INTRODUCTION

Leptin is a cytokine-type peptide which is mainly produced by fat tissue. It regulates fat mass by decreasing food intake and increasing resting energy expenditure, so an increase of serum leptin could be an indicator of malnutrition. Our objective was to determine serum leptin levels in chronic alcohol misusers, hospitalized by somatic complications, who drink more than 80 g ethanol/day, and to analyse its relationships with nutritional status assessed by anthropometry and dual-energy X-ray absorptiometry (DEXA), insulin-like growth factor (IGF-1) and its binding protein (IGF1BP-3); acute phase reaction assessed by C-reactive protein (CRP), interleukin-6 (IL-6) and type II soluble receptor of tumour necrosis factor (TNF) (sTNFRII); serum oestradiol and testosterone; and the amount and duration of ethanol intake, the smoking habit and the presence of liver cirrhosis.

Methods: Patients were admitted through the emergency room, and blood for the above-mentioned determinations was taken at 08.00 on the following day, so none of the patients was acutely intoxicated at this time. The control group was composed of 32 healthy male (age-matched) subjects. Results: Malnutrition was frequent among alcoholics. Serum leptin levels were closely related to total fat both in controls and in alcoholics. Serum leptin levels were decreased in alcoholics, even after adjusting for the amount of fat. Those alcoholics who reported anorexia and weight loss showed decreased leptin levels. After 15 days of hospitalization, serum leptin did not increase, in contrast with LDL cholesterol, serum albumin, prealbumin, IGF-1, IGF1BP-3 and testosterone which increased, whereas oestradiol and acute phase reactants, such as CRP, IL-6 and sTNFRII, were decreased. Serum leptin was not related to gonadal hormones at admission, but on day 15 we found a negative correlation between leptin and testosterone, and a positive one with oestradiol.

Conclusions: Serum leptin levels are related to many factors, e.g. fat mass, age, smoking, serum testosterone and oestradiol levels, growth factors such as IGF-1 and CRP, and cytokines, such as IL-6 and sTNFRII. The most important of these is fat mass, as shown by multivariate analysis. Since serum leptin levels are decreased in alcohol misusers, we consider this decrease to be a consequence of a low fat mass.
SUBJECTS AND METHODS

Seventy-nine consecutive hospitalized male alcohol misusers, who drink more than 80 g ethanol/day, were included in the study (mean age ± SD: 49.2 ± 1.4 years; range 25–78 years). All the patients were admitted through the emergency room to the internal medicine unit of the General University Hospital, a reference centre on Tenerife Island. Patients with raised serum creatinine or increased blood glucose levels were excluded. The principal causes of admission were: in 23 cases an infection; pneumonia, 12 cases; bronchial infection, three cases; cellulitis and spontaneous bacterial peritonitis, two cases; and urinary infection, osteomyelitis, pulmonary tuberculosis and undetermined sepsis, one case each; 24 cases were admitted with an withdrawal syndrome; 10 cases with acute alcoholic hepatitis; eight cases with ascites-decompensated liver cirrhosis; eight cases with alcoholic pancreatitis (non-severe); and five cases with gastrointestinal bleeding. The following data were recorded.

Ethanol intake and liver function assessment

Ethanol intake during the last weeks and the duration of the intake were recorded by recall, and calculated as follows: grams of ethanol = volume of beverage (cc) × strength (v/v; %) × 0.8 (specific gravity of ethanol). All the patients have drunk regularly until the onset of the illness which caused hospital admission. None of them was acutely intoxicated on arrival at the hospital. The presence of alcohol withdrawal data in the first days of admission was recorded, as well as smoking habit and the number of packets/year. Alcohol withdrawal syndrome was evaluated by the presence of tremor, hallucinations or delirium, and it was treated with vitamin B₆ and diazepam. Liver cirrhosis was present in 15 patients, in 10 of them it was decompensated by ascites. Besides the physical and biological data, we performed abdominal ultrasonography, liver scintigraphy and liver biopsy, when necessary.

