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Clinical Profile of Diabetic Patients with Liver Dysfunction

Ghouse Pasha[1], Prashanth G.[2]

Author's Affiliation:
[1]Assistant Professor [2]Professor, Department of General Medicine, Basaveshwara Medical College, Chitradurga, Karnataka 577502, India.

Corresponding Author:
Prashanth G.,
Professor, Department of General Medicine, Basaveshwara Medical College, Chitradurga Karnataka 577502, India.
E-mail:
doctor.kotresh@gmail.com

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Abstract

The spectrum of clinical disease in fatty liver with steatohepatitis varies from the asymptomatic elevation of liver enzymes to severe liver disease with fibrosis and nodular regeneration. Patients with nonalcoholic steatohepatitis can develop progressive liver disease and complications to the point that they may need liver transplantation.Nonalcoholic steatohepatitis should be considered as a cause for chronically elevated liver enzymes in asymptomatic diabetic patients particularly if they are obese and have hyperlipidemia.This study was carried out among 100 diabetic patients diagnosed to be with hepatic dysfunction attending tertiary care hospital during the study period. Maximum number of patients had diabetic nephropathy (17%), followed by diabetic retinopathy (15%), peripheral neuropathy (11%) and peripheral vascular disease (4%). Neuropathy, Nephropathy, PVD and Retinopathy were present in patients who had diabetes for more than 10 years.

Keywords: Diabetes; LFT; NAFLD.

Introduction

The knowledge of diabetes dates back to centuries before Christ. Polyuric disease, resembling diabetes was described as early as 150 BC in ancient Egyptian records discovered by George Beers. Celsus (30 BC – 50 AD) had recognized the disease.

Diabetes, a Greek term, which literally means to 'run through' or a 'siphon' was initially used by Aretaeus in first century AD for the generic description of a condition causing increased urine output Roman physicians thought of diabetes as a "wonderful affection, not very frequent among men, being melted down of flesh and limbs into urine. The patient never stopped making water, but the flow of urine is incessant as if from a opening of aqueducts- Aretaeus, the Cappadocian [1,2].

The association of polyuria with a sweet tasting substance in the urine was first reported in Sanskrit literature dating from fifth to sixth centuries AD at the time of two noted Indian physicians Susrutha and Charaka [3].

It was in the seventeenth century that Thomas Willis (1621-1675) made the observation "as if imbibed with honey and sugar about the diabetic urine". A century after Willis, Mathew Dobson (1735-1784) demonstrated that the sweetness of urine was indeed due to sugars. It was John Rollo who was one of the first to use the adjective mellitus (mellitus = honey) to distinguish it from other polyuric states in which the urine was unsavory (Greek – insipidus). Over the centuries, gradually the causes and complications of this disease were recognized. Avicenna, an Arab physician at around the tenth century had described gangrene [1,2].

The diabetes world was overwhelmed with joy in 1921 when young physician and surgeon Frederick Grant Banting (1891-1941) and Charles Best, his graduate student assistant, working in Toronto through the summer on an almost non-existent budget in alab loaned to them temporarily by a vacating professor, prepared active extracts ofpancreas which lowered the elevated level of sugars in diabetic dogs. The first patient tobe treated with pancreatic extract was Leonard Thomson in 1922.The long acting

insulinpreparation (isophane) was introduced in 1936 by Hans Christian Hagedorn andcolleagues.

The testing of Sulfonylureas was done by Auguste Loubatieres in 1944. Thefirst therapeutic use of a Biguanide was done by G. Ungar in 1957. The efficacy of insulinin preventing the complications and retarding multisystem involvement was heralded bythe fact that the untreated cases in the pre-insulin era had a high mortality rate which wasmostly due to diabetic ketoacidosis [4].

Most patients of NAFLD (45-100%) have no symptoms or signs of liver disease at the time of diagnosis. In these patients, abnormal liver function tests are often discovered incidentally. When symptoms occur, they are non-specific – like persistent fatigue (50-73%), pruritus (0–6%), oedema (2–10%), malaise, and right upper quadrant discomfort or pain. Other features like GI bleeding (0 – 3%), jaundice (0 – 5%), ascites (0 – 3%), pruritus, and oedema point towards severe liver disease. Ascites, hepatic encephalopathy, and variceal bleeding indicate cirrhosis of liver due to progressive NASH. When the disease is not advanced, diffuse non-tender smooth hepatomegaly is present in 25-53% of patients. Such patients are usually obese and/or diabetic. Advanced disease may present with right hypochondrium tenderness, jaundice, palmar erythema, spider angioma, portal hypertension, ascites, varices and splenomegaly. The spectrum of clinical disease in fatty liver with steatohepatitis varies from the asymptomatic elevation of liver enzymes to severe liver disease with fibrosis and nodular regeneration. Patients with nonalcoholic steatohepatitis can develop progressive liver disease and complications to the point that they may need liver transplantation [5].

Nonalcoholic steatohepatitis should be considered as a cause for chronically elevated liver enzymes in asymptomatic diabetic patients particularly if they are obese and have hyperlipidemia [6].

