

Association of micro and macrovascular complications with fatty liver in patients with type 2 diabetes mellitus

Suresh V¹, Gupta NSRC², Bhargavi EU³

¹Dr Vaddadi Suresh

Associate professor, Medicine
GSL General Hospital
Rajahmundry, India

²Dr NSRC Gupta

Assistant professor, Medicine
GSL General Hospital
Rajahmundry, India

³Dr E Usha Bhargavi

Assistant professor, Pathology
GSL General Hospital
Rajahmundry, India

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Correspondence to:

Dr Vaddadi Suresh

9848149870

sureshvaddadi@yahoo.co.in

ABSTRACT

Background: Fatty liver is a fairly common entity seen in the diabetic population. Studies showed that liver adiposity is independently associated with Insulin Resistance and can substantially increase the risk of various micro and macrovascular complications of diabetes mellitus.

Aims: Identifying various micro and macrovascular complications and finding their association with fatty liver disease in type 2 diabetes patients.

Material and methods: 141 diabetic patients admitted in a tertiary care center 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. All patients were investigated for complications like nephropathy, neuropathy, retinopathy, cardiac and peripheral vascular disease. Statistical analysis was done to find the association of 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 statistical 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.

Keywords: Fatty liver, Diabetes, vascular complications

Introduction

When nonalcoholic fatty liver disease (NAFLD) was first identified in 1980 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 poly cystic 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, γ GT, 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 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, monofilament 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.

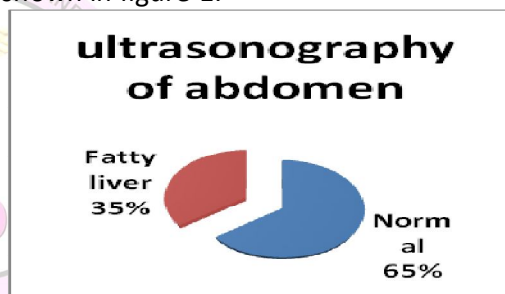


Fig.1 Showing prevalence of fatty liver in type 2 diabetics

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: Showing various overall complications observed in 141 diabetic patients

DIABETIC COMPLICATION	PREVALENCE (n=141)	Overall %
Neuropathy	44	31.2 %
Nephropathy	16	11.3 %
Retinopathy	15	10.6 %
Cardiovascular disease	13	9.2 %
Peripheral Vascular Disease (PVD)	5	3.5 %

Most patients with neuropathy had a loss or reduction of touch sensation when tested with monofilament (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.

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)

Table 2 : Comparison of complications between the two groups

COMPLICATION	FL (n=49)	NON FL (n=92)	P value
1. Neuropathy	20 (40.8%)	22 (23.9%)	0.034*
2. Nephropathy	6 (12.2%)	10 (10.8%)	0.43
3. Retinopathy	5 (10.2%)	10 (10.8%)	0.574
4. Cardiac disease	8 (16.3%)	5 (5.4%)	0.037*
5. PVD	2 (2.04%)	3 (3.2%)	0.348

* statistical significant PVD- peripheral vascular disease

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.

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

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 dyslipidemia. 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 demonstrated 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 microalbuminuria.^[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, gastroenterologists, 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 prevalence 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.

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