NON ALCOHOLIC FATTY LIVER DISEASE AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS IN SULAIMANI GOVERNORATE

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ABSTRACT

Background

Nonalcoholic fatty liver disease (NAFLD) is a common hepatic disorder characterized by accumulation of fat in the liver parenchyma of patients who do not drink excessive amount of alcohol. The prevalence of NAFLD is high in conditions associated with insulin resistance, such as obesity, type 2 DM, dyslipidemia and the metabolic syndrome. NAFL is very common in type-2 diabetic patients, with 50-75% demonstrating fat in the liver by ultrasound.

Objectives

To assess the frequency of NAFLD in patients with type 2 DM in Sulaimani and its relation with age, gender, duration and state of glycaemic control compared to non diabetic subjects.

Methods

This is across sectional study, conducted in Sulaimani General Teaching Hospital from December. 2013 to December 2014. A total of 102 patients were enrolled in the study, sixty seven were diabetic and 35 were nondiabetic as control. Patients with chronic viral hepatitis B, C, autoimmune hepatitis, excessive alcohol ingestion, and drugs with adverse effect on liver were excluded. These patients were evaluated by abdominal ultrasonography to determine the presence of fatty liver. They were divided into fatty liver group and non-fatty liver group. They were further evaluated for BMI, waist/hip ratio, blood pressure, lipid profile, liver function test. The data obtained was analyzed using SPSS-21.

Results

61% of diabetic patients had fatty liver on ultrasonography; of those 17% fulfill the criteria of NASH, compared to 48%, 6% in the control group respetively. BMI, serum triglyceride and ALT were significantly higher in group with fatty liver than non fatty liver in both diabetic and control (P-value= 0.001, 0.027, and 0.006 respectively).The frequency of NAFLD increases with age. Diabetes was associated with more severe degree of NAFL and fibrosis score.

Conclusion

NAFLD is more common in type 2 DM than nondiabetic. Obesity, hypertriglyceridemia, and HbA1c are independent predictors of NAFLD.

Keywords: *Type 2 DM, NAFLD, NASH, Obesity, Sulaimani.*

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) was first described in the 1950s when fatty liver was first characterized in a group of obese patients. In 1980, Ludwig and colleagues at the mayo clinic described 20 obese, diabetic, nonalcoholic patients who had similar findings on liver biopsy to patients with alcoholic liver disease, and the term nonalcoholic steatohepatitis was introduced [1].

NAFLD is subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). In NAFL, hepatic steatosis is present without evidence of significant inflammation, whereas in NASH, hepatic steatosis is associated with hepatic inflammation that may be indistinguishable from alcoholic steatohepatitis [2, 3].

Studies suggest that 20-30% of individuals in Western countries have NAFLD [4]. NAFLD may represent the majority of unexplained cases of aminotransferase elevation [5] .The prevalence increases from 16.5% in lean persons to 75% in obese persons [6]. The disease is reported in all age groups, even in pediatric patients in which it is strongly associated with obesity [7].

NAFLD also is strongly associated with type 2 DM and glucose intolerance, with or without superimposed obesity. Type 2 DM, hyperglycemia, or glucose intolerance has been described in 20% to 75% of adult patients with NASH, and may increase the risk of NASH more than twofold compared with nondiabetic persons [8, 9].

Obesity is strongly associated with NAFLD. Studies have shown a significant correlation between the risk of the metabolic syndrome, degree of hepatic steatosis, and waist-to-hip ratio, thus highlighting the importance of intra-abdominal or visceral fat as a predictor of NAFLD [10].

The primary laboratory abnormality is the elevated serum AST and ALT levels. However, liver aminotransferase levels are seldom higher than 3 or 4 times the upper limit of normal. The ALT levels are higher than the AST levels in most instances, but reversal of the ALT/AST ratio to more than 1 had been reported to predict the presence of more advanced fibrosis [11].

The diagnosis of NAFLD requires all of the following [12, 13]:

- Demonstration of hepatic steatosis by imaging or biopsy.
- Exclusion of significant alcohol consumption.
- Exclusion of other causes of hepatic steatosis.

