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Cardiovascular Disease (CVD) risk factors among patients of type2 Diabetes Mellitus (DM) with Non–Alcoholic Fatty Liver Disease (NAFLD)

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Abstract

Background: Global pandemics of cardiovascular disease (CVD) and diabetes mellitus (DM) are spreading quickly. CVD continues to be a pressing global health issue, standing as a prominent cause of both mortality and morbidity. Among its diverse risk factors, type2 DM and Non–Alcoholic Fatty Liver Disease (NAFLD) stand out as pivotal contributors. This research endeavors to delve into the multifaceted relationship between type2 DM, NAFLD, and cardiovascular health. **Material & Methods:** From July 1 to December 31, 2012, a hospital-based observational study was conducted in the Department of Medicine at Cumilla Medical College and Hospital in Bangladesh. This study comprised 50 type2 DM patients with NAFLD who had been hospitalized. Their medical history, physical exam, and laboratory study (fasting and 2-hour post-meal blood glucose, blood urea, serum creatinine, liver function tests, and fasting lipid profile) were included. Based on a liver ultrasound examination, NAFLD was identified. **Results:** Out of 50 patients, 18(36%) were males and 32(64%) were females, with mean age 58.89 ± 8.38 and 54.6 ± 10.1 years, respectively. Grade -1 NAFLD cases were 54%, grade -2 was 32%, and grade -3 was 14%. On statistical analysis, we found increasing grades of NAFLD were significantly associated with hypertension ($p=0.0083$), obesity ($p=0.0006$), increasing levels of total cholesterol ($p<0.0001$), ALT ($p<0.0001$), AST ($p<0.0001$) and ALP ($p<0.0001$). **Conclusions:** NAFLD combines with CVD risk factors among people with type2 diabetes. It is a substitute and a reliable CVD risk marker in type2 diabetes patients. Ultrasonography was used to detect NAFLD.

Keywords:- Type2 Diabetics Mellitus, NAFLD, CVD risk factors, metabolic syndrome.

INTRODUCTION

Cardiovascular Disease (CVD) and Type2 Diabetes Mellitus (DM) represent two major public health challenges of the 21st century. They are both chronic conditions associated with significant morbidity, mortality, and healthcare costs.[1] Over the past few decades, an alarming increase in the prevalence of both conditions has been observed globally. Moreover, a noteworthy association has been

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Page no- 151-162 | Section- Research Article (Medicine)

established between type2 DM and Non-Alcoholic Fatty Liver Disease (NAFLD), further complicating the clinical management of affected individuals.[2]

Type2 DM is characterized by insulin resistance and impaired glucose metabolism, leading to elevated blood sugar levels. It is a complex metabolic disorder with multifactorial origins, involving both genetic and environmental factors.[3] The condition is often accompanied by a cluster of comorbidities, including obesity, dyslipidemia, and hypertension, collectively referred to as the metabolic syndrome. This constellation of risk factors significantly heightens the likelihood of developing CVD, which encompasses a range of conditions affecting the heart and blood vessels, such as coronary artery disease, heart failure, and stroke.[4]

Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as the most common chronic liver disorder worldwide. It is characterized by the accumulation of excess fat in hepatocytes, not attributable to excessive alcohol consumption.[5] NAFLD is closely linked to insulin resistance, obesity, and metabolic syndrome, which makes it highly prevalent among individuals with type2 DM.[6] NAFLD exists on a spectrum, ranging from simple steatosis (accumulation of fat) to non-alcoholic steatohepatitis (NASH), which is characterized by inflammation and hepatocellular injury. In severe cases, NASH can progress to cirrhosis and even hepatocellular carcinoma.[7]

The coexistence of type2 DM and NAFLD poses a formidable clinical challenge, as these conditions synergistically exacerbate the risk of CVD.[8] The interplay between insulin resistance, dyslipidemia, chronic inflammation, and endothelial dysfunction creates a fertile ground for atherosclerosis and other cardiovascular complications. Furthermore, both type2 DM and NAFLD share common pathogenic pathways, including abnormal lipid metabolism, chronic low-grade inflammation, and oxidative stress.[9]