Nutritional assessment

Weight and height were recorded at admission, with further calculation of body mass index (BMI) as weight/height², classifying the patients as undernourished when BMI was under 20 kg/m², normal when it was 20–25 kg/m², overweight if it was 25–30 kg/m² and obese if it was over 30 kg/m². BMI was not considered in patients with ascites. We also determined the mid-arm circumference (MAC) and the triceps skinfold (TSF) by a Holtain lipocalliper and further calculated the mid-arm muscle area (MAMA = MAC – πTSF² / 4π) (Blackburn et al., 1977). Anthropometric parameters were compared with those of the population of the Western Canary Islands for adults of the same sex and age. We used as standards the 50th percentiles of these parameters in men of the same age (González-Hermoso et al., 1990). We also recorded the intake of the main groups of food: meat and fish, milk, eggs, cereals, legumes and vegetables, and also if there was vomiting, diarrhoea, anorexia or weight loss.

Body composition analysis was performed in 64 patients by DEXA using a hologic QDR-2000 system (software v5.54), considering the six following regions: left and right arm, left and right leg, trunk and head. We considered for the nutritional analysis the fat and the lean mass (Lohman, 1996). We selected the arms as the more representative region to study the lean mass in alcoholic and cirrhotic patients (Santolaria et al., 2000). We also performed a DEXA study in 32 healthy male controls (BMI 26.1 ± 2.7 kg/m²) selected from the staff of our hospital, all of them drinkers of less than 10 g of ethanol/day; six (18%) were smokers. The selection was age-matched to the patients’ group (mean age 48.7 ± 2 years; range 28–71 years).

Blood tests

Blood samples of patients and controls were taken at 08.00 on the day after the admission (none of the patients was acutely intoxicated at the time of venesection), under fasting conditions. Serum was frozen at −40°C for further determination of lepton levels, by immunoradiometric assay (IRMA) (Diagnostic Systems Laboratories, Webster, TX, USA) with a sensitivity of 0.1 ng/ml; IGF-1 by IRMA with a sensitivity of 2.06 ng/ml; IGF1BP-3 by IRMA with a sensitivity of 0.5 ng/ml; sTNFRII by ELISA (Inmunotech, Marseille, France) with a sensitivity of 0.01 ng/ml; IL6 by chemiluminescent enzyme immunometric assay (Diagnostic Products Corporation, Los Angeles, CA, USA) with a sensitivity of 5 pg/ml; CRP by fluorescence polarization immunoassay (Diagnostic Division Abbott, Wiesbaden, Germany) with a sensitivity of 0.1 mg/dl; LH by chemiluminescent enzyme immunometric assay (Diagnostic Products Corporation) with a sensitivity of 0.7 UI/ml; oestradiol by chemiluminescent enzyme immunometric assay (Diagnostic Products Corporation) with a sensitivity of 20 pg/ml; and free testosterone by RIA (Diagnostic Products Corporation) with a sensitivity of 0.15 pg/ml. All the assays were of high standard quality with very low cross reactivity. Lepton values were expressed as absolute values and as a ratio to the total fat assessed by DEXA. We also determined triglycerides, cholesterol [total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL)], total serum proteins, prealbumin and albumin levels, in order to assess visceral proteins. In order to detect changes related to withdrawal, all these tests were repeated, in 67 patients, after 15 days of hospitalization, during which the patients ate a normal hospital diet. The study was approved by the institutional review board of the hospital; informed consent was obtained from all patients.

Statistical analysis

A Kolmogorov–Smirnov test was performed to assess if variables were normally distributed. As most variables, especially lepton, IGF-1, cytokine, CRP, LH and oestradiol, did not fit the normal distribution, we have performed the non-parametric chi-square test, Mann–Whitney U-test, Kruskal–Wallis, Spearman correlation and Wilcoxon test for repeated measures. We performed a two-way analysis of variance (ANOVA) with previous logarithmic transformation to assess if serum lepton levels were dependent on diverse factors, such as alcohol, tobacco or infection. We performed a covariance analysis with previous logarithmic transformation of the variables to compare the slope of the regression lines. Stepwise multiple regression analysis was performed to discern which parameters yielded independent predictive values on serum lepton levels. All the tests were two-tail performed. Results are expressed as means ± SD.
RESULTS

Leptin and nutritional status

Nutritional assessment. Fifty-eight per cent of the patients complained of anorexia and 46% of weight loss above 5% (mean weight loss percentage, 16 ± 6%). Regarding BMI, after exclusion of patients with ascites or oedema (10), 12.5% were under 20 kg/m² (undernourished), 50% were between 20 and 25 kg/m², 30% between 25 and 30 kg/m² (overweight) and 7% over 30 kg/m² (obese). As shown in Table 1, lean and fat mass, assessed by DEXA, of the alcohol misusers were significantly decreased when compared with those of controls.