Aims of the study

To assess the frequency of NAFLD in patients with type 2 DM in Sulaimani and its relation with age, gender, Duration and state of glycaemic control compared to non diabetic subjects.

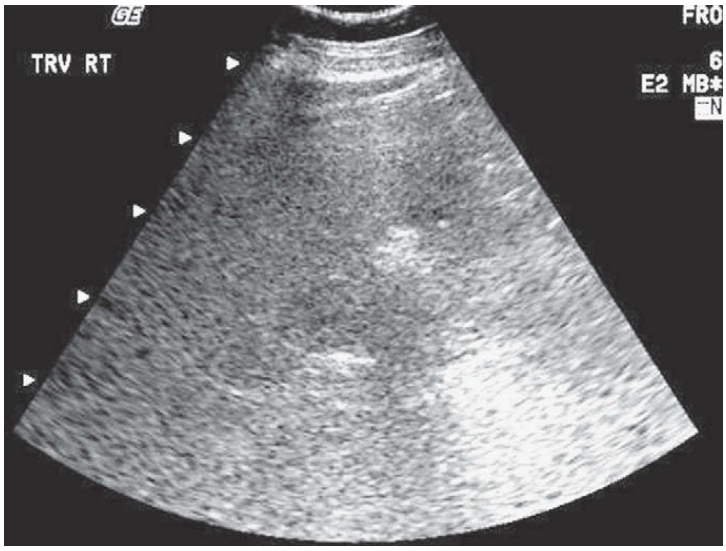

Figure 1. Ultrasound demonstrating increased echogenicity in a patient with NAFL.

PATIENTS AND METHODS

This is cross sectional case control study conducted in Sulaimani governorate from December 2013 to December 2014. During this period 102 participants were collected randomly, 67 patients have type 2 DM, while the remaining 35 patients were nondiabetic as control.

Ethical and Scientific approval were achieved from Iraqi Board for Medical Specialty. All participants were agreed to participate in the study. They were asked to attend the hospital after an overnight fasting, patients were subjected to detailed history and standard questionnaire was designed.

Thorough general examination performed. Anthropometric measurements were taken including height, weight, waist and hip circumference, blood pressure was also checked. Body mass index was calculated Overweight was defined as BMI of 25-29, 9 kg/m^{2}and obesity as BMI > 30 kg/m^2 according to WHO criteria [14].

According to National Institute of Diabetes, Digestive, and Kidney diseases (NIDDK) waist/hip ratio > 0.8 in female and > 1 in male is considered as high or abnormal according to WHO criteria [15] .

According to guidelines from the National Heart, Lung, and Blood institute (NHLBI) and the American Heart Association (AHA) [16], metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions:

- Fasting glucose ≥100 mg/dl(or receiving drug therapy for hyperglycemia)
- Blood pressure ≥130/85 mmHg (or receiving drug therapy for hypertension)
- Triglycerides ≥150 mg/dl (or receiving drug therapy for hypertriglyceridemia)
- HDL-C < 40 mg/dl in men or <50 mg/dl in women.
- Waist circumference ≥ 102 cm in men or ≥ 88 cm in women.

Exclusion criteria included patients with drugs like (amiodarone, methotrexate, Tamoxifen, Glucocorticoids and valproate) that are known to cause fatty liver.

Significant alcohol consumption [17] which is defined as an average consumption > 210 grams of alcohol / week in men or > 140 grams of alcohol /week in women over at least a two year period.

Patients were sent for the following investigations: complete blood count{ HORIBA medical - ABX Micro ES_{60}), biochemical tests like FBS ,ALT ,AST, TC, TG,HDL , LDL, Albumin{KENZA 240TX Bio LABO }, HBs Ag, HCVAb.{ Vidas using ELISA method }, ANA {Chorus - fluorescent assay}, HbA_{1C} {HLC 723GX using high performance liquid chromatography} .

Transabdominal ultrasonography (US) was performed using (SIEMENS, Korea, ACUSON X300, CH5-2 Probe). All the ultrsonographic evaluations were performed by one experienced radiologist.

