Liver disease in patients with diabetes mellitus

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Summary

Liver function tests were assessed in 60 unselected out-patient diabetics stabilized on insulin or oral hypoglycaemic agents. Routine liver function tests, particularly plasma concentrations of γ -glutamyl transpeptidase and alkaline phosphatase were elevated occasionally but rarely to more than twice the upper limit of normal. There was no correlation between measures of diabetic control and results of liver function tests. Twelve (20%) patients had evidence of gall stones, a prevalence above the expected from the community. Fourteen (23%) patients had an abnormally bright liver ultrasound echo pattern, probably indicative of fatty infiltration of the liver. This echo pattern was associated with only a minimal rise in plasma alanine amino transferase and alkaline phosphatase concentrations. It is concluded that functionally significant liver disease is uncommon amongst stabilized diabetic patients.

Introduction

Disturbance of liver function in some patients with diabetes mellitus is well recognized (Bradley, Sagild and Schertenleib, 1955; Camerini-Davalos, Marble and Muench, 1962) but the precise relationship of diabetes mellitus to liver dysfunction has not been simply established. The liver is probably the single most important regulatory site of glucose metabolism (Felig and Sherwin, 1976) and, in patients with liver disease, disturbance of carbohydrate metabolism is common (Johnston and Alberti, 1976). Various authors have reported a prevalence of cirrhosis in diabetics from 6 to 21%

at post-mortem (Creutzfeld, Frerichs and Sickinger, 1970), but it is likely that this figure is falsely elevated by inclusion of patients with hepatogenous diabetes whose prognosis may be very different from that of those with 'genetic' diabetes mellitus (Felig and Sherwin, 1976). Other studies have sought to exclude patients known to have liver disease (Camerini-Davalos *et al.*, 1962).

This confusing situation has been compounded by the development and widespread application of new liver function tests since much of the previous work was completed. Moreover, it is difficult to avoid bias in selecting patients for study of liver function, particularly when biopsy is required to establish a pathological diagnosis. For these reasons the authors have sought to establish the frequency and severity of liver disease using modern techniques in an unselected population of established diabetics undergoing modern treatment. In particular, they have used grey scale ultrasound examination of the liver to derive information of the state of the liver parenchyma. They previously demonstrated a close correlation between the presence of an abnormally bright reflective echo pattern from the liver and either cirrhosis or fatty infiltration (Joseph, Dewbury and Maguire, 1979).

Methods

Sixty unselected diabetic patients requiring treatment with insulin or oral hypoglycaemic agents and attending a diabetic clinic were studied consecutively. Patients are usually referred to the clinic from local general practitioners for control of their diabetes and only a minority are referred for specific complications. Patients were interviewed and examined. A Vickers M300 autoanalyser was

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used routinely to measure plasma creatinine (by pseudo-kinetic Jaffé reaction), albumin (by a modified bromocresol green method), bilirubin (by diazoreaction with dichloraniline and Brij 35 as surfactant), aspartate and alanine amino transferase (by optimized methods using the respective ketoacid and tris buffer at 37°C), and alkaline phosphatase (using nitrophenylphosphate as substrate). Plasma γ -glutamyl transpeptidase was measured by a kinetic method using γ -glutamyl nitro anilide as substrate with glycylglycine as acceptor. Plasma was used for random measurement of glucose by glucose oxidase method. Blood Hb A₁ concentration, which is believed to reflect diabetic control (Peterson and Jones, 1977) was measured by the spectrophotometric method of Fluckiger and Winterhalter (1976), after storage for no more than 5 days as whole blood at 4°C with lithium heparin as anti-coagulant. Preliminary studies showed fairly constant levels of Hb A₁ under these conditions after an initial rapid decay of about 6% of total Hb A₁. Twenty-four-hr collections of urine for urinary glucose excretion were also made. Ultrasound examinations of the liver and gall bladder were

performed by an experienced operator (KD) in a standard manner using a Picker 80 L analogue B scanner with a focused 3 mHz transducer. Examples of liver echo pattern regarded as normal or bright are shown in Figs 1 and 2 respectively. It was impractical to undertake ultrasound examination on a normal population. A retrospective survey was therefore made of the frequency of a bright echo pattern in 60 non-diabetic patients referred for ultrasonography for suspected gall stones which were not detected. These control subjects were matched for age and sex with the diabetic patients.

Weight was expressed as percent. ideal body weight (IBW) using the midpoint of the reference range for subjects of medium frame in the Metropolitan Life Insurance Co. Tables (Anonymous, 1964). For the purposes of assessment of alcohol intake, one 'drink' was taken to be half a pint of beer, one glass of wine or one measure of spirits. Results are expressed as mean $\pm$ s.e. mean. Significance tests were made using Student's 't' test and χ^2 test. Linear correlations were sought between variables. Logarithmic transformation of grossly positively skewed data was used where appropriate.

FIG. 1. Longitudinal scan through the right lobe of the liver showing the normal appearance. Note that the normal liver parenchyma (L) is interspersed with portal and hepatic veins, the walls of which can be identified. The kidney (K) is slightly less reflective than the liver. The diaphragm (D) stands out brightly in comparison with the liver.

