

## Original Articles

### HEPATOMEGALY IN DIABETES MELLITUS

Zulfiqar Haider, Aziza Rasul and Kishwar Zafar Moeen

#### Abstract

18 diabetic patients (14 with maturity onset and 4 with juvenile diabetes) with hepatomegaly were investigated. The distribution of histological findings on liver biopsy were: fatty infiltration (5); fatty changes with cell necrosis (2); fatty changes with inflammatory changes (2); chronic active hepatitis (2); nutritional cirrhosis (2) and a miscellaneous group comprising of diverse conditions in 5 patients. Apart from fatty infiltration no other abnormality specifically related to diabetes was detected. The implications of these findings are discussed.

#### Introduction

The inter-relationship between diabetes mellitus and hepatic disorders has remained speculative. It was thought that the cases of so called "tropical diabetes" may be due to hepatic dysfunction and hence the concept of hepatopathic diabetes has been put forward (Ibrahim 1962). Also there is a clinical impression that in this region, liver enlargements are encountered frequently in patients suffering from diabetes mellitus. While liver enlargement in diabetes mellitus during the phase of metabolic decompensation is well known, there are a certain number of diabetics in whom the cause of hepatomegaly remains obscure. In this short study the results of investigations in patients with liver enlargement associated with diabetes mellitus are reported.

#### Material and Methods

18 patients suffering from diabetes mellitus and hepatomegaly were studied. Diabetes mellitus was diagnosed on the basis of glucose tolerance test under standard conditions after 50 gms of glucose load and using capillary blood for glucose estimation. The results were interpreted according to the criteria laid down by the College of General Practitioners (1962). Hepatomegaly was diagnosed on clinical grounds and was defined as enlargement of liver above 6th intercostal space in mid clavicular line while the patient is examined in the supine position and there is no evidence of emphysema and viscerotoposis. Liver enlargement was always confirmed by radio-isotopic liver scan. Liver function tests which were done in every case included serum

bilirubin, transaminases, alkaline phosphatase, serum protein, albumin: globulin ratio and thymol turbidity. HB/AG was done in 4 cases. The results of SGOT & SGPT were expressed as karman units (normal values: SGOT 8-40 and SGPT 8-35 units) and alkaline phosphatase as K.A. units (normal 3-13 K.A. units). Serum protein and serum bilirubin were done by the methods described by King and Wooten (1964). Test for HB/AGs was done by counter current immunoelectrophoresis. Liver biopsy was done in all cases using menghini aspiration needle.

#### Results

Age and sex distribution is shown in Table I. There were 14 females and 4 males. All except 3 patients were above 30 years of age; the other 3 were below 20 years of age. Some features relevant to diabetes mellitus are shown in Table II. There were 14 patients with maturity onset diabetes and 4 with juvenile type of diabetes mellitus. 11 patients were over weight and 7 were under weight. Seven patients were on insulin therapy and 11 were taking oral hypoglycaemia agents. Diabetes mellitus was well controlled in 4 patients (post parandial blood glucose <200 mg%) and was poorly controlled in the rest.

The distribution of histological changes on liver biopsy along with results of investigation and clinical features relevant to liver enlargement were as follows (Table III).

Table I: Age and Sex Distribution in 18 Patients of Diabetes Mellitus with Hepatomegaly.

Age and Sex	Female	Male
10-20 years .. .. .	2	1
21-30 years .. .. .	0	0
31-40 years .. .. .	5	0
41-50 years .. .. .	3	2
51-60 years .. .. .	4	1
61 and above .. .. .	0	0
Total: .. .. .	14	4

Table II: Features related to Diabetes Mellitus in 18 Patients with Hepatomegaly.

Clinical Features	No. of Patients
1. Type of Diabetes	
(a) Juvenile .. .. .	4
(b) Maturity onset .. .. .	14
2. Weight Changes	
(a) Over weight .. .. .	11
(b) Under weight .. .. .	7
3. Therapy .. .. .	
(a) Insulin .. .. .	7
(b) Oral Hypoglycaemic Agents .. .. .	11
4. State of Control	
(a) Uncontrolled .. .. .	14
(b) Good control .. .. .	4

Table III: Distribution of Histological Findings, Clinical and Biochemical Features relevant to Liver Disease in 18 Diabetics with Hepatomegaly.