We calculated NAFLD fibrosis score according to Angulo et al [18] in order to determine those patients with significant risk of fibrosis, the following formula was used: NAFLD fibrosis score = -1.675 + 0.037 ×age (years) +0.094× BMI (kg/m^2) +1.13 × IFG/diabetes (yes=1, no = 0) + 0.99 × AST/ALT ratio 0.013×platelet (×10^9 /L) -0.66 ×albumin (g/dl). values greater than 0.676 and lower than -1.455 were considered as the presence and absence of fibrosis, respectively, values between these cut-offs considered as intermediate risk.

Statistical analysis: Data were entered in to excel sheet, then transferred to SPSS-21 Descriptive analysis was performed for all variables. Analytic analysis was conducted to association and differences between compared variables by using t- test, chi square and fisher exact test. P value ≤ 0.05 was regarded as a significant level.

RESULTS

A total of 102 cases were enrolled in the study, 67 of them were having type 2 DM and the remaining 35 cases were non diabetic as control.

Overall 56 patients (55%) were male and 46 patients (45 %) were female. In the diabetic group 32(47.7%) patients were male and 35(52.3%) patients were female while in the control group 24(68.5%) subjects were male and 11 (31.5%) subjects were female, Figure 2.

Mean age among diabetic group was 53.92 (age range 34-77 years), while mean age among control group was 49.11 (age range 32- 66 years, the metabolic syndrome features were significantly different among both groups as showed in Table 1.

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NAFLD was diagnosed in 41(61%) diabetic patients compared to 17 (49%) subjects in the control group, Figure 3.

32 (78%) patients had elevated ALT (upper limit of normal range is 30 IU/L in male, 19 IU/L in female) and 7 (17%) fulfill the criteria of NASH, while in control group NAFLD was diagnosed in 53%, of these 7 (41%) subjects had elevated ALT, and 1 (6%) subject had NASH . According to the NAFLD fibrosis score, which was a noninvasive score to detect fibrosis among NAFLD, there was a high percentage of indeterminate score (73%) in diabetic group in comparison to control group which was (53%), but the percentage of significant fibrosis in control group was (3%) , in diabetic group (6%) as shown in Figure 4.

Clinical and biochemical characteristics among fatty liver and non-fatty liver between both groups, Table 2, Table 3.

Nonalcoholic fatty liver disease was more prevalent, but not significantly, in males (55.2%) than females (44.8%), Figure 5.

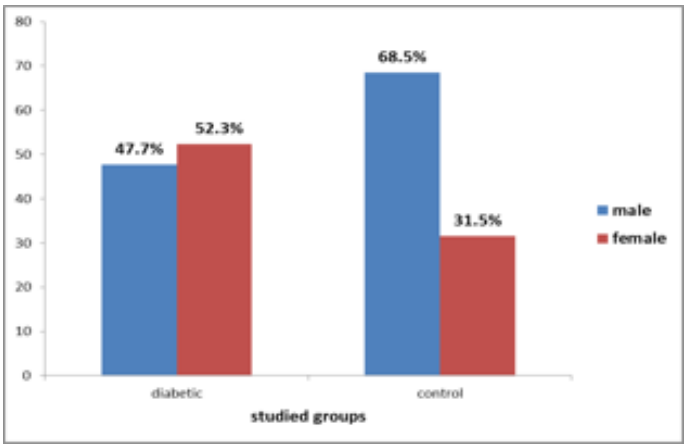

Figure 2. Sex distribution among studied groups.

Table 1. Clinical characteristics of study groups.

Variables	Studied groups		P values
	Diabetic N (%)	Control N (%)	
Mean Age (yr.)	53.92	49.11	0.024
Metabolic Syndrome			
No	8 (11.9)	15 (42.9)	0.001
Yes	59 (88.1)	20 (57.1)	
BMI			
Normal	10 (14.9)	8 (22.9)	0.422
Overweight	28 (41.8)	16 (45.7)	
Obesity	29 (43.3)	11 (31.4)	
Waist/Hip ratio			
Normal	15 (22.4)	15 (42.9)	**0.031**
Abnormal	52 (77.6)	20 (57.1)	
Hypertension			
No	20 (29.9)	20 (57.1)	**0.007**
yes	47 (70.1)	15 (42.9)	
NAFL	34 (83)	16 (94)	**0.261**
NASH	11 (17)	2 (6)	

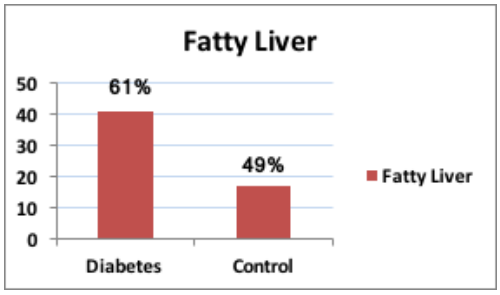

Figure 3. Ultrasound finding of NAFLD frequency in study population.

