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FATTY LIVER DISEASE IN TYPE 2 DIABETES AMONG SAMPLE OFIRAQI PATIENTS

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ABSTRACT

Objective: To assess the prevalence of non-alcoholic fatty liver disease in type II diabetes mellitus patients. **Study Design:** A Prospective cross-sectional Study. **Place and Duration:** Department of Medicine in Al-Yarmouk teaching hospital Baghdad, from 1st September 2020 to 1st March 2021. **Methodology:** Patients presenting with diabetes mellitus type II were divided into two groups based on the presence or absence of non-alcoholic fatty liver disease depending on abdominal ultrasound examination. Age, gender, body mass index, presence of hypertension, plasma aspartate aminotransferase, plasma alanine aminotransferase, plasma alkaline phosphatase, plasma gama glutamyl transferase, serum albumin, plasma cholesterol, plasma triglycerides, plasma low density lipoprotein, plasma high densitylipoprotein and glycosylated haemoglobin HbA1c were the variables calculated. **Results:** Out Of 100 patients with T2DM, 52 patients (52%) were found to have changes of fatty liver disease in abdominal ultrasonography examination. The mean age of fatty liver group was 54.58±7.42 year and that of non-fatty liver group was 51.33± 9.69 year. The mean BMI of fatty liver group was 27.54±3.17 and that of non-fatty liver group was 24.58± 1.60. The mean HbA1c of fatty liver group was 8.97±0.777 and that of non-fatty liver group 7.37± 0.744.The mean serum bilirubin of fatty liver group was 1.08±0.255 and that of non-fatty liver group was 0.850±0.185 .The mean AST of fatty liver group was 42.35±5.691 and that of non-fatty liver group was 31.417± 3.426.The mean ALT of fatty liver group was 42.19±11.472 and that of non-fatty liver group was 32.08± 6.283.The mean ALP of fatty liver group was 139.65±34.325 and that of non-fatty liver group was 143.5± 52.625.The mean GGT of fatty liver group was 22.65±12.15 and that of non-fatty liver group was19.58± 9.35.The mean total cholesterol of fatty liver group was 210.115± 21.406 and that of non- fatty liver group was 175.5± 8.570.The mean total TG of fatty liver group was 201.65 ± 32.75 and that of non-fatty liver group 139± 23.4).The mean total HDL of fatty liver group was 39.154 and that of non-fatty liver group was 44.333.The mean LDL of fatty liver group was 117.731 and that of non-fatty liver group was 93.667. **Conclusion:** NAFLD is highly prevalent among patients with T2DM. Overweight or obesity, abnormal cholesterol levels and poor glycaemic control were significantly associated with NAFLD. **Keywords:** Non-alcoholic fatty liver disease, Diabetes mellitus, Prevalence.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most highly prevalent chronic liver disorders worldwide, irrespective of age, gender, and ethnicity.[1] NAFLD is characterized by the deposition off at in the liver, leading to a spectrum of disorders including simple steatosis, steatohepatitis, cirrhosis, and hepatocellular carcinoma (HCC) in the absence of excessive alcohol intake.[2] The prevalence of NAFLD is variable depending on the diagnostic criteria used to define NAFLD in the general population. The prevalence is almost 15–20 % based on derangement of hepatic transaminase levels and reaches to20–46 % when hepatic ultrasonographic changes were used to define NAFLD.[3,4] Diabetes mellitus (DM) is a well-known risk factor for NAFLD, in addition to obesity, hyperlipidaemia, and metabolic syndrome.[1] The prevalence of NAFLD in patients with type 2 diabetes mellitus (T2DM) worldwide was estimated at 34–94 %.[5] This common association could be explained by the defective lipid metabolism with triglyceride deposition in the liver, as a result of insulin resistance.[6] Patients with T2DM who have NAFLD are at a higher risk of developing advanced stages of liver disease, including fibrosis, cirrhosis, and hepatocellular carcinoma, in comparison to non-diabetic patients.[1,7] The two key pathophysiologic abnormalities associated with insulin resistance that play a role in the genesis of a fatty liver are hyperinsulinemia and increased free fatty acid delivery to the liver.[8] The mortality rate of diabetic patients due to cirrhosis is more than twice the general population and patients with both NAFLD and DM have a poorer prognosis in terms of higher rates of cirrhosis and mortality.[9] NAFLD is strongly associated with