Understanding the intricate relationship between type2 DM, NAFLD, and CVD is of paramount importance for developing effective prevention and management strategies. Early identification and intervention are crucial in mitigating the risk of cardiovascular events in this high-risk population. Lifestyle modifications, including dietary changes, regular physical activity, and weight management, are fundamental components of any comprehensive treatment plan.[10] Additionally, pharmacological interventions targeting glucose metabolism, lipid profiles, and liver health may play a pivotal role in reducing CVD risk among patients with type2 DM and NAFLD.[11]

The convergence of type2 DM, NAFLD, and CVD represents a significant healthcare challenge with far-reaching implications. A comprehensive understanding of the underlying mechanisms and risk factors is imperative in developing targeted interventions to improve the clinical outcomes of affected individuals.[12] The integration of multidisciplinary approaches involving healthcare providers, researchers, and patients themselves is essential in addressing this complex interplay of metabolic disorders.

Pathophysiological changes in NAFLD: Although the exact cause of NAFLD is

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unknown, the observation that not all patients with steatosis progress to hepatic inflammation and hepatocellular damage have given rise to the hypothesis that various pathogenic factors first cause hepatic steatosis before progressing to hepatic impairment (also known as "the second hit") in some patients.[13] Hepatic fat accumulation and insulin resistance are intimately related. Nearly 98% of those with NAFLD have insulin resistance, and more than 80% of NAFLD patients fit the essential criteria for metabolic syndrome.[14] Insulin resistance causes peripheral adipose tissue to lypolyze more often, increasing the amount of free fatty acids entering the liver. Additionally, insulin resistance stimulates the production of new triglycerides in the liver and prevents the oxidation of fatty acids, which leads to triglyceride buildup.[15] Although many factors, including oxidative stress, mitochondrial abnormalities, and hormonal imbalances involving leptin and adiponectin, have been linked to the development of liver damage, it is unknown what constitutes a "second hit" that causes liver damage. NAFLD has a range of histological alterations; simple steatosis is>5% hepatic steatosis without substantial hepatocellular injury, inflammation, or fibrosis.[16]

Biochemical abnormalities in NAFLD: These enzymes (ALT and AST) that are chronic, variable, and mildly to moderately high are the most prevalent biochemical abnormalities in NAFLD.[17] There must be no remaining reasons for elevated aminotransferases.[18] Alcohol misuse, drug use, chronic hepatitis B and C, hereditary haemochromatosis, Wilson's disease (in patients under 40), and Alpha 1 - antitrypsin deficiency are all hepatic reasons for chronically high aminotransferase levels. The non-hepatic causes, on the other hand, include Coeliac sprue, genetic muscle metabolism problems, acquired muscle illness, and intense activity. Elevated total cholesterol, LDL-C, triglycerides, blood sugar, and decreased HDL-C are abnormal biochemical tests linked to insulin resistance, as are elevated triglycerides and blood sugar. After ruling out other causes of hepatitis, the diagnosis of NAFLD or NASH might be considered.

Imaging in NAFLD: Although ultrasound is very inexpensive and widely accessible, it is less sensitive at detecting people with mild (30%) steatosis or obesity (BMI of 35–40 kg/m2). Therefore, NAFLD is not necessarily excluded if ultrasonography is negative. A high-quality ultrasound can be extremely sensitive and precise when detecting fatty liver. A hyperechoic liver (bright) is the typical finding. However, this discovery is exposed (85–95%) but non-specific (positive predictive value: 62%).[19]

The sonographic findings are graded as follows:[20]

- **Grade 0:** normal echogenicity.
- **Grade 1:** slight diffuse increase in fine echo's in liver parenchyma with normal visualization of the diaphragm and intra hepatic blood vessels borders.
- **Grade 2:** moderate diffuse increase in fine echo's in liver parenchyma with slightly impaired visualization of the diaphragm and intra hepatic blood vessels borders.
- **Grade 3:** marked diffuse increase in fine echo's in liver parenchyma with poor or non-visualization of the diaphragm, intra hepatic

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blood vessels borders and posterior lobe of the liver.