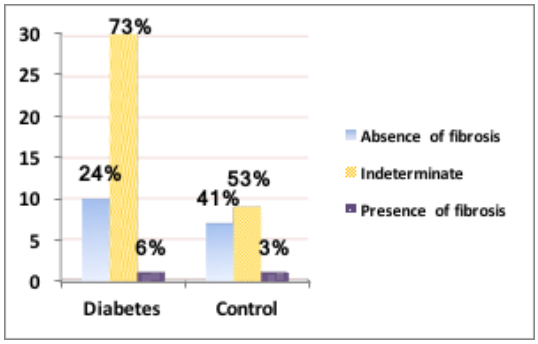

Figure 4. NAFLD fibrosis score among NAFLD between two groups.

Table 2. Clinical characteristics among fatty liver and non-fatty liver between diabetics and controls.

Variables	Diabetic		Control		P values
	Fatty liver (N=41)	No fatty liver (N=26)	Fatty liver (N=17)	No fatty liver (N=18)	
Age (mean ± SD)	52.5 ± 9.9	56.2±11.3	47.8±10	50.3±8	0.049
Male sex	21	11	11	13	0.11
Female sex	20	15	6	5	0.42
Duration of DM (mean ± SD)	5.3±4.3	7.4±7.3	NA	NA	0.19
Metabolic syndrome	39	20	12	8	0.41
Abnormal waist/hip ratio	32	21	13	9	0.43
Body Mass Index (mean ± SD)	30.9 ± 4	27.8±5.7	30.3±4	26.4±3.4	**0.001**
Systolic BP (mean ± SD)	145±27	136±24	133±20	135±30	0.277
Diastolic BP (mean ± SD)	89±13.5	85±10.3	88±13	82±12	0.206

Table 3. Biochemical characteristics among fatty liver and non-fatty liver group between diabetics and controls.

Variables (mean ± SD)	Diabetic		Control		P values
	Fatty liver (N=41)	No fatty liver (N=26)	Fatty liver (N=17)	No fatty liver (N=18)	
ALT	37±21	23±9.8	34±16	29.3±8.2	0.006
AST	38±43	27±11.8	29±4.3	30.4±7.8	0.415
TC	197±53	186±45.2	192±34	186±39	0.749
TG	213 ±126	137±78	189±73	170±78	0.027
HDL	41.2±12	43.3±11	38±8	41±10	0.48
HbA_{1c}%	9.4±1.8	8.7±2.4	NA	NA	0.17

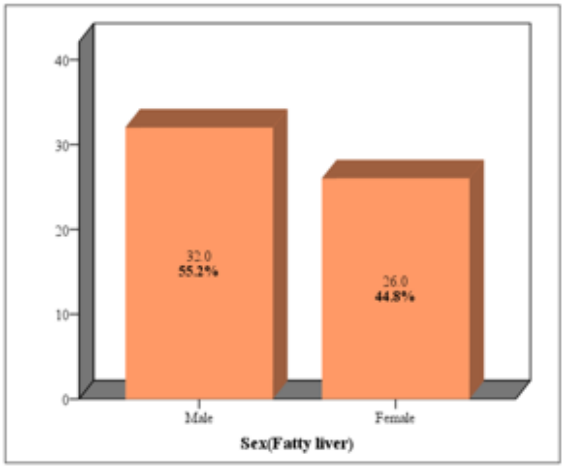

Figure 5. Sex difference in NAFLD.

There was a statistically significant increase of NAFLD with increasing BMI with p value 0.001, Figure 6

The percentage of NAFLD increases with advancing age in both groups, with peak prevalence in the fifth decade of life in diabetic group versus forth decade in control group, Figure 7.