overweight/obesity and insulin resistance. However, it can also occur in lean individuals and is particularly common in those with a paucity of adipose depots (i.e., lipodystrophy).[10] NAFLD is histologically similar to alcoholic liver disease, but by definition it occurs in the absence of excessive alcohol consumption (typically, a threshold of < 20 g/day for women and < 30 g/day for men is adopted) and is not due to other identifiable causes of fatty liver such as hepatitis C and certain medications.[11]

Histological NASH has been found in 3–16% of apparently healthy potential living liver donors in Europe and 6– 15% in the USA. Overall, NAFLD is estimated to affect 20–30% of the general population in Western countries and 5–18% in Asia, with about 1 in 10 NAFLD cases exhibiting NASH.[11] The risk of developing cirrhosis is extremely low in individuals with chronic hepatic steatosis but increases as steatosis becomes complicated by histologically conspicuous hepatocyte death and inflammation (i.e., non-alcoholic steatohepatitis).[12]

NASH itself is also a heterogeneous condition; sometimes it improves to steatosis or normal histology, sometimes it remains relatively stable for years, but sometimes it results in progressive accumulation of fibrous scar that eventuates in cirrhosis.

NAFLD is the leading cause of liver dysfunction in the non-alcoholic, viral hepatitis-negative population in Europe and North America and is predicted to become the main aetiology in patients undergoing liver transplantation during the next 5 years.[11] The high NAFLD burden is caused not only by these hepatic complications but also by the associated increased cardiovascular morbidity and mortality in patients with NAFLD.[13,14] Therefore, it is important for physicians to be aware of the high likelihood that their patients with type 2 diabetes have NAFLD, as this is another potential complication that requires attention.

PATHOGENESIS AND PATHOPHYSIOLOGY

The mechanisms underlying the pathogenesis and progression of NAFLD are not entirely clear. The initiating events in NAFLD are basedon the development of obesity and insulin resistance, leading to increased hepatic free fatty acid flux. This imbalance between the rate of import/synthesis and the rate of export/catabolism of fatty acids in the liver leads to the development of steatosis. Cellular damage triggers cell death and inflammation, which leads to stellate cell activation and development of hepatic fibrosis that culminates in cirrhosis. As with many other liver diseases, heritable and environmental factors clearly impact susceptibility to hepatic steatosis, NASH, and disease progression to liver fibrosis, and liver cancer.[15]

Several genetic modifiers of disease severity have been identified, with PNPLA3 (a gene that encodes an enzyme involved in intracellular trafficking of lipids) and its product, adiponutrin, being the best validated.[16] Certain variants in PNPLA3 consistently correlates with susceptibility to hepatic steatosis, cirrhosis, and liver cancer. Polymorphisms in other genes involved in lipid homeostasis (e.g., TM6SF2 and MBOAT7) are also emerging as potential genetic risk factors for NAFLD. Like cirrhosis caused by other liver diseases, cirrhosis caused by NAFLD increases the risk for primary liver cancer.[17]

Both hepatocellular carcinoma and intrahepatic cholangiocarcinoma (ICC) have also been reported to occur in NAFLD patients without cirrhosis, suggesting that NAFLD per se may be a premalignant condition. NAFLD-related cirrhosis is not limited to adults. It has been well documented in children. As in adults, obesity and insulin resistance are the main risk factors for paediatric NAFLD. Thus, the rising incidence and prevalence of childhood obesity suggests that NAFLD is likely to become an even greater contributor to society's burden of liver disease in the future.[18]

