INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that has been a major health problem and a socio-economic burden for the developing world. Currently, 240 million people worldwide have diabetes and this number is projected to increase up to 380 million by 2025, with 80% of cases in low and middle income countries including Pakistan. Pakistan belongs to high diabetes prevalence area, with rates ranging from 7.6 to 11% and currently having 6.9 million affected people, ranking at 7th position in the list of countries with major burden of diabetes mellitus with projected estimates expected to double by 2025, which will affect about 11.5 million people.

Non-alcoholic fatty liver disease (NAFLD) is defined as a wide spectrum of liver diseases with fat accumulation ranging from simple steatosis to nonalcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma in the absence of excessive alcohol intake. Patients with type 2 diabetes have an increased risk for developing NAFLD and later on advanced fibrosis and cirrhosis. Approximately 60 to 70% of persons with type 2 diabetes have some form of NAFLD. About 20% of such patients with NAFLD have nonalcoholic steatohepatitis (NASH), which constitutes approximately 80% of cryptogenic cirrhosis and progressed to advanced fibrosis in 32 - 37% of patients. NAFLD and NASH are linked with standardised mortality rate for death, greater than that for cardiovascular disease (CVD) in diabetics.

Gupte et al. in a study of 100 non-alcoholic individuals with type 2 DM noted that 49 patients had fatty liver on ultrasound abdomen, and 28 out of 32 patients undergoing biopsy (87.5%) showed steatohepatitis with mild, moderate, and severe grades in 65.5%, 12.5%, and 9.35%, respectively. Prashant et al. reported 87% patients had NAFLD on histology with 62.6% steatohepatitis and 37.3% fibrosis. Kaifra et al. identified 522 (56.5%) cases of NAFLD out of a total of 924 type 2 diabetic patients with higher prevalence in females (60%) than in males (54.3%).

Most of the studies done previously in Pakistan used ultrasound for diagnosis; and not the liver biopsy, which is the gold standard and necessary for a definite diagnosis of NASH.
The rationale of this study was to determine the frequency of nonalcoholic steatohepatitis detected on histopathology, as early detection of nonalcoholic steatohepatitis leading to prompt treatment early in the course can prevent debilitating complication of developing cirrhosis as well as reduce morbidity and, in turn, improve the economic burden. Furthermore, this study will be helpful in strengthening the result of the only previous similar study, which included a small number of patients.12

The objective of this study was to determine the frequency of nonalcoholic steatohepatitis (NASH) on histopathology in patients of type 2 diabetes mellitus with duration of more than 5 years.

**METHODOLOGY**

This was a cross-sectional study, conducted in the Department of Medicine, Dow Medical College, Civil Hospital, Karachi, from November 2013 to April 2014 after permission from Ethical and Research Board of the University. Patients diagnosed with type 2 diabetes mellitus of more than 5 years’ duration, having raised alanine transaminases level and fatty liver on ultrasonography, were selected. Informed consent was obtained from all the patients after explanation of the study protocol. Transabdominal liver biopsy was performed in all patients by experienced physicians at Civil Hospital Karachi, under ultrasound guidance with strict sterile protocol, using 18 G Trucut biopsy needle. The patients were monitored until they were hemodynamically stabilised and no evidence of bleeding was noted. All biopsy specimens of adequate size were sent to a single centre for histopathology. Those patients with any form of liver disease like hepatitis B, C and D, autoimmune hepatitis, metabolic liver disease, and steatosis like alcoholic and hypertriglyceridemia and contraindication to liver biopsy like > 3 seconds upper limit of normal, and any bleeding tendency, were not enrolled in the study.

Non-alcoholic fatty liver disease (NAFLD) was defined as a wide spectrum of liver diseases with fat accumulation ranging from simple steatosis to non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma in the absence of excessive alcohol intake.4 Non-alcoholic steatohepatitis (NASH) was defined as the presence of > 5% fat droplets and hepatocyte ballooning along with periportal and lobular inflammation on biopsy of liver tissue.4 Type 2 diabetes mellitus was defined as diabetes with duration of more than 5 years treated by oral hypoglycemic agents or insulin, which was diagnosed after the age of 30 years with presence of either HbA1C of more than 6.5%, fasting blood sugar level of more than 126 mg/dl or random blood sugar of more than 200 mg/dl, while alanine aminotransferase (ALT) > 33 IU/L in males and > 19 IU/L in females was considered abnormal.

Data was collected and analysed on software SPSS version 17. Descriptive statistics included mean ± standard deviation and median of continuous data, like age, duration of diabetes, HbA1c level, fasting blood sugar levels and random blood sugar levels. Frequencies and percentages were calculated from the categorical data in patient with NASH. Multivariate analysis was done on liver enzymes. Effect modifiers were controlled by stratification of age in groups, gender (male and female), type of treatment (on oral hypoglycemic, on insulin, on both oral hypoglycemic and insulin), duration of diabetes in groups (more than 5 years, 5 to 10 years, more than 10 years) to observe outcome, chi-square test was applied to all the aforementioned variables and p-value of ≤ 0.05 was taken as significant

