Liver in obesity

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SUMMARY We report on clinical, nutritional, and hepatic histological findings in 50 non-selected obese subjects (mean overweight +74%; range +21–138%). The pathogenesis of the liver damage was assessed with the help of multidimensional analysis of a number of clinical variables. According to the severity of the hepatic lesions, the patients have been ranged in five groups: 0 (normal liver) 10%; I (fatty liver) 48%; II (fatty hepatitis) 26%; III (fatty fibrosis) 8%; IV (fatty cirrhosis) 8%. The more severe changes (groups III and IV) were constantly associated with excessive alcohol intake. The multidimensional analysis was unable to find a relationship between obesity and the development of fibrosis and cirrhosis whereas it showed that: (a) there was a highly significant correlation between the daily ethanol intake and the degree of overweight, (b) severe fatty metamorphosis was significantly associated with the degree of overweight, the existence of diabetes mellitus, and the amount of alcohol and fat intake, (c) nutritional factors, in particular deficient protein intake, have only an accessory effect in the development of mild inflammation and fibrosis, (d) the consumption of potentially hepatotoxic drugs, very high in the obese (about five drugs per day) could have a role in the development of cirrhosis. In conclusion in our study, there was no evidence that obesity per se could result in severe liver damage.

Controversy exists in the literature about the incidence and nature of liver lesions in obese patients. In most studies fatty liver was the only significant abnormality, but recent reports have suggested that severe liver damage, sometimes mimicking the entire histological spectrum of alcoholic liver disease, could be found in obesity. In most of these studies, however, information on the potential hepatotoxic factors occurring in obesity was usually lacking. Thus, we undertook a cross-sectional study of the liver histology in 50 non-selected obese patients with the aims: (a) to define precisely the prevalence, the nature, and the severity of the liver lesions in obesity; (b) to determine, by the multidimensional analysis, the quantitative and/or qualitative clinical variables which were related to the observed histological abnormalities.

Methods

PATIENTS Fifty obese patients, consecutively hospitalised in a nutrition department for weight reduction and complications related to obesity, were investigated. Their main characteristics are indicated in Table 1.

CLINICAL METHODS Clinical and nutritional data were obtained for all patients. Duration of obesity, maximum, and current overweight were assessed. Past history of weight reduction diets and weight reduction could not be determined with sufficient accuracy in contrast with other data. Diabetes mellitus was defined on the basis of the National Diabetes Data Group’s standards. Drug consumption was carefully screened, with special reference to hepatotoxic medications. Dietary interviews were all performed by a trained dietician using standardised techniques and protocols. The dietician recorded protein intake (g/day), lipid intake (% of dietary intake), dietary calorie intake (Cal/day), which did not include ethanol, ethanol intake (g/day and % of total Cal intake). Ethanol consumption was carefully screened: two physicians and the dietitian separately questioned each patient, and often his family. Hepatitis B antigen and tissue autoantibodies were looked for in each patient. Real
time ultrasonography was used for the diagnosis of
calculous gall bladder disease.

HISTOLOGICAL METHODS
A percutaneous biopsy of the liver was performed in
each patient with his oral consent regardless of the
results of the usual liver 'function' tests, because it
has been shown that these tests are not sufficiently
reliable to identify correctly and consistently both
moderate and severe histological lesions. Liver
biopsy specimens were immediately fixed in Bouin's
solution, and sections were stained with
haematoxilin-eosin, Masson's trichrome, PAS and
reticulin. Each set of five coded slides was
independently examined by two pathologists on the
basis of 10 features and graded with different levels
of severity: steatosis (-:<10% of hepatocytes; +:
10–20%; ++:20–50%; +++: >50%); acidophilic
necrosis, Mallory's bodies, swollen or clarified
hepatocytes, cirrhosis (-: absent; +: present);
glycogen nuclei, centrolobular inflammation,
centrolobular fibrosis, portal inflammation, portal
fibrosis (-: none; +: slight; ++: moderate; +++:
severe). In case of discrepancy between the two
examiners, the more important lesion was
considered. All cases could be arranged in five
categories according to the association and the
severity of the basic lesions (steatosis, inflammation,
fibrosis), as follows: Group 0: normal liver (none or
slight change(s) or steatosis <10%); Group I: fatty
liver (steatosis >10% and only slight changes);
Group II: fatty hepatitis (inflammation: moderate or
severe); Group III: fatty fibrosis (fibrosis: moderate
or severe); Group IV: fatty cirrhosis (fibrotic septa
arranged around regenerative nodules of
parenchyma).