Obesity stimulates hepatocyte triglyceride accumulation by altering the intestinal microbiota to enhance both energy harvest from dietary sources and intestinal permeability. Reduced intestinal barrier function increases hepatic exposure to gut-derived products, which stimulate liver cells to generate inflammatory mediators that inhibit insulin actions. Obese adipose depots also produce excessive soluble factors (adipokines) that inhibit tissue insulin sensitivity. Insulin resistance promotes hyperglycaemia. This drives the pancreas to produce more insulin to maintain glucose homeostasis. However, hyperinsulinemia also promotes lipid uptake, fat synthesis, and fat storage. The net result is hepatic triglyceride accumulation (i.e., steatosis). Triglyceride per se is not hepatotoxic. However, its precursors (e.g., fatty acids and diacylglycerols) and metabolic by- products (e.g., reactive oxygen species) may damage hepatocytes, leading to hepatocyte lipotoxicity. Lipotoxicity also triggers the generation of other factors (e.g., inflammatory cytokines, hormonal mediators) that deregulate systems that normally maintain hepatocyte viability. The net result is increased hepatocyte death. Dying hepatocytes, in turn, release various factors that trigger wound healing responses that aim to replace (regenerate) lost hepatocytes. Such repair involves transient expansion of other cell types, such as myofibroblasts and progenitor cells, that make and degrade matrix, remodel the vasculature, and generate replacement hepatocytes, as well as the recruitment of immune cells that release factors that modulate liver injury and repair.[19]

NASH is the morphologic manifestation of lipotoxicity and resultant wound healing responses. Because the severity and duration of lipotoxic liver injury dictate the intensity and duration of repair, the histologic features and outcomes of NASH are variable. Cirrhosis and liver

cancer are potential outcomes of chronic NASH. Primary liver cancers develop when malignantly transformed liver cells escape mechanisms that normally control regenerative growth. The mechanisms responsible for futile repair (cirrhosis) and liver carcinogenesis are not well understood.[20]

Because normal liver regeneration is an overly complex process, there are multiple opportunities for deregulation and thus pathogenic heterogeneity. To date, this heterogeneity has confounded development of both diagnostic tests and treatments for defective/deregulated liver repair (i.e., cirrhosis and cancer). Hence, current strategies focus on circumventing misrepair by preventing and/or reducing lipotoxic liver injury.[21]

INVESTIGATIONS

Investigation of patients with suspected NAFLD should be directed first towards exclusion of excess alcohol consumption and other liver diseases (including viral, autoimmune, and other metabolic causes) and then at confirming the presence of NAFLD, discriminating simple steatosis from NASH, and determining the extent of any hepatic fibrosis that is present.

Biochemical tests

There is no single diagnostic blood test for NAFLD. Elevations of serum ALT and AST are modest, and usually less than twice the upper limit of normal. ALT levels fall as hepatic fibrosis increases and the characteristic AST: ALT ratio of < 1 seen in NASH reverses (AST: ALT > 1) as disease progresses towards cirrhosis, meaning that steatohepatitis with advanced disease may be present even in those with normal-range ALT levels. Other laboratory abnormalities that may be present include non-specific elevations of GGT, low-titre antinuclear antibody (ANA) in 20–30% of patients and elevated ferritin levels. Although routine blood tests are unable to determine the degree of liver fibrosis/cirrhosis accurately, calculated scores, such as the NAFLD Fibrosis Score and FIB-4 Score, which are based on the results of routinely available blood tests and anthropometrics, have a high negative predictive value for advanced fibrosis/cirrhosis and so can be used to rule out advanced fibrosis in many NAFLD patients. This allows care to focus on those most likely to have advanced disease.[22]

Imaging

Ultrasound is most often used and provides a qualitative assessment of hepatic fat content, as the liver appears 'bright' due to increased echogenicity; sensitivity is limited when fewer than 33% of hepatocytes are steatotic, however. CT, MRI, or MR spectroscopy offer greater sensitivity for detecting lesser degrees of steatosis, but these are resource-intensive and not widely used. No routine imaging modality can distinguish simple steatosis from steatohepatitis or accurately quantify hepatic fibrosis short of cirrhosis.[23]

