

A Study of Non-Alcoholic Fatty Liver Disease (NAFLD) in Type 2 Diabetes Mellitus in a Tertiary Care Centre, Southern India

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ABSTRACT

Background: Type 2 diabetes mellitus is a common disease. The spectrum of liver diseases which ranges from innocuous enzyme elevation to progressive chronic liver disease has been described in association with type 2 diabetes mellitus. Mild chronic elevations of transaminases often reflect the underlying insulin resistance. NAFLD is a liver condition that is being recognized with an increasing frequency and it may progress to end stage liver disease.

Aims: To study the Non-Alcoholic Fatty Liver Disease in type 2 diabetic patients and the correlation between glycaemic control (FBS) and the duration of diabetes with respect to the ALT levels.

Study Design: A randomized case control study

Materials and Methods: Fifty type 2 diabetics and fifty non diabetics who were taken as age, sex and body mass index (BMI) matched controls were studied. Subjects with a history of icterus, alcohol consumption and HBsAg positivity were excluded from the study. NAFLD was diagnosed if "fatty liver" was found on ultrasonography (USG). Fasting blood sugar (FBS), post prandial blood sugar (PPBS)

and liver function test (LFT) were done. The results were compared by using suitable statistical methods. (Student's unpaired "t"-test and Pearson's correlation co-efficient).

Results: NAFLD was noted in 60% of the cases and in 20% of the controls. A body mass index of $> 25\text{kg/m}^2$ was significantly associated with NAFLD in both the cases and the controls. The duration of diabetes was significantly associated with NAFLD ($p = 0.0054$). A significant relationship was found between the presence of NAFLD and the female sex in the cases ($p=0.0392$), but not in the controls ($p = 0.2790$). The levels of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were significantly high in the cases as compared to those in the controls. There was a positive co-relation between FBS, PPBS and the duration of diabetes with respect to the ALT levels.

Conclusion: Non-alcoholic fatty liver disease (NAFLD), as determined by ultrasound, is common in type 2 diabetics. There is a positive correlation between FBS (Fasting blood sugar), PPBS (post prandial blood sugar), and the duration of diabetes with respect to the ALT levels.

Key Words: Diabetes mellitus, Non-alcoholic fatty liver disease (NAFLD), Liver function tests (LFT), ALT, ALP, Ultrasonography, FBS, PPBS

INTRODUCTION

The spectrum of liver diseases which ranges from innocuous enzyme elevation to progressive chronic liver disease has been described in association with type 2 diabetes mellitus. The chronic elevation of the transaminases often reflects the underlying insulin resistance. NAFLD is a liver condition that is being recognized with an increasing frequency and it may progress to end stage liver disease [1]. The presence of type 2 diabetes mellitus significantly increases the risk and the severity of NAFLD [1].

The prevalence of NAFLD in type 2 diabetes mellitus has not been well studied and there has been an epidemic rise in type 2 DM. Its association with chronic liver disease in the form of NAFLD makes it an important health problem.

The present study was undertaken to study the incidence of NAFLD in type 2 DM.

MATERIALS AND METHODS

Fifty patients with type 2 diabetes mellitus of one year's duration who attended the Medical Outpatients Department at Karnataka Institute Medical Sciences Hospital, Hubli, south India from 1st November 2005 to 31st October 2006 were taken up for the study,

after considering the inclusion and exclusion criteria. The reasons for the exclusion were prior icterus, a h/o alcohol consumption, an HBs Ag positive status and a h/o the use of drugs which caused LFT abnormalities (glitazone, acarbose, tamoxifen, amiodorone, diltiazem, steroids and statins).

Age, sex and body mass index (BMI) matched patients who did not have type 2 diabetes mellitus were included as the controls. This study was approved by the institutional ethics committee (IEC) and an informed consent was obtained from the study participants.

A complete clinical examination was done, with special reference to the presence of the right upper quadrant (RUQ) abdominal discomfort and hepatomegaly.

All the patients were investigated for blood counts, FBS (fasting blood sugar) PPBS (post prandial blood sugar), fasting lipid profile and ultrasonography of the abdomen.

