Relationship between hepatic morphology and clinical and biochemical findings in morbidly obese patients

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SYNOPSIS This study was undertaken to determine the interrelations between clinico-biochemical parameters and hepatic morphology in markedly obese patients. One hundred and sixty-six women and 52 men comprise this series. There was a statistically significant association of carbohydrate metabolism disturbance with increasing age and corpulence and, in women, with hyperuricaemia and morphological alterations of the liver. Menstrual irregularities also correlated well with hepatic morphology. The livers frequently exhibited steatosis, but other morphological changes were mild. Compared with women, men had higher triglyceride values, more severe hepatic involvement, and poorer correlation of carbohydrate disturbances with hepatic histology. The results indicate a central role of the impaired carbohydrate utilization in the biochemical and hepatic alterations of obesity.

Few studies in the severely obese correlating clinical and biochemical data with morphology of the liver are available. The early reports of Zelman (1952) and Westwater and Fainer (1958) were based on small series with limited laboratory data and all but one of the patients were males. The introduction of small bowel bypass to achieve weight reduction stimulated considerable controversy about the effects of these surgical procedures on the liver (Payne and DeWind, 1969; Drenick, Simmons, and Murphy, 1970; Juhl, Christoffersen, Baden, and Quaade, 1971; Salmon, 1971; Shibita, Mackenzie, and Huang, 1971; Meyerowitz, 1972). However, the influence of diverse factors (age, sex, corpulence, metabolic alterations) on hepatic morphology is not well known. In this paper, we study the interrelations among several biochemical parameters, and we seek possible links between biochemical and clinical information with hepatic morphology.

Materials and Methods

The subjects studied were hyperphagic individuals undergoing jejunoileal bypass. The criteria for selection included obesity mainly due to hyperphagia, a minimum of 50 kg overweight, and a

good surgical risk. Clinical data were obtained through questioning by one of the authors in more than half of the patients and from medical records or mailed questionnaires in the remainder. Except for diabetes and obesity, no patient had conditions known to alter hepatic histology (active gastrointestinal disease, anaemia, history of alcoholism, hepatitis, or drug addiction). Few patients were taking medicines. Seventeen women taking oral contraceptives were included because after analysis of the data their inclusion did not significantly affect the results.

The corpulence was expressed as percentage obesity which was calculated by dividing patient's weight by medium frame ideal weight of the Metropolitan Life Insurance Company as given by Geigy (1962); 0 represents the ideal and 100 is double the desired weight.

Fasting serum calcium, phosphorus, cholesterol, uric acid, blood urea nitrogen, total protein, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, and glutamic oxalacetic transaminase (GOT) were done in all patients on the Technicon SMA 12/60¹. The three-hour glucose tolerance test (OGTT) was carried out following the recommendations of the University Diabetes Program and the American Diabetes Association Committee on

Statistics (1969). The plasma glucose was determined by the alkaline ferricyanide method in the Auto-Analyzer. In the bromsulphalein (BSP) retention test, 5 mg of dye per kg of body weight was injected in patients weighing 100 kg or less. Heavier subjects received 500 mg. Retention of the dye was measured by spectrophotometry. Fasting triglycerides (Tg) were determined enzymatically using a commercially available kit². The method of Noble (1969) was used for the electrophoretic separation of plasma lipoproteins in agarose gel. The prothrombin time (PT) was estimated by the method of Biggs and Macfarlane as modified by Gaston, Brooks, Blumenthal, and Miller (1971). Serum folates were assayed by a microbiological technique employing *Lactobacillus casei*.

The upper limits of normal in this laboratory, established from healthy blood donors, are: cholesterol, 260 mg/100 ml; uric acid, 8.3 mg/100 ml in men and 7.7 mg/100 ml for females; GOT, 50m U/ml. The lower limits of normal for serum folates is 6 ng/ml. We consider an OGTT result 'normal' when plasma glucose at one hour is less than 175 mg/100 ml and at two hours less than 130 mg/100 ml; 'diabetic' if the sum of the fasting, one-, two-, and three-hour values (in mg/100 ml) is 600 or more (University Group Diabetes criteria); and 'abnormal' when the values fall between 'normal' and 'diabetic'.