Liver biopsy

Liver biopsy remains the 'gold standard' investigation for diagnosis and assessment of degree of inflammation and extent of liver fibrosis. The histological definition of NASH is based on a combination of three lesions (steatosis, hepatocellular injury, and inflammation; with a mainly centrilobular, acinar zone 3 distribution. Specific features include hepatocyte ballooning degeneration with or without acidophil bodies or spotty necrosis and a mild, mixed inflammatory infiltrate. These may be accompanied by Mallory–Denk bodies (also known as Mallory's hyaline). Perisinusoidal fibrosis is a characteristic feature of NASH.[24]

Histological scoring systems are widely used to assess disease severity semi-quantitatively. It is important to note that hepatic fat content tends to diminish as cirrhosis develops and so NASH is likely to be under-diagnosed in the setting of advanced liver disease, where it is thought to be the underlying cause of 30–75% of cases in which no specific aetiology is readily identified (so-called 'cryptogenic cirrhosis').[25]

PATIENTS AND METHODS

This cross-sectional study was conducted at the medical department of Al-Yarmouk teaching hospital from September 2020 to March 2021, where 100 patients of both sexes suffered from type 2 diabetes mellitus were checked for fatty liver changes proved by abdominal ultrasound study. The patients with known chronic liver disease (hepatitis B surface antigen or Anti HCV positive), pregnancy, and history of alcohol or drugs which may cause fatty liver were excluded.

A check list was filled after full history, clinical examination and essential laboratory investigation were done.

The check list included: age, gender, hypertensive status of the patients. The patients were divided into fatty liver and non- fatty liver group and were further evaluated by the measurement of BMI, glycosylated haemoglobin (HbA1c), total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), total cholesterol (TC) triglycerides (TG), low density lipoprotein (LDL) and high- density lipoprotein (HDL). Each patient was exposed to abdominal ultrasound examination looking for fatty liver changes using Voluson E6 ultrasound machine in the department of radiology in Al-Yarmouk teaching hospital.

Ethical consideration

This research proposal was fully discussed and approved by the ethical and scientific committee in the Arab board of internal medicine. The agreement of health authority in Al- Yarmouk teaching hospital was taken before starting data collection. A consent was taken from each patient after full explanation of aim of study and ensuring them about confidentiality of the collected data

which would be anonymous and would not be used for any purpose other than this current study.

Statistical analysis

The collected data was entered and analysed into SPSS V24 statistical program.

Descriptive statistics were presented using tables and graphs.

Analytic statistics were presented using chi square test to find out significancy of associations between related categorical variables. Independent samples T test was used to find out significancy of differences between related numerical variables. P value less than 0.05 was considered as discrimination point of significancy.

RESULTS

A total 100 patients with T2DM were enrolled during the study period.

Out of 100 patients, 44 were males and 56 were females. Noneof the subjects enrolled in this study had histories of alcohol consumption. Of 100 patients with T2DM, 52 (52%) were found to have changes of fatty liver disease in abdominal ultrasonography examination. Figure (1)

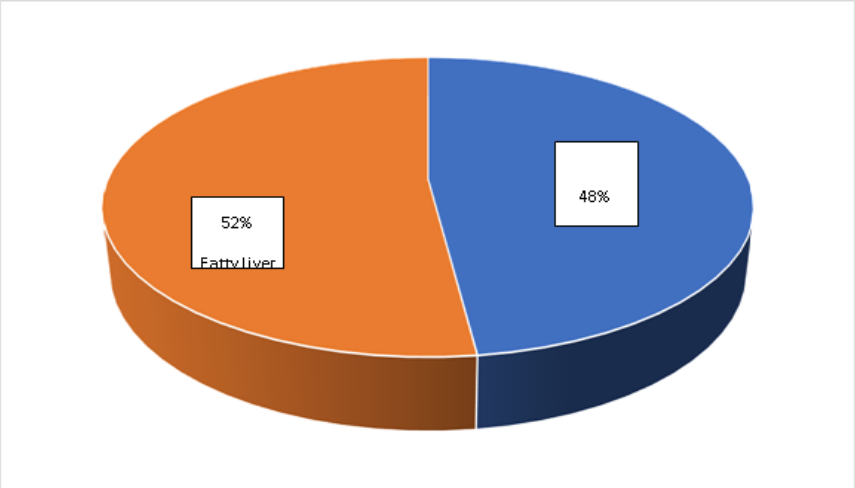

Figure 1: distribution of cases according to studied group.