A liver iron deposit may make a CT scan less accurate in identifying fatty liver or even the level of fat infiltration. Hepatic steatosis reduces the CT attenuation of the liver. Because of those characteristics, it can be diagnosed with a 76% positive predictive value. The finest and most expensive imaging test for fatty liver is an MRI.[21] The limited benefits of MRI are weighed against the more widely available and cheaper ultrasonogram.[22]

MATERIAL AND METHODS

This study was set up as a hospital-based exploratory investigation at the Cumilla Medical College and Hospital's Department of Medicine in Cumilla, Bangladesh, for six months, from July 1 to December 31, 2012. 50 (Fifty) admitted adult patients (male and female) with type2 DM, and NAFLD had been considered. Our sampling strategy was purposeful.

Inclusion criteria

From July to December 2012, all patients with type2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease (NAFLD) were admitted to the Cumilla Medical College and Hospital's Department of Medicine and were prepared to provide informed permission.

Exclusion criteria

Alcoholism, established hepatic illness, HBsAg and Anti-HCV positivity, a history of ingesting hepatotoxic drugs, and a refusal to provide informed permission were the exclusion criteria.

Age, sex, height, weight, waist-hip ratio (WHR), body mass index (BMI), smoking, blood pressure (BP), and fasting lipid profile were significant factors. Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), HBsAg, Anti-HCV, ECG, and Blood Glucose Fasting and 2 hours after breakfast/75gm glucose load were vital variables.

Operational definitions

Non-alcoholic fatty liver disease (NAFLD) was diagnosed by ultrasound examination of the liver and sonographic findings23 graded as follows, Grade 0, Grade 1, Grade 2 and Grade 3.

Dyslipidemia

Total cholesterol - >200mg/dl

HDL- cholesterol- <40 mg/dl (male), <50mg/dl (female)

Triglyceride- >150mg/dl

LDL- cholesterol- >130mg/dl

Hypertension: Patients who used antihypertensive medication upon admission or whose blood pressure was higher than 140/90 mmHg were considered to have hypertension.

Data collection tool and technique

A medical history, clinical examination, and following laboratory tests were used to gather information. All participants were made aware of the study, and their consent was obtained using a consent form. Data were collected using a deliberate non-probability sampling technique. For each patient, a completed data collection form was used to capture

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demographic information such as age, sex, WHR, BMI, hypertension, diabetes, smoking habit, family history, and previous CVD history. All patients had complete physical examinations. Blood glucose (fasting and 2 hours after breakfast/75gm glucose load), fasting lipid profile, ECG, serum creatinine, Anti-HCV, HBsAg, and liver enzymes (ALT, AST, ALP) were all tested. Ultrasonogram of the hepatobiliary system was carried out in all patients in Radiology Department using GE LOGIQ 200 pro series ultrasonography machine. All the information was recorded in the data collection form.

Statistical analyses

Quantitative data were expressed as mean and standard deviation, while qualitative data were expressed as frequency distribution and percentage. All data were systematically recorded. Version 17.0 of SPSS (Statistical Program for Social Science) was used for the statistical analysis. If comparisons were required between the two groups or between two categories within the same group, categorical data were subjected to the chi-square test (with correction if values in the cells were less than five). Statistically significant differences were those with a p-value of 0.05 or less.

Ethical considerations

The Bangladesh College of Physicians and Surgeons (BCPS) approved the research protocol before the start of this investigation. Informed consent was obtained from each participant after each patient had been informed of the study's goals and objectives in a readily understood local language. It ensured that everyone was informed and that records were kept private. The technique enabled the doctor and the patients to develop a logical strategy for patient care.