The percentage of NAFLD increases with duration of diabetes, Figure 8.

Diabetes was positively associated with the severity of fatty liver .In diabetic group 19.6% of patients have mild fatty liver versus 12.7% in control group ,While moderate-sever fatty liver was found in 20.6% of diabetic group versus only 3.9% in control group, Figure 9.

Glycated hemoglobin (HbA1C) level strongly correlated with fatty liver among diabetics, Figure 10.

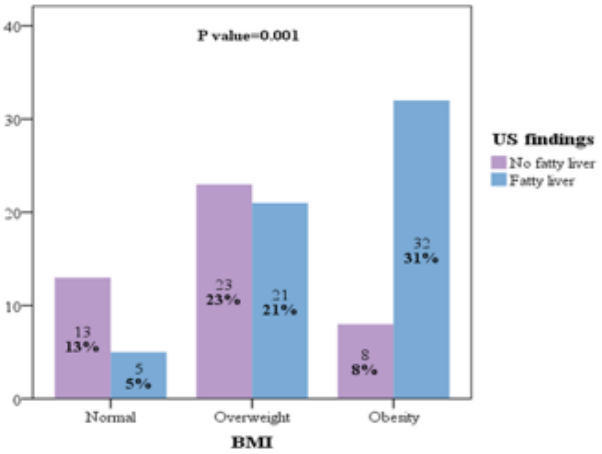

Figure 6. Association of NAFLD with BMI.

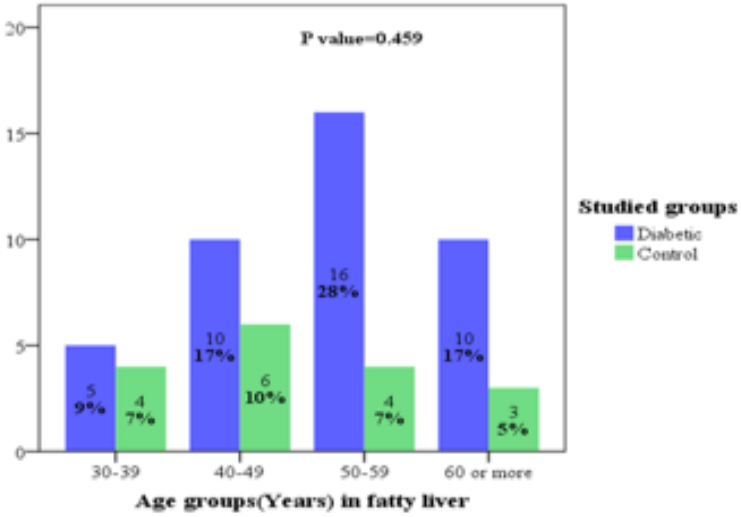

Figure 7. Relationship of NAFLD with age.

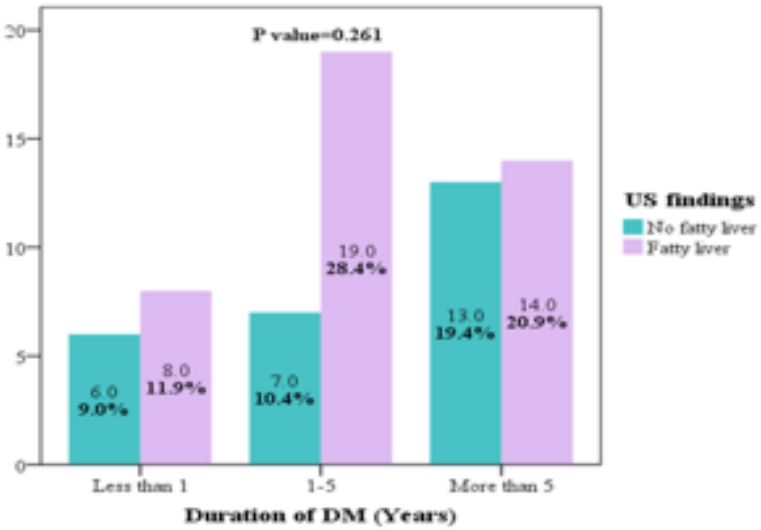

Figure 8. Relationship of NAFLD with duration of DM.