Prevalence of fatty liver disease was not significant according to the gender (20 males and 32 females) P value 0.246, as shown in table (1) and figure (2).

Table1: Association between gender and fatty liver status.

	Normal		Fatty liver		
	N	%	N	%	P Value
Male	24	54%	20	46%	
Female	24	43%	32	57%	0.246

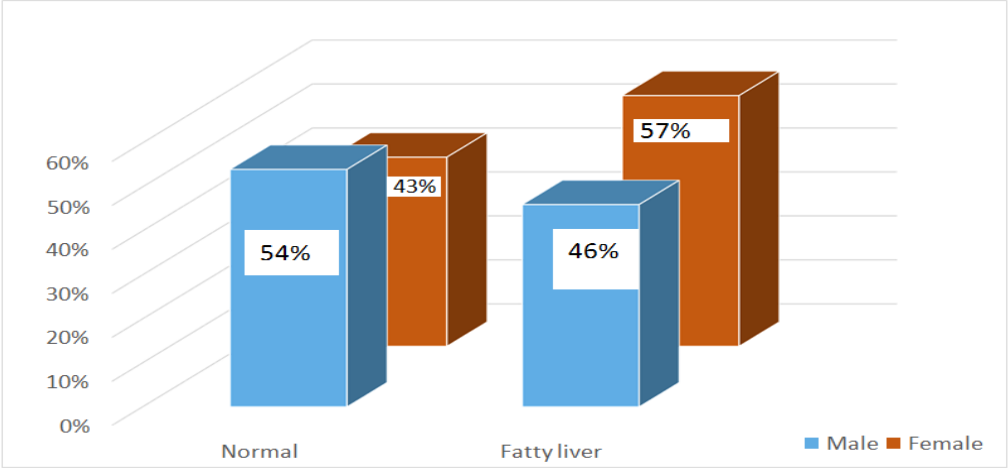

Figure 2: Association between gender and fatty liver status.

The mean age of fatty liver group was 54.58±7.42 year which is not significantly higher than that of non-fatty liver group (51.33± 9.69 year), p value=0.065.

The mean BMI of fatty liver group was 27.54±3.17 which is significantly higher than that of non-fatty liver group (24.58± 1.60), p value=0.001.

The presence of hypertension is more in patients with fatty liver than in normal patients, figure (3).

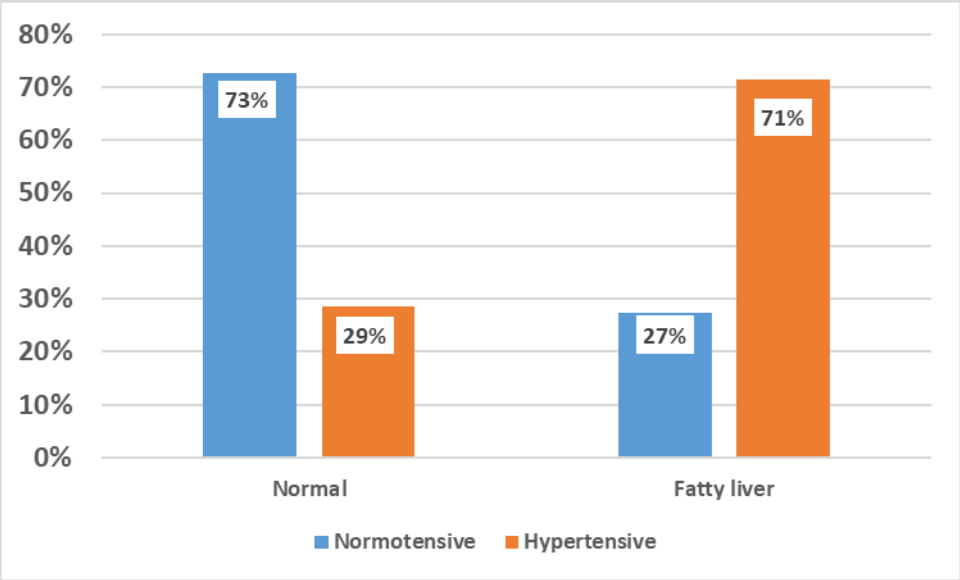

Figure 3: Association between fatty liver and Hypertension.