RESULTS

Patients were stratified according to their grade of NAFLD into Group A (grade-1 NAFLD), Group B (grade –2 NAFLD) and Group C (grade -3 NAFLD) and they were analyzed as follows:

Table 1: Prevalence of demographic &clinical profile of patients according to grade of NAFLD

Parameter	Group A		Group B		Group C		p values*
	Number	%	Number	%	Number	%	
Total number (n= 50)	27	54	16	32	7	14	_
Male	9	33.33	6	37.5	3	42.86	_
Female	18	66.66	10	62.5	4	57.14	_
Age (years)	52.89 ± 12.17		55.44 ± 6.6		60.29 ± 9.14		_
Family history of CVD risk factors	13	48.15	9	56.25	5	71.42	0.1204
Smoking	11	40.74	8	50.00	4	57.14	0.2254
Hypertension	17	62.96	11	68.75	7	100	0.0083
WHR (≥ 0.9 –male; ≥0.8 -female)	23	71.88	16	100	7	100	0.0091
BMI ≥ 23kg/m2	15	55.56	16	100	7	100	0.0006

*Chi-square test was done to measure the level of significance.

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Patients of Group B and Group C were with higher age than Group A. Hypertension (p value = 0.0083), WHR (p value = 0.0091) and obesity (p value = 0.0006) were significantly higher in Group B and Group C. No significant association were found between smoking or family history of CVD risk factors (p value> 0.05) and increasing grade of NAFLD.

Table 2: Prevalence of biochemical profile of patients according to grade of NAFLD

Parameter	Group A		Group B		Group C		p values*
	Number	%	Number	%	Number	%	
Total number	27	100	16	100	7	100	_
Total Cholesterol ≥200mg/dl	6	22.22	8	50	5	71.42	<0.0001
HDL-C <40 mg/dl(male) <50mg/dl(female)	25	92.59	14	87.5	7	100	0.6804
LDL-C >130 mg/dl	23	85.19	15	93.75	7	100	0.5888
Triglyceride ≥150 mg/dl	20	74.07	14	87.5	7	100	0.1433
ALT (10 – 50) U/L	3	11.11	10	62.5	7	100	<0.0001
AST (10 – 45) U/L	4	14.81	9	56.25	6	85.71	<0.0001
ALP (40 – 125) U/L	1	3.7	2	12.5	4	57.14	<0.0001

*Chi-square test was done to measure the level of significance.

Table showing increasing grades of NAFLD were significantly associated with increasing levels of serum total cholesterol and liver enzymes (p value< 0.0001).

