EVALUATION OF RISK FACTORS OF NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IN A TERTIARY CARE HOSPITAL AT RAWALPINDI, PAKISTAN: A LOCAL EXPERIENCE

Uzma Bano, Murtaza Gondal, Shaheen Moin

Department of Medicine, Foundation University
Medical College and Hospital, Rawalpindi, Pakistan

ABSTRACT

Objective: *To document the frequency of risk factors for nonalcoholic fatty liver disease, such as gender, diabetes mellitus, hypercholestrolemia, hypertriglyceridemia, obesity and metabolic syndrome.*

Material and Method: *This descriptive study was carried out at Department of Medicine Fauji Foundation Hospital Rawalpindi from January 2007 to December 2007 One hundred nonalcoholic patients with elevated ALT and negative viral serology and diagnosed as having fatty liver on ultrasound were evaluated for the presence of diabetes, hypercholestrolemia, hypertriglyceridemia, obesity and metabolic syndrome. Patients with suspected autoimmune hepatitis, hemochromatosis and Wilsons disease were excluded.*

Results: *The mean age was 45.39 years. Out of 100 patients, 63% were females and 37% were males. Sixty six percent patients were obese. Other risk factors included hypertriglyceridemia in 48%, diabetes mellitus in 34%, hypercholesterolemia in 28% and metabolic syndrome in 28% cases.*

Conclusion: *Nonalcoholic fatty liver disease is associated with a high prevalence of obesity, hypertriglyceridemia, hypercholestrolemia, diabetes and female gender.*

Key words: *Nonalcoholic Fatty Liver Disease, Steatohepatitis, Obesity, Hypertriglyceridemia, Metabolic Syndrome.*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a clinico-histopathological entity with histological features that resemble alcohol-induced liver injury, but by definition, occurs in patients with little or no history of alcohol consumption. It encompasses a histological spectrum that ranges from fat accumulation in hepatocytes without concomitant inflammation or fibrosis (simple hepatic steatosis) to hepatic steatosis with a necroinflammatory component (steatohepatitis) that may or may not have associated fibrosis. The latter condition, referred to as nonalcoholic steatohepatitis (NASH), may progress to chronic hepatitis, cirrhosis, and hepatocellular carcinoma.[1,2] NASH is now recognized to be a leading cause of cryptogenic cirrhosis.[3] NAFLD affects 10-25% of the general population in various countries and 3-6% of the US population has some degree of NAFLD with the diagnosis based on raised aminotransferases in the absence of any alternative etiologies.[4,5] The prevalence increases to 50-75% in obese individuals. The traditional risk factors for NAFL are generally considered to be female sex, type 2 diabetes mellitus, obesity, and hyperlipidemia.

The diagnosis of NAFLD rests on clinicohistological criteria including absent low alcohol consumption and a compatible liver biopsy showing steatosis, hepatocyte ballooning, apoptosis, Mallory bodies, mixed inflammation associated or not with fibrosis and cirrhosis. Radiological imaging may also help to identify patients with NAFLD. All three imaging modalities including ultrasound, CT scan and MRI are sensitive (93-100%) for detecting a significantly fatty liver. NAFLD is among the most common etiologies of altered liver function tests and otherwise unexplained alanine aminotransferase (ALT) elevation has been adopted as a surrogate marker of NAFLD in epidemiological studies.[6] To determine the frequency of different risk factors in

NAFLD population we carried out a study at Fauji Foundation Hospital Rawalpindi and documented the proportion of NAFLD population that was female had diabetes, hypertriglyceridemia, hypercholestrolemia, obesity and metabolic syndrome. Objective of this study was to determine the frequency of various risk factors in patients of NAFLD.

MATERIAL AND METHODS

Study was carried out at Fauji Foundation Hospital Rawalpindi in Department of Medicine and Nephrology recruiting patients from most of Punjab and Northern areas of Pakistan which are Ex-army personnel and their dependents (beneficiaries patients mostly females as retired army personnel themselves are entitled in Military Hospital). It was a descriptive study on 100 patients with non-probability convenience sampling. The demographic details, clinical presentation, investigations, and risk factors of NAFLD were recorded on a Performa attached as annex I. The study was completed in a period of one year from January to December 2007.