FIG. 2. Longitudinal scan through a brightly reflective liver (L). The overall amplitude of the echoes is higher than normal, the diaphragm (D) no longer appears so bright and the kidney (K) appears darker. The liver has a uniform appearance with loss of visualization of vessel walls.

Patients

Thirty-four insulin-dependent (18 male, 16 female) and 26 insulin-independent patients (19 male, 7 female) were studied. None had symptoms of uncontrolled diabetes mellitus. The mean age was 53 ± 2 years (range 17 to 73 years), mean duration of diabetes 11 ± 2 years, (range 0.3 to 36 years) and mean weight $116 \pm 2\%$ IBW (range 77–170% IBW). Insulin-dependent diabetics were younger but no less obese than the insulin-independent patients. Seven patients gave a history of previous viral hepatitis and 3 had undergone cholecystectomy. The patients estimated their current alcohol intake at 4 ± 1 drinks/week (range 0 to 28 drinks) with a previous maximum intake of 11 ± 3 drinks/week (range 0 to 40 drinks/week). Twelve patients had retinopathy, 12 had symptoms of ischaemic heart or peripheral vascular disease and 14 patients had evidence of either peripheral or autonomic neuropathy. Only one patient was known to have nephropathy and mean plasma creatinine was $91 \pm 3 \mu\text{mol/l}$ (range 35–171 $\mu\text{mol/l}$).

Results

In Table 1 results of liver function tests in the

diabetic patients are compared with normal reference ranges established for the methods used in this laboratory. Random blood glucose was increased, and Hb A₁ was significantly higher in the diabetics than in 15 healthy subjects ($7.6\% \pm \text{s.e. mean } 0.3$, $P < 0.01$). Few patients had liver function test results consistently outside the reference range. There were no significant correlations between random blood glucose, 24-hr urinary glucose excretion, Hb A₁ weight or alcohol consumption and liver function tests.

Fourteen (23%) of the diabetics had a bright liver echo pattern, but only one of the control subjects had this echo pattern ($\chi^2 = 11.0$, $P < 0.01$). The control subject with a bright echo pattern had clinical, biochemical and histological evidence of alcoholic hepatitis. Fifteen of the 60 control subjects proved to have peptic ulcers, 6 to have cardiovascular disease, 4 irritable bowel syndrome, 13 had a variety of different conditions and in 20 patients the symptoms resolved spontaneously before a diagnosis was established.

Diabetics with a brightly reflective liver echo were heavier and had higher alanine amino transferase and alkaline phosphatase activity than those without

a bright liver echo (Table 2). Seven of the 14 patients with a bright echo pattern had a liver edge palpable more than one cm below the costal margin compared with 12 of the 46 patients with a normal echo pattern ($P < 0.05$).

Twelve of the diabetic patients (20%) had either undergone cholecystectomy or were shown unequivocally to have gall stones by ultrasound examination. Eight of the patients with gall stones

were in the insulin-independent group. Patients with gall stones tended to be older and to have lower 24-hr urine glucose excretion and had lower random blood glucose concentrations (Table 2).

Discussion

This study confirms that a few diabetic outpatients have mild disturbance of routine liver function tests. It should be emphasized that these

TABLE 1. Liver function tests in 60 diabetic patients with reference ranges for methods used in this laboratory

	Laboratory reference range	Diabetic patients*	No. of diabetic patients outside reference range
Weight (% ideal body weight)	—	116 ± 2	
Random plasma glucose (mmol/l)	3.0–8.6	9.9 ± 0.7	27
24-hr urine glucose (mmol/24 hr)	—	43 ± 11	
HbA _{1c} (% total Hb)	—	11.3 ± 0.4	
Bilirubin (μmol/l)	0–17	11 ± 1 (1–46)	6
Albumin (g/l)	32–50	41.7 ± 0.7 (38.1–47.1)	0
Alanine amino transferase (i.u./l)	5–37	25 ± 2 (10–67)	6
Aspartate amino transferase (i.u./l)	5–42	23 ± 2 (11–100)	2
Alkaline phosphatase (i.u./l)	50–275	216 ± 19 (91–415)	11
γ-glutamyl transpeptidase (i.u./l)	6–29 (f) 10–46 (m)	27 ± 2 (8–83)	10

* Figures in parenthesis indicate ranges; (f) female; (m) male.

TABLE 2. Characteristics of diabetic patients with and without abnormalities on liver ultrasound