NAFLD (non-alcoholic fatty liver disease) was diagnosed if the person showed "fatty liver" on ultrasonography as a diffuse increase in the echogenicity. The upper limit of the normal liver size was taken as 16cm in the longitudinal plane. Any measurement above this was considered as hepatomegaly. LFT (liver function test)-

The liver enzymes were measured as per the IFCC's (International Federation for Clinical Chemistry's) kinetic method and total bilirubin was measured by using the Diphylline diazonium salt method.

STATISTICAL ANALYSIS

The statistical analysis was done by using the Student's unpaired [Table/Fig-1] 't'-test and the Pearson's correlation co-efficient.

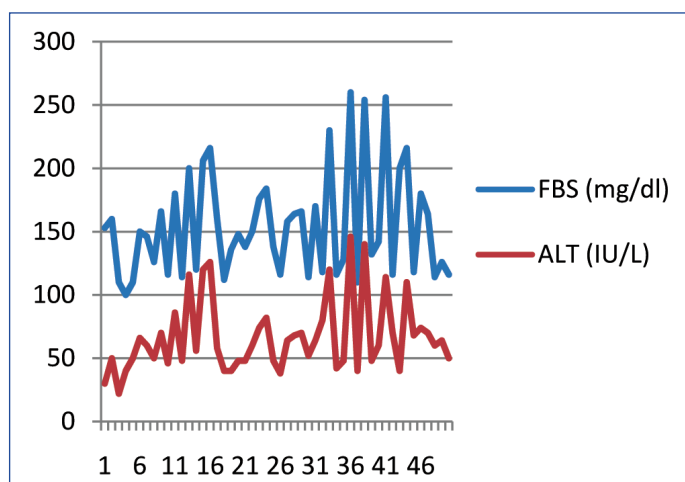
RESULTS

Fifty cases and controls were compared. The mean age of the subjects was 46.7 years in both the groups. Of the 50 cases of type 2 DM, 30(60%) had NAFLD and of the 50 non-diabetics 10(20%) had NAFLD, which was statistically significant.

Parameter	Cases	Controls
Mean Age	46.74 Yrs	46.72 Yrs
Sex distribution		
Male	30 (60%)	30 (60%)
Female	20 (40%)	20 (40%)
Mean BMI (Kg/m ²)	24.46	24.54
Prevalence of NAFLD	30 (60%)	10 (20%)
Liver size in cm.	16.94	14.74
Prevalence of ALT elevation (>44IU/L)	41 (82%)	4 (8%)

[Table/Fig-1]: Shows the different parameters between cases and controls

Among the cases, 18(60%) and among the controls, 9(90 %) had a BMI of > 25 kg/m². Fatty liver was present in 5, 9 and 16 cases where the duration of diabetes was 5 yrs, 6-10 yrs, and > 10 yrs respectively. Of the 30 cases of NAFLD in type 2 DM, 14(46.7%) were males and 16 (53.3%) were females. The p value was 0.0392, which was statistically significant. Of the 30 cases of NAFLD in type 2 DM, 9 (30%) had RUQ discomfort. None of the patients without fatty liver disease had RUQ discomfort. The Chi-square value for this was 5.426 and the p value was 0.0198, which was statistically significant. The average liver size in the cases and controls was 16.94 cm and 14.74 cm respectively. The level of ALT in the cases and controls was 66.68 IU/L and 32.58 IU/L respectively, which was statistically significant. The prevalence of an elevated ALT level of >44IU/L in the cases was 41 (82%) and in the controls, it was 4 (8%). Of the 50 cases of type 2 DM, 22 had a BMI of >25 kg/m² (over



	Cases Mean ± SD	Controls Mean ± SD
FBS	153.98 ± 41.82mg/dl	77.48 ± 11
ALT	66.68 ± 28.90IU/L	32.58 ± 7