Histological Findings	No.	Clinical Features			Liver Function Tests (mean values)						
		Past History of jaundice	Jaundice	Ascites	Serum Bilirubin mg%	SGOT	SGPT	Alkaline Phosphatase	Protein Gm%	A/G	HB/AG
1. Fatty Changes											
(i) Fatty Infiltration	5	—	—	—	0.55	38.7	43	12.2	7.7	1.12	Not Done
(ii) Fatty Changes with Cell Necrosis	2	1	—	—	0.7	35	36	8.5	6.5	0.6	Not done
(iii) Fatty Changes with Inflammatory Reaction	2	2	—	—	3.1	105	110	15.0	7.0	1.0	Negat. in one
2. Chronic Active Hepatitis and Post-Necrotic Cirrhosis	2	1	1	1	8.15	117.5	311.5	14.1	6.65	0.85	Negat. in both
3. Nutritional Cirrhosis	2	—	—	2	0.9	99	85	13.5	5.6	0.6	—
4. Miscellaneous											
(i) Normal	1	—	—	—	1.2	20	18	7.2	7.5	1.0	—
(ii) T.B. Granuloma	1	—	—	—	0.8	20	30	8.0	7.1	1.3	Negat.
(iii) Malignancy (possible)	1	—	—	—	0.4	45	45	21.0	7.2	1.1	—
(iv) Chronic Venous Congestion	1	—	—	—	0.6	90	90	10	7.5	1.1	—
(v) Malarial Pigment	1	—	—	—	0.6	25	30	14.0	7.0	0.7	—

## 1. Fatty Changes

### (i) Fatty infiltration:

Fatty infiltration in liver parenchyma was found in 5 patients; 4 had maturity onset diabetes and 1 juvenile diabetes. Diabetes was uncontrolled in all at the time of biopsy. Significant elevation of transaminases (770 units) was noted in only 1 patient and past history of jaundice was not obtained in any of the cases.

### (ii) Fatty changes with cell necrosis:

There were 2 patients in this category both of whom had maturity onset diabetes. One patient had a history of an attack of jaundice 2 months prior to biopsy. The illness simulated viral hepatitis with documented rise of transaminases values. However, she had been taking some unspecified indigenous medicine at the time of illness and as such it was difficult to rule out drug induced jaundice.

### (iii) Fatty changes with portal tract infiltration:

There were 2 patients and both had a history of jaundice during the past one year. There was a moderate elevation of serum transaminases at the time of biopsy. The transaminase levels returned to normal after a year on subsequent follow up.

## 2. Chronic Active Hepatitis and Post Necrotic Cirrhosis

There were 2 middle aged females with

maturity onset diabetes in this group. There was past history of an attack of jaundice in one. There was evidence of disturbed liver function in both and one patient subsequently died of hepatic failure. HB/AG was negative in both these patients.

## 3. Nutritional Cirrhosis

Histological evidence of nutritional cirrhosis was present in 2; one a middle aged male and the other a girl of 14 years with juvenile diabetes mellitus. Both had clinical evidence of hepatic impairment in the form of ascites, oedema and splenomegaly. Transaminases were significantly elevated in the young girl with juvenile diabetes.

## 4. Miscellaneous Group

This group comprised of 5 patients and the histological diagnosis included: normal (1), T.B. granuloma (1), malignancy (1), chronic venous congestion (1) and malarial pigment (1).

## Discussion

Before the advent of insulin, gross hepatic enlargement was frequently noticed in the young ketosis prone diabetics (Marble et al., 1938). Treatment with insulin was followed by reduction in the liver size (White et al., 1938). The hepatic enlargement in young patients with uncontrolled ketosis has been found to be due to fatty changes, accumulation of water in the intracellular spaces and to some extent accumulation of glycogen (Creutzfeldt et al., 1970; Warren et al., 1966).