Wedge biopsies of the liver were taken at the beginning of the bypass operation by one of us (G.B.S.). Sections were routinely stained with haematoxylin and eosin (H&E) and occasionally by other techniques (Oil red O for lipids; PAS stains for reticulin and collagen fibres and for iron). Hepatic histology was assessed without knowledge of laboratory data; two of us (J.L.M. and H.B.T.) agreed on the histological interpretation. Fatty change was graded minimal (< 5% of hepatocytes had visible fatty droplets), mild (5-25%), moderate (25-50%), and marked (> 50%). We recorded nuclear vacuolization only if it affected more than 5% of parenchymal cell nuclei. Other histological findings (fibrosis, inflammation, pigments, lipogranulomas) were graded mild, moderate, and marked.

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Results

CLINICAL FINDINGS

The distribution by age and sex is shown in table I. The mean age of the females was 35.7 and that of the males 34.9 years. The heaviest subject weighed 241 kg and the lightest 94.2 kg. In males, the mean percentage overweight was 117.3 ± 36.1 ; in females it was 134 ± 36.9 . Table II shows the corpulence. Thirteen patients were Negro and the remainder were Caucasian. Cholelithiasis, past or present, was noted in 72 (33%) subjects. In 59 women with this information available (all under 37 years of age) 32 either had abnormal menstrual periods or complained of sterility. Two diabetic patients were taking insulin and four others were on oral anti-diabetic medication. Clinical gout was present in five males and two females. About a fourth of the individuals gave a history of transient hypertension but very few were receiving antihypertensive medication. Less than 10% of the patients had minor ECG changes and/or a history of angina pectoris. (Exertional dyspnoea, encountered fairly often, was usually attributed to overweight.)

Age	Males	Females
16-29	14 (27.0%)	46 (27.7%)
30-39	21 (40.4%)	63 (38.0%)
40-60	17 (32.6%)	57 (34.3%)
Total	52 (100.0%)	166 (100.0%)

Table I Distribution by sex and age

Percentage Overweight	Males	Females
<120	29 (55.8%)	65 (39.2%)
120-149	13 (25.0%)	51 (30.7%)
150 & over	10 (19.2%)	50 (30.1%)

Table II Corpulence

LABORATORY DATA

The fasting and one-, two-, and three-hour values in the OGTT are given in table III. Table IV shows the relationship of OGTT with uric acid and Tg in women. In men there was no obvious association among these three parameters. Table V shows the

OGTT	Males					Females				
	No.	Fasting Mean SD	One Hour Mean SD	Two Hour Mean SD	Three Hour Mean SD	No.	Fasting Mean SD	One Hour Mean SD	Two Hour Mean SD	Three Hour Mean SD
Normal	10	92 $\pm$ 10	143 $\pm$ 15	102 $\pm$ 18	78 $\pm$ 18	43	90 $\pm$ 9	137 $\pm$ 19	106 $\pm$ 18	80 $\pm$ 19
Abnormal	21	98 $\pm$ 10	188 $\pm$ 26	134 $\pm$ 29	82 $\pm$ 18	60	100 $\pm$ 10	190 $\pm$ 33	149 $\pm$ 25	91 $\pm$ 21
Diabetic	15	148 $\pm$ 62	261 $\pm$ 89	260 $\pm$ 110	173 $\pm$ 104	38	152 $\pm$ 55	284 $\pm$ 78	258 $\pm$ 95	178 $\pm$ 73

Table III Results of oral glucose tolerance test (OGTT)

	Uric Acid		Tg ¹	
	Normal	High	Normal	High
Normal	39	4	26	11
Abnormal	48	12	28	20
Diabetic	24	14	16	18
Significance ²	P < 0.025		P > 0.1	

Table IV Relationship of OGTT to uric acid and Tg (women only)

¹Upper limits of normal are those given by Frederickson *et al* (1967)²All analysis of data for significant differences in this study was by the χ^2 test of contingency tables.

OGTT	Age Group			Percentage Overweight		
	16-29	30-39	40-60	<120	120-149	150 & Over
Normal	24	15	14	27	20	6
Abnormal	17	35	29	38	22	21
Diabetic	7	25	21	15	10	28
Significance	P < 0.005			P < 0.001		

Table V Relationship of OGTT to age and corpulence (all patients)

Age Group	Males		Females	
	No. of Cases	Tg (mg%) Mean SD	No. of Cases	Tg (mg%) Mean SD
16-29	12	205 ± 73	33	141 ± 58
30-39	20	231 ± 92	54	170 ± 87
40-49	13	274 ± 180	36	176 ± 87
50-60	2	67 ± 0.6	10	123 ± 57

Table VI Triglycerides (Tg) by age and sex

relationship of OGTT with age and corpulence. As tables IV and V indicate, there was a statistically significant association between the degree of abnormality of the OGTT and corpulence and age in both sexes and with uric acid in females; the link Tg-OGTT did not reach statistical significance (table IV).

