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RESEARCH ARTICLE

FATTY LIVER AND VASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Among diabetic patients Fatty liver disease is of common occurance. Various studies showed that liver adiposity is independently associated with Insulin Resistance and its presence can significantly increase the risk of various micro and macrovascular complications of diabetes mellitus.

Aims: Evaluating type 2 diabetes patients for micro and macrovascular complications and correlating their association with fatty liver disease in these patients.

Material and methods: 141 diabetic patients admitted in a King George Hospital and Andhra medical College, Visakhapatnam of Andhra Pradesh, Indiax over a two year period were screened for fatty liver by ultrasonography of the abdomen and were classified into FL (fatty Liver) group and NFL (non fatty liver) group, with and without fatty liver, respectively. All patients were investigated for complications like nephropathy, neuropathy, retinopathy, cardiac and peripheral vascular disease. Statistical analysis was done to find the association of these complications with fatty liver.

Results: Out of 141 patients, 49 (35%) had fatty liver. Leading complication was neuropathy (31.2%), followed by nephropathy (11.3 %), retinopathy (10.6 %), cardiac disease (9.2%) and peripheral vascular disease (3.55%). Between FL and NFL groups, Diabetic neuropathy (40.8% vs 23.9%) and cardiac disease (16.3% vs 5.4%) showed statical significance ($p<0.05$), while other complications were more or less equally prevalent in the two groups.

Conclusions: Fatty liver is seen in one third of diabetic patients. Vascular complications like neuropathy and cardiac disease are more commonly seen in diabetic patients with fatty liver than those without fatty liver.

INTRODUCTION

In 1980, when nonalcoholic fatty liver disease (NAFLD) was first identified in obese children, it was thought to be a rare entity. But now, it is increasingly seen in the diabetic population with a prevalence of 20-40%.[1] Rising incidence of obesity among type 2 diabetics is the biggest contributing factor for this. The risk factors for NAFLD are central obesity, type 2 diabetes mellitus, dyslipidemia – major components of metabolic syndrome. In fact, fatty liver is considered to be the hepatic manifestation of the metabolic syndrome. It is more common in men, the majority of cases occurring between the ages of 40 to 60 years.[2,3] The prevalence of NAFLD is increasing in India and other Asian countries due to westernization of the lifestyle, such as a high-fat and high-calorie diet and less physical activity. The association of various complications of diabetes like neuropathy nephropathy, and retinopathy with fatty liver is an emerging concept that is under further validation.[4] Fatty liver, as an independent risk factor for cardiac disease has been well studied.[5] Of late, the extra-hepatic association of NAFLD and chronic kidney disease (CKD), colorectal cancer, obstructive sleep apnea, osteoporosis, hypothyroidism and polycystic ovarian disease is also gaining interest.[6 -11] Even though NAFLD requires liver biopsy for accurate diagnosis, Steatosis is readily made out by ultrasonography of abdomen as high amplitude echoes from the liver. Different studies have used different entities for defining fatty liver like AST, ALT, γGT, liver biopsy etc.[12]. The wide variation in the prevalence of complications and their associations with fatty liver in diabetics vary in different regions of the world. Given the complexity of pathogenesis and varied geographical and ethnic factors, further studies are required from all over the world for better understanding of the concept of systemic complications associated or coexisting with NAFLD in diabetes. Our study aims at identifying the prevalence of various micro and macrovascular complications

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and tracing the association of these complications with fatty liver disease in type 2 diabetic population.

MATERIAL AND METHODS

This study was done in patients admitted with type 2 diabetes in a tertiary hospital over a two year period. Patients aged >18 years were selected with characteristic symptoms of diabetes like polyuria, polydipsia, polyphagia. Age, gender, body mass index was noted. Diabetic patients with obvious liver disease due to other causes (Hepatitis B,C), patients with a history of exposure to hepatotoxic agents like alcohol, Statins, Thiazolidinediones, Anti tubercular therapy etc. were excluded from the study. All patients underwent Ultrasonography of the abdomen. Specific evaluations included fundus examination for retinopathy, cardiac examination with 12 lead ECG and 2D ECHO, monofillament testing for neuropathy, urine analysis and s.creatinine for nephropathy and vascular doppler of lower limbs for symptomatic patients of peripheral vascular disease or patients with abnormal peripheral pulses. Patients were classified based on their abdominal ultrasonography report into fatty liver group (FL+) and Non fatty liver (FL-) group. The prevalence of various complications were noted and compared between the two groups and were statistically analyzed. All the statistical work was performed by using SPSS trail version 16 and excel 2007.