In well controlled juvenile diabetics, fatty liver is rare and liver enlargement if present is due to glycogen infiltration (Vaishnava et al., 1970). In the maturity onset diabetics fatty liver is more often associated with obesity (Creutzfeldt et al., 1970). However, non-diabetic obese patients have also been reported to have similar frequency of fatty changes (Berkowitz 1964). There is a general agreement that diabetes per se does not produce any specific liver disease but certain liver conditions such as viral hepatitis (Creutzfeldt et al., 1970; Droller, 1945), and cirrhosis (Muting et al., 1966; Conn et al., 1969) are more often associated with diabetes. The small group of 18 diabetics with hepatomegaly investigated by us were a highly selective material. On liver biopsy fatty infiltration was the single most common abnormality being present in 5 patients with uncontrolled diabetes. In other patients in whom fatty changes were associated with either cell necrosis or inflammatory cell infiltration in the portal tracts, a past history of an illness simulating viral hepatitis was present in 3 out of 4 patients. Chronic active hepatitis with early post-necrotic cirrhosis was seen in 2 patients both of whom had a history of an attack of jaundice. It is not certain whether jaundice followed an attack of serum hepatitis but Australia Antigen (HB/AG) was negative in both. Histological evidence of nutritional cirrhosis was obtained in 2 patients with uncontrolled diabetes and evidence of hepatic failure in the form of ascites and oedema. Both of these patients were under weight but detailed investigations to rule out conditions like malabsorption could not be undertaken. In all probability the liver condition was unrelated to diabetes mellitus per se. The remaining 5 patients had unrelated miscellaneous abnormalities on liver biopsy.

In conclusion, in this study comprising of 18 diabetics with hepatomegaly, fatty infiltration was the most common abnormality. Apart from this, other findings were for the most part unrelated to diabetes mellitus as such. Thus, in this small group of patients suffering from diabetes mellitus, apart from fatty infiltration, there was no single or specific cause contributing to hepatic enlargement.

### Acknowledgements

We wish to express our gratitude to Dr. S.J. Zuberi, PMRC Research Centre Jinnah Post-graduate Medical Centre, Karachi for her kind help in performing Australia Antigen Test. Thanks are also due to Mr. Khalid Maqbool for performing biochemical test and to Messrs Asadullah Khan, S.N. Iqbal and Mahmood Ahmad for their technical help.

### References

Berkowitz, D. (1964) Metabolic changes associated with obesity before and after weight reduction. *JAMA.*, 187:399.

Conn, H.O., Schreiber, W., Elkington, S.G. and Johnson, T.R. (1969) Cirrhosis and diabetes. I. Increased incidence of diabetes in patients with Leanne's cirrhosis. *Am. J. Dig. Dis.*, 14:837.

Creutzfeldt, W., Frerichs, H. and Sickinger, K. Liver disease in diabetes mellitus. In Popper, H. and Schaffner, F. eds: *Progress in Liver Disease*. Vol. 3. New York Grune and Stratton, 1970, pp. 371-407.

Droller, H. (1945) Outbreak of hepatitis in diabetic clinic. *Br. Med. J.*, 1:623.

Ibrahim, M. (1962) Diabetes in East Pakistan. *Br. Med. J.*, 1:837.

King, E.J. and Wooten, I.D.P. *Micro-analysis in medical biochemistry*. 4th ed. London, Churchill, 1964.

Marble, A., White, P., Bogan, I.K. and Smith, R.M. (1938) Enlargement of the liver in diabetic children. *Arch. Intern. Med.*, 62:740.

Muting, D., Lackas, N., Reikowski, H. and Richmond, S. (1966) Cirrhosis of the liver and diabetes mellitus. A study of 140 combined cases. *German Med. Monthly*, 11:385.

Report of a working party appointed by the College of General Practitioners (1962) A diabetic survey. *Br. Med. J.*, 1:1497.

Vaishnava, H., Gulati, P.D. and Damodaran, V.N. (1970) Observations on the structure and function of liver in Indian diabetics. *Diabetologia*, 6:21.

Warren, S., LeCompte, P.M. and Legg, M.A. *Pathology of Diabetes Mellitus*. 4th ed. Philadelphia, Lea and Febiger, 1966.

White, P., Marble, A., Bogan, I.K. and Smith, R.M. (1938) Enlargement of the liver in diabetic children. II. Effect of raw pancreas, Betaine hydrochloride and pro-tamine insulin. *Arch. Intern. Med.*, 62:751.