Serum leptin. Levels were decreased in alcohol misusers. As serum leptin levels were closely related to total fat both in alcohol misusers and controls (P < 0.0001), leptin differences between alcohol misusers and controls were also assessed after adjusting for total fat by covariance analysis, the alcohol misusers showing again lower serum leptin levels than the controls (P = 0.001) (Fig. 1). Similar results were found when serum leptin was related to BMI. Serum leptin levels, both in alcohol misusers and controls, increased with age, in a similar fashion to the increase of fat with age. Alcohol misusers who reported anorexia and weight loss showed lower leptin levels than the remaining patients (3.18 ± 4.2 vs 5.15 ± 7.4 ng/ml; P = 0.02). After 15 days of abstinence, serum leptin levels showed a slight, but not significant, increase (Table 2).

Intensity of ethanol misuse, smoking habit and leptin

Mean alcohol intake was 191 ± 73 g/day during 28 ± 11 years. We did not find any relationship between the reported amount of daily intake of ethanol and serum leptin levels. Furthermore, the 24 (30%) patients who developed a withdrawal syndrome showed slightly lower (though not significantly), serum leptin concentrations (3.6 ± 3 ng/ml) when compared with those of the 55 remaining patients (4.5 ± 6.9 ng/ml).

A smoking habit was more frequent among alcohol misusers (50/79, 63%) than in controls (6/32, 18%) (P < 0.001). Serum leptin levels were lower in alcohol misusers who smoked than in non-smokers (P = 0.002), showing a similar trend in healthy

### Table 1. Nutritional status of alcohol misusers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alcohol misusers Mean ± SD (n)</th>
<th>Controls Mean ± SD (n)</th>
<th>Mann–Whitney U-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49 ± 13 (79)</td>
<td>49 ± 12 (31)</td>
<td>0.18</td>
</tr>
<tr>
<td>BMI (kg/m²)×</td>
<td>24 ± 5 (62)</td>
<td>26 ± 3 (32)</td>
<td>3.23</td>
</tr>
<tr>
<td>Lean mass (g) assessed by DEXA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left arm</td>
<td>2656 ± 605 (64)</td>
<td>3077 ± 511 (31)</td>
<td>3.34</td>
</tr>
<tr>
<td>Right arm</td>
<td>2753 ± 604 (64)</td>
<td>3165 ± 525 (31)</td>
<td>3.25</td>
</tr>
<tr>
<td>Head</td>
<td>3722 ± 457 (64)</td>
<td>4063 ± 340 (31)</td>
<td>3.68</td>
</tr>
<tr>
<td>Total</td>
<td>49 977 ± 7456 (64)</td>
<td>53 785 ± 6230 (31)</td>
<td>2.46</td>
</tr>
<tr>
<td>Fat mass (g) assessed by DEXA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left arm</td>
<td>972 ± 570 (64)</td>
<td>1352 ± 518 (31)</td>
<td>3.14</td>
</tr>
<tr>
<td>Right arm</td>
<td>1013 ± 588 (64)</td>
<td>1453 ± 574 (31)</td>
<td>3.44</td>
</tr>
<tr>
<td>Trunk</td>
<td>8471 ± 4940 (64)</td>
<td>11 015 ± 4049 (31)</td>
<td>2.49</td>
</tr>
<tr>
<td>Head</td>
<td>826 ± 119 (64)</td>
<td>912 ± 119 (31)</td>
<td>3.38</td>
</tr>
<tr>
<td>Total</td>
<td>16 315 ± 8316 (64)</td>
<td>21 351 ± 6641 (31)</td>
<td>2.96</td>
</tr>
<tr>
<td>Total serum proteins (g/dl)</td>
<td>6.9 ± 0.8 (79)</td>
<td>7.2 ± 0.3 (27)</td>
<td>2.38</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.5 ± 0.6 (79)</td>
<td>4.2 ± 0.2 (27)</td>
<td>5.40</td>
</tr>
<tr>
<td>Serum prealbumin (mg/dl)</td>
<td>20.1 ± 10.0 (78)</td>
<td>30 ± 4 (27)</td>
<td>4.90</td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>58 ± 73 (79)</td>
<td>183 ± 91 (32)</td>
<td>6.08</td>
</tr>
<tr>
<td>IGF1BP-3 (ng/ml)</td>
<td>1569 ± 786 (79)</td>
<td>3729 ± 1363 (32)</td>
<td>7.45</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>4.2 ± 6.0 (79)</td>
<td>8.1 ± 5.8 (32)</td>
<td>4.73</td>
</tr>
<tr>
<td>Leptin/total fat</td>
<td>23 ± 20 (64)</td>
<td>36 ± 16 (31)</td>
<td>4.45</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>170 ± 56 (79)</td>
<td>220 ± 47 (32)</td>
<td>4.53</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>115 ± 115 (79)</td>
<td>130 ± 64 (32)</td>
<td>2.28</td>
</tr>
<tr>
<td>z</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