NAFLD was diagnosed to be present in patients with elevated ALT in the presence of fatty liver on ultrasound as suggested by presence of a diffuse hyperechoic echotexture (bright liver), increased liver echotexture compared with the kidneys, vascular blurring, deep attenuation plus exclusion of other known causes like excessive alcohol intake, positive HBsAg, positive anti-HCV or any other known etiologies of liver disease. Liver biopsy was used to confirm the diagnosis only in those patients who gave consent. The histopatological criteria of diagnosis of NAFLD were macrovesicular fatty change in hepatocytes with displacement of the nucleus to the edge of the cell. Additional presence of features like Mallory bodies, ballooning degeneration, predominantly lobular neutrophilic inflammation, and Rappaport zone III perisinusoidal fibrosis were considered as supportive of diagnosis of fatty liver. Obesity was defined by a body mass index (BMI) >30 kg/m2 at least 2 occasions Metabolic syndrome was defined according to National Cholesterol Education Program Guidelines developed by the 2001 National Cholesterol Education Program (Adult Treatment Panel [ATP] III) focused explicitly on the risk of cardiovascular disease, and did not require evidence of insulin or glucose abnormalities.[7]

Patients in all age groups with elevated ALT and fatty liver on USG were included in study, while patients with positive serology for hepatitis B and C, alcoholic hepatitis, diagnosed cases of Wilson's disease, hemochromatosis and autoimmune hepatitis were excluded from study. Detail plan of study is shown in Figure 1. Patients were registered from medical outpatient department and screened with ALT. Those with elevated ALT were checked for HBsAg and antibodies to HCV and patients having a negative viral serology were sent for an ultrsonography. Patients were questioned about any history of alcohol intake and an attempt was made to quantify the weekly intake in grams. Detail history and physical examination was carried out according to a Performa including demographic