The mean HbA1c of fatty liver group was 8.97±0.777 which is significantly higher than that of non-fatty liver group (7.37± 0.744), p value=0.001.

The mean serum bilirubin of fatty liver group was 1.08±0.255 which is significantly higher than that of non-fatty liver group (0.850± 0.185), p value=0.001.The mean AST of fatty liver group was 42.35±5.691 which is significantly higher than that of non-fatty liver group 31.417± 3.426), p value=0.001.

The mean ALT of fatty liver group was 42.19±11.472 which is significantly higher than that of non-fatty liver group 32.08± 6.283), p value=0.001.The mean ALP of fatty liver group was 139.65±34.325 which is not significantly differs that of non- fatty liver group 143.5± 52.625), p value=0.669.

The mean GGT of fatty liver group was 22.65±12.15 which is not significantly differs that of non-fatty liver group 19.58± 9.35), p value=0.162.

The mean total cholesterol of fatty liver group was 210.115± 21.406 which is significantly higher than that of non-fatty liver group 175.5± 8.570), p value=0.001.The mean total TG of fattyliver group was 201± 21.654 which is significantly higher than that of non-fatty liver group 139± 23.4), p value=0.001.

The mean total HDL of fatty liver group were found to be significantly lower than that of non-fatty liver group, p value=0.001.The differences between means of studied numerical variables are shown in table (2).

Table 2: Differences between means of studied numericalvariables according to fatty liver state.

	Group	N	Mean	Std. Deviation	P value
Age	Fattyliver	52	54.58	7.421	0.065
	Normal	48	51.33	9.696	
BMI	Fattyliver	52	27.535	3.1701	0.001
	Normal	48	24.583	1.6004	
HbA1c	Fatty liver	52	8.973	0.7769	0.001
	Normal	48	7.371	0.7435	
Bilirubin	Fattyliver	52	1.084	0.2547	0.001
	Normal	48	0.850	0.1849	
AST	Fattyliver	52	42.346	5.6910	0.001
	Normal	48	31.417	3.4260	
ALT	Fattyliver	52	42.192	11.4721	0.001
	Normal	48	32.083	6.2835	
ALP	Fatty liver	52	139.654	34.3259	0.669
	Normal	48	143.500	52.6255	

GGT	Fatty liver	52	22.654	12.1524	0.162
	Normal	48	19.583	9.3532	
Totalchol.	Fatty liver	52	210.115	21.4061	0.001
	Normal	48	175.500	8.5701	
TG	Fatty liver	52	201.654	32.7569	0.001
	Normal	48	139.000	23.4003	
HDL	Fatty liver	52	39.154	5.5356	0.001
	Normal	48	44.333	6.2068	
LDL	Fatty Liver	52	117.731	14.0798	0.001
	Normal	48	93.667	12.3725	

DISCUSSION

In the present study, the prevalence of NAFLD in 100 patients of Type 2 diabetes mellitus was 52% based on abdominal ultrasound examination. This is similar to other studies that have reported the prevalence of NAFLD among DM patients at approximately 50% (ranged between 29.6% and 87 %).[26]

There were no significant differences in sex distribution between the two groups. This contrasts with previous studies where the prevalence of NAFLD among men and women were found to be varied. Whereas in some, NAFLD was considered to be more common among women[27,28], in others it was reported to be more prevalent among men.[29,30] In recent studies, as in ours, it has been suggested that both sexes might be afflicted equally.[27]

BMI was significantly higher in patients with NAFLD (27.54±3.17) than those without NAFLD (24.58± 1.60 *P* = 0.001). Obesity is the most common entity associated with NAFLD that has been reported in various other studies.[31,32,33]

This study found that glycaemic control in term of HBA1C in patients with NAFLD were statistically significant as compared to non-NAFLD. (*P* = 0.001). This observation suggests a causal relationship between glycaemic control and fatty liver and corresponds with the results of previous studies.[34,35]

