Journal of Conventional Knowledge and Holistic Health
(Contents available at www.globalscitechocean.com)

Research article

Exploring the role of type II diabetes mellitus and obesity as risk factors in patients afflicted with fatty liver disease

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Article history

Received : October 16, 2023
Accepted : November 20, 2023

Keywords

Cirrhosis
Cross-sectional study
Fatty liver disease
Steatositis score
Type II diabetes mellitus

DOI: 10.53517/JCKHH.2581-3331.722023237

ABSTRACT

Fatty Liver Disease (FLD) frequently coexists with Type 2 Diabetes Mellitus (T2DM) and Obesity, often considered as a manifestation of the metabolic syndrome. FLD encompasses a spectrum of presentations, ranging from simple steatosis to steatohepatitis and cirrhosis, with a staggering prevalence of 75% among T2DM patients. Overweight/obesity and insulin resistance (IR) are closely associated with FLD. Noninvasive assessment and disease staging rely on factors such as age, sex, lipid profile, BMI, and diagnostic modalities like Steatositis scores and Stiffness values, aiding early FLD detection and fibrosis prediction. The management of FLD in the context of T2DM and Obesity primarily targets improving IR and glycemia, serving as a key treatment approach. This study aimed to investigate the relationship between T2DM and Obesity as risk factors for Fatty Liver Disease patients. A cross-sectional study was conducted from November 2022 to March 2023, involving 90 patients aged ≥30 years with a history of FLD, comprising 45 with T2DM and 45 with Obesity, selected from the Gastroenterology and Hepatology Teaching Hospital in Al-Najaf City, Iraq. All patients were diagnosed by physicians, and Fibro Scan results were used for examination and assessment. The FLD patient group was categorized into subgroups based on the presence of T2DM and Obesity. Fasting blood glucose and lipid profiles were measured using the colorimetric method. The study findings revealed no statistically significant difference in mean age between the two groups. However, significant differences were observed between the T2DM and Obesity groups in terms of mean BMI, Steatositis score, Stiffness, Fasting blood sugar, triglycerides, total cholesterol, LDL, and HDL. Steatositis score demonstrated a significant correlation with BMI (r=0.286, p=0.006), a negative association with serum TG level (r=-0.07, p=0.01), and a positive correlation with TC level (r=0.80, p=0.0001). Furthermore, the steatositis score positively correlated with Stiffness level (r=0.387, p=0.0001). This study underscores the elevated prevalence of FLD in patients with T2DM and Obesity, shedding light on the risk factors associated with FLD. It emphasizes the need for further large-scale studies to assess the impact of lifestyle modifications, including physical activity and dietary changes, on FLD and glycemic control status.

INTRODUCTION

Fatty liver disease (FLD) and type 2 diabetes (T2DM) often coexist. The prevalence of FLD is 59.67% in T2DM patients (Katsiki et al., 2018). This results in adverse outcomes such as higher rates of mortality due to cirrhosis. FLD includes a spectrum of pathological conditions, which range from simple steatosis (NAFL), nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (Sao and Aronow, 2018).

Fatty liver is also known as hepatic steatosis, it happens when fat builds up in the liver. The liver is the second-largest organ in the body (Katsiki et al., 2018). It helps process nutrients from food and drinks, and filters harmful substances from blood (Sao and Aronow, 2018). Too much fat in the liver can cause liver inflammation, which can damage the liver and create scarring. In severe cases, this scarring can lead to liver failure (Pirmoazen et al., 2020) (Fig. 1). When fatty liver develops in someone who drinks a lot of alcohol, it's known as alcoholic fatty liver disease (AFLD). In someone who doesn't drink a lot of alcohol, it's known as nonalcoholic fatty liver disease (NAFLD) (Han et al., 2020).

Symptoms of fatty liver

Fatty liver can progress through four stages:

1. *Simple fatty liver:* There's a buildup of excess fat in the liver. Simple fatty liver is largely harmless if it doesn't progress.
2. *Steatohepatitis:* In addition to excess fat, there's also inflammation in the liver.

3. *Fibrosis:* Persistent inflammation in the liver has now caused scarring. However, the liver can still generally function normally.
4. *Cirrhosis:* Scarring of the liver has become widespread, impairing the liver's ability to function. This is the most severe stage and is irreversible.

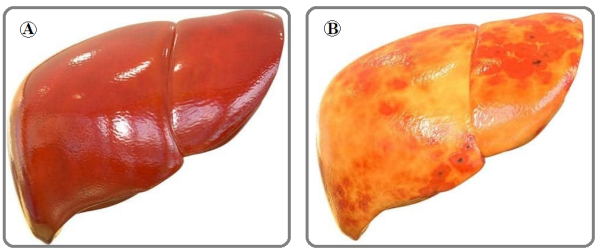

Fig. 1. Liver anatomy. (A). Healthy liver, (B). Fatty liver

Both AFLD and NAFLD present similarly. However, in many cases, fatty liver causes no noticeable symptoms (Lutsiv et al., 2023). Some people with fatty liver disease develop complications, including liver scarring. Liver scarring is known as liver fibrosis (Huang et al., 2021).