STATISTICAL METHODS
The explanatory multidimensional analysis used
multiple linear regression analysis and partial
correlation analysis. The pragmatic multi-
dimensional analysis used linear discriminant
analysis. These analyses were performed with
programs from Université Catholique de Louvain
(MAH, personal communication).

Multiple linear regression analysis is a method
used to try to describe a set of explained variables
using a set of explanatory variables. Here it consists
in finding the linear combination of the variables
which explains the cause of histological features of
the liver. The specific influence of each explanatory
variable is tested by comparing with zero the
the corresponding coefficient of the linear combination.

The analysis of the coefficient of partial
correlation shows the degree to which each variable
is a source of additional information about the cause
of the histological feature.

Linear discriminant analysis yields, for a given set
of variables, the linear combination of those which
separate a group of subjects with a particular
histological feature from others. This analysis is
carried out step by step, which allows the successive
determination of the one, two, three or more
variables which discriminate between the groups
according to the previous variable chosen.

The informational indices used are the sensitivity
and the positive predictive value.

Results

CLINICAL DATA
Thirty one patients had obese non-insulin
dependent diabetes. Among them 10 had mild and
seven had severe uncontrolled diabetes, and were
treated by diet and oral hypoglycemic drugs.

The mean consumption of drugs, taken for
chronic condition, was 5-6 different types of drug
per day. Among these drugs some have a potential
hepatotoxicity: it included methyldopa in 11 cases,
perhexilene maleate in one, antidepressants and

<table>
<thead>
<tr>
<th>Table 1 Clinical data of the patients under study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Mean (range)</td>
</tr>
<tr>
<td>Current overweight* (%)</td>
</tr>
<tr>
<td>Mean (range)</td>
</tr>
<tr>
<td>Duration of obesity (yr)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>

* overweight = \frac{observed\ weight - theoretical\ weight}{theoretical\ weight}

theoretical weight (kg) = height (cm) - 100 - \frac{\text{height} - 150}{x}

x=2 \text{ (female)}

x=4 \text{ (male)}
tranquillisers in 15, oxyphenisatin in three, clometacin in six, acetaminophen in three, papaverin in two, sulphonyleureas (mainly antidiabetics) in 19, tinacryfen in three. A past history of INH was noted in one case. In some cases, there was an association between inducers of the drug metabolising enzyme system and substances producing toxic metabolites in the liver.

The nutritional status of the patients is summarised in Table 2. The nutrient intakes were compared with the Recommended Dietary Allowances adapted for a French population. Regular consumption of alcohol was recorded in 17 patients: the consumption was estimated as excessive in 11 (daily ethanol intake >80 g in men or >60 g in women) and moderate in six patients. HBS antigen and tissue autoantibodies were not identified in any serum sample. Cholecystectomy was previously performed in seven women and choledolithiasis was detected by ultrasonography in 12 women and one man.

**PATHOLOGICAL DATA**

**General analysis**

The prevalence of the histological groups is indicated in Table 3, with particular reference to alcohol consumption. Fatty liver was observed in 24 patients (48%). In 14 of these cases, there was severe steatosis affecting at least 50% of hepatocytes. Three excessive drinkers were noted in this group. Fatty hepatitis was diagnosed in 13 patients (26%), who were not excessive drinkers. Fatty fibrosis and cirrhosis were observed in eight patients (16%), with four patients in each group; all were excessive alcohol drinkers.