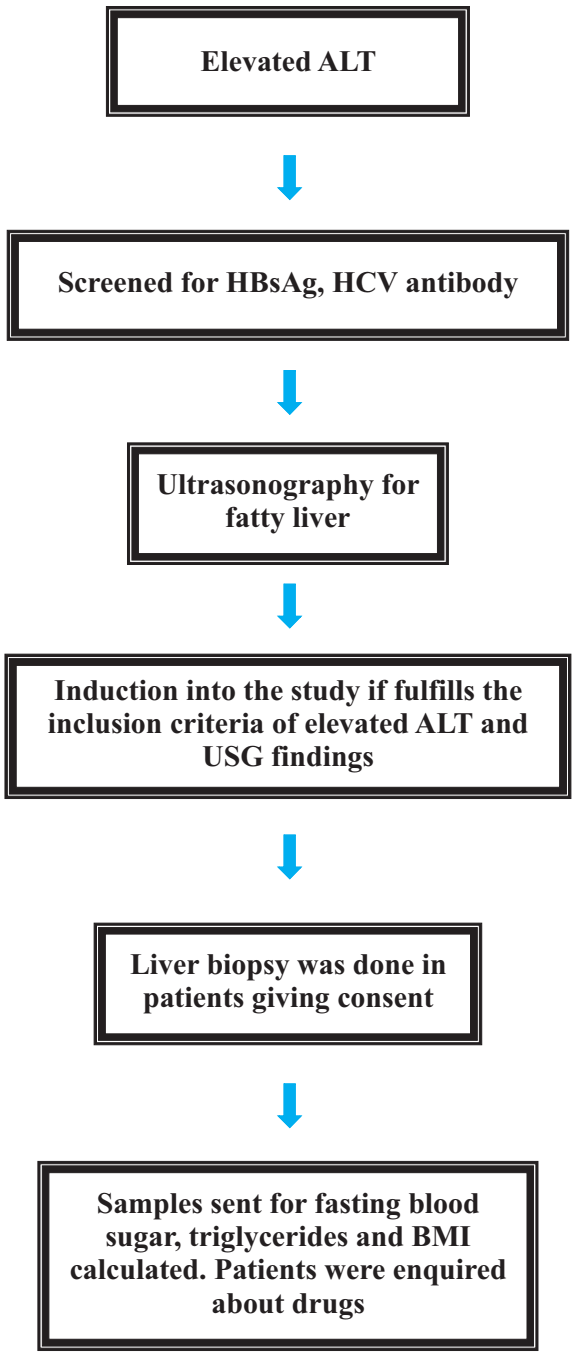

Figure 1- Study Plan

details of age gender, contact information and hospital registration number. Patients were asked about history of diabetes, hypertension or intake of oral hypoglycemics, insulin, anti-hypertensives, amiodarone, diltiazem or tamoxifen (common drugs that cause hepatitis). After the initial screening patients were explained about the importance, technique and possible complications of liver biopsy. Those who consented to biopsy had their blood samples sent for blood complete picture, coagulation profile, and biopsy was taken using the surecut liver biopsy needle under ulrtrasound guidance. The samples were sent to department of pathology for reporting. Patients' blood samples were sent for fasting blood sugar, random blood sugar, fasting cholesterol and fasting triglyceride levels. On the same visit their weight was done with the shoes, sweaters, coats shawls and hats off. Their height was measured in centimeters and their Body Mass Index (BMI) was calculated.

The data was entered and analyzed by using SPSS version 11 software. Descriptive statistics included continuous variables of age, ALT, BMI, fasting triglycerides, fasting and random blood sugar levels. Categorical data included gender and presence or absence of symptoms (like anorexia, dyspepsia, right upper quadrant pain), fatty liver on ultrasound, ANF, KF rings, fatty change on histopathology, obesity, diabetes, hypertension, and hypertriglyceridemia. Analysis was done and the continuous data was expressed as mean with standard deviation, and categorical data was reported as frequencies and percentages. Data is presented using pie and bar graphs.

RESULTS

The study enrolled 210 patients of elevated ALT with negative viral serology, these were sent for ultrasound and 104 patients were found to have bright liver suggestive of fatty liver on ultrasound, three patients were excluded due to positive serology for autoimmune hepatitis and one due to suspicion of Wilson's disease. The remaining 100 patients were evaluated for presence of risk factors of obesity, diabetes, dyslipidemias and drugs. Patients ranged from 15 to 77 years with a mean age of 46.50 13.58 years. Sub group analysis showed that the mean age did not differ between the males and females (47.0811 versus 46.137; p= 0.743). Sixty three percent were females and 37% were males. Most patients were asymptomatic, 28% had dyspepsia, 5% had right hypochondrial pain and 36% had fatigue as the main presenting symptom. Only 19% patients had hepatomegaly and none had signs of portal hypertension.

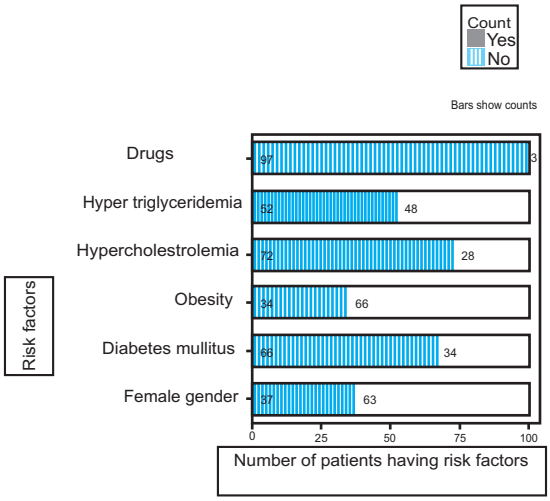

Figure 2– Stacked bar chart showing distribution of different risk factors among patients with NAFLD

The mean ALT of the study population was 83 28.5 IU/L. All patients had normal serum bilirubin and albumin. Only four patients consented to get a liver biopsy, in all four histopathology confirmed steatohepatitis. Thirty four percent of the study population was diabetic, more prevalent among the obese (39.39% patients were diabetic among obese as opposed to 23.5% among non-obese; p= 0.113) and was more common among the females (39.7% were diabetic among the females versus 24.32% diabetics among males (p= 0.118). These differences, however were not statistically significant; p>0.05.

Various factors associated with NAFLD in our study population are shown in Figure 2. Forty eight percent patients with NAFLD had hypertriglyceridemia and 28% were hypercholestrolemic. These dyslipidemias were more common in obese patients; (hypertriglyceridemia was present in 59% versus 26.4% of obese and non-obese respectively, p=0.002; and hypercholestrolemia was present in 34.8% versus 14.7 of obese and non-obese patients respectively, p= 0.03). Similarly, these dyslipidemias were more frequent among the diabetics; (hypertriglyceridemia was present in 61.76% versus 40.9% in diabetics and non-diabetic patients respectively, p= 0.048; and hypercholestrolemia was present in 47% versus 18.18% in diabetic and non-diabetic patients respectively, p= 0.002). Mean triglyceride of females was 186.23 mg/dl versus 172.4865 in males (p= 0.251). 34 females (54%) and 14 males (37.8%) had hypertriglyceridemia. This difference was not statistically significant (p= 0.119); although females were 1.9 times more likely to have hypertriglyceridemia as compared to men (OR 1.96; 95% CI 0.841- 4.412). Mean cholesterol

of females was 199.4762 mg/dl versus 193.97 in males (p= 0.543). Sixteen females (25.4%) and 12 males (32.4%) had hypercholestrolemia. This difference was not statistically significant (p= 0.449); although females were less likely to have hypercholestrolemia as compared to men (OR 0.709; 95% CI 0.291- 1.73).