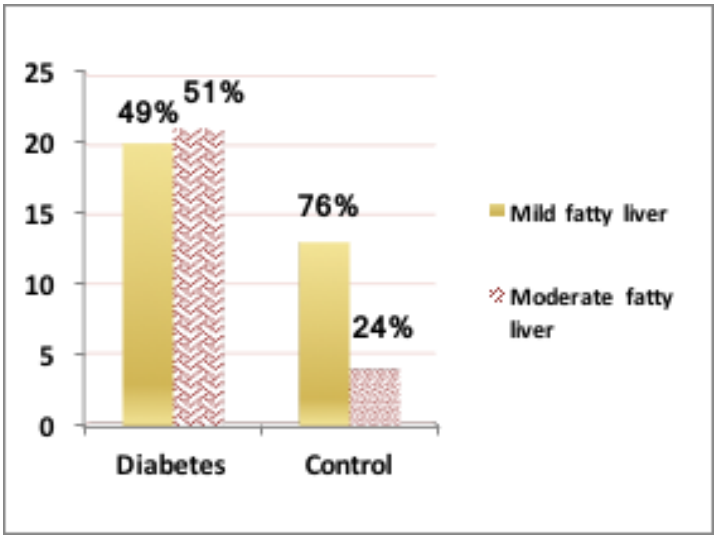

Figure 9. Severity of Fatty liver by U.S in diabetic and control groups.

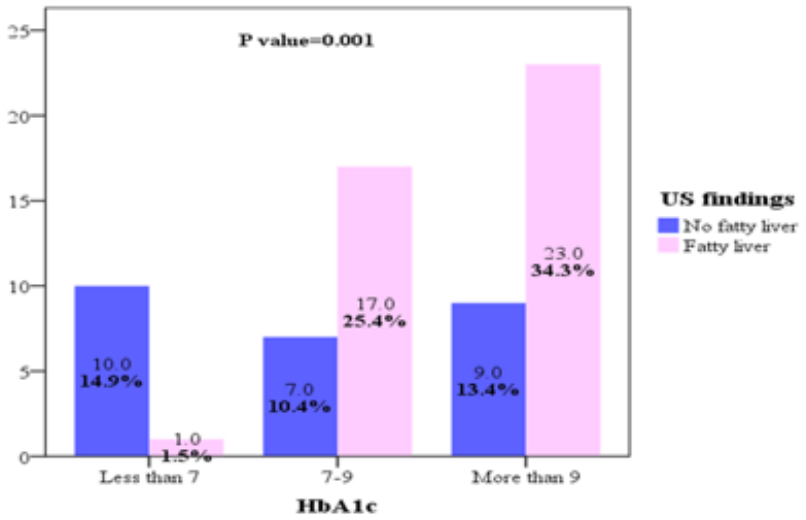

Figure 10. Correlation of HbA1c with fatty liver among diabetics.

DISCUSSION

NAFLD is a Clinicopathological syndrome characterized by wide spectrum of liver damage ranging from benign fatty infiltration to steatohepatitis, advanced fibrosis and cirrhosis [18]. The prevalence of NAFLD is high in conditions associated with insulin resistance, such as obesity, type 2 DM, dyslipidemia and metabolic syndrome [18]. It is very common in type-II diabetic patients, with 50% to 75% subjects demonstrating fat in the liver by ultrasound [8].

In this study the prevalence of fatty liver was 61% among type II DM which correlates with study conducted by Shobha et al [19] 60.8% in Pakistan and by Akbar and Kawther et al [20] 55% in Saudi Arabia, while the prevalence of fatty liver in our study among nondiabetic is 48% , which is higher than other studies, this can be explained by high waist/hip ratio (57.1%) and metabolic syndrome features (57.1%) among control group, this correlate with 40% in study conducted by Kirovski et al [21] 40% in Germany.

Among fatty liver in diabetics 78% of patients have elevated ALT above normal compare to 59% in control, this is comparable to Jayarama and Sudha [22] in Hubli, south Indian which ALT was elevated above normal range in 82% of diabetic.