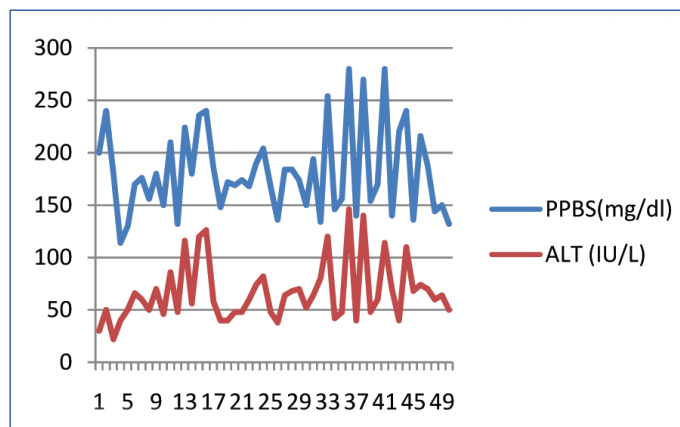
[Table/Fig-2]: Shows Analysis of co-relation between glycaemic control (FBS) and ALT levels in types 2 diabetes

weight). All these patients had an ALT level of >44IU/L for which the Chi-square value was 6.583 and the p value was 0.01103, which was statistically significant. The Pearson's correlation co-efficient was calculated for the FBS level and the ALT levels. The value of the correlation co-efficient (r) was 0.8451 (p<0.001), which showed a positive correlation. The Pearson's co-relation co-efficient was calculated for the duration of type 2 DM and the ALT levels. The value of the correlation co-efficient (r) was 0.3804 (p=0.0064), which showed a positive correlation. The Pearson's co-relation co-efficient was calculated for PPBS and the ALT levels. The value of the correlation co-efficient (r) was 0.3907 (p=0.005), which showed a positive correlation.

The Pearson's correlation co-efficient was calculated for the FBS level and the ALT levels. The value of the correlation co-efficient (r) was 0.8451 (p<0.001), which showed a positive correlation [Table/Fig-2].

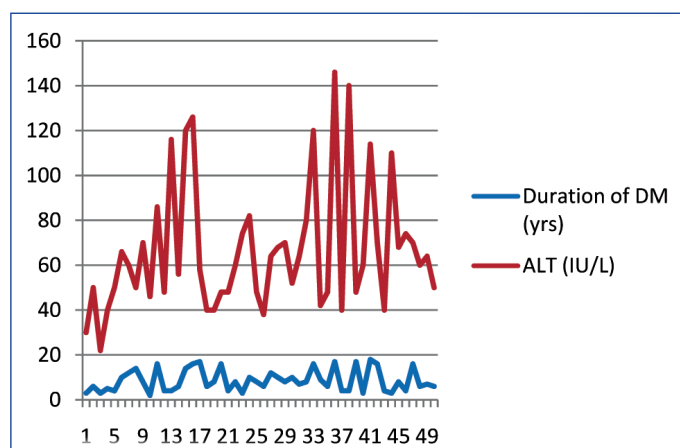
The Pearson's correlation co-efficient was calculated for PPBS and the ALT levels. The value of the correlation co-efficient (r) was 0.3907 (p=0.005), which showed a positive co-relation [Table/Fig-3].

The Pearson's correlation co-efficient was calculated for the duration of type 2 DM and the ALT levels. The value of the correlation



	Cases Mean ± SD	Controls Mean ± SD
PPBS	221.38±29.41mg/dl	138.96 ±19mg/dl
ALT	66.68±28.90IU/l	32.58±7IU/L

[Table/Fig-3]: Shows Analysis of co-relation between PPBS and ALT levels in type 2 diabetes



	Mean ±SD
Duration of type 2 diabetes	8.64 ± 8.64 yrs
ALT	66.68 ± 28.90IU/l

[Table/Fig-4]: Shows analysis of co-relation between duration of type 2 diabetes and ALT levels

co-efficient (r) was 0.3804 ($p=0.0064$), which showed a positive co-relation [Table/Fig-4].

DISCUSSION

In the present study, the mean age of the cases was 46.74 ± 10.35 yrs. In the study of Akbar DH et al [2], the mean age of the study group was 54 ± 12.8 yrs. In the present study, the mean duration of diabetes mellitus was 8.64 years, which is comparable to the duration of 8.65 yrs in the study which was done by Akbar DH et al [2].

