $p<0.005$ ). Serum leptin (odds ratio (OR) 1.12, 95% CI 1.03 to 1.22) was a better predictor than % body fat (OR 0.92, 95% CI 0.76 to 1.1) for the presence of hypercapnia.

**Conclusions:** Hyperleptinaemia is associated with hypercapnic respiratory failure in obesity. Treatment with leptin or its analogues may have a role in OHS provided central leptin resistance can be overcome.

## INTRODUCTION

Obesity is rapidly increasing in prevalence with a major impact on ill health and health costs.<sup>1</sup> Sleep disordered breathing, usually manifest by obstructive sleep apnoea (OSA), is common in obesity. However, some patients with obesity and OSA develop daytime hypercapnia (obesity hypoventilation syndrome, OHS).<sup>2</sup>

Leptin is a protein hormone produced by mammalian adipocytes. It acts within the hypothalamus via a specific receptor to reduce appetite and increase energy expenditure.<sup>3</sup> Serum levels correlate positively with total body fat mass. In obesity there may be a failure of central feedback mechanisms leading to leptin resistance.<sup>3</sup> There is evidence, for example, that obese humans have a relative deficiency of CNS leptin compared with lean controls.<sup>4</sup> Recent data have shown, however, that leptin replacement reverses the hypoventilation that occurs in the leptin deficient mouse model of obesity.<sup>5</sup>

We further characterised this relationship by measuring leptin levels and arterial blood gas tensions in patients with various degrees of obesity and sleep disordered breathing, including patients with awake hypercapnia.

## METHODS

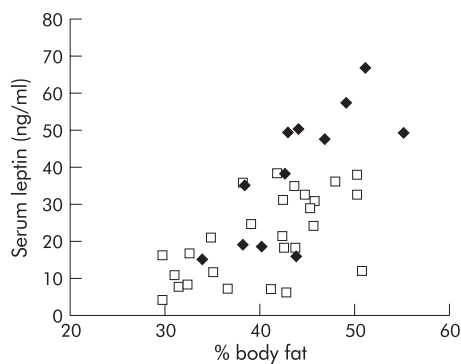
Consecutive patients undergoing diagnostic sleep studies at Royal Prince Alfred Hospital between July and December 1999 were studied. Anthropometric measurements, spirometric tests, and arterial blood gas sampling were performed in the afternoon before a nocturnal sleep study. The following morning venous blood was drawn for measurement of fasting serum leptin (Radioimmunoassay, Linco Research Inc, Missouri, USA). The reproducibility of the assay was  $\pm 5\%$  and the accuracy was  $\pm 0.5$  ng/ml. Daytime hypercapnia was defined as arterial carbon dioxide tension ( $P_{aCO_2}$ ) of  $>6.0$  kPa (in the

absence of metabolic and acute respiratory alkalosis) and hypoxaemia as arterial oxygen tension ( $P_{aO_2}$ ) of  $<10.7$  kPa in patients aged  $<60$  years and  $<10.0$  kPa in those aged  $>60$  years. Obesity was defined as a body mass index (BMI) of  $>28$  kg/m<sup>2</sup>.<sup>4</sup> Patients were excluded from the study if they were  $<20$  or  $>80$  years of age, had airways disease or FEV<sub>1</sub>/FVC ratio of  $<75\%$ , neuromuscular disease, severe left ventricular failure, untreated thyroid disease, or were currently on a strict weight reducing diet. Patients were also excluded if arterial blood gas tensions could not be measured (patient declined, poor sample volume, venous sample, difficulty in collecting sample). The percentage body fat was calculated using Garrow's formula<sup>6</sup> which corrects for sex differences in BMI and was used for the comparison with fasting leptin.

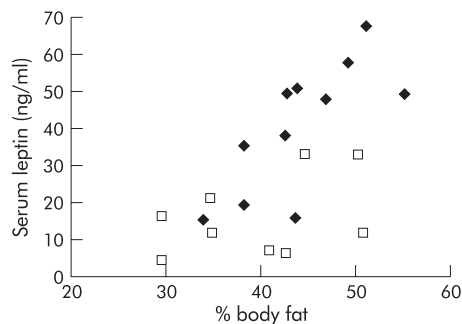
Logistic regression analysis was performed with  $P_{aCO_2}$  as the dependent variable and leptin and % body fat as explanatory variables (SPSS for Windows 10.0, SPSS Inc, USA). Odds ratios with 95% confidence intervals were calculated for both variables. Statistical significance was taken at the 5% level.