The Tg results are shown in table VI. Note the higher values in men than in women. Secondly, the peak levels are in the 30-50 age group in both sexes. Contraceptive hormones may have affected Tg (Stokes and Wynn, 1971), but numbers were too small and scattered in subgroups to draw conclusions or to affect the overall results.

In 21 patients (9.6%) the serum cholesterol was between 261 and 300 mg/100 ml and in 11 patients (5%) it was over 300 mg/100 ml. No relationship was evident between hypercholesterolaemia and other factors, except possibly age.

Lipoprotein electrophoresis usually revealed normal or type IV patterns (of Fredrickson, Levy, and Lees, 1967). As expected, the type IV patterns occurred in subjects with highest Tg levels.

A single determination revealed hyperuricaemia in 20 (38.4%) men and in 35 (20.7%) women, which

is a significant sex difference ($P < 0.025$). After taking into account the abnormalities of carbohydrate metabolism, no association was found between uricaemia and corpulence, age, or Tg (or among the last three parameters).

The BSP retention test was done on 111 occasions; 50 patients retained between 7 and 20% of the dye at 45 minutes, 10 subjects had over 20% retention, and in 51 patients the results were normal.

Serum folates between 2 and 5.9 ng/ml occurred in 40 (29.8%) of 134 patients who were not anaemic. No other abnormalities (clinical, metabolic, or histology of the liver) could be associated with low folates.

Protein electrophoresis, as well as tests to evaluate endocrine (thyroid, adrenals) and haematological status, consistently gave normal results. The alkaline phosphatase, PT, albumin, and total bilirubin were abnormal in less than 5% of the patients, therefore, they were not compared with other functions.

HISTOLOGICAL FINDINGS OF THE LIVER

The microscopic findings are summarized in table VII.

Histological Change	Steatosis			Lipogranulomas	Lobular and Portal Fibrosis		Inflammation		'Ballooned' Nuclei (>5%)
	<25%	25-50%	>50%		Slight	Moderate	Portal	Lobular	
Males (%)	40.0	32.7	27.3	36.4	7.6	11.5	21.1	11.7	23.2
Females (%)	63.2	20.0	16.8	15.0	7.2	2.4	16.8	8.4	22.9

Table VII Histological findings in the liver

Fatty change

This was the most prominent abnormality. In over half of the instances, especially in mild and moderate steatosis, the fat was in the form of large droplets mostly in a central and midlobular position (fig 1). When fatty metamorphosis became severe, it was either diffuse or predominantly centrilobular. If some portal fibrosis supervened, fat was often located at the periphery of the lobules and some of it was trapped within the enlarged portal tracts (fig 2). Small and medium size fatty droplets tended to be diffusely distributed (fig 3).

Lipogranulomas

These are defined as groups of Kupffer cells,

lipophages, and a mixed inflammatory infiltrate (lymphocytes with some eosinophils and neutrophils). A single, large vacuole of lipid surrounded by leucocytes is here considered a fatty cyst. Lipogranulomas were usually small and only two contained giant cells. Lipogranulomas were most abundant and conspicuous in centrilobular areas (fig 4). Livers containing lipogranulomas usually also exhibited steatosis (not always severe) with large globules of fat.

Parenchymal inflammation

Lymphocytic or neutrophilic infiltrates frequently occurred in clumps coexisting with fatty cysts and lipogranulomas. These changes were usually mild.

Fig 1 Moderate fatty change. Note the predominantly midlobular and centrilobular large lipid vacuoles. H&E, 40

Fig 2 Marked fatty metamorphosis and fibrosis. Globules of fat have coalesced, ruptured, or have been engulfed in poorly demarcated portal triads. H&E, 100

Fig 3

Fig 4

Fig 5

Fig 3 Diffuse distribution of small and medium size droplets of lipids. H&E, 150

Fig 4 Lipogranuloma near a central vein. Fat vacuoles and mixed cellular component. H&E, 250

Fig 5 Thin fibrous strands bridging mildly enlarged portal tracts. The steatosis is here mostly periportal. H&E, 100

Fibrosis (portal and lobular)

A few, thin fibrous strands were often seen in the centre of the lobules. However, more severe involvement with portal and portal-central vein bridging were uncommon (fig 5). Fibrosis was associated, in decreasing order of frequency, with polymorpho-nuclear leucocytic infiltrates, lipogranulomas, and fatty change.

