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RESEARCH ARTICLE

DYSFUNCTION OF LIVER AND KIDNEY IN DIABETES MELLITUS AN OBSERVATIONAL STUDY

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ABSTRACT

Introduction: Liver disorder is known to be a risk factor for diabetes and diabetic patients are at risk of developing liver disorders. Association of liver and renal disease is less explored in the field of research. **Aim:** To estimate prevalence of abnormal Liver function in diabetes, and to study prevalence of nephropathy in diabetes categorized as: at <5yrs; 5-10 yrs; >10 yrs. **Materials and Methods:** The study and observation was done in sample of 300 subject of type II Diabetes mellitus from March 2012 to Aug 2013. Based on duration of Diabetes mellitus, subject were distributed according to <5yrs, 5-10yrs and >10yrs of illness. Out of 300 type II Diabetes mellitus subject 75% were male and female group was 25%. **Results:** With reference to liver function test 21% patient were having abnormal liver function test. The prevalence of diabetes nephropathy i.e. 35% overall. Prevalence of nephropathy increased with increasing duration of Diabetes mellitus. **Conclusion:** In the study Liver enzyme was elevated overall 21 % more than 3 times, 0.66% were detected with HCV reactive, fatty liver disease was most common finding, Macroalbuminuria present in 7.3 % of subject.

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INTRODUCTION

International Diabetes Federation 2009 report reveals that the total number of diabetic subjects in India is 50.8 million. India is often referred as the diabetes capital of the world. Over 30 million have now been diagnosed with diabetes mellitus in India. The CPR in the urban is estimated to be 9% and in rural areas prevalence rate is around 3%. The prevalence of IGT (impaired glucose tolerance) is around 8.7% and 7.9% in urban and rural areas respectively (International Diabetes Federation Atlas, 2009). The world health statistics 2012 report states that one 3 adults worldwide has hypertensive, one in 10 adults has diabetes mellitus.

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Liver disease is an important cause of death in type 2 diabetes (World Health Organization Media Centre, 2014). In the population based Diabetes Study, cirrhosis was the fourth leading cause of death and accounted for 4.4% of diabetes related deaths (Amos, 2010). Virtually the entire spectrum of liver disease is seen in patients with type II diabetes. This includes abnormal liver enzymes, NAFLD, cirrhosis, hepatocellular carcinoma, and acute liver failure. In addition, there is an unexplained association of diabetes with hepatitis C. Finally, the prevalence of diabetes in cirrhosis is 12.3-57%. Thus, patients with diabetes have a high prevalence of liver disease and patients with liver disease have a high prevalence of diabetes. The management of diabetes in patients with liver disease is theoretically complicated by liver-related alterations in drug metabolism,

