Impaired lung function and serum leptin in men and women with normal body weight: a population based study

D D Sin, S F P Man

Background: Impaired lung function is a risk factor for cardiovascular morbidity. Whether circulating factors are responsible for this association is unknown. A study was undertaken to determine whether leptin, a hormone that can promote atherothrombosis, is raised in individuals with impaired lung function.

Methods: Data from non-obese participants in the Third National Health, Nutrition, and Examination Survey (n=2808) were analysed to determine the relationship between circulating leptin levels and forced expiratory volume in 1 second (FEV1) values divided into quintiles (quintile 1, FEV1 predicted <85.2%; quintile 2, 85.3–94.3%; quintile 3, 94.4–101.4%; quintile 4, 101.5–110.0%; and quintile 5, ≥110.1%).

Results: Serum leptin levels changed along the FEV1 gradient. The highest leptin levels were found in quintile 1 (geometric mean (GM) 5.42; interquartile range (IQR) 3.00–9.60 fg/l) and the lowest in quintile 5 (GM 4.94, IQR 2.80–9.10 fg/l). Adjustments for age, body mass index, and other confounders strengthened this relationship. Compared with quintile 5, the odds of having an increased serum leptin level in quintiles 1, 2, 3, and 4 were 2.26 (95% confidence interval (CI) 1.54 to 3.31), 2.20 (95% CI 1.52 to 3.17), 1.46 (95% CI 1.01 to 2.09), and 1.28 (95% CI 0.90 to 1.83), respectively.

Conclusion: Individuals with impaired lung function have raised serum leptin levels. Leptin may play a role in the pathogenesis of cardiovascular morbidity and mortality related to impaired lung function.

METHODS

Study participants

The detailed methods for NHANES 3 have been described previously. Briefly, it comprised a cross sectional, multistage probability sample representative of the total non-institutionalised civilian population in the US. The sample was selected from households in 81 counties between 1988 and 1994. The original NHANES 3 sample included 20 050 adults aged 17 years and older. The present analysis was restricted to non-obese participants (body mass index (BMI) <26 kg/m²) aged 20 years and older who performed spirometric tests that met acceptability and reliability criteria of the American Thoracic Society (ATS). To adjust for height, age, sex, and race, we used published prediction equations for FEV1, and forced vital capacity (FVC) derived from the NHANES population.

We divided the cohort into quintile groups based on percentage predicted FEV1; quintile 1 was defined as FEV1 <85.2% predicted (mean 70.8%); quintile 2, 85.3–94.3% (mean 90.1%); quintile 3, 94.4–101.4% (mean 98.0%); quintile 4, 101.5–110.0% (mean 105.6%); and quintile 5, ≥110.1% predicted (mean 118.6%).

Laboratory measurements

Using a radioimmunoassay of polyclonal antibodies raised in rabbits against highly purified recombinant human leptin, leptin concentrations used in this analysis were measured from serum samples of 6415 participants in NHANES 3 who...
provided a morning blood sample after an overnight fast. The minimum detectable concentration of this assay was 0.5 fg/l and the limit of linearity was up to 100 fg/l. Recovery of leptin was not determined, but the limit of detection was up to 100 fg/l. Recovery of leptin was determined using standard laboratory techniques. The assay had a minimum detectable concentration of 0.5 fg/l and a limit of linearity up to 100 fg/l. Recovery of leptin was not determined, but the limit of detection was up to 100 fg/l.

### Covariates

Age was classified into six strata (20–29; 30–39; 40–49; 50–59; 60–69; and 70 years and older), race was divided into two categories (white and non-white), and smoking status was divided into three strata (current, former, and never smokers). For current and former smokers the total cigarette consumption was estimated using pack year equivalents (average daily consumption of cigarettes divided by 20 and multiplied by the number of years smoked). BMI was calculated using standard laboratory techniques, and the limit of linearity was up to 100 fg/l. Recovery of leptin was determined using standard laboratory techniques. The assay had a minimum detectable concentration of 0.5 fg/l and a limit of linearity up to 100 fg/l. Recovery of leptin was not determined, but the limit of detection was up to 100 fg/l.