In the present study; 17% of diabetic fatty liver met the criteria of nonalcoholic steatohepatitis (NASH), which is comparable to the result of study (22%) conducted by Vikash Kumar et al [23] in New Delhi. 6% of control met the criteria of NASH which is higher than the result

(3.3%) of a study reported in Iran done by Mehran Rogha et al [24].

The presence of NAFLD correlates significantly with BMI [25, 26]. In our study the prevalence of NAFLD correlates significantly (P-value0.001) with BMI in diabetics and control, the result is similar to study done by Shobha et al [19].

Although overall obesity is clearly associated with NAFLD, body fat distribution appears to play an important role in the pathogenesis of NAFLD, via both its strong association with insulin resistance and possibly as source of free fatty acids. Increased intra abdominal fat deposition is also associated with what are commonly considered to be clinical manifestation of insulin resistance including type 2 DM, impaired glucose tolerance, dyslipidemia and metabolic syndrome [25]. Among fatty liver in both diabetics and controls, a great percentage 78% ,76.5% respectively, have high waist/hip ratio ,this is positively correlates with the presence of fatty liver in both groups this supported by study conducted by Arunkumar et al [26] which stated that high waist/ hip ratio significantly associated with fatty liver but in current study it was not significant, because the two groups almost similar in high waist/ hip ratio.

In addition , we also found that higherHbA_{1C}level was significantly associated with fatty liver in diabetics ,as the percentage of fatty liver increases from 1.5% in those who had HbA_{1C} below 7% to 25.4% in those with HbA_{1C} between 7-9% ,and then to 34.3% in patients with HbA_{1C}above 9% (P value 0.001) ,this comparable to study reported by Ma et al [27] and Shobha et al [19]. Based on this point, HbA_{1C} level can be considered as an independent risk for NAFLD.

The relationship between fatty liver, impaired glucose tolerances, DM and hyperlipidemia is well established [19, 28]. It has been demonstrated that insulin resistance leads to higher free fatty acid load to the liver, consequently higher triglyceride synthesis and increased secretion of triglyceride rich very low density lipoprotein (VLDL) from the liver. In fact, hypertriglyceridemia have been strongly correlated with liver fat accumulation [19, 29]. Our study has also showed there is a statistically significant difference (P-value= 0.027) in mean triglyceride levels among fatty liver and non-fatty liver groups in both diabetics and controls, this is comparable to study done by Hajieh et al [30] in Iran and Arunkumar et al [26] in India.

The current study confirmed that the prevalence of NAFLD increases with increasing age and the peak prevalence of NAFLD was between 50-60 years, comparable to study done by Xiaona Hu et al [31] and by Sanjay aKalra et al [32] in India.

In this study, we found that fatty liver was more common(statistically not significant) in male (55%) than female (45%) , this is probably due to high percentage of male in study population and small size of control (35 subjects) in comparison to diabetics (67 patients) this support the study reported in Iran by Hossein et al [33] in which gender is not a risk factor for fatty liver but in that study fatty liver was more common in female (65.5%) than male (35.5%) ,while in another study done by Akbar and Kawther et al [20] in Saudi Arabia found that presence of fatty liver was significantly associated with female sex.

This study showed that fatty liver increased with longer duration of DM, majority of cases of fatty liver were among those who had DM for more than 1-5 years, but the result was statistically not significant, this agree with the results reported by Hossein panah et al [33] in Iran and Akbar, Kawther et al[20] in Saudi Arabia.

Diabetic patients had a higher percentage of moderate-severe fatty liver (51%) versus (24%) in control on ultrasound and also they had a higher indeterminate score of fibrosis (73%) than control (53%) when assessed by NAFLD fibrosis score these results are in accordance to Shahbazian et al study [30].

In conclusions: NAFL is common in type 2 DM, obese and in individual with dyslipidemia. ALT elevation was seen more frequently in fatty liver than in non-fatty liver type 2 diabetic patients. The independently associated risk factors for diabetic fatty liver were high HbA_{1c}, raised BMI, and increase triglyceride levels. NAFL increased with age and male gender. So, it is recommended to assess all diabetic patients for NAFLD.

The author discloses no conflict of interest.

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