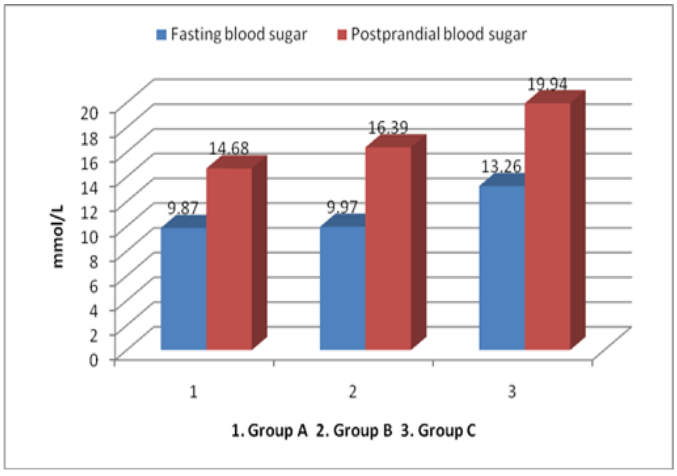

Figure 1: Average blood glucose status in different grade of NAFLD

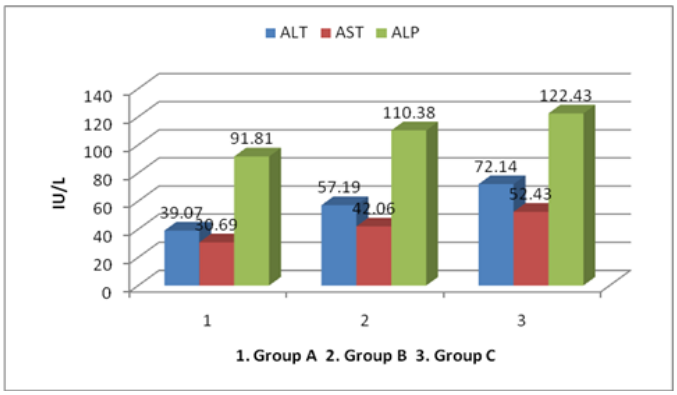

Figure 2: Pattern of average liver enzymes levels in different grade of NAFLD

This figure shows that glycemic control was poor with increasing grade of NAFLD. The average Fasting Blood Sugar in Group A, Group B and Group C were 9.87±2.6, 9.97±2.95 and 13.26±5.48 (mmol/L) respectively and post prandial /after 75 gm glucose load were

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Page no- 151-162 | Section- Research Article (Medicine)

14.68±4.1, 16.39±3.93 and 19.94±5.79 (mmol/L) respectively.

The above figure indicates mean liver enzyme (ALT, AST & ALP) levels were within normal limit in Group A. In Group B only mean ALT level was raised. But in Group C mean ALT, AST levels were raised and mean ALP level was at upper normal limit.

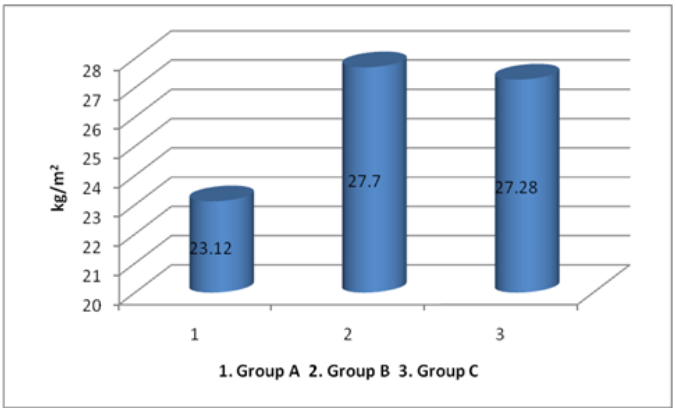

Figure 3: Average BMI statuses in different Groups of patients

The figure shows average BMI was higher in all three groups and with increasing the grade of NAFLD (Group B and Group C), BMI were also raised.

DISCUSSION

Accumulating evidence suggest that NAFLD could be linked to accelerated atherogenesis through the presence of abnormal lipoprotein metabolism. We also have found that a significant proportion of our study population are dyslipidemia, as 41 (82%) and 46 (92%) patients have serum triglyceride >150mg/dl and serum HDL <40mg/dl (in male) and <50mg/dl (in female) respectively. These findings were much higher than reported by AK Agarwal et al.[24] They found 54.9% and 50.7% patients to have hypertriglyceridemia and low serum HDL levels respectively. On the other hand, high levels of serum total cholesterol are present in 19 (38%) patients in our study. Similar observation was reported by Duseja et al,[25] who reported hypercholesterolemia in 32% of patients. In current study, serum LDL cholesterol level is elevated in 18% of study subjects. Roli Agrawal et al reported similar observation.[26] Previous studies have shown that diabetes mellitus increases the risk of cardiovascular disease in women to a greater extent than in men. It seems that DM may alter lipid profiles more adversely in women compared to men.[27] Among our study population, we also find that prevalence of dyslipidemia is higher in females than in males, as 84.38% and 93.75% female patients have hypertriglyceridemia and low HDL level respectively, compared to 77.78% and 88.89% of male patients.