Portal spaces

Mononuclear, and less often neutrophilic, infiltrates were present to a variable degree. If only an isolated subcapsular portal tract appeared abnormal, it was not considered significant. Mild proliferation of bile ducts was seen in a few biopsies.

Nuclear vacuolization

In H and E preparations, 'empty'-appearing, completely 'ballooned' nuclei were seen in periportal areas, often with a patchy distribution (fig 6). Less commonly, small vacuoles were noticed within pleomorphic nuclei of hepatocytes; the location in the lobule of this type of nuclear inclusion was not constant.

Pigments

Ceroid (lipochrome) was normal or decreased. The few bile plugs and iron which were found occurred in the most abnormal livers.

Other histological findings

Proliferation of Kupffer cells and necrosis of hepatocytes were uncommon. As expected, the latter often coexisted with neutrophilic inflammation. No alcoholic hyaline (Mallory bodies) was identified in any biopsy.

Correlation of Hepatic Morphology with Clinical and Biochemical Data

In this series, in women, abnormal carbohydrate metabolism is the single most important finding associated with hepatic changes (table VIII). This link is stronger in females over 30 years old than

Fig 6 'Ballooned' type of nuclear vacuolization. Observe its patchy and periportal distribution. H&E, 250

in younger women. Nuclear vacuolization ('ballooned' nuclei) is supposedly a common histological feature in livers of diabetics. We found it in 45% of the 'diabetic', in 18.3% of the 'abnormal', and in 14% of the 'normal' women. It was usually associated with fatty metamorphosis of the liver. Sixteen of 32 patients with menstrual irregularities had over 25% hepatic steatosis; by contrast only three of 27 normally menstruating women showed a similar degree of liver involvement. This difference was not explained by the degree of carbohydrate tolerance. After making allowance for the role of carbohydrate metabolism alteration and for gynaecological history, neither the clinical (corpulence, age)

OGTT	Hepatic Abnormalities			
	Steatosis		Fibrinosis	
	<25%	25% & Over	None	Present
Normal	37	6	42	1
Abnormal	39	21	55	5
Diabetic	10	28	30	8
Significance	P < 0.0001		NC ¹	

Table VIII Correlation between OGTT and hepatic morphology (women only)

¹ χ^2 test not calculated because one or more expected values is less than 5.

condition nor the metabolic (lipids, uric acid) parameter correlated well with hepatic morphology.

In men, histological changes of the liver were more severe (table VII) and could not statistically be linked to any clinical or metabolic dysfunction.

Thirty-seven patients had slightly elevated GOT, and of these, eight had no or mild pathological findings in the liver, 15 showed some hepatic fibrosis, 22 had marked fatty change, and 16 parenchymal or portal inflammation. Conversely, 15 out of 24 subjects with hepatic fibrosis and 22 of 40 with marked hepatic steatosis had elevations of the GOT. Mild or moderate hepatic steatosis was not associated with GOT elevations. Bromsulphalein was not reliable in predicting hepatic alterations in this study.

Discussion

The results of this study underscore the importance of carbohydrate metabolism in exogenous obesity. The majority of the patients had either an 'abnormal' or a 'diabetic' OGTT. Moreover, diabetes, when present, was mild in most patients. These facts are interpreted as evidence of the obesity-associated character of the carbohydrate disturbance. A key mediator, extensively studied in recent years, is insulin. Hyperinsulinism has been linked to corpulence, hyperglycaemia, and hypertriglyceridaemia (Rosselin, Claude, Eschwege, Patois, Warnet, and Richard, 1971). The relationship between insulin and adipose tissue has been extensively studied (Björntorp, Berchtold, Holm, and Larsson, 1971), and the hyperinsulinism of obesity has been thought as mainly due to the 'resistance' of the adipocyte to the action of insulin. Surprisingly little is known about the role that the liver may play in this hyperinsulinism. Abnormal glucose tolerance and high insulin levels also occur in cirrhosis, but it has been suggested that these are caused by shunting of insulin-containing portal blood (Conn, Schreiber, and Elkington, 1971; McCullough, Tzargournis, Greenberger, and Linscheer, 1971).