×Patients with ascites or oedema have been excluded.

![Graph showing lower serum leptin levels in alcohol misusers.](https://example.com/fig1.png)

**Fig. 1.** Lower serum leptin levels in alcohol misusers. In alcohol misusers (——— ○; R² = 0.6008), serum leptin levels (after logarithmic transformation) were significantly lower than in healthy controls (——— •; R² = 0.6826) after adjustment for total fat mass by covariance analysis.
controls. Since smokers showed a lower fat mass than non-smokers we performed a two-way ANOVA. We found that leptin depended mainly on fat mass \((P < 0.0001)\) and, to a lesser extent and in a negative fashion, on excessive alcohol intake \((P = 0.001)\), but not on smoking habit.

**Liver cirrhosis, nutritional status and serum leptin**

As shown in Table 3, cirrhotic patients (especially those with ascites) showed a more impaired nutritional status than non-cirrhotic alcoholics. So, arm lean mass was significantly decreased in non-cirrhotic alcohol misusers and in both cirrhotic groups when compared with control subjects, and in cirrhotics with ascites when compared with non-cirrhotic alcohol misusers. Liver-synthesized proteins, such as serum albumin, prealbumin, IGF-1 and its binding globulin IGF1BP-3, were all decreased in alcohol misusers and in both cirrhotic groups when compared with controls, and also in both cirrhotic groups when compared with alcohol misusers, but showed no differences between cirrhotics with and without ascites. However, fat mass was reduced in alcoholics and cirrhotics with ascites, but not in cirrhotics without ascites. In a parallel fashion, serum leptin was decreased in alcohol misusers and cirrhotics with ascites, when compared with controls, but not in cirrhotics without ascites; similar results were obtained when we analysed the leptin/total fat ratio.

We did not find differences regarding serum LH levels. However, serum testosterone levels were decreased, and serum oestradiol levels were increased in alcohol misusers and in both cirrhotic groups when compared with controls, and also in both cirrhotic groups when compared with the non-cirrhotic alcohol misusers. The oestradiol/testosterone \((O/T)\) ratio showed a pattern similar to that of oestradiol, but with better