Patients with NAFLD are often identified by asymptomatic elevation of liver enzymes, most frequently of serum alanine aminotransferase (ALT), and nonalcoholic hypertransaminasemia, in which viral or other causes of liver disease are excluded, has been used as a surrogate marker for NAFLD.[28] The results of several recent studies have shown the relationship between ultrasound features of steatosis and elevated liver transaminase levels in patients with diabetes.[29] Our findings confirm these observations. In our study, serum ALT, AST and ALP levels are raised in 38.89%, 38.89% and 11.11% patients among males respectively and 40.63%, 37.5% and 15.63% patients among females respectively.

In current study, patients are subcategorized according to ultrasonography grading of

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Page no- 151-162 | Section- Research Article (Medicine)

NAFLD into group A, group B and group C having grade 1, grade 2 and grade 3 NAFLD respectively. Among 50 patients, 27 (54%) patients are in group A, 16 (32%) patients are in group B and 7 (14%) patients are in group C. Similar observations were reported by Roli Agrawal et al and Mahaling et al.[30,31]

In group A, 13 (48.15%) patients have positive family history of CVD risk factors, compared to 9 (56.25%) patients in group B and 5(71.42%) patients in group C. 11(40.74%) patients in group A are smoker, compared to 8(50%) patients in group B and 4(57.14%) patients in group C. These observations indicate that no significant association is present between smoking or family history of CVD risk factors (p value> 0.05) and increasing grade of NAFLD. Similar findings were reported by Acikel et al.[32] They found 53% smoker in grade 1 and 60% smoker in grade 2-3 NAFLD patients.

Among our study subjects, 62.96%, 68.75% and 100% patients are hypertensive in group A, group B and group C respectively, indicating positive association between hypertension and increasing grades of NAFLD (p value – 0.0083). These findings didn't match with study where reported 20% hypertensive patients in grade 1 and 23.5% in grade 2-3 (p value – 0.69).[33]

Using a cut off point for abdominal or central obesity of WHR ≥ 0.9 for males and ≥ 0.8 for females, the prevalence is significantly higher in group B and C subgroup, as compared to group A (100% vs 71.88%) (p value <0.0091). Mean WHR ≥ SD is 0.91 ± 0.39, 0.97 ± 0.41 and 0.98 ± 0.35 in group A, group B and group C respectively. Similar observations were seen by AK Agarwal et al.[34,35] In present study, average BMI among different subgroups of patients is 23.12 ± 3.0 kg/m2, 27.7 ± 3.5 kg/m2 and 27.28 ± 3.9 kg/m2 in group A, group B and group C respectively.

Using a cut off point for obesity of BMI ≥ 23 kg/m2, the prevalence is significantly higher in group B & C, as compared to group A (100% vs 55.56%) (p value–0.0006). So, it is observed that higher grade of fatty infiltration is significantly associated with increased grade of obesity. These findings resemble with the findings of Wanless36 who reported that the degree of fatty liver correlate with degree of obesity.

In current study, raised level of serum total cholesterol is present in 22.22% patients in group A, compared to 50% patients in group B and 71.42% patients in group C. So, it is observed that increasing grade of NAFLD is significantly associated with increasing level of serum total cholesterol (p value < 0.0001). Similar finding was reported by Mahaling et al.[33] They observed that increasing grades of NAFLD were significantly associated with increasing level of serum total cholesterol (p value – 0.001). But Acikel et al,[34] found no significant association (p value – 0.093).