The other two frequently elevated values in this study were the Tg and uric acid. To interpret Tg levels, the influence of age (Schaefer, 1964) and probably sex should be taken into account; age-adjusted criteria are used to determine the upper limits of 'normal' (Fredrickson *et al.*, 1967). However, there is little information on the possible influence of sex on Tg values. In our material, hypertriglyceridaemia was more closely associated with sex and age variation than with corpulence, abnormal carbohydrate metabolism, or hyperuricaemia. These findings tend to parallel those of other studies in normal, mildly obese and diabetic

individuals (Allard and Goulet, 1968; Plauchu, Pousset, Montgolfier, Guibert, and Kressmann, 1971).

Inasmuch as the method used by us is not very specific for uric acid, and furthermore, serum urate levels fluctuate fairly widely even in the same subject (Goldstein, Becker, and Moore, 1972), the uric acid values should be interpreted with caution. Even recognizing such limitations, our data show higher uric acid levels in men than in women.

The coexistence of high Fg, hyperglycaemia, and obesity is well known (Emmerson and Knowles, 1971; Mertz, 1972), although a precise link among these factors is difficult to establish. Except between uricaemia and hyperglycaemia (and only in females) we were unable to find a statistically significant association among these parameters.

Elevations of GOT, even slight, correlated well with hepatic fibrosis and inflammation, and to a lesser extent with hepatic steatosis. Determinations of GOT have more practical value when there are no other conditions known to affect the GOT, as in our patients. In contrast to GOT, BSP was a poor test in predicting the severity of hepatic alterations. This may be explained by the difficulty in calculating an adequate dose and by the irregular distribution of the dye in the obese.

Hepatic steatosis in obesity has long been recognized. In the first studies, carried out in males, no relationship could be established between hepatic pathology and any biochemical data. We report here similar findings in men. However, it should be pointed out that the number of males in the present and in previous studies is relatively small. To our knowledge, no comparison of biochemical and clinical information with histology of the liver has been previously attempted in markedly obese females. In investigations on diabetic patients, mostly mildly obese females, the degree of hepatic fatty metamorphosis depended on the degree of overweight not on the severity of diabetes (Berlinger and Thaler, 1970; Wasastjerna, Reissell, Karjalainen, and Ekelund, 1972). In our material impairment of carbohydrate metabolism seems more important than corpulence in producing hepatic changes. Perhaps it might be concluded that, at least in females, the coexistence of both obesity and 'diabetic' alteration is much more likely to cause fatty liver than if only one factor is present.

Gout has been implicated as a cause of fatty liver (Hennecke and Südhoff, 1970), but it remains unclear whether the uric acid alteration or the frequently coexisting obesity and 'diabetes' are responsible for the hepatic steatosis. Our data are inconclusive in this respect, but carbohydrate alterations seem to play a more important role than gout. Hypercholesterolaemia (Leevy, 1962).

hypertriglyceridaemia, or high fatty acids, per se, are not known to be associated with liver damage. This is also evident in the present work.

We report here a close association between menstrual disturbances and hepatic abnormalities in young obese females. This, to our knowledge, has not been previously described, and further studies are needed.

Our data suggest both unpredictable and more severe liver involvement in obese men than in women. Review of other reports (Zelman, 1953; Westwater and Fainer, 1958; Meyerowitz, 1972) appears to support this view. The reason for this sex difference is not clear. Seemingly, the alterations which should coexist with obesity to cause hepatic abnormalities are less common or less severe in females.

Histologically, although fatty change in the liver was common, significant fibrosis was infrequent, and when the latter occurred, necrosis and inflammation often coexisted. Thus, the last two factors, rather than steatosis, are the important fibrogenetic stimuli in the liver. This concept is held by most investigators (Schaffner and Popper, 1970; Smetana, 1972) studying fatty livers of diverse aetiology. The role of lipogranulomas (Christoffersen, Braendstrup, Juhl, and Poulsen, 1971), if any, awaits further investigation (in our material it did not seem to be prominent). The pathway leading to cirrhosis in the obese—a relatively uncommon event—is probably similar to the one operating in other micronodular cirrhosis.

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