potential interactions between the drugs, and a low, albeit real, incidence of hepatotoxicity. Liver disease occurring as a consequence of DM- Glycogen deposition, NAFLD and NASH, Fibrosis and cirrhosis, Biliary disease, cholelithiasis, Cholecystitis (Turner, 2010). DM and abnormalities of glucose homeostasis occurring as a complication of liver disease- Hepatitis, Cirrhosis, Hepatocellular carcinoma, Fulminant hepatic failure, Postarthotopic liver transplantation; Liver disease occurring coincidentally with DM and abnormalities of glucose metabolic- Haemochromatosis, Glycogen Storage disease, Autoimmunobiliary disease. In four clinical trials involving 3,701 patients with type 2 diabetes, between 2 and 24% of screened patients had liver enzyme tests above the upper limit of normal (ULN). 5% of the patients had concomitant liver disease at baseline. In another report involving 13 clinical trials and 5,003 patients with type 2 diabetes, in which patients with serum ALT, aspartate aminotransferase, or alkaline phosphatase>2.5 times ULN. 98% of asymptomatic patients with raised ALT revealed liver disease – most commonly NAFLD and chronic hepatitis[5]. The most common chronic liver disease in the U.S. is NAFLD. It is defined as fatty liver disease in the absence of <20g alcohol/day. NAFLD, which resembles alcoholic liver disease, consists of a spectrum of liver disease from steatosis (fatty infiltration of the liver) to NASH (steatosis plus inflammation, necrosis, and fibrosis). The prevalence of NAFLD in diabetes is estia at 34-17% and, in cirrhosis and, in some case, to hepatocellular carcinoma. 50% have NASH, 19% have cirrhosis at the time of diagnosis. Dyslipidemia with elevated plasma triglycerides, decreased HDL in increased lipolysis and free fatty acids overloading the mitochondrial beta oxidation system and accumulation of fatty acids in the liver[5]. Cirrhosis is an important cause of death in diabetes. In the Verona study, the SMR for cirrhosis was 2.52, greater than the 1.34 for CVD. The SMR increased to 6.84 in patients on insulin. The association of cirrhosis and diabetes is complicated by the fact that cirrhosis itself is associated with insulin resistance. Impaired glucose tolerance is seen in 60% and overt diabetes in 20% of patients with cirrhosis. Insulin-mediated glucose disposal has been shown to be reduced by 50% in cirrhotic patients. Numerous studies have confirmed a fourfold increased prevalence of hepatocellular carcinoma in patients with diabetes as well as an increased prevalence of diabetes in patients with hepatocellular carcinoma (Turner, 2010). The prevalence of HCV is higher in patients with diabetes than in the general population. Specifically, the prevalence of HCV antibodies is 4.2% in the diabetic population compared with 1.6% in the comparator group. The relative odds of HCV- infected patients developing diabetes is 2.1 (95% CI 1.12-3.90). Patients with HCV are more likely to develop diabetes (21%) than patients with hepatitis B (10%), suggesting that HCV, rather than liver disease per se, predisposes patients to diabetes. Furthermore, patients who are transplanted for HCV (and universally become infected again) are more likely to develop diabetes than those who are transplanted for other liver disease. Taken together, these observations suggest that HCV may play a pathogenic role in type II diabetes. Recent studies suggest that the core protein of HCV impairs insulin receptor substrate signaling, which plays an important role in the metabolic effects of insulin. There is an association of diabetes with $^{\alpha}$-interferon treatment of HCV infection. Type I diabetes occurs more frequently in patients treated with interferon for HCV versus other conditions. The latency of diabetes ranges from 10 days to 4 years after starting treatment (Simo, 1996; Manka, 2016). Management of diabetes is must to prevent long and short term complication these including in this section because some of medicine having directly or indirectly effect of liver and kidney as well. Low-glycemic, low-calorie diets with a weight loss of 1-2 kg/week seems reasonable. Some have suggested that a Mediterranean diet (i.e., high complex carbohydrates, high monounsaturated fats, moderate amounts of wine, and low amounts of red meat) is preferred in patients with type II diabetes and NAFLD. Exercise improves peripheral insulin sensitivity, although not specific to patients with diabetic liver disease (Bojesting, 1996). Pharmacologic therapy of type II diabetes in patients with liver disease is, for the most part, the same as that without liver disease. While there are theoretical concems about altered drug metabolism and hepatotoxicity, only patients with evidence of liver failure such as ascites, coagulopathy. Or encephalopathy have altered drug metabolism. Furthermore, there is no evidence that patients with liver disease are predisposed to hepatoxicity. Metformin may be particularly useful in obese patients in whom it may cause mild weight loss. It is relatively contraindicated in patients with advanced live disease or in binge drinkers because it may predispose to lactic acidosis. Glucosidase inhibitors- They may be particularly useful in patients with liver disease because they act directly on the gastrointestinal tract to decrease carbohydrate digestion and thus glucose absorption, thereby decreasing postprandial hyperglycemia. A RCT of 100 patients with compensated liver cirrhosis and type II diabetes treated with insulin to evaluate the use of acarbose for post parandial hyperglycemia was carried out. Glycemic control improved significantly in both the fasting and postprandial state. Acarbose frequently cause mild transient elevations of ALT elevations or rare occasions, severe liver disease. While the labeling of acarbose has a warning for patients with liver disease, it appears to be safe and effective in patients with hepatic encephalopathy and type 2 diabetes. Miglitol, another glucosidase inhibitor, has not been associated with hepatotoxicity. TZDS may be especially useful because they enhance insulin sensitivity, the underlying defect in NAFLD. There has been concern about their potential hepatotoxicity because of the experience with troglitazone (since withdrawn from the U.S. market.) It is currently recommended that serum ALT levels be evaluated before the initiation of rosiglitzone and pioglitazone therapy and that therapy not are initiation if there is evidence of active liver disease or if the serum ALT level exceeds 2.5 times ULN. Monitoring is recommended periodically thereafter as clinically indicated rather than every 2 months as previously recommended. Paradoxically, TZDs are emerging as the treatment of choice for NASH (Bojesting, 1996; Salmela, 1984). Insulin requirements may vary. For instance, in patients with decompensated liver disease, the requirement may be decreased due to reduced capacity for gluconeogenesis and reduced hepatic breakdown. However, patients with impaired hepatic function may have an increased need for insulin due to insulin resistance. Thus, careful glucose monitoring and frequent dose adjustments of insulin may be necessary. The chronic complications of DM affect may organ systems and are responsible for the majority of morbidity and mortality associated with the disease (Gakdo, 2014). Chronic complications of DM are micro vascular- Retinopathy, Neuropathy, and Nephropathy; Marco Vascular- Coronary