In group A, group B and group C patients, low serum HDL level is present in 92.59%, 87.5% and 100% patients respectively, and high LDL level is present in 85.19%, 93.75 and 100% patients respectively. These observations indicate that no significant association is present between low HDL levels (p value – 0.6804) or high LDL levels (p value – 0.58) and increasing grades of NAFLD. Similar findings were reported by Acikel et al.[34] They also found no significant association between low HDL levels (p value – 0.11) or high LDL levels (p value – 0.08) and increasing grades of

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Page no- 151-162 | Section- Research Article (Medicine)

NAFLD. But our findings didn't match with Mahaling et al.[33] They found that increasing level of serum LDL (p value – 0.000) and decreasing HDL (p value – 0.000) were significantly associated with increasing grades of NAFLD.

In our study we see that no significant association is present between increasing serum triglyceride levels (p value – 0.1432) and increasing grades of NAFLD. This resembles with the report of Mahaling et al.[33] But Acikel et al34 found significant association between increasing serum triglyceride level (p value – 0.0001) and increasing grade of NAFLD. Another Indian study by Sen A et al,[37] found that increasing grades of NAFLD were significantly associated with increasing levels of serum total cholesterol (p value < 0.0001), triglyceride (p value < 0.0001) and decreasing HDL (p value – 0.002). But they found no significant association between serum LDL level (p value – 0.19) and increasing grades of NAFLD.

An Indian study by AK Agarwal et al,[28] demonstrated that liver enzymes were higher in grade 2 than in grade 1 NAFLD patients. These resembles with our observations. In our study we find that in group A 11.11% patients have raised serum ALT level compared to 62.5% in group B and 100% in group C. Serum AST level is raised in 14.81%, 56.25% and 85.71% patients in group A, group B and group C respectively. Serum ALP level is raised in 3.7% group A patients compared to 12.5% group B and 57.14% group C patients. So, it is observed that, in current study increasing grades of NAFLD are significantly associated with increasing levels of serum ALT (p value <0.0001), AST (p value < 0.0001) and ALP (p value < 0.0001). But Acikel et al,[34] found no significant association between liver enzymes and increasing grades of NAFLD.

As NAFLD is strongly associated with insulin resistance, patients with type2 DM and NAFLD often have poor glycemic control compared to their counterparts without NAFLD.[38,39,40] The presence of NAFLD in people with type2 DM often makes it difficult to obtain good glycemic control. The intrahepatic triglyceride content is the major determinant in explaining the amount of insulin needed to achieve good glycemic control in type2 DM patients. In fact, in insulin treated T2DM patients with stable glycemic control, it has been demonstrated that the intrahepatic triglyceride content was more closely correlated with the daily insulin dose and the ability of insulin to suppress hepatic glucose production and better explained the interindividual variation in insulin requirements.[41]

In our study we see that, mean fasting blood glucose is 9.87 ± 2.6, 9.97 ± 2.95 and 13.26 ± 5.48 mmol/L in group A, group B and group C patients respectively. Mean postprandial blood glucose is 14.68 ± 4.1 mmol/L in group A compared to 16.39 ± 3.93 mmol/L in group B and 19.94 ± 5.79 mmol/L in group C. So, these observations indicate that glycemic control is poorer in group B and C than in group A. Similar findings were reported by AK Agarwal et al,[28] who found that patients with grade 2 disease had poorer glycemic control.

CONCLUSIONS

NAFLD is associated with an increased risk of developing cardiovascular disease, which augments as the hepatic damage progresses.

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The presence of NAFLD would predict a higher atherogenic risk regardless of the other components of the MS. It is probable that NAFLD may not be a marker of CVD. Still, it may indeed be involved in its pathogenesis. Regardless of their liver function tests, patients with NAFLD should be considered at a higher risk of developing CVD complications.

Limitations of the study

Most crucially, there were a few participants in the study group. Confirming these findings in an expanded population is crucial. However, the study's subjects were all from the same ethnicity, which validates the results. However, it is also important to emphasize that liver biopsy was not used to confirm the diagnosis of NAFLD, which was made based on ultrasonography. Although research indicates that diagnosing NAFLD rarely requires a liver biopsy.[41]

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Page no- 151-162 | Section- Research Article (Medicine)

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