### Statistical analyses

The baseline characteristics of the study participants across the FEV1 quintile groups were compared using a test for trend.

### Table 1: Baseline characteristics of study participants stratified according to severity of FEV1 impairment

<table>
<thead>
<tr>
<th>Quintile</th>
<th>(n=561)</th>
<th>Quartile 2</th>
<th>(n=562)</th>
<th>Quintile 3</th>
<th>(n=561)</th>
<th>Quintile 4</th>
<th>(n=562)</th>
<th>Quintile 5</th>
<th>(n=562)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% predicted)</td>
<td>70.8 (14.9)</td>
<td>90.1 (2.6)</td>
<td>98.0 (2.1)</td>
<td>100.5 (2.4)</td>
<td>115.8 (8.3)</td>
<td>0.001</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.5 (2.4)</td>
<td>22.6 (2.2)</td>
<td>22.9 (2.2)</td>
<td>23.2 (2.2)</td>
<td>23.5 (2.2)</td>
<td>0.001</td>
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<tr>
<td>Serum albumin (g/l)</td>
<td>40.9 (3.4)</td>
<td>41.6 (3.5)</td>
<td>41.9 (3.6)</td>
<td>41.6 (3.5)</td>
<td>41.6 (3.5)</td>
<td>0.001</td>
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<tr>
<td>Serum folate (nmol/l)</td>
<td>15.4 (14.2)</td>
<td>14.8 (14.7)</td>
<td>15.6 (15.6)</td>
<td>14.1 (12.3)</td>
<td>15.8 (12.8)</td>
<td>0.952</td>
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<tr>
<td>Males</td>
<td>297 (52.9%)</td>
<td>278 (49.5%)</td>
<td>259 (46.2%)</td>
<td>249 (44.3%)</td>
<td>252 (44.8%)</td>
<td>0.001</td>
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<tr>
<td>Weight (kg)</td>
<td>63.4 (10.6)</td>
<td>64.2 (10.0)</td>
<td>63.9 (9.9)</td>
<td>64.1 (10.0)</td>
<td>63.1 (9.7)</td>
<td>0.685</td>
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<tr>
<td>Triceps skinfold (mm)</td>
<td>13.8 (6.6)</td>
<td>14.7 (6.9)</td>
<td>14.8 (6.6)</td>
<td>14.3 (6.6)</td>
<td>13.2 (6.1)</td>
<td>0.068</td>
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</table>

### Table 2: Log transformed serum leptin values stratified according to severity of lung impairment

<table>
<thead>
<tr>
<th>Severity of lung impairment</th>
<th>Quintile 1</th>
<th>(n=561)</th>
<th>Quintile 2</th>
<th>(n=562)</th>
<th>Quintile 3</th>
<th>(n=561)</th>
<th>Quintile 4</th>
<th>(n=562)</th>
<th>Quintile 5</th>
<th>(n=562)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log transformed leptin values (fg/l)</td>
<td>1.69 (0.78)</td>
<td>1.67 (0.81)</td>
<td>1.68 (0.78)</td>
<td>1.65 (0.80)</td>
<td>1.60 (0.79)</td>
<td>0.059</td>
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<tr>
<td>Unadjusted partial regression coefficient</td>
<td>0.093 (0.047)</td>
<td>0.069 (0.047)</td>
<td>0.085 (0.047)</td>
<td>0.0565 (0.047)</td>
<td>0.0 (reference)</td>
<td>0.059</td>
<td></td>
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<tr>
<td>Partial regression coefficient adjusted for sex</td>
<td>0.182 (0.034)</td>
<td>0.119 (0.034)</td>
<td>0.099 (0.034)</td>
<td>0.050 (0.034)</td>
<td>0.0 (reference)</td>
<td>0.001</td>
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<tr>
<td>Partial regression coefficient adjusted for sex and BMI</td>
<td>0.250 (0.029)</td>
<td>0.174 (0.029)</td>
<td>0.141 (0.029)</td>
<td>0.056 (0.029)</td>
<td>0.0 (reference)</td>
<td>0.001</td>
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<tr>
<td>Fully adjusted partial regression coefficient</td>
<td>0.236 (0.029)</td>
<td>0.190 (0.029)</td>
<td>0.160 (0.029)</td>
<td>0.077 (0.029)</td>
<td>0.0 (reference)</td>
<td>0.001</td>
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</table>