The liver damage due to cirrhosis is permanent. Cirrhosis may cause symptoms such as abdominal pain, loss of appetite, weight loss, weakness or fatigue, nausea, itchy skin, yellow skin and eyes, easy bruising or bleeding, dark-colored urine, pale stools, fluid accumulation in the abdomen, swelling (edema) of your legs, web-like clusters of blood vessels under your skin, breast enlargement in men, and confusion.

Environmental factors affect the expression of genes, inducing weight gain. When the capacity of expansion of subcutaneous adipose tissue (AT) is reached, an increased free fatty acids (FFAs) mobilization arises, resulting in visceral and ectopic fat deposition (Huang et al., 2021). One ectopic site is the muscle, where increased FFAs deposition promotes insulin resistance (IR), inhibiting insulin-mediated glucose uptake. On the other hand, AT insulin resistance facilitates lipolysis and increases the flux of FFAs to the liver, inducing hepatic IR and enhancing glucose production, de novo hepatic lipogenesis (Roca-Fernández et al., 2021), VLDL release and atherogenic dyslipidemia. FFAs spill over into the pancreas, causing β-cell dysfunction by lipotoxicity, hyperglycemia and diabetes (the twin cycle hypothesis). Increased liver fat also promotes hepatic glucagon resistance (GR) over the amino acids (AAs) metabolism, reducing ureagenesis and resulting in hyper-aminoacidemia. Increased AAs stimulate glucagon production to compensate for hepatic GR, and a vicious cycle is installed (the liver-pancreas axis). This hyperglucagonemia also leads to an increased hepatic glucose release. The global IR state results in hyperinsulinemia, which may enhance sodium reabsorption and increase sympathetic nervous system activity, contributing to hypertension. Inflamed dysfunctional AT becomes more insulin resistant and releases pro-inflammatory adipokines, while decreasing anti-inflammatory adiponectin (Roca-Fernández et al., 2021).

In the liver, triglycerides and toxic metabolites induce lipotoxicity, mitochondrial dysfunction and endoplasmic reticulum stress, leading to hepatocyte damage, apoptosis and fibrosis. These dysfunctional hepatocytes synthesize and secret the dipeptidyl peptidase 4 (DPP4), which promotes inflammation of AT macrophages and more IR. AAs amino acids, AT adipose tissue, DPP4 dipeptidyl peptidase 4, FFA free fatty acid, GR glucagon resistance, HDL high-density lipoprotein, IR insulin resistance, LDL low-density lipoprotein, NAFLD nonalcoholic fatty liver disease, SAT subcutaneous adipose tissue, SNS sympathetic nervous system, VAT visceral adipose tissue, VLDL very low-density lipoprotein (Roca-Fernández et al., 2021).

Types of fatty liver disease

There are two main types of fatty liver disease: nonalcoholic and alcoholic. Fatty liver can also happen during pregnancy, although this is uncommon.

Nonalcoholic fatty liver disease (NAFLD): NAFLD occurs when fat builds up in the liver of people who don't drink a lot of alcohol (López-Sánchez et al., 2021). If have excess fat in the liver and no history of heavy alcohol use, may receive a diagnosis of NAFLD. If there's no inflammation or other complications, the condition is known as simple NAFLD (Lutsiv et al., 2023). Nonalcoholic steatohepatitis (NASH) is a type of NAFLD. It's when a buildup of excess fat in the liver is accompanied by inflammation.

Alcoholic fatty liver disease (AFLD): Drinking a lot of alcohol damages the liver. Alcoholic fatty liver disease (AFLD) is the earliest stage of alcohol-related liver disease. Alcoholic steatohepatitis (ASH) is a type of AFLD (Lutsiv et al., 2023).

Acute fatty liver of pregnancy (AFLP): Acute fatty liver of pregnancy (AFLP) is when excess fat builds up in the liver during pregnancy. When AFLP develops, it usually appears in the third trimester of pregnancy (López-Sánchez et al., 2021).

Causes of fatty liver disease

In fatty liver disease, excess fat is stored in liver cells, where it accumulates. A variety of factors can cause this fat buildup. Drinking too much alcohol can cause AFLD. Heavy alcohol use can alter certain metabolic processes in the liver. Some of these metabolic products can combine with fatty acids, leading to the formation of types of fat that can accumulate in the liver (Hillenbrand et al., 2015).

In people who don't drink much alcohol, the cause of fatty liver disease is lesser. For these people, it's possible their body produces too much fat or doesn't metabolize fat efficiently enough (Hillenbrand et al., 2015). One or more of the following factors may play a role in people who don't consume much alcohol and develop fatty liver disease: obesity; type 2 diabetes; insulin resistance; high levels of fat, especially triglycerides, in the blood; and metabolic syndrome. Other potential causes of fatty liver include pregnancy, side effects from some types of medications, some types of infections, such as hepatitis C, and certain rare genetic conditions.