Table no.: 1 Case distribution

Duration of type 2 DM	No. of Subject	Percentage
<5 yr	157	52.3%
5-10yr	110	36.6%
>10yr	33	11%
Total	300	100

Table No.: 2 Age Distribution

Duration of type 2 DM	Total no. of subjects	Age Group			
		35-49 years	50-59 years	60-69 years	70+ years
<5yr	157	45	54	50	8
5-10 yr	110	42	38	20	10
>10 yr	33	4	8	16	5
Total	300	91	100	86	23

Table No.: 3 Sex distributions

Duration of type 2 DM	Total no. of Subjects	Male	%	Female	%
<5yr	157	125	79.8	32	20.4
5-10 yr	110	77	70	33	30
>10 yr	33	23	70	10	30
Total	300	225	75	75	25

Table No.: 4 Bilirubin Distributions

Duration of type 2 DM	no. of subjects	Increased Bilirubin			
		1-2mg%	>2 mg%	Total	%
<5yr	157	5	4	9	5.70
5-10 yr	110	8	7	15	13.60
>10 yr	33	4	2	6	18.10
Total	300	17(5.6%)	13(4.3%)	30	10.0

Table No.: 5 Liver Enzyme Distributions

Duration of type 2 DM	Increased liver enzyme	AST/ALT		AST/ALT>2ULN	
		No.	%	No.	%
<5yr	157	25	15.90	6	3.89
5-10 yr	110	29	26.36	10	9.1
>10 yr	33	9	27.27	5	15.2
Total	300	63	21.00	21	7

Table No.: 6 Hepatitis B and C Virus Distributions

Duration of type 2 DM	Total no. of subjects	HBsAg Positive		HCV Positive	
		No.	%	No.	%
<5yr	157	04	0.63	01	0.63
5-10 yr	110	03	0.90	01	0.91
>10 yr	33	02	6.06	02	6.07
Total	300	09	3.0	04	1.33

Table No.: 7

Duration of type 2 DM	Total no. of subjects	Abnormal USG	
		No.	%
<5yr	157	24	15.93
5-10 yr	110	28	25.5
>10 yr	33	8	24.3
Total	300	60	20.0

Table No.: 9

	Total no. of subjects	Micro albuminuria	Macro-albuminuria	Total
<5yr	157	40 (25.4%)	1(10.6%)	41(26.11%)
5-10 yr	110	37 (33.6%)	5(4.5%)	42(38.18%)
>10 yr	33	6(18.11%)	16(48.4%)	23(69.6%)
Total	300	83(27.66%)	22(7.3%)	105(35.0%)

artery disease, Peripheral vascular disease, and Cerebro vascular disease (Fernando, 1998; Krahules, 2002). In addition to the above complications, there is strong association between diabetes and obesity, hypertension and dyslipidemia.

Renal abnormalities in Diabetes were first recorded in 19th century. Today DN contributes significantly to morbidity and premature mortality in DM. the prevalence o fn ephropathy is about 20-40% in patients with DM. smoking accelerates the decline in renal function.