	Gall stones		'Bright echo'	
	Patients without	Patients with	Patients without	Patients with
Number	48	12 (20%)	46	14 (23%)
Age (years)	51 ± 2	59 ± 3	52 ± 2	56 ± 2
Weight (% ideal body weight)	116 ± 2	118 ± 8	114 ± 2	126 ± 6*
Alcohol intake (drinks/week)	4 ± 2	2 ± 1	3 ± 2	3 ± 2
Palpable hepatomegaly	18	1	12	7
Creatinine (μmol/l)	92 ± 3	88 ± 10	96 ± 9	98 ± 5
Random plasma glucose (nmol/l)	10.6 ± 0.8	6.9 ± 0.8*	8.8 ± 0.5	10.6 ± 0.6
24-hr urine glucose (mmol/l)	50 ± 12	8 ± 3	38 ± 11	61 ± 25
Haemoglobin A _{1c} (%)	11.1 ± 0.5	11.9 ± 1.0	11.2 ± 0.5	11.4 ± 1.1
Bilirubin (μmol/l)	12 ± 1	9 ± 1	11 ± 1	12 ± 1
Albumin (g/l)	42.3 ± 0.3	42.5 ± 0.5	42.0 ± 0.3	43.3 ± 0.5
Aspartate amino transferase (i.u./l)	23 ± 2	23 ± 2	24 ± 2	22 ± 2
Alanine amino transferase (i.u./l)	24 ± 2	26 ± 6	23 ± 2	32 ± 4*
Alkaline phosphatase (i.u./l)	212 ± 73	218 ± 18	203 ± 8	250 ± 27*
γ-glutamyl transpeptidase (i.u./l)	26 ± 2	33 ± 7	26 ± 2	35 ± 2

* Significant difference, $P < 0.05$.

abnormalities were mild, rarely above twice the accepted upper limit of normal. As noted by others (Belfiore, Napoli and Lo Vecchio, 1973; Rosalki, 1975), elevation of plasma concentrations of alkaline phosphatase and γ -glutamyl transpeptidase were the abnormalities most often encountered, but these abnormalities remained minor and did not correlate with changes in other measures of liver function or measures of diabetic control. It seems unlikely that these minor abnormalities reflect clinically significant liver dysfunction in all cases. Coincidentally, none of the patients was known to have liver disease before the study and it would appear that such disease is uncommon in unselected diabetic patients. The authors suggest that the finding of more than mild disturbance of routine liver function in diabetic patients should prompt investigation just as in non-diabetic patients. Disturbance of metabolic functions of the liver appear to correlate with routine liver function tests (Johnston and Alberti, 1976) and thus impairment of the metabolic capacity of the liver is unlikely to contribute significantly to poor control of diabetes in the majority of diabetics.

None of the patients reported in this study had symptoms of uncontrolled diabetes although in some cases control was not satisfactory. The results may well differ from those in patients with uncontrolled diabetes. In a preliminary study of uncontrolled diabetic patients admitted to hospital the authors have noted more frequent disturbance of liver function tests, notably elevation of plasma alkaline phosphatase and γ -glutamyl transpeptidase concentrations and depression of plasma albumin. The latter probably reflects the cachexic effects of uncontrolled diabetes mellitus.

The authors used ultrasonography both to investigate the prevalence of gall stones and to assess the state of the liver parenchyma. This technique is particularly suited to screening large numbers of patients without bias imposed by fear of possible side effects. The accuracy of the technique in experienced hands in detecting gall stones is well recognized (Crade, 1979; Bastrum, Crow and Foote, 1977). For logistic reasons it was not possible to submit matched healthy control subjects to ultrasound examination but the observed overall prevalence of gall stones of 20% and the prevalence of 33% in the small number of maturity onset diabetics studied are undoubtedly higher than expected. In a careful study covering 9 towns in England, Barker and his colleagues (1979) found prevalences of 6% for women aged <45 years rising to 25% in those >75 years and of 4% and 17% in men of the same age ranges. The present study confirms evidence previously only available from post-mortem studies (Heaton, 1973). Creutzfeld and his co-workers (1970) suggested that the increased prevalence of gall

stones in diabetics might be due to obesity but this was not evident in the present patients, although all the authors' patients receive dietary advice to achieve their IBW. Surprisingly, gall stones were possibly associated with better control and it is of interest that bile saturation has been reported decreased in uncontrolled diabetes (Bennion and Grundy, 1977).

The frequency of a bright echo pattern in normal subjects is not known but is almost certainly very low. In contrast, approximately 90% of patients with either micronodular cirrhosis or moderate to severe fatty infiltration have bright echo patterns (Dewbury and Clark, 1979; Foster *et al.*, 1980). Only one of the control group had a bright echo pattern despite bias imposed by using a group selected for investigation of the biliary tract, and that subject subsequently proved to have alcoholic liver disease. Previously the authors examined a group of 40 patients selected by finding normal liver histology on biopsy. Despite the bias arising from a group selected for investigation of the liver, only 2 had a bright echo pattern (Foster *et al.*, 1980). In both groups the rate was significantly lower than the 23% rate observed in out-patient diabetics. The authors believe that in the majority of cases the bright echo pattern indicated fatty infiltration because of the lack of evidence of disturbed liver function, splenomegaly or clinical signs of chronic liver disease and because of the correlation with obesity. In no case did they think liver biopsy was justified on clinical grounds. Thus, the findings on liver ultrasound do not contradict the remarks made above on the basis of liver function tests about the frequency of functionally significant liver disease, although alanine amino transferase and alkaline phosphatase levels were marginally higher in the bright echo group. The prognostic significance of fatty infiltration of the liver is uncertain and they intend to follow the progress of these patients with a bright echo pattern.

Acknowledgment

Dr P. Todd kindly allowed us to study patients under his care.

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