Only 13% patients of NAFLD had normal weight (BMI 18-25) and 21% were over weight (BMI 25-30). The rest of 66% patients were obese with 48% having grade I obesity (BMI 30-35), 17% having grade II obesity (BMI 35-40) and only 1% being morbidly obese (BMI >40) as shown in Figure 3. Among the 66 obese patients 26 (39.4%) were diabetic, 23 (34.8%) had hypercholestrolemia, 39 (59%) had hypertriglyceridemia and 24 (36.7%) had metabolic syndrome. On the other hand among the 34 non-obese patients only 8 (23%) were diabetic, 5 (14.7%) had hypercholesterolemia, 9 (26.4%) had hypertriglyceridemia and 2 (5.8%) had metabolic syndrome. Obesity was much more common among females with fatty NAFLD, 49 females (77.8%) as compared to 17 males (46%) were obese (BMI >30); this difference was statistically significant (p= 0.001). Females were 4 times more likely to be obese if they have fatty liver on ultrasound (OR 4.118; 95% CI 1.711-9.907). Mean BMI of females was 31.35 and that of males was 27.78; ths difference was statistically significant (p= 0.001).

When analyzed for the existence of metabolic syndrome, we documented the presence of diabetes, obesity, hypertriglyceridemia and hypertension, and found that 26% patients had metabolic syndrome (defined as co-existence of three of more of these traits). 17%, 21%, 36%, 18% and 8% had none, one, two, three and four traits respectively as shown in Figure 4. The frequency of metabolic syndrome was higher in females in whom 21 out of 63 (33.3%) had at least 3 traits of the "deadly quartet" as compared to males in which 5 out of 37 (13.5%) had metabolic syndrome. This difference between the two genders was statistically significant (p= 0.029). Females had a 3.2 times higher risk of having metabolic syndrome if they are found to have a fatty liver on ultrasound (OR3.2; 95% CI 1.089-9.4). Three patients in the study group were found to be using drugs implicated n causing fatty liver. Two patients were using diltiazem for hypertension and heart disease and one was on tamoxifen for breast cancer for more than one year.

DISCUSSION

Formerly called nonalcoholic steatohepatitis, nonalcoholic 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. Nonalcoholic fatty liver disease is the most common cause of elevated liver enzymes7 and the most common cause of cryptogenic cirrhosis.8 NAFLD is known to affect 10-39 percent of the general global population with an average incidence of 20 percent. 9 It is the second most common diagnosis after chronic viral hepatitis10 and this prevalence is still probably an underestimate. 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 proportions11. Early recognition of these risk factors and their adequate management can lead to reduction in proportion of patients progressing to cirrhosis. The most prevalent risk factors for the development of steatosis in our study were female gender, obesity, diabetes, and hypertriglyceridemia. Many local published data have also reported similar results.12 Our data show 63% patients of NAFLD to be females and 66% to be obese. Many international and local studies have also shown similar results. In most series, the typical patient with nonalcoholic fatty liver disease is a middle-aged woman, but some have found a higher prevalence of nonalcoholic fatty liver disease in males than in females.[13]

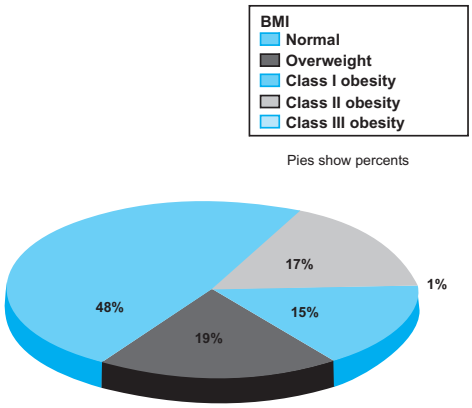

Figure 3 – Pie chart showing distribution of various classes of obesity among the study population of NAFLD