Descriptive statistics were presented in the form of percentages. Various diabetic micro or macrovascular complications have been studied in the two groups to find any significant differences in their prevalence by using Fisher's Exact-test. A p value < 0.05 is taken as statically significant.

RESULTS

Out of 141 diabetic patients, 92 (65%) were males and 49 (35%) were females. Most common age group affected was between 51-60 yrs**.** Abdominal sonography was normal in 92 (65%), showed fatty liver in 49 (35%) as shown in figure-1. The most common overall complication observed was diabetic neuropathy in 44 followed by nephropathy in 16. Various complications identified are presented in Table.1.

Table 1 Comparision of FBS in study & Control groups.

Group	No. Of Cases	Mean ±SD in mg/dl	P <0.05*
Dm +GBS Vs DM-GBS	20 30	179.65±71.55 129.73 ± 58.90	<0.55*
DM+GBS Vs Controls	20 25	179.65 ± 71.55 96.27 ± 14.62	<0.001**
DM-GBS Vs Controls	30 25	129.73 ± 58.90 96.27 ± 14.82	<0.01*

*Significant **Highly significant DM=Diabetes Mellitus, GBS=Gallbladder Stone/Sludge

Incidence of gallbladder disease was higher in The mean total serum cholesterol level in the study group was 166.6±30.82 mg/dl while in the control group it was 148.96±20.75 mg/dl. On further analysing the levels in diabetics with gallbladder disease it was found that mean total serum cholesterol level was 177.15±32.69 mg/dl. In diabetics without gallbladder disease the mean level was 159.56±27.88 mg/dl. It was concluded that total serum cholesterol levels positively correlated with the presence of gallbladder disease in diabetics. (Table 2)

Table 2 Comparision of Serum Cholesterol levels in Test and Conteol groups.

Group	No. Of Cases	Mean±SD	P
Dm + GBS Vs DM-GBS	20 30	177.15±32.69 159.56±27.88	<0.05*
DM + GBS Vs Controls	20 25	177.15±32.69 148.96±20.75	<0.01**
Dm – GBS Vs Controls	30 25	159.56±27.88 148.96±20.75	>0.05*

*Significant **Highly Significant DM-Diabetes Mellitus GBS-Gallbladder Stone/Sludge.

There were 20 cases (40%) of gallbladder disease in the study group and only 1 case (4%) had gallbladder disease in the control group. It was concluded that the incidence of gallbladder disease was significantly more in diabetics. The mean duration of diabetes in diabetics with gallbladder disease was found to be 7.77±5.0 years and 3.56±3.08 years in diabetics without gallbladder disease. Gallbladder disease positively correlated with the longer duration of diabetes. The fasting gallbladder volume was 28.27±12.7 cm3 in diabetics with gallbladder disease, 27.79±7.63 cm3 in diabetics without gallbladder disease and 32.85±14.27 cm3 in controls. The postprandial volume was 18.75±8.51cm3 in diabetics with gallbladder disease, 12.14±4 88 cm3 in diabetics without gallbladder disease and 13.69±5.95 cm3 in controls. The mean percentage contraction was calculated from the above values and was found to be 31.25±15.34% in diabetics with gallbladder disease, 56.84±9.02% in diabetics without gallbladder disease and 55.96±14.58% in controls. (Table 3)

Table 3 Comparision of Mean percentage of Volume Contraction in test & controls.

Group	No of Cases	Mean ± SD	p
DM+GBS VS	20 30	31.52±15.34 56.84±9.02	<0.001**
DM+GBS Vs Controls	20 25	31.52±15.34 55.96±14.58	<0.001**
DM-GBS	30 25	56.84±9.02 55.96±14.58	<0.05*

*Significant **Highly significant DM-Diabetes Mellitus GBS-Gallbladder with Stone/Sludge.