### Table 3. Nutritional and hormonal alterations according to alcohol misuse and liver disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls Mean ± SD ((n))</th>
<th>Alcohol misuse Mean ± SD ((n))</th>
<th>Cirrhosis Mean ± SD ((n))</th>
<th>Cirrhosis with ascites Mean ± SD ((n))</th>
<th>Kruskal–Wallis (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat (kg)</td>
<td>21.3 ± 6.5 (31)</td>
<td>16.7 ± 8.8 (53)</td>
<td>17.0 ± 6.1 (4)</td>
<td>12.7 ± 3.8 (7)</td>
<td>3.14 0.002</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>8.1 ± 5.8 (32)</td>
<td>4.4 ± 6.5 (64)</td>
<td>5.8 ± 3.6 (5)</td>
<td>2.8 ± 2.2 (10)</td>
<td>25.2 0.000</td>
</tr>
<tr>
<td>Leptin/day 15 (ng/ml)</td>
<td>8.1 ± 5.8 (32)</td>
<td>4.3 ± 7.4 (52)</td>
<td>9.57 ± 5.9 (5)</td>
<td>3.2 ± 1.5 (10)</td>
<td>27.5 0.000</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>4.3 ± 0.2 (32)</td>
<td>3.7 ± 0.5 (64)</td>
<td>2.9 ± 0.6 (5)</td>
<td>2.6 ± 0.4 (10)</td>
<td>58.7 0.000</td>
</tr>
<tr>
<td>Serum prealbumin (mg/dl)</td>
<td>30.6 ± 5.8 (32)</td>
<td>23.0 ± 8.7 (63)</td>
<td>9.2 ± 4.5 (5)</td>
<td>7.7 ± 3.2 (10)</td>
<td>48.9 0.000</td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>183 ± 91 (32)</td>
<td>71 ± 76 (64)</td>
<td>3.7 ± 3.6 (5)</td>
<td>2.2 ± 0.4 (10)</td>
<td>51.8 0.000</td>
</tr>
<tr>
<td>IGF1BP-3 (ng/ml)</td>
<td>3792 ± 1363 (32)</td>
<td>1785 ± 679 (64)</td>
<td>715 ± 296 (5)</td>
<td>615 ± 311 (10)</td>
<td>70.0 0.000</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>3.0 ± 2.2 (32)</td>
<td>3.7 ± 2.5 (60)</td>
<td>3.2 ± 0.9 (5)</td>
<td>4.4 ± 6.7 (10)</td>
<td>2.37 0.498</td>
</tr>
<tr>
<td>Testosterone (pg/ml)</td>
<td>18.1 ± 4.3 (32)</td>
<td>15.1 ± 8.2 (61)</td>
<td>3.72 ± 2.3 (5)</td>
<td>3.2 ± 1.9 (10)</td>
<td>36.6 0.000</td>
</tr>
<tr>
<td>Oestradiol (pg/ml)</td>
<td>33.9 ± 8.1 (32)</td>
<td>45 ± 23 (63)</td>
<td>57 ± 12 (5)</td>
<td>105 ± 125 (10)</td>
<td>35.3 0.000</td>
</tr>
<tr>
<td>O/T</td>
<td>2.0 ± 0.6 (32)</td>
<td>12 ± 40 (61)</td>
<td>21 ± 11 (5)</td>
<td>50 ± 74 (10)</td>
<td>44.4 0.000</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.5 ± 0.5 (32)</td>
<td>6.7 ± 8.0 (63)</td>
<td>2.2 ± 1.0 (5)</td>
<td>6.7 ± 7.0 (10)</td>
<td>57.8 0.000</td>
</tr>
<tr>
<td>sTNFRII (pg/ml)</td>
<td>2.3 ± 0.5 (32)</td>
<td>5.4 ± 2.5 (64)</td>
<td>6.5 ± 2.0 (5)</td>
<td>10 ± 2 (10)</td>
<td>67.8 0.000</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>5.8 ± 1.4 (32)</td>
<td>20 ± 31 (63)</td>
<td>20.4 ± 10 (5)</td>
<td>62 ± 130 (10)</td>
<td>45.9 0.000</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein; IGF-1, insulin-like growth factor; IGF1BP-3, the binding protein of insulin-like growth factor; LH, luteinizing hormone; CRP, C-reactive protein; sTNFRII, type II soluble receptor of TNF; IL-6, interleukin-6; O/T, oestradiol/testosterone ratio.
statistical significance. Serum leptin was not related to
gonadal hormones at admission, but was on the 15th day,
when a negative correlation between leptin and testosterone
\((P = 0.013)\), and positive correlations between leptin and
oestradiol \((P = 0.020)\) and O/T ratio \((P = 0.005)\) were
observed. These correlations were also significant when serum
leptin was expressed as a ratio to total fat. In the control group,
the correlation was not significant.

**Infection**

Although serum leptin levels of alcohol misusers admitted
with an infection were moderately increased, compared with
those of the non-infected patients \((5.3 \pm 1.8 \text{ vs } 3.8 \pm 0.6 \text{ ng/ml})\),
differences were not significant, and, moreover, serum leptin
levels of infected patients were lower than those of the
controls \((8.0 \pm 1 \text{ ng/ml})\). Acute phase markers were altered in
infected patients, who showed decreased serum albumin and
prealbumin levels, and increased serum CRP \((P < 0.001)\) and
IL-6 \((P < 0.01)\) levels. Serum leptin levels on the 15th day, but
not on the first day, directly correlated with CRP \((P = 0.048)\),
sTNFRII \((P = 0.001)\) and IL-6 (a trend, \(P = 0.087)\) and
inversely with serum albumin \((P = 0.029)\). In healthy controls,
we also found a positive correlation between leptin and CRP
\((P = 0.001)\), and a trend between leptin and IL-6 \((P = 0.051)\).