**Partial correlation analysis**

Analysis of the partial correlations mainly showed:

(1) a significant correlation between the degree of overweight and the ethanol intake (r=0.49, p<0.001); (2) a significant correlation between the ratio of ethanol calorie intake to total calorie intake and the deficiency of protein intake on the one hand and the excess of fat intake and the deficiency of protein intake on the other hand (r=0.27, p<0.05 and r=0.49, p<0.001, respectively).

**Multiple linear regression analysis**

(a) **Basic lesions** (Table 4). Absolute ethanol intake (g/day) and the ratio of ethanol calorie intake to total calorie intake were the only explanatory variables with a significant positive predictive value found in the three groups of elementary histological lesions, steatosis, inflammation, and fibrosis. A deficiency of protein intake had a significant positive predictive value for the development of inflammation and fibrosis. Finally, diabetes mellitus had a highly significant positive predictive value for the diagnosis of severe steatosis. For this last basic lesion, maximum overweight was a borderline variable.

(b) **Histological groups** (Table 5). Lipid intake, duration of obesity and existence of diabetes mellitus were the only explantory variables with a significant positive predictive value in group I (fatty liver). Absolute ethanol intake, the ratio of ethanol calorie intake to total calorie intake, but also current overweight, were the only explanatory variables with significant positive predictive value in group II (fatty hepatitis). Ethanol intake had a significant positive predictive value in group III (fatty fibrosis) and IV (fatty cirrhosis).

**Discriminant analysis** (Table 6)

Recording of three variables obtained from clinical evaluation (duration of obesity, diabetes mellitus and lipid intake) enabled 95% of these obese subjects in group I to be correctly classified. By contrast, the association of three or four variables did not enable the group II patients to be easily distinguished. The results were better in groups III and IV, but of poor help in clinical discrimination of the patients.

**Other histological findings**

Acidophilic necrosis was found in three alcoholic patients and in one non-alcoholic subject. Alcoholic hyalin was observed in three patients, all excessive drinkers. Swollen hepatocytes were seen in four excessive drinkers with or without diabetes mellitus. The presence of glycogen nuclei was related to diabetes mellitus and/or to steatosis. A moderate inflammation was observed in nine of the 33
Table 3  Pathological findings in patients under study

<table>
<thead>
<tr>
<th>Group*</th>
<th>Patients no (%)</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Mean current overweight (%)</th>
<th>Duration of obesity (yr)</th>
<th>Diabetes mellitusExcessive drinkers†</th>
<th>Daily drinker</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5 (10)</td>
<td>50</td>
<td>5 F</td>
<td>53</td>
<td>24</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>24 (48)</td>
<td>50</td>
<td>21 F</td>
<td>81</td>
<td>22</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>13 (26)</td>
<td>47</td>
<td>11 F</td>
<td>72</td>
<td>21</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>4 (8)</td>
<td>46</td>
<td>3 F</td>
<td>52</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>4 (8)</td>
<td>55</td>
<td>4 M</td>
<td>63</td>
<td>26</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

* For definition, see methods.
† Excessive alcohol intake >80 g/day for males (M) or >60 g for females (F).

 abstinent patients, but, in five cases, the role of drug toxicity (methyldopa clometacin, acetaminophen, oxyphenisatin, perhexiline maleate) could not be excluded. A slight centrolobular fibrosis was shown in six of the 33 abstinents, but, in two cases, drug hepatotoxicity (acetaminophen, perhexiline maleate) was possible. In three of these six patients, diabetes mellitus with degenerative vascular lesions was present.