In type 2 diabetic patients with or without obesity, up to 30% have fat with inflammation, 25% have associated fibrosis, and 1–8% have cirrhosis [7].

Methodology

This study was carried out among 100 diabetic patients diagnosed to be with hepatic dysfunction attending tertiary care hospital during the study period. Seriously ill patients and patients who did not give their consent for participation in study were excluded.

Liver function test (LFT) was done by enzyme kinetic and end point assay through the determination of the activity of serum enzyme from blood samples. Blood samples were collected by venepuncture after an aseptic measure. The samples were allowed to clot and the serum was separated by centrifugation at 10,000 rpm for 15 minutes at room temperature. Serum samples were stored at 2-40C until tested. For enzyme kinetic assay, commercially available kits (ROBONIK prietest™ clinical chemistry reagents. Mumbai(INDIA) PVT.LTD, Transasia Bio-Medicals LTD, Solan,(HP) in technical collaboration with ERBA diagnostics Mannheim Gmbh, Germany.) were used. Absorbance of reaction mixture was measured after performing the assay according to the supplied instruction. Then absorbance was converted by plotting a standard curve to determine sample values. All tests were done at 37^0 C.

The total bilirubin test was determined by the Diazo method, Bilirubin reacts with diazotisedsulpanilic acid in acidic medium to form pink colored azobilirubin with absorbance directly proportional to Bilirubin concentration. Direct Bilirubin, being water soluble directly reacts in acidic medium. However indirect or unconjugated Bilirubin is solubilised using a surfactant and then it reacts similar to direct Bilirubin. The instrument automatically calculates and prints the activity of total bilirubin in mg/dl.

Serum AST test method is an adaptation of the methodology recommended by the International Federation of Clinical Chemistry (IFCC) (Carter P, 1970). The change in absorbance with time due to the conversion of NADH to NAD is directly proportional to the AST activity and is measured using a bichromatic (340,700 nm) rate technique. The instrument automatically calculates and prints the activity of AST in U/L.

Serum ALT test method is an adaptation of the recommended procedure of the IFCC as described by Bergmeyer (Bergmeyer HU at al., 1998). The change in absorbance is directly proportional to the ALT activity and is measured using a bichromatic (340,700 nm) rate technique. The instrument automatically calculates and prints the activity of ALT in U/L.

The alkaline phosphatase test method is based Kinetic UV test- optimised IFCC method. Alkaline phosphatase (ALP) catalyses the hydrolysis of p-nitrophenyl phosphate at alkaline pH, liberating

p-nitrophenol and phosphate. The rate of p-Nitrophenol formation, measured photometrically, is proportional to the catalytic concentration of alkaline phosphatise present in sample. The instrument automatically calculates and prints the activity of alkaline phosphatase in U/L.

Serum total protein method is a modification of the bi-uret reaction first introduced by Kingsley (kingslsy GR, 1942). The blue (II) protein complex thus formed is proportional to the protein concentration in the sample and is measured using bichromatic 546nm (520-560nm) endpoint technique. The instrument automatically calculates and prints the activity of TP in gm/L.

Serum albumin test method is an adaptation of the Bromocresol green (BCG) dye method. Albumin binds with Bromocresol green (BCG) at pH 4.2 causing a shift in absorbance of the yellow BCG dye. The blue-green color formed is proportional to the concentration of albumin present, when measured photometrically between 580-630nm with maximum absorbance at 625 nm. The instrument automatically calculates and prints the activity of Alb in gm/L.

Results

Three patients were in the age of 31-34, 21 patients were in the age of 45-50, 21 patients were in the age of 51-55, 17 patients were in the age of 56-60, 15 patients were in the age of 61-65, 6 patients were in the age 66-70, 12 patients were in the age of 71-75, 3 patients were in the age of 76-80, 2 patients were in the age group more than 80 years. The mean age of the patients was 59.32 years ranging from 32 to 87 years. Majority of type 2 patients belonged to 51 – 60 years age group in this study. Females outnumber males in this study (Table 1).

In this study, maximum duration of diabetes mellitus was 20 years and minimum duration was one year. Majority of males and females had diabetes for 1- 5 years (Table 2).

In this study, H/O complications caused by diabetes were also assessed. Maximum number of patients had diabetic nephropathy (17%), followed by diabetic retinopathy (15%), peripheral neuropathy (11%) and peripheral vascular disease (4%) (Table 3).

Neuropathy, Nephropathy, PVD and Retinopathy were present in patients who had diabetes for more than 10 years (Table 4).

42.9% of patients in the age of 41-50,57.9% of patients in the age of 51-60, 61.9% patients in the age of 61-70, 53.3% of patients in the age of 71-80, 100% of patients in the age >80 had minimum of 1 LFT abnormality (Table 5).