**Recovery after hospitalization**

After 15 days of hospitalization and withdrawal, blood tests
were repeated (Table 2). Serum leptin levels were increased
very slightly but not significantly, whereas LDL cholesterol
was significantly increased, and HDL decreased. Serum
proteins, such as albumin, prealbumin, IGF-1 and IGF1BP-3,
were significantly increased, as was testosterone, whereas
oestradiol and acute phase reactants (CRP, IL-6 and sTNFRII)
were decreased. By an ANOVA with repeated measures (days
1 and 15), we did not find differences between alcohol mis-
users with and without withdrawal syndrome.

We studied which factors leptin depended on by stepwise
multiple regression analysis. At admission, leptin was only
related to age, and anthropometric and body composition
variables. With multivariate analysis, only the total amount of
fat assessed by DEXA was independently related to serum
leptin levels. On the 15th day, leptin also correlated positively
with the acute phase reactants CRP, sTNFRII and IL-6, and
with oestradiol, and inversely with testosterone. However,
by multivariate analysis, only the total body fat and, inversely,
serum testosterone levels showed independent relationships
with serum leptin levels.

**DISCUSSION**

We have included only male alcohol misusers in order to
obtain a more homogeneous group and to simplify the study.
Serum leptin levels are physiologically higher in females (Wei
et al., 1997; Donahue et al., 1999). Females are more easily
affected by ethanol and their body composition and nutritional
status are not comparable with those of males. Furthermore,
alcohol misuse in females is less prevalent and difficult to
assess. All patients were heavy drinkers.

The patients of our study were frequently, although not very
intensely, malnourished, since the BMI was under 20 kg/m²
only in 12% of the patients. Serum leptin levels were reduced
in alcohol misusers, both as raw values and when serum leptin
was adjusted by total fat (Fig. 1). Patients with anorexia and
weight loss, or with a BMI under 20 kg/m² showed lower
leptin values. Therefore, since leptin inhibits the NPY and
appetite (Inui, 1999), it does not seem to play a role as an
inducer of anorexia in our alcoholics. Moreover, after 2 weeks
of withdrawal, and despite the increase of serum albumin,
prealbumin, IGF-1 and cholesterol, serum leptin levels did not
significantly increase, speaking against any role of ethanol as
a cause of blunted serum leptin levels.

Nicolas et al. (2001) reported increased circulating leptin
levels in chronic active alcoholics. Active alcoholics had
significantly higher serum leptin concentrations than controls,
despite a lower fat area for the arm. In many respects, our
study is similar to that of Nicolas et al. (2001), as it deals with
chronic alcoholics and alcoholic cirrhotics, and analyses
nutritional status, but there are some differences which may
explain the disparate results. Although, the BMI of active
alcoholics is similar in both studies, the BMI of the control
group was higher in our study \((26.1 \text{ vs } 24.7 \text{ kg/m²})\). This
figure \((26.1 \text{ kg/m²})\) is close to that reported in the anthropo-
metric study of the population of the Western Canary
Islands, which yielded a BMI of 25.4 kg/m² as the 50th
percentile of the male population of 40–49 years. So, our
control group must be considered as slightly overweight. All
the alcoholics in the Nicolas et al. (2001) study were out-
patients assisted for dependence and without acute
complications, whereas our patients were heavy drinkers
admitted mainly for infection or the withdrawal syndrome.
Alcoholics assisted for dependence are active drinkers and
may serve as a model of sustained ethanol effects. However,
alcoholics, because of organic complications, presumably
stopped drinking shortly before admission. Indeed, none of
our patients was acutely intoxicated when blood was obtained;
we can therefore exclude the acute effect of ethanol, despite
the heavy alcohol misuse of our patients. If hyperleptinaemia
in alcoholism is really an acute effect of ethanol, it is possible
that our clinical model is not the best one to detect this acute
effect on serum leptin, but detects the effect of chronic ethanol
misuse, malnutrition and chronic and acute illness. However,
regarding the acute effect of ethanol, Röjdmark et al. (2001)
have shown that acute ethanol intake (three consecutive doses
of 0.45 g/kg each) by healthy individuals is followed by
decreased serum leptin levels.