It was concluded that there was reduced contractility post-fatty meal in diabetics with gallbladder disease as compared to the other two groups. diabetics with poor sugar control. Most patients with neuropathy had a loss or reduction of touch sensation when tested with monofillament (33/44). Others had sensory as well as motor neuropathy (22/44), autonomic neuropathy (11/44) and loss of vibration and joint position sense (8/44). Diabetic nephropathy was seen in 16 (11.3%) patients who had proteinuria (13/16) and elevated S.Creatinine (4/16). Fundus examination revealed evidence of retinopathy in 15 (10.6%) in the form of microaneurysms or exudates or cotton wool spots. Cardiac evaluation showed abnormalities in 13 (9.2%) patients. The prevalence of diabetic neuropathy and cardiovascular disease is significantly higher in patients with fatty liver (p<0.05) whereas other complications have shown equal prevalence in both groups. Gallbladder wall thickness was measured and found to be 2.76± 1.19 mm in diabetics with

gallbladder disease, 2.04±0.35 mm in diabetics without gallbladder disease and 2.06±0.47 mm in controls. It was concluded that gallbladder thickness positively correlated with the presence of gallbladder disease.

Autonomic neuropathy was assessed in the study and the control group and it was found that 13 diabetics (26%) had autonomic neuropathy while all the controls were negative for autonomic neuropathy. It was concluded that the incidence of autonomic neuropathy was 26% and was strongly correlated with the presence of diabetes. Of the 13 cases of autonomic neuropathy it was found that 5 had early parasympathetic dysfunction and 3 had definite parasympathetic dysfunction and 5 had combined sympathetic and parasympathetic dysfunction.

The fasting, postprandial gallbladder volume and percentage contraction were further analysed with respect to the presence or absence of autonomic neuropathy. Fasting gallbladder volume was 28.56+ 12.45 cm3 In diabetics with ANP with gallstones, 36.46±5.98 cm3 in diabetics with ANP with dysmotility, 24.34±14.65 cm3 in diabetics without ANP with gallstone 27.79±7 .63 cm3 in normal diabetics and 32.85±14.2 cm3 in controls. Although there was no statistical difference but it was found that ANP was positively correlated with higher fasting volumes. Mean postprandial gallbladder volume was 20.56±8.87 cm3 in diabetics with ANP with gallstones, 26.16±1.24 cm3 in diabetics with ANP with dysmotility 13.0±6.26 cm3 in diabetics with gallstones without ANP, 12.14±4.88 cm3 in normal diabetics and 13.60±5.95 cm3 in controls.

The percentage contraction post fatty meal was calculated from these values and found to be 24.73±14.64% in diabetics with ANP with GBS, 26.38±17 .04% in diabetics with ANP with dysmotility, 43.48±8.45% in diabetics with gallstones without AN, 56.84±9.02% in normal diabetics and 57.64±9.92% in controls. (Table: 4) It was concluded that diabetics with ANP had significantly impaired gallbladder emptying.

Table 4 Comparision of Pre-prandial(fasting) and post-prandial gall bladder volume in study and control groups in relation to gallstone disease & Autonomic Neuropathy

Group	No of Cases	Pre-prandial Mean±SD in Cm^3	Post-prandial Mean±SD in Cm^3	Mean Percentage Contraction post Fatty meal
DM+ANP+GBS	10	28.56±12.45	20.56 ± 8.87	24.73 ± 14.64%
DM+ANP+Dys	3	36.46 ± 5.98	26.16 ± 1.24	26.38 ± 17.04%
DM-ANP+GBS	7	24.34 ±14.65	13.30 ± 6.26	43.48 ± 8.45%
DM-ANP-GBS	30	27.79 ± 7.63	12.14 ± 14.88	56.84 ± 9.02%
Controls	25	32.85 ± 14.27	13.60 ± 5.95	57.64 ± 9.92%

DISCUSSION

Type 2 diabetes imparts multitude of complications to the patients which are determined partially by the duration, severity and associated comorbid issues. There are far many factors that are believed to accelerate the complication rate in these patients, and fatty liver is one amongst those, which holds a special place. The recent surge in the interest in various micro and macrovascular complications seen in diabetic patients with fatty liver should help in unveiling the association. The prevalence of fatty liver in diabetes in our study is 35% with majority of patients being males. This is supported by studies, showing reported prevalence of NAFLD in type 2 diabetes mellitus ranging from Electrocardiographic changes included ST segment depression or T inversions (11/13) and 2D Echo showed regional wall motion abnormalities (5/13). In selected patients, treadmill testing was done which was positive for ischemia in 2/13 patients. Peripheral vascular disease was the least common complication seen in 5 patients (3.5%). All of them had abnormal dorsalis pedis pulsations and reduced flows in the distal vessels. All these diabetic complications were compared between the two groups and the results are tabulated as follows. (Table 2)