Discussion

Table 1: Age and Sex distribution of the study population

Age group	Sex		Total
	Male n (%)	Female n (%)	n (%)
31 – 44 years	2 (4.1)	1 (2.0)	3 (3.0)
45 – 50 years	6 (4.1)	15 (29.4)	21 (21.0)
51 – 55 years	8 (16.3)	13 (25.5)	21 (21.0)
56 – 60 years	9 (18.4)	8 (15.7)	17 (17.0)
61 – 65 years	9 (18.4)	6 (11.8)	15 (15.0)
66 – 70 years	3 (6.1)	3 (5.9)	6 (6.0)
71 – 75 years	7 (14.3)	6 (9.8)	12 (12.0)
76 – 80 years	3 (6.1)	0	3 (3.0)
More than 80 years	2 (4.1)	0	2 (2.0)
Total	49 (100)	51 (100)	100 (100)

Table 2: Duration of diabetes mellitus among the cases

Duration of Diabetes	Sex		Total
	Male n (%)	Female n (%)	
1 – 5 years	29 (59.2)	32 (62.7)	61 (61.0)
6 – 10 years	2 (24.5)	13 (25.5)	25 (25.0)
11 – 15 years	6 (12.2)	5 (9.8)	11 (11.0)
16 – 20 years	2 (4.1)	1 (2.0)	3 (3.0)
Total	49 (100)	51 (100)	100 (100)

Table 3: Complications of diabetes mellitus in study population

Complications	Sex		Total
	Male n (%)	Female n (%)	n (%)
Neuropathy	7 (14.3)	4 (7.8)	11 (11.0)
Nephropathy	10 (20.4)	7 (13.7)	17 (17.0)
PVD	3 (6.1)	1 (2.9)	4 (4.0)
Retinopathy	8 (16.3)	7 (13.7)	15 (15.0)

Table 4: Relation of complications of diabetes mellitus with duration of diabetes

Duration of DM (yrs)	Complications of DM			
	Neuropathy	Nephropathy	PVD	Retinopathy
1 – 5 years	0	1	0	0
6 – 10 years	0	3	1	1
11-15 years	8	10	2	11
16 – 20 years	3	3	1	3

This study evaluated 100 diabetic patients. In this study maximum patients were in the age group of 51-60 years. It is well known that diabetes is common after the age 50 years .Females were predominant in this study.

A study conducted by Shobhaluxmi et al reported that the prevalence of NAFLD is higher in type 2 diabetes (60.8%) [8]. Merat et al. concluded that the prevalence of NAFLD was 55.8% [9].

Table 5: Relation of age of patient with minimum of 1 abnormal LFT

Age in years	No. of cases	No. of cases with minimum of 1 abnormal LFT
31 – 40 years	3	0
41 – 50 years	21	9 (42.9)
51 – 60 years	38	22 (57.9)
61 – 70 years	21	13 (61.9)
71 – 80 years	15	8 (53.3)
More than 80 years	2	2 (100)

In our present study overall 44% cases were found to have one or other hepatic abnormalities (NAFLD). Out of this, 18% of the patients had fatty changes of the liver, 26% cases had both hepatomeagaly and fatty changes of the liver ultrasonologically.

A Clinical study conducted by ISMAIL et. al. concluded that NAFLD are more among male patients as compared to females, patients with Diabetic duration >5 yrs were found to have fatty liver, unsatisfactory control (>7%) of HbA1c level are at a greater risk for developing fatty liver [10].

This study found that, those who were in the Diabetic duration >5yrs were found to have more incidence of USG liver abnormalities 27cases (69.23%) (NAFLD), Patients with glycemic control HbA1c value > 7 are at a greater risk for developing fatty liver and LFT abnormality.

Of all the complications of diabetes mellitus , the involvement of pheripheral nerve is least understood. It is termed as neuropathy because its nature is degenerative rather than inflammatory. This is a common long term complication of diabetes mellitus.

In this study 11% of the cases had diabetic peripheral neuropathy, either sensory or mixed peripheral neuropathy. The main stay of treatment of diabetic neuropathy is optimal control of hyperglycemia.

Renal disease is a leading cause of death and morbidity in diabetics. About half of the end stage renal disease is considered now due to diabetic nephropathy.

In this study, nephropathy, either in the form of proteinuria or elevated renal parameters was present in 17% of the cases. Diabetic retinopathy is a leading cause of blindness. The frequency of retinopathy varies with the age of onset and duration of diabetics. In this study, 15% cases had either grade I or II diabetic retinopathy.

Diabeticsis one of the commonest disease which affects the blood vessels causing atherosclerosis and various changes in the vessel wall. All vessels are affected by diabetics, but peripheral vessels are also commonly affected causing various signs and symptoms in the peripheries and may lead on to gangrene of the limbs.

In this study, only 4% of the cases are found to have peripheral vascular disease, even though the incidence is much higher in the diabetic population. The reason for this may be that patients with peripheral vascular disease present to surgical specialities usually.

Conclusion

Abnormal liver function tests in diabetes patients can be attributed to several factors, the most common cause being non alcoholic fatty liver disease (NAFLD) associated with insulin resistance and metabolic syndrome in diabetes.

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