FATTY LIVER AND VASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS

Srinivas P.S.S and ShobaDevi K
RESEARCH ARTICLE

FATTY LIVER AND VASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS

Srinivas P.S.S¹ and ShobaDevi K²

¹Andhra Medical College, Visakhapatnam
²Biochemistry RangaRaya Medical College, Kakinada, Andhra Pradesh, India

ABSTRACT

Background: Among diabetic patients Fatty liver disease is of common occurrence. 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, India 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 nephropathy (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.

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 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 nephropathy, neuropathy, and retinopathy with fatty liver is an emerging concept that is under further validation.³ Fatty liver, as an independent risk factor for cardiac disease has been well studied.⁴ 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.⁵-¹⁰ 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.¹¹ 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

*Corresponding author: Srinivas P.S.S
Andhra Medical College, Visakhapatnam

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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 nephropathy in 44 followed by nephropathy in 16. Various complications identified are presented in Table.1.

Table 1 Comparison of FBS in study & Control groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. Of Cases</th>
<th>Mean±SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dm±GBS</td>
<td>20</td>
<td>179.65±71.55</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>vs</td>
<td></td>
<td>129.73±58.90</td>
<td></td>
</tr>
<tr>
<td>DM-GBS</td>
<td>30</td>
<td>179.65±71.55</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>vs</td>
<td></td>
<td>129.73±58.90</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>25</td>
<td>96.27±14.62</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Dm-GBS</td>
<td>30</td>
<td>96.27±14.62</td>
<td>&lt;0.01*</td>
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<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

*Significant **Highly significant DM-Diabetes Mellitus GBS-Gallbladder Stone/Stludge

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±8.51 cm3 in diabetics with gallbladder disease, 12.14±8.8 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 Comparison of Mean percentage of Volume Contraction in test & controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>No of Cases</th>
<th>Mean ± SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM+GBS</td>
<td>20</td>
<td>31.52±15.34</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>vs</td>
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<td>vs Controls</td>
<td>25</td>
<td>55.96±14.58</td>
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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 nephropathy 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 without ANP with dysmotility,
12.14±4.88 cm³ in normal diabetic 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
GBS and dysmotility, 43.48±8.45% in diabetics with gallstones
without AN, 56.84±9.02% in normal diabetics and 57.64±9.92%
without AN in controls. (Table: 4) It was concluded that diabetics with ANP
had significantly impaired gallbladder emptying.

<table>
<thead>
<tr>
<th>Group</th>
<th>No of Cases</th>
<th>Pre-prandial Mean±SD in Cm³</th>
<th>Post-prandial Mean±SD in Cm³</th>
<th>Mean Percentage Contraction post Fatty meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM+ANP+GBS</td>
<td>10</td>
<td>28.56±12.45</td>
<td>20.56±8.87</td>
<td>24.73 ± 14.64%</td>
</tr>
<tr>
<td>DM+ANP+Dys</td>
<td>3</td>
<td>36.46±5.98</td>
<td>26.16±1.24</td>
<td>26.38 ± 14.64%</td>
</tr>
<tr>
<td>DM+ANP+GBS</td>
<td>7</td>
<td>24.34±14.65</td>
<td>13.30±6.26</td>
<td>43.48 ± 8.45%</td>
</tr>
<tr>
<td>DM-ANP-GBS</td>
<td>30</td>
<td>27.79±7.63</td>
<td>12.14±14.88</td>
<td>56.84 ± 9.02%</td>
</tr>
<tr>
<td>Controls</td>
<td>25</td>
<td>32.85±14.27</td>
<td>13.60±5.95</td>
<td>57.64 ± 9.92%</td>
</tr>
</tbody>
</table>

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 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 antioxidiant capacity. [13,19]
This can cause axonal injury, longer axons being effected more
distinguishing 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 demon-strated demyelinating
neuropathy. [13] 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
demonstrating 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 EXTRAPERICARDIAL FAT ACCUMULATION ARE FOUNDED TO BE HIGHER IN FATTY LIVER PATIENTS. 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.[20] INOUR STUDY, THE PREVALENCE OF NEPHROPATHY IS SLIGHTLY HIGHER IN THE FL GROUP BUT STATISTICALLY SIGNIFICANT. PREVIOUS STUDIES SHOWED CONFlicting results with studies done in china on diabetics with fatty liver and framingham Offspring Heart Study documenting no clear association.[21,22] 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. 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. 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 type 2 diabetes and NAFLD. Fatty liver disease represents a pro inflammatory state with high levels of plasma CRP, fibrinogen, vWF and plasminogen activator inhibitor-1 (PAI-1) activity. Along with them, decreased plasma levels of adiponectin, which possess anti atherogenic properties may promote vascular disease in NAFLD patients. 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.

**Acknowledgements**

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**References**

17. Langner CA, EH Birkenmeier, KA Roth, Bronson RT, Gordon JL. Characterization of the peripheral neuropathy in neonatal and adult mice that are homozygous for the fatty liver dystrophy (fld) mutation. J Biol Chem 1991; 266(18):11955-64.


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