## RESULTS

Results are expressed as mean (SD). A total of 56 patients were studied (16 women) with a mean age of 46 years (range 22-80). Forty four patients were eucapnic ( $P_{aCO_2}$  5.5 (0.4) kPa) and 12 were hypercapnic ( $P_{aCO_2}$  6.5 (1.1) kPa). Twenty patients were obese and hypoxic ( $P_{aO_2}$  8.8 (1.6) kPa). As expected, fasting serum leptin levels were closely related to % body fat in the entire patient group ( $r=0.77$ ). In the obese group (n=39) hypercapnic patients had significantly higher fasting serum leptin levels than eucapnic patients, with leptin levels of 39.1 (17.9) and 21.4 (11.4) ng/ml, respectively ( $p<0.005$ , fig 1). There was no difference in degree of body fat



**Figure 1** Fasting serum leptin levels versus % body fat in obese hypercapnic (diamonds) and eucapnic (squares) patients. Hypercapnic patients had significantly higher leptin levels ( $p < 0.005$ ).



**Figure 2** Fasting serum leptin levels versus % body fat in obese hypoxic patients. Hypercapnic patients (OHS, diamonds) had significantly higher leptin levels than eucapnic patients (squares,  $p < 0.005$ ).

between the hypercapnic (% body fat 43.8 (6.0)%) and eucapnic (% body fat 40.8 (6.2)%) patients ( $p > 0.4$ ). Serum leptin ( $b = 0.113$ ,  $SE(b) = 0.044$ ,  $p = 0.01$ , OR 1.12 (95% CI 1.03 to 1.22)) but not % body fat ( $b = -0.087$ ,  $SE(b) = 0.094$ ,  $p = 0.4$ , OR 0.92 (95% CI 0.76 to 1.1)) was a predictor for the presence of hypercapnia. The results were similar in the obese hypoxic group of patients (fig 2). There was no difference in the apnoea-hypopnoea index (AHI) between the two groups (mean 47/hour for eucapnic patients and 57/hour for hypercapnic patients,  $p > 0.2$ ).

## DISCUSSION

We have observed that serum leptin is a better predictor than % body fat for the presence of hypercapnia in patients with OHS. This suggests that, in patients with obesity and sleep disordered breathing, a higher leptin level predisposes to the development of OHS. We are not aware of previous work examining both serum leptin levels and the presence of OHS in patients with obesity.

OHS occurs in a minority of obese subjects secondary to severe upper airway obstruction and altered central control of breathing.<sup>2</sup> Recent data have suggested a potential role for

leptin in the pathogenesis of OHS. In the *ob/ob* mouse, a genetically mutated mouse model of obesity that is leptin deficient, there is an increased  $Paco_2$  and a reduced hypercapnic ventilatory response.<sup>5</sup> Leptin administration reversed hypoventilation in this model, presumably by stimulation of central respiratory control centres.<sup>5</sup> Conversely, in wild type mice with diet induced obesity and increased endogenous leptin levels, ventilation was appropriately compensated.<sup>5</sup> In humans leptin levels can fall by up to 53% after a 10% loss of body weight,<sup>3</sup> and in eucapnic obese patients the hypercapnic respiratory drive also falls after weight loss.<sup>7</sup> These results suggest that leptin may act to maintain alveolar ventilation to compensate for the increased ventilatory load in obesity.<sup>8</sup> Our finding that hypercapnic patients have higher leptin levels may indicate a failure of that compensatory mechanism.

Leptin may be only one of many predictors for hypercapnia in the obese population. This study did not measure hypercapnic ventilatory responses which would have been useful to help elucidate the direct effects of hypoventilation on leptin levels. Also, our study was not large enough to analyse the subgroup of patients with OSA who may have a greater degree of hypercapnia, although there was no statistical difference in AHI between the two groups studied.

These data support a role for hyperleptinaemia in the pathogenesis of hypercapnic respiratory failure in obesity. There is a potential rationale for treatment with leptin or its analogues in OHS, provided central leptin resistance<sup>4,5</sup> can be overcome.

## ACKNOWLEDGEMENTS

E Starritt is supported by the Community Health and Tuberculosis Association, Australia. Supported by NHMRC of Australia.

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