Additional susceptibility factors remain unidentified. This prevalence of Diabetic nephropathy is increasing such that an epidemic of ESRD has developed over the past 20 years, particularly in patients with type II DM, without any signs of leveling off. With type II DM becoming more common among young adults and in pediatric population, one may infer that the burden of ESRD will increase even further unless more effective clinical measures are formed. Patients with type I DM, approx 20-30% will develop ESRD, whereas about 10-20% of those with type II DM will do so. It is known that DN can be detected before the onset of decrease in GFR, in most patients by detecting abnormal amounts of albumin in the urine[14]. Two stages have been designated micro albuminuria- urine albumin between (30 and 300 mg/24hr, (20-200 gm/min in a timed sample or spot urine albumin to creatinine (ACR) ratio 30-300 mg/gm); macro albuminuria- also termed clinical albuminuria and overt nephropathy. Urine albumin- (>300mg/24hr, >200ugm/min in a timed sample or spot urine albumin to creatinine (ACR) ratio >300 mg/gm) (Mogensen, 1995). This study aims at studying nephropathy in newly diagnosed diabetics, both type I and type II and to estimate prevalence of abnormal LFT in diabetes and prevalence of nephropathy in diabetes categorized as: at <5yrs; 5-10 yrs; >10 yrs as well.

MATERIALS AND METHODS

The present study was conducted on subjects attending the diabetes clinic in the department of Medicine, as well as the General Medicine OPD and on the patients admitted in the wards of Department of Medicine, MLB Medical College, Jhansi in 300 subjects from March 2012 to Aug 2015. The sample size calculated with Standard deviation and mean difference between Diabetes mellitus and liver and kidney disease the mean value based on previously published articles[16]. The Subject were type II DM distributed according to duration of illness <5yrs, 5-10 years and >10 years. The age group started from 35 yrs to >70yrs with maximum in group 50-60 yrs. Out of 300 type II DM subject 75% were male and female group was 25%. The inclusion criteria for the study were any patient who has been diagnosed diabetes mellitus, and the exclusion criteria were diagnosed diabetes with a preexisting renal disease, due to some other pathology, patients developing nephropathy due to some other pathology and any confounding factor or comorbidity like hepatotoxic drug, alcoholism etc need to be exclude.

A detailed history with regard to age, sex and symptoms of the patient was taken. A physical examination to assess the general condition of the patient was carried out. The history was recorded in detail for each patient including history of amount of urine output, pedal edema, swelling of body, breathlessness etc. Each patient was inquired about the duration of symptoms, personal history, past history, family history, dietary history, drug history. General examination was done to know the general condition, pulse rate, respiratory rate, blood pressure, temperature, pallor, icterus, cyanosis, clubbing, edema, hydration, lymphadenopathy, JVP etc. Ankle brachial pressure index was calculated. Systemic examination included central nervous system, respiratory system, abdominal and genitourinary system. Fundus examination was done to do evaluation of diabetic changes in eyes. Related investigations like Complete blood count, S. bilirubin, Urine Routine/Microscopy, Blood Sugar, Fundus, Lipid profile, S. Creatinine, Specific Investigation, HCV reactivity, HBsAg reactivity, Serum Bilirubin, SGOT, SGPT, Serum albumin, PT/PC/APPTT/INR, Creatinine Clearance, Microalbuminuria, macroalbuminuria, Serum Na^+/K^+, USG abdomen and Kidney Urinary Bladder, Blood urea- 24 hr urinary protein, Renal biopsy was done.

RESULTS

The study analyzed in sample of 300 with type II DM from August 2015. Based on duration of DM subject were distributed according to <5yrs, 5-10yrs and >10yrs of illness. Out of 300 type II DM subject 75% were male and female group was 25%. Hyperbilirubinemia was present in 10% of 300 subject overall group wise 5.7% in <5yrs duration, 13.6% in 5-10 yrs duration and 18.1% in >10 yrs. Duration of DM. Out of the 30 patients type II DM 9 were HBsAg Positive, and 24 were HCV positive, rest were asymptomatic. Elevated liver enzymes (AST/ALT) was found in 21% overall the rise in symptomatic individual (non HBV,HCV reactive, non cirrhotic subjects was mild not beyond 3 times of ULN)>. 24 out of 300 subject i.e. overall 8% were detected to be HCV reactive. Of 24 HCV reactive type II DM subject 3 had cirrhosis of liver and asymptomatic at the time of diagnosis with deranged LFT. 16 subject had mild rise in transaminase only 5 subject were healthy carrier with normal LFT.