In our study, there was 27% of normotensive patients had fatty liver changes, while 71% of hypertensive patients had fatty liver changes, highly significant statistical association was noticed between being hypertensive and getting fatty liver, p value=0.001 We observed mean cholesterol, triglyceride, HDL, and LDL levels defer significantly between the two groups. Dyslipidaemias are commonly associated with NAFLD. Previous Studies have shown that 20–92% of patients diagnosed with NAFLD have hyperlipidemia[30], including hypertriglyceridemia, hypercholesterolemia, or both.[36]

Hyperlipidaemia along with diabetes and obesity increases the risk ofNAFLD development.[37]

We found that transaminase levels were statistically significant between the NAFLD and non-NAFLD groups (*P* = 0.001 for both). Previous studies have shown that mild to moderate elevations of serum aminotransferase are common in NAFLD[38], and normal values can be found in up to 78% of patients at any time, even when complete histological findings are present[39], suggesting a poor correlation between transaminase levels and disease severity.[38]It is known that NASH and significant fibrosis occurs in NAFLD patients with normal ALT range.[40,41] One possibility is that those were falseresults because of the use of inappropriate ALT cut-offs. In a retrospective study of 51 NAFLD patients with normal ALT range, 12 had bridging fibrosis and six had cirrhosis.[41] However, the ULN of ALT in that study was 75 IU/l for men and 52 IU/l for women. Mean ALT in the 'normal ALT' group was 41 IU/l, which would be considered abnormal according to current standard. Another study including 64 patients with normal ALT (<40U/l) showed that patients with normal ALT had less severe steatosis and necroinflammation, but the fibrosis was similar to that of patients with increased ALT.[42] In another retrospective study of 233 obese women undergoing liver biopsies during bariatric surgery, although patients with ALT below 19 U/l appeared to have less severe disease, 23% and 5% still had NASH and advanced fibrosis respectively. Even among patients with ALT below 0.5 × ULN, 42% had possible NASH and 16% had significant fibrosis. Low-normal ALT may give clinicians and patients false reassurance of inactive disease. In a recent multi-centre study including 733 patients with biopsy-proven NAFLD, ALT level was not found to be an independent factor discriminating the presence of advanced fibrosis.[42] NAFLD patients with normal ALT are still at risk of progressive and severe hepatic disease.

CONCLUSION

NAFLD is highly prevalent in T2DM patients. Obesity, low HDL level, elevated TG level and poor glycaemic control are associated with an increased risk for developing NAFLD. Attention should be paid to minimize the burden of NAFLD among diabetic patients. Weight reduction, with lifestyle modification and health education for T2DM patients, are recommended strategies that play a crucial role in the prevention of NAFLD. Early treatment of abnormal lipid parameters in the form of controlling HDL and TG levels is important

to prevent NAFLD and its negative impact on the patient's life.

Recommendation

1- Clinical spectrum of NAFLD needs continued research to determine its pathogenesis and to improve diagnostic modalities.

2- It is hoped that improved imaging techniques and the discovery of new serum biomarkers, as well as the development of clinical algorithms, will enable a more accurate diagnosis of NASH without the need for a liver biopsy.

3- A multimodal treatment plan that targets obesity, insulin resistance,hyperlipaemia, and hypertension might be the best option.

Limitation

A limitation of this study is that the diagnosis of NAFLD was done by ultrasonography and exclusion of known etiologic factors of chronic liver disease, but it was not confirmed by liver biopsy. It is known that none of the radiological features can distinguish precisely between steatohepatitis and other types of NAFLD and only liver biopsy can assess the severity of hepatic damage and the prognosis. However, liver biopsy is not easily applied in large epidemiological studies. On the contrary, ultrasonography is by far the most common tool of diagnosing NAFLD in clinical practice and has a very good sensitivity and specificity in detecting moderate and severe steatosis in patients with the biopsy-proven disease. Indeed, it has been reported that the presence of >33% fat on liver biopsy is optimal for ultrasound detection of steatosis, although ultrasonography isn't completely sensitive, particularly when hepatic fat infiltration is <33%.

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