Discussion

Most published series¹-⁴ ⁹ ¹⁰ of histological studies of the liver in obese patients before or at the time of small bowel bypass reported fatty metamorphosis in approximately 90% of cases, minimal or slight portal fibrosis and/or inflammation in 30-50% of cases, mild centrolobular, pericellular fibrosis in 10-25% of cases, and 'early' cirrhosis in 3-5% of cases. Moreover, a new pathological entity was recently described, mainly in the female obese patient, mimicking the whole spectrum of alcoholic liver disease with fatty hepatitis (steatonecrosis), fibrosis, and cirrhosis, polymorphonuclear cell infiltrates, and Mallory's bodies.⁵-⁶ ¹¹ ¹² In most of these studies, heavy drinkers were excluded, but moderate alcohol intake was often tolerated. It is, however, well established that precise recording of alcohol intake, especially in women, is very difficult¹³ and that low doses of alcohol (20 g/day in women, 60 g/day in men) can induce the development of cirrhosis.¹⁸ The drug consumption, always important in morbid obesity, and the results of serologic testing for hepatitis B virus were generally not specified. In some young patients having fatty cirrhosis with or without Mallory's bodies, the usual causes of juvenile cirrhosis - that is, Wilson's disease, α₁-antitrypsin deficiency - were not documented. Finally, although the role of nutritional factors, in particular protein malnutrition, in the development of the hepatic lesions has been suggested,⁵ precise dietary history
Liver in obesity

Table 5  Multiple linear regression analysis (II) (Histological groups)

<table>
<thead>
<tr>
<th>Group</th>
<th>Row</th>
<th>Variable</th>
<th>Partial correlation coefficient</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (21 females)</td>
<td>1</td>
<td>Lipid intake</td>
<td>0·58</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Duration of obesity</td>
<td>0·52</td>
<td>&lt;0·02</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Diabetes mellitus</td>
<td>0·51</td>
<td>&lt;0·02</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Maximum overweight</td>
<td>0·38</td>
<td>&lt;0·07</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>ETOH intake</td>
<td>0·37</td>
<td>&lt;0·09</td>
</tr>
<tr>
<td>II (11 females)</td>
<td>1</td>
<td>ETOH intake</td>
<td>0·79</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>ETOH CI/TCI</td>
<td>0·77</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Current overweight</td>
<td>0·67</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Age</td>
<td>0·51</td>
<td>&lt;0·07</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>TCI</td>
<td>0·47</td>
<td>&lt;0·09</td>
</tr>
<tr>
<td>III (3 females)</td>
<td>1</td>
<td>ETOH intake</td>
<td>0·96</td>
<td>&lt;0·02</td>
</tr>
<tr>
<td>IV (4 males)</td>
<td>1</td>
<td>ETOH CI/TCI</td>
<td>0·99</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>ETOH intake</td>
<td>0·99</td>
<td>&lt;0·01</td>
</tr>
</tbody>
</table>

CI: Calorie intake; ETOH: Ethanol; TCI: Total calorie intake; ETOH CI/TCI: Ratio of ethanol calorie intake to total calorie intake.

and detailed nutrient intake were exceptionally reported. With all these methodological restrictions, it was difficult to precisely identify the aetiological factor(s) involved in the pathogenesis of the hepatic lesions found in the obese patient and to know if obesity per se could induce severe, sometimes pseudoalcoholic, liver damage.

In our French population of 50 non-selected obese subjects, severe liver damage (fibrosis and cirrhosis) was observed in eight patients (16%) and was constantly associated with excessive alcohol intake. Fatty change was present in 90% of liver biopsies and was the only significant abnormality in 48% of cases. Moreover, multidimensional statistical analysis of the relationship showed that: 1° the degree and/or, perhaps chiefly, the duration of obesity did not induce per se the development of fibrosis and cirrhosis. Overweight could only be incriminated in the appearance of both steatosis and inflammation (group II) but not on inflammation alone; 2° the role of the ratio of ethanol calorie intake to total calorie intake appeared as important as the role of absolute ethanol intake in the development of liver damage; 3° severe steatosis was correlated with the maximum overweight, the existence of diabetes mellitus, and the absolute and relative ethanol intake; 4° nutritional imbalance, especially poor protein intake, had a significant