Partial regression coefficients were derived from linear regression models. Each cell represents the mean (SE) expected increase in serum leptin values (on a logarithmic scale, fg/l) for each quintile group relative to the reference category (quintile 5). Adjusted for age, sex, smoking status, race, body mass index, and lung function (see methods).

BMI=body mass index; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; CRP=C reactive protein.

Continuous variables are shown as mean (SD) and dichotomous variables are shown as number (% of column totals) unless otherwise indicated. Geometric mean.

†Adjusted for age, sex, smoking status, race, body mass index, and lung function.
There is a growing body of evidence indicating that leptin may have an important role in upregulating the inflammatory system. Recent evidence indicates that macrophages, when exposed to leptin, markedly increase production of proinflammatory mediators such as tumour necrosis factor (TNF-α) and interleukins 6 and 12, indicating a positive feedback mechanism. Since leptin is a potent inflammatory promoter it may exacerbate existing lung and systemic inflammation, contributing to the poor clinical outcomes of patients with various lung diseases.
Leptin is also an important risk factor for coronary events. It has a pressor effect on blood vessels through increased activation of the sympathetic nervous system which is thought to mediate obesity related hypertension. Because excess adrenergic activity has also been noted in advanced lung disease, our findings raise the possibility that leptin may play an important role in increasing the risk for poor cardiovascular outcomes in such patients. Other adverse effects of leptin have been demonstrated including increased risk of thrombosis through its action on platelets and of osteoporosis through its action on the central hypothalamic pathways. The risks of cardiovascular morbidity and mortality are markedly increased in the presence of low FEV1. In view of the wide array of harmful cardiovascular and neurohumoral effects of leptin, its role in the pathogenesis of cardiovascular outcomes of lung disease need to be further explored.

Superficially, our findings appear to differ from those of previous reports. In one study serum leptin levels were found to be lower in those with advanced lung disease than in healthy controls, a finding that was difficult to understand since, in the same study, TNF-α levels (a positive feedback mediator for leptin) were much higher in those with lung disease than in the control group. This study, however, was small and the noise associated with the measurement of leptin could have confounded the findings. In a subsequent study by the same group of investigators serum leptin levels were found to be higher in patients with chronic obstructive pulmonary disease (COPD) than in controls, but only in a subgroup of patients who were non-cachectic and had similar BMI to the healthy controls, suggesting that BMI is a critical confounder of this relationship. Our study was designed to minimise the potential for confounding. In our analysis we excluded overweight and obese individuals in the NHANES 3 study. To control for any residual confounding by age, sex, and (in particular) weight we used multiple regression techniques in which age, sex, and BMI were considered as covariates. By doing so, we avoided the shortcomings of previous studies.

Our study has several limitations which need to be highlighted. Firstly, the cross sectional nature of the NHANES 3 data precludes any inferences regarding the temporal nature of the relationship between FEV1, impairment and serum leptin levels. Secondly, there were insufficient numbers of patients with very severe lung disease, so the relationship between serum leptin levels and very severe lung disease remains unknown.

In summary, our findings indicate that, when adjusted for BMI, age, sex, and other potential confounders, patients with impaired FEV1 have higher serum leptin levels than normal controls in a “severity dependent” manner. The growing body of evidence demonstrating the important deleterious effects of circulating leptin on the neurohumoral and cardiovascular systems raises the possibility that this hormone may contribute to poor outcomes of patients with common lung diseases such as COPD. Future work is needed to confirm our findings and to determine whether interventions that reduce circulating leptin in lung disease can improve the health status and outcomes of these patients.

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REFERENCES