30–75%.[13] Diabetic microvascular complications that were studied include neuropathy, nephropathy and retinopathy whereas macrovascular complications include cardiovascular disease and PVD. The most common complication seen in this study in both the groups is diabetic neuropathy. The prevalence of neuropathy is significantly higher in FL group than in NFL group (40.8% vs 23.9%, p <0.05). This is supported by similar studies done in south india.[14] Hyperglycemia can predispose to the formation of advanced glycation end products (AGE) which can alter cellular signalling and enhances the synthesis of NAD(P)H oxidase which generates superoxides and thereby causing oxidative stress. Also, excess glucose is shunted through alternate metabolic pathways such as the aldose reductase, hexose, and lactate pathways, all of which alter the redox balance and deplete cellular antioxidant capacity.[15,16] This can cause axonal injury, longer axons being effected more causing distal neuronal damage. Fatty liver represents an insulin resistant state featuring dyslipedemia.

Nerve sheath is made of myelin and it is proposed that dyslipidemia will have profound effects on myelin structure. Studies in mice homozygous for the autosomal recessive fatty liver dystrophy (fld) mutation demon-strated demyelinating neuropathy.[17] However the cause and effect relation is yet to be established. Cardiac disease has shown statically significant association with fatty liver in our study (FL vs NFL = 16.3% vs 5.4%, p < 0.05). ECG abnormalities include ST-T changes and 2D Echo abnormalities include areas of hypokinesia both indicating ischemic heart disease (IHD).

Cardiovascular disease is the most important cause of mortality in fatty liver patients as documented in many studies. There is evidence that NAFLD is associated with altered cardiac energy metabolism, abnormal left ventricular structure, and impaired diastolic function. Intra and extra pericardial fat accumulation are found to be higher in fatty liver patients.[18-20] In addition, fatty liver and CAD share common risk factors like diabetes, obesity, dyslipidemia hypertension etc. Also, carotid Doppler studies revealed higher intima media thickness in fatty liver patients which confirms the role of atherosclerosis causing similar plaques in coronary vessels and IHD[21]. In our study, the prevalence of nephropathy is slightly higher in the FL group but statically insignificant. Previous studies showed conflicting results with studies done in china on diabetics with fatty liver and framingham Offspring Heart Study documenting no clear association. [22,23] On the contrary, four of the five prospective studies suggested that NAFLD is independently

associated with an increased risk of chronic kidney disease or microalbumin- uria.[24-27] The slightly lower prevalence of retinopathy in FL group in our study (10.2% vs 10.8, p=0.57) indicate that factors related to diabetes (duration, severity etc.) are more important in the development of retinopathy suggesting that fatty liver cannot stand as an independent risk factor for diabetic retinopathy.

This is partly supported by most recent study conducted on korean population showing lower prevalence of nephropathy and retinopathy in patients with NAFLD.[28] Fatty liver as an independent risk factor for PVD is barely studied. Our study showed no association between fatty liver and PVD. However, a study conducted in Italy showed increased prevalence of peripheral vascular disease (12.8% vs. 7%) in people with type2 diabetes and NAFLD.[29] Fatty liver disease represents a pro inflammatory state with high levels of plasma CRP, fibrinogen, v-WF and plasminogen activator inhibitor- 1 (PAI-1) activity.[30] Along with them, decreased plasma levels of adiponectin, which possess anti atherogenic properties may promote vascular disease in NAFLD patients.[31] Considering the variability of results from different corners of the world, it is difficult to achieve a common agreement regarding the scope of fatty liver as an independent risk factor for various micro and macro vascular complications of diabetes.

Large scale randomized multicentric studies from all over the world with wide discussions encompassing endocrinologists, nephrologists, neurologists, gastroentero -logists, physicians and ophthalmologists is the need of the hour for the better appreciation of this issue. The occurrence of NAFLD is very high in diabetic population. There is increased revalence of macrovascular complications like CAD and microvascular complications like neuropathy and nephropathy in diabetic patients with fatty liver. Type 2 Diabetic patients with fatty liver should be screened for these complications for early diagnosis and timely prevention or treatment.[31,32]

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