**RESULTS**

A total of 262 patients of type 2 diabetes mellitus were selected. On multivariate analysis, only ALT was shown to be significantly associated with NASH. The mean age of the patients was 50.72 ±8.48 years. The median duration of diabetes was 9 years. Gender distribution of the NASH patients showed that out of 148 cases, 56.1% (83/148) were males and 43.9% (65/148) were females. While 97 (65.6%) of patients had 5 - 10 years history of

| Table 1: Frequency of non alcoholic steatohepatitis on histopathology in patients of type 2 diabetes mellitus for age groups, gender, duration of diabetes and type of therapy. |
|---------------------------------|-----------------|-----------------|-----------------|
| Variables                      | Stratifications | Non-alcoholic steatohepatitis | Chi-square | p-value |
|--------------------------------|-----------------|-----------------------------|-------------|
|                               | n=262 | yes (n=148) | no (n=114) |          |         |
| Age group (years)              |       |             |              |         |         |
| 36 to 40 years                 | 17 (11.5%) | 15 (13.2%) | 0.83 | 0.84 |
| 41 to 50 years                 | 68 (45.9%) | 56 (49.1%) |              |         |         |
| 51 to 60 years                 | 40 (27.1%) | 29 (25.4%) |              |         |         |
| > 60 years                     | 23 (15.5%) | 14 (12.3%) |              |         |         |
| Gender                         |       |             |              |         |         |
| Male                           | 83 (56.1%) | 62 (54.4%) | 0.07 | 0.78 |
| Female                         | 65 (43.9%) | 52 (45.5%) |              |         |         |
| Duration of diabetes           |       |             |              |         |         |
| 5-10 years                     | 97 (65.5%) | 75 (65.8%) | 0.002 | 0.96 |
| >10 Years                      | 51 (34.5%) | 39 (34.2%) |              |         |         |
| Type of therapy for diabetes   |       |             |              |         |         |
| On oral hypoglycemics          | 70 (47.3%) | 45 (39.5%) | 1.62 | 0.44 |
| On Insulin                     | 50 (33.8%) | 45 (39.5%) |              |         |         |
| On Both                        | 28 (18.9%) | 24 (21.1%) |              |         |         |
diabetes and 51 (34.3%) had more than 10 years of diabetes. One hundred fifteen (43.89%) were taking oral hypoglycemic, 95 (36.25%) were taking insulin, and 52 (19.85%) were on both treatments.

The rate of nonalcoholic steatohepatitis in type 2 diabetes complication was not significant among different age groups (p=0.84) as shown in Table I. Similarly, insignificant difference was observed in the frequency of nonalcoholic steatohepatitis in male and female (p=0.78, Table I). Rate of nonalcoholic steatohepatitis was also compared with respect to duration of diabetes and type of treatment, but significant difference was not observed as presented in Table I. No complications were encountered during or post procedure owing to the meticulous care taken in every step of the process.

DISCUSSION

Formerly called non-alcoholic steatohepatitis, non-alcoholic fatty liver disease (NAFLD) now refers to a spectrum of diseases of the liver ranging from steatosis (i.e., fatty infiltration of the liver) to NASH (i.e., steatosis with inflammation and hepatocyte necrosis) to cirrhosis. Non-alcoholic steatohepatitis is the most common cause of elevated liver enzymes and the most common cause of cryptogenic cirrhosis.13,14 NAFLD is known to affect 10 - 39% of the general global population with an average incidence of 20 percent.15 It is the second most common diagnosis after chronic viral hepatitis, and this prevalence is still probably an underestimate.16 This high prevalence of NAFLD, however, is not exclusive to the white western population. Jimba et al. using liver ultrasonography reported a prevalence of NAFLD of 29% among healthy Japanese adults, indicating that NAFLD has reached epidemic proportions.17 Early recognition of these risk factors and their adequate management can lead to reduction in proportion of patients progressing to cirrhosis.

In present study, out of 262 patients, 56.49% (148/262) showed non-alcoholic steatohepatitis. The prevalence of type 2 diabetes varied between 10 and 75 percent in other international studies.18 Presence of type 2 diabetes mellitus significantly increases the risk and severity of NAFLD regardless of body-mass index.19 In the study by Jimba et al, the prevalence of NAFLD increased from 27% in subjects with normal fasting glucose to 43% in those with impaired fasting glycaemia and to 62% in patients with newly diagnosed diabetes.17 Although initial studies emphasised that NASH occurred mostly in women, but more recent studies have shown that NASH occurs with equal frequency in men20,21, as is also seen in this study.

In different studies of obese subjects undergoing bariatric surgery, the factors independently associated with NASH were male gender, insulin resistance, aspartate aminotransferase (AST), and type 2 DM.22,23 On multivariate analysis, only alanine aminotransferase (ALT) was shown to be associated with NASH in the present group of patients with type 2 DM. The most dreaded outcome of longstanding NASH is hepatic fibrosis and subsequently, cirrhosis. In various studies, the factors independently associated with fibrosis on histology were older age, obesity, diabetes, raised AST and ALT, and ALT : ALT ratio > 1 and presence of Mallory bodies.24 Silverman et al., have reported a prevalence of 21 - 60% of hyperlipidemia in NAFLD. These dyslipidemias were more common in obese patients, diabetics and females. Hypertriglyceridemia rather than hypercholesterolemia was found to increase the risk of non-alcoholic fatty liver disease.19 Non-alcoholic fatty liver disease has a strong association with metabolic syndrome in observational studies and has been described as the “hepatic component of this syndrome”. Over 90% of patients with NAFLD have at least one feature of the metabolic syndrome, with approximately one-third having the complete syndrome defined as any three of central obesity impaired fasting glucose, hypertriglyceridaemia, low high-density lipoprotein cholesterol and hypertension. The likelihood of NAFLD increases as the number and severity of metabolic risk factors increase. The metabolic syndrome in NAFLD patients increases the likelihood of severe disease, conferring an odds ratio (OR) of 3.2 for the presence of NASH and 3.5 for advanced fibrosis.

CONCLUSION

Non-alcoholic steatohepatitis disease is an important chronic liver disease which has a higher frequency in type 2 diabetes.

REFERENCES