The mean BMI of the cases in the present study was $24.46 \pm 1.53 \text{ kg/m}^2$. In the study which was done by Akbar DH et al [2], the mean BMI of the study group was $30 \pm 5.5 \text{ kg/m}^2$.

In the present study, the prevalence of NAFLD among the cases was 60% and among the controls, it was 20%. The prevalence of NAFLD with type 2 DM in the study which was done by Akbar DH et al [2] and Suparna Pal et al [3] was 55% and 70% respectively, which is comparable to that which was found in the present study.

In the present study, NAFLD was significantly associated with the female sex among the type 2 diabetics ($p = 0.0392$) but not in the control group ($p = 0.2790$). Akbar DH et al [2] found a significant relationship between the presence of NAFLD and the female sex ($p = 0.05$). Although previous studies had emphasized that non-alcoholic steatohepatitis occurred mostly in women, the more recent studies have shown that non-alcoholic steatohepatitis occurs with an equal frequency in men, [4,5].

In the present study, the average liver size was 17.83cm in the diabetics with NAFLD and it was 15.6cm in the diabetics without non-alcoholic fatty liver disease. In the study of Akbar DH et al [2], the average liver size was 17.2cm in the patients with NAFLD and it was 13 cm in the non-NAFLD patients, which was comparable to that which were seen in our study.

In the present study, elevated ALT ($> 44 \text{ IU/L}$) levels were seen in 82% of the type 2 diabetics and in 8% of the control group. The elevated ALT ($>44 \text{ IU/L}$) levels were significantly related to a BMI of $> 25 \text{ kg/m}^2$ among the type 2 diabetics ($p=0.0103$), but not in the control group ($p = 0.6612$).

A growing body of evidence shows a close relationship between non-alcoholic steatohepatitis and the components of the metabolic syndrome. As insulin resistance is the central factor in non-alcoholic steatohepatitis, there is a possibility that the pathogenesis of NAFLD may have started long before the diagnosis of the type 2 diabetes mellitus [4].

Erbey JR et al [6] found that the prevalence of elevated ALT levels among the U.S. type 2 diabetics was 7.8% and that the prevalence of the elevated ALT levels was 10.6% in the obese diabetics ($\text{BMI} > 25 \text{ kg/m}^2$) as compared to a prevalence of 6.6 in the non-obese diabetics. Salmela et al [7] found that the prevalence of elevated ALT levels

among the type 2 DM patients was 22.9%. He also showed that a BMI of $> 25 \text{ kg/m}^2$ and a poor diabetic control ($\text{FBS} > 216 \text{ mg/dl}$) were significantly associated with elevated ALT levels. Elevated ALT levels were also associated with the onset of diabetes within the past 4 years. In the present study, there was a positive correlation between FBS, PPBS, the duration of type 2 diabetes and the ALT levels among the cases.

The aminotransferase values and the common imaging tests such as liver ultrasound, computed tomography and magnetic resonance imaging are used in predicting the liver histology. Recently, numerous circulating biomarkers like the cytokeratin 18 (CK-18) fragments and serum dehydroepiandrosterone (DHEA) have been investigated to non-invasively predict the hepatic histology in patients with NAFLD. It has been suggested that the CK-18 fragment levels of $> 380.2 \text{ IU/L}$ can predict non-alcoholic steatohepatitis in a very precise fashion. The DHEA levels have a consistent and stepwise inverse relationship with the degree of hepatic fibrosis [8].

CONCLUSION

Non-alcoholic fatty liver disease (NAFLD), as determined by ultrasound, was common in the type 2 diabetic subjects. The prevalence of NAFLD increases with the duration of diabetes mellitus and an increase in the BMI (body mass index). LFT abnormalities were common in diabetes. The ALT and ALP levels were significantly elevated. There was a positive correlation between the glycaemic control (FBS and PPBS) and the duration of diabetes mellitus with respect to the ALT levels.

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