3% i.e. out of 300 were detected to be HBsAg reactive, 3 out of 9 were cirrhotic with deranged LFT at the time of diagnosis. Both HBsAg and HCV positivity showed positive relation to the duration of illness or observed the random pattern of distribution in different group categorized according to the duration of illness (<5yrs, 5-10yrs and >10yrs). USG abdomen revealed positive finding i.e. fatty liver hepatomegaly, cirrhosis/Cholecystitis. In overall 20% i.e. 60 subject out of 300 subjects. The most common finding were fatty liver diagnosed 39 out of 60 individual i.e. 66% Of remaining 3 were HCV reactive cirrhosis. 3 were HBsAg reactive cirrhosis, Remaining 15 were having CC/CL The prevalence of diabetic nephropathy was 35% overall. Prevalence of Microalbuminuria– 27-66% Prevalence of Macroalbuminuria- 7.3%. Among <5yrs group- Prevalence of microalbuminuria– 25.4%; Prevalence of macroalbuminuria– 0.6%; Total proteinuria- 26%. Among 5-10yrs group- Prevalence of microalbuminuria– 33.6%; Prevalence of macroalbuminuria– 4.5%; Total proteinuria- 38.18%; Among >10yrs group- Prevalence of microalbuminuria– 18.11%; Prevalence of macroalbuminuria– 48.4%; Total proteinuria- 69.61%. Prevalence of albuminuria increased with increased duration of DM. The results were accordance with the studies[15,17].

Conclusion

In our study mild elevation of liver enzyme was detected overall in 21% (<3 time ULN). Raised ALT was the most common pattern this was in concordance with the finding with 22.7% estimated. A direct correlation was observed between increased ALT duration of illness, BMI>25, fatty liver and dyslipidemia[9]. In our study 0.66% i.e. 2 patient were detected HCV reactive, 1 out of 2 had progressed cirrhosis by time diagnosis was reached. This is not in concordance with other studies.

A study of 100 subject showed HCV prevalence to be 19%, in 1996 showed HCV prevalence rate in T2DM 4.39 time higher (Simo, 1996). In another study the rate was highest in group having duration of illness 5-10 yrs. The HBsAg prevalence rate overall was 3% in our study or opposed to 5-20% in normal population this is concordance with the studies. We had overall 20% rate with USG finding (i.e. hepatomegaly/fatty liver, cholecysterol/cholelithiasis, cirrhosis). Fatty liver was the most common finding (Prashant, 2009). In our study duration of diabetes was directly correlated with albuminuria. Prevalence of albuminuria was 69.6% in group>10 yrs of DM, 38.18% in group 5-10 yrs of DM and 38.18% in group <5 yrs of DM. Overall prevalence of proteinuria was 25%. Microalbuminuria was present in 18.1% of group >10yrs duration of DM, 33.6% in group 5-10yrs of DM, 25.4% in group <5yrs of DM. Overall microalbuminuria was present in 27.66% subject. Macroalbuminuria was present in 48.4% of group >10yrs of DM, 4.5% of group 5-10 yrs of DM, 0.6% of<5yrs of DM. Overall macroalbuminuria was present in 7.3% of subject. This was in accordance with study prevalence of stages of diabetic nephropathy (Krolewski, 1996; Ritz, 1996).

Abbreviationns:

ALT- Alanine Aminotransferase; **CPR-** Crude Prevalence; **DM-** Diabetes Mellitus; **DN-** Diabetic Nephropathy; **ESRD-** End Stage Renal Disease; **GFR-** Glomerular Filtrate Rate; **HCV-** Hepatitis C Virus; **IGT-** Impaired Glucose Tolerance; **JVP-** Jugular Venous Pressure; **NAFLD-** Non Alcoholic Fatty Liver Disease; **NASH-** Non Alcoholic Steato Hepatitis; **ULN-** Upper Limit of Normal

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