Table 6  Step-by-step discriminant analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Variables (no)</th>
<th>Variable</th>
<th>D²</th>
<th>Correctly classed (%)</th>
<th>Max PPV (%)</th>
<th>Se (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>Duration of obesity</td>
<td>1·52</td>
<td>66</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1+ Diabetes mellitus</td>
<td>1·87</td>
<td>86</td>
<td>92</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1+2+Lipid intake</td>
<td>1·99</td>
<td>95</td>
<td>67</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1+2+3+ Maximum overweight</td>
<td>2·11</td>
<td>100</td>
<td>52</td>
<td>41</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>ETOH CI/TCI</td>
<td>0·99</td>
<td>39</td>
<td>47</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1+ ETOH intake</td>
<td>1·37</td>
<td>48</td>
<td>59</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1+2+Age</td>
<td>1·47</td>
<td>56</td>
<td>67</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1+2+3+ current overweight</td>
<td>1·52</td>
<td>63</td>
<td>82</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Variables</td>
<td>1·56</td>
<td>78-5</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>Lipid intake</td>
<td>1·59</td>
<td>47</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1+ ETOH intake</td>
<td>2·12</td>
<td>62</td>
<td>67</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1+2+Protein intake</td>
<td>2·19</td>
<td>74</td>
<td>79</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1+2+3+ ETOH CI/TCI</td>
<td>2·23</td>
<td>79</td>
<td>89</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Variables</td>
<td>2·28</td>
<td>87</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>Lipid intake</td>
<td>2·29</td>
<td>74</td>
<td>75</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1+ ETOH CI/TCI</td>
<td>2·37</td>
<td>79</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1+2+Protein intake</td>
<td>2·39</td>
<td>83</td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1+2+3+ ETOH intake</td>
<td>2·40</td>
<td>85-5</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Variables</td>
<td>2·43</td>
<td>89</td>
<td>100</td>
<td>62</td>
</tr>
</tbody>
</table>

PPV: Positive predictive value; CI: Calorie intake; ETOH: Ethanol; TCI: Total calorie intake; ETOH CI/TCI: Ratio of ethanol calorie intake to total calorie intake.
positive predictive value for the development of mild inflammation and fibrosis, but not for the more severe histological groups III and IV; 5° drug consumption is extraordinarily high in our patients (mean daily ingestion of 5 different types of drugs) and some of these drugs may cause chronic liver disease or cirrhosis. Similar results were recently reported by Gluud et al19 in 61 morbidly obese patients: fatty change was present in 85% of the biopsies; only one biopsy showed fibrosis, in a patient with the highest alcohol consumption; no cirrhosis was found; in this series, 20% of the patients admitted previous excessive alcohol consumption.

An interesting finding in our study was the significant relationship between fatty liver and non-insulin dependent diabetes, at constant level of the other variables. Clearly, diabetes mellitus may induce the development of steatosis, irrespective of the degree and duration of obesity. This was different from the conclusions of Creuzfeldt et al20 who stated that the so called diabetic fatty liver was in fact the consequence of overweight. The mechanism of liver steatosis in non-insulin dependent diabetes might be attributed to the decrease of tissue insulin sensitivity in overweight patients.21 So, the steatosis of non-insulin dependent diabetes might be similar to that observed in insulin dependent diabetes, when insulin treatment is inadequate.22 Moreover we found a slight centrolobular (perivenular) fibrosis in three non-alcoholic patients with non-insulin dependent diabetes and degenerative lesions. This lesion, recently described in insulin dependent diabetes,23 24 could hypothetically be, by analogy with alcoholic liver disease,25 an early index of progressive liver injury that might eventually lead to cirrhosis. These patients must be regularly followed.

In conclusion, using a high powered statistical method, which allows the role of each variable to be independently assessed, we did not find any argument supporting the hypothesis that obesity or nutrition imbalance could determine severe liver damage. So, we would like to underline that the hypothetical role of obesity in severe liver damage may have been overestimated. Thus, the discovery of a non-alcoholic liver damage in an obese patients must need detailed examination in order to find a cause which might allow a specific treatment. This cause might be: (a) a drug hepatotoxicity, and we emphasise the high drug consumption in these patients; (b) a metabolic disorder, as diabetes mellitus, which needs a perfect control; (c) an intestinal bacterial overgrowth which might be the cause of lesions similar to that observed after jejunioileal bypass.26

The authors thank Pr J Quichaud, Dr J D Lalau, Dr T Poynard, for their helpful comments, Mme Pawlak for technical assistance, and Martine Hazebroucq for manuscript preparation.

References