Data over the last decade show that 57-74 percent of obese persons, and 90 percent of morbidly obese persons (over 200 percent of ideal body weight) are affected with NAFLD 14 The prevalence of NAFLD increases by a factor of 4.6 in obese people. The reported prevalence of obesity in several series of patients with NAFLD varied between 30 and 100 percent.15 The prevalence of NAFLD in obese individuals is 76% as compared with 16% in non-obese individuals.16

Truncal obesity seems to be an important risk factor for nonalcoholic fatty liver disease, even in patients with a normal body-mass index.17 We estimated obesity by BMI; however measuring the waist hip ratio as a measure of truncal obesity probably would have increased the prevalence of obesity in the study population.

Our data showed 34% patients of NAFLD to be diabetic. In other international studies prevalence of type 2 diabetes varied between 10 and 75 percent.18 Even some children with type 1 diabetes mellitus have been found to have NAFLD.19 Presence of type 2 diabetes mellitus significantly increases the risk and severity of NAFLD regardless of body-mass index.20 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.12. Forty eight percent patients with NAFLD in our study had hypertriglyceridemia and 28% were hypercholestrolemic. 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 nonalcoholic fatty liver disease.21 Nonalcoholic 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 three of either: 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. [22]

A study in Saudi Arabia reviewed 235 patients of NAFLD and found that diabetes and obesity were the main risk factors in the study group. Metabolic syndrome was reported in 14.9% and hypothyroidism in 3.8% of the subjects.23 In one local study on forty eight patients, 58% of NASH patients were female and > 90% were obese. The average ALT & AST levels were 87 and 71 u/l, respectively. Bilirubin and Serum Albumin were normal in all patients. 63% of patients had diabetes. Fasting lipid profile showed hypercholesterolaemia in 79% and raised triglycerides in 88%.24 A local study by Umer et al showed that the mean age of NAFLD patients was 31 years and the mean BMI was 32. Mean serum ALT was 88 u/L. Data of lipid profile showed mean cholesterol of 219-mg/dl and mean triglyceride of 170 mg/dl.25 In a recent series reported by Khurram et al, obesity, hepatomegaly, diabetes, and hypertriglycedemia were characteristic features of NAFLD patients that were more common in females. [26]

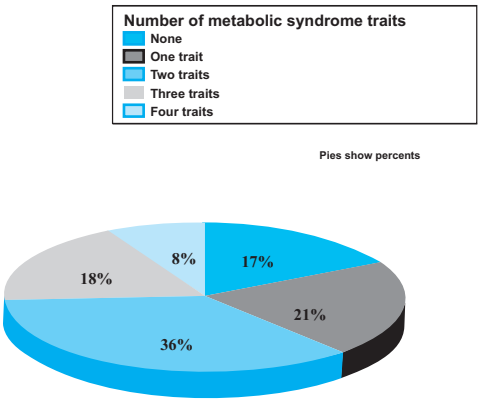

Figure 4– Pie chart showing distribution of different traits of metabolic Syndrome among the study population of NAFLD

Results of our study were comparable to other locally published data and also match the data of other internationally published studies. However, our study had certain limitation, it is a descriptive study which is a weaker study design; whereas a comparative study comparing normal and NAFLD population for prevalence of risk factors would have been a stronger study design that would have provided a more robust evidence of association between these risk factors and NAFLD. All our patients were diagnosed on the basis of ultrasound that has a sensitivity of 89 percent and a specificity of 93 percent27 in detecting steatosis. Results could have been improved by confirming the diagnosis with liver biopsy. With ultrasound diagnosis we can detect a fatty liver, but cannot provide data on steatohepatitis, which requires a liver biopsy for confirmation. Including serum ferritin, ceruloplasmin and alfa1 antitrypsin levels in the screening procedure for exclusion of patients would have increased the specificity of diagnosis. A further problem was the small sample size for a very common disease. These limitations can lead to spurious associations and to inflated estimations of the strength of any real association. Moreover further studies are required on a larger scale to document the prevalence of various risk factors in NAFLD population accurately.

CONCLUSION

Non-alcoholic fatty liver disease is an

increasingly important chronic liver disease associated with high prevalence of obesity, hypertriglyceridemia, hypercholestrolemia, diabetes, female gender and metabolic syndrome. Recognition of these risk factoers in patients of NAFLD can help in early implimentation of statergies that halt the progression of this disease. Future work is required to better define its natural history, elucidate the pathogenesis and develop effective treatment options for this, often progressive, disease.