Kiefer et al. (2001) have suggested that leptin may play a
role as a modulator of alcohol craving. They found raised
serum leptin concentrations in in-patients admitted for ethanol
detoxification, which decreased after 14 days. Our results are
not in accordance with these findings, since we have not found
increased serum leptin levels in alcoholics who developed
withdrawal. Moreover, in this group, we did not observe any
significant decrease of serum leptin levels after 2 weeks of
hospitalization.

The smoking habit has been related to lower serum leptin
levels (Wei et al., 1997; Mantzoros et al., 1998; Donahue
et al., 1999; Chu et al., 2001). In our study, smoking was also
related to lower serum leptin levels and to a decreased fat
mass. But as smoking was also more prevalent among alcohol
misusers (60%), than among controls (18%), when we
corrected for fat mass, the smoking habit lost its relation to
serum leptin. Therefore, the reduced serum leptin levels of smokers seem to be a consequence of a reduced fat mass.

Hyperleptinaemia has been reported in liver cirrhosis too (Shimizu et al., 1998; Henriksen et al., 1999; Testa et al., 2000). Our results vary in relation to ascites decompensation. Cirrhotics with ascites showed a very impaired nutritional status, with decreased lean and fat mass, and the lowest serum leptin levels, whereas cirrhotics without ascites showed more fat, and their serum leptin levels were similar to those of control subjects, although the number of the latter was too small to draw firm conclusions.

Epidemiological studies have shown that serum leptin levels are directly related to oestriadiol (Lagiou et al., 1999) and inversely to serum testosterone levels in men (Vettor et al., 1997; Lagiou et al., 1999; Chu et al., 2001). Chronic ethanol intake increases serum oestriadiol, and decreases testosterone, levels; an effect which is more intense when liver cirrhosis exists (Van Thiel and Gavalier, 1990). Serum testosterone levels were decreased in our alcoholic patients, whereas serum oestriadiol and the O/T ratio were increased. And, although testosterone, oestriadiol or the O/T ratio showed no correlation with leptin on the first day of the study, all three did show a significant correlation on the 15th day. After 2 weeks of withdrawal, and after resolution of acute complications, leptin relations with testosterone and oestriadiol became more evident.

Serum leptin levels are increased in several situations characterized by an acute phase reaction, such as sepsis or surgery, and this increase is related to proinflammatory cytokines (Arnalich et al., 1999; Moses et al., 2001; Papanathanassoglou et al., 2001). In our study, alcoholics admitted with an infection showed higher CRP and IL-6 levels, but not higher serum leptin levels. In many common disorders leading to malnutrition and cachexia, serum leptin levels are decreased, despite an inflammatory response. In the wasting syndromes of pancreatic and lung cancer, serum leptin levels are decreased, despite increases in TNF, IL-6 and sTNFRII (Mantovani et al., 2000; Brown et al., 2001). The same occurs in chronic obstructive pulmonary disease, in which, despite raised TNF, low leptin levels are related to a decreased fat mass (Schols et al., 1999; Takabatake et al., 1999). In advanced cachectic chronic heart failure, ‘inappropriate’ low leptin levels have been reported in the face of raised serum TNF and IL-1 levels (Murdoch et al., 1999; Filippatos et al., 2000). Also, a similar situation has been described in chronic inflammatory bowel disease and in wasting AIDS, in which serum leptin levels are low or normal despite an increase of sTNFRII (Yarasheki et al., 1997; Ballinger et al., 1998). In advanced malnutrition, serum leptin levels are more dependent on fat mass than on cytokines. Low serum leptin levels in malnourished alcoholics resemble the above-mentioned diseases. In all these cases, hyperleptinaemia does not seem to be the cause of anorexia and malnutrition.

In conclusion, serum leptin levels depend on many factors such as fat mass, age, ethanol, smoking habit, serum testosterone and oestriadiol levels, growth factors such as IGF-1 and CRP, and cytokines such as IL-6 and sTNFRII, but the most important of these is fat mass, as suggested by multivariate analysis. We consider that the decreased serum leptin levels in the alcoholics is a consequence, rather than a cause, of low fat mass. As our patients were not acutely intoxicated at the time of leptin determination, our study dealt with alcoholic malnutrition and organic complications, rather than with the acute effect of ethanol on serum leptin levels. Further studies will be necessary to assess and dissociate the acute and chronic effects of ethanol misuse on serum leptin levels, taking into consideration fat mass and possibly also other confounders.

REFERENCES