REFERENCES

1. Skelly MM, James PD, Ryder SD. Findings on liver biopsy to investigate abnormal liver function tests in the absence of diagnostic serology. J Hepatol 2001; 35:195–9.
2. Matteoni CA, Younossi ZM, Gramlich T. Nonalcoholic fatty liver disease: A spectrum of clinical pathological severity. Gastroenterology 1999; 116:1413.
3. Caldwell SH, Oelsner DH, Iezzoni JC. Cryptogenic cirrhosis: Clinical characterization and risk factors for underlying disease. Hepatology 1999; 29:664.
4. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol 2003;98:960–7.
5. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterology 2003; 124: 71–9.
6. Sanyal AJ. American Gastroenterological Association. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology 2002;123:1705-25.
7. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285:2486.
8. Clark JM, Diehl AM. Nonalcoholic fatty liver disease: An under-recognized cause of cryptogenic cirrhosis. JAMA 2003; 289:3000-4.
9. Collantes R, Ong JP, Younossi ZM. Nonalcoholic fatty liver disease and the epidemic of obesity. Cleve Clin J Med 2004; 71:657-64.
10. Byron D, Minuk G. Clinical hepatology: Profile of an urban, hospital-based practice. Hepatology 1996; 24:813-5.
11. Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, Wasada T. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med 2005; 22:1141–5.
12. Ansari A, Bilal N. Frequency of Non-Alcoholic Steatohepatitis (NASH) in patients with type 2 Diabetes Mellitus. Ann Pak Inst Med Sci 2005; 1(4): 227-9
13. Nomura H, Kashiwagi S, Hayashi J, Kajiyama W, Tani S, Goto M. Prevalence of fatty liver in a general population of Okinawa, Japan. Jpn J Med 1988; 27:142-9.
14. Ratziu V, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, et al. Liver fibrosis in overweight patients. Gastroenterology 2000; 118:1117-23.
15. Bellentani S, Saccoccio G, Masutti F. Prevalence of and risk factors for hepatic steatosis in northern Italy. Ann Intern Med 2000; 132:112-7.
16. Bellentani S, Saccoccio G, Masutti F, Croce LS, Brandi G, Sasso F. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000; 132: 112–7.
17. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. Diabetes 1998;47:699-713
18. Schaffner F, Thaler H. Nonalcoholic fatty liver disease. Prog Liver Dis 1986;8:283-98
19. Manton ND, Lipsett J, Moore DJ, Davidson GP, Bourne AJ, Couper RTL. Non alcoholic steatohepatitis in children and adolescents. Med J Aust 2000; 173:476-9.
20. Silverman JF, O'Brien KF, Long S. Liver pathology in morbid obese patients with and without diabetes. Am J Gastroenterol 1990; 85:1349-55
21. Assy N, Kaita K, Mymin D, Levy C, Rosser B, Minuk G. Fatty infiltration of liver in hyperlipidemic patients. Dig Dis Sci 2000; 45:1929-34.
22. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R. Non-alcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003; 37: 917–23.
23. Qari FA, Alghamdi A. Fatty liver in overweight and obese patients in western part of Saudi Arabia: A study of sonological prevalence Pak J Med Sci 2005;21(2):143-7.

24. Adam T, Lakhnana NK. Non Alcoholic Steatohepatitis - A study of forty eight cases. J Pakistan Inst Med Sci 2004; 15(1):849-82.

25. Umar M, Chohan S, Khaar HB, Zahid M, Amir Chohan, Seema Kanwal, et al. Clinical Spectrum of Non-Alcoholic Steatohepatitis (NASH) in Non Diabetic Population. Pakistan J Gastroenterol 2003;17(1):30-2.

26. Khurram M, Shakoor A, Arshad MM, Khaar HB, Hasan Z. Characteristic features of 50 patients with NAFLD. Rawal Med J 2004; 29(1):8-12.

27. Joseph AE, Saverymuttu SH, Al-Sam S, Cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol 1991; 43:26-31.

Address for Correspondence:
Dr. Ghulam Murtaza Gondal
Assistant Professor
Department of Medicine,
Foundation University Medical College & Hospital,
Rawalpindi.
E-mail: drgmgondal@hotmail.com