Risk factors

The main risk factor for AFLD is drinking heavy amounts of alcohol when defines heavy drinking as 15 or

more drinks per week for men and 8 or more drinks per week for women. Research Trusted Source has found that men who consume 40 to 80 grams of alcohol per day and women who consume 20 to 40 grams of alcohol per day over 10 to 12 years are at a higher risk of severe alcohol-related liver disease (Roerecke et al., 2019). In addition to heavy alcohol consumption, other risk factors for AFLD (Mukhtar et al., 2020) are older age, genetics, obesity, smoking, and a history of certain infections, such as hepatitis C.

The major risk factors for NAFLD are overweight or obesity, insulin resistance, type 2 diabetes, high cholesterol, high triglycerides, and metabolic syndrome (Alam et al., 2021). Other risk factors for NAFLD include older age, having a family history of liver disease, taking Certain medications, such as methotrexate (Trexall), tamoxifen (Nolvadex), and amiodarone (Pacerone), pregnancy, a history of certain infections, such as hepatitis C, polycystic ovary syndrome (PCOS), obstructive sleep apnea, exposure to certain toxins, rapid weight loss, and rare genetic conditions, like Wilson disease or hypobeta-lipoproteinemia (Hillenbrand et al., 2015).

Fatty liver diagnosis

To diagnose a fatty liver, a doctor will take a medical history, conduct a physical exam, and order one or more tests (Gupta et al., 2022).

1. *Physical exam:* To check for liver inflammation a doctor may palpate or press on your abdomen.
2. *Blood tests:* In many cases, fatty liver disease is diagnosed after blood tests show elevated liver enzymes. For example, a doctor may order the alanine aminotransferase test (ALT) and the aspartate aminotransferase test (AST) to check liver enzymes. Elevated liver enzymes are a sign of liver inflammation. Fatty liver disease is one potential cause of liver inflammation, but it's not the only one (Abdullatif et al., 2022).
3. *Imaging studies:* A doctor may use one or more of the imaging tests to check for excess fat or other problems with the liver including an ultrasound exam, CT scan, and MRI scan. They might also order a test known as vibration-controlled transient elastography (VCTE, FibroScan). This test uses low-frequency sound waves to measure liver stiffness.
4. *FibroScan:* (liver elastography) is a type of liver elastography. FibroScan is a special ultrasound technology that measures liver stiffness (hardness) and fatty changes in the liver (Table 1; Fig. 2). FibroScan results are as follows.

    a. Fibrosis (fy-BROH-sis): Scarring in the liver.
    b. Liver stiffness: Hardness of the liver related to liver scarring.
    c. Fatty change: An abnormal buildup of fat in the liver.
    d. Steatosis (STEE-uh-toh-sis): A condition caused by having too much fat in the liver.
    e. CAP score: The way the percentage of fatty change in the liver is measured.
    f. *Liver biopsy:* A liver biopsy is considered the best way to determine the severity of liver disease.

Table 1. FibroScan results

Diagnosis	Liver stiffness result	Fibrosis score	Liver
Fatty Liver Disease (NAFLD or NASH)	2 to 7 kPa	F0 to F1	Normal
	7.5 to 10 kPa	F2	Moderate scarring
	10 to 14 kPa	F3	Severe scarring
	14 kPa or higher	F4	Cirrhosis

Fig. 2. FibroScan (liver elastography)

Controlled Attenuation Parameter (CAP) score is a measurement of fat accumulation in liver for your doctor to further determine steatosis grade. The CAP score ranges from 100 to 400 decibels per meter (dB/m). The table below will help categorize CAP scores into a certain steatosis grade and the range of percentage of fatty change (Table 2).

Table 2. CAP scores into a certain steatosis grade and percentage ranges of fatty change

CAP Score	Steatosis grade	% of liver with fatty change
238 to 260 dB/m	S1	11% to 33%
260 to 290 dB/m	S2	34% to 66%
>260 dB/m	S3	67% or more

MATERIALS AND METHODS

The current cross-sectional study was performed from November 2022 to March 2023. Conducted 90 patients who were ≥30 years old and had a history of fatty liver disease with T2DM (45) and Obesity (45) recruited from Gastroenterology and Hepatology Teaching Hospital in Al–Najaf City, Iraq. All patients were diagnosed by physicians and FibroScan examination reports. The study was approved by the Institutional Ethics Committee with approval number 4959, dated 18/12/2022.

All participants completed a standardized questionnaire to capture clinical and demographic data. Blood samples were collected after a 10-hour or longer overnight fast to measure various factors including Spectrophotometry was utilized to measure levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, as well as serum levels of Glucose.

The statistical analysis was conducted using SPSS 24.0 software. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages. Group characteristics were compared using Student's t-tests for independent samples and one-way ANOVA. Correlation analysis, specifically Pearson Correlation, was performed to determine the correlation coefficients between variables.

RESULTS AND DISCUSSION

This study offers a novel examination in the Najaf population of the role of diabetes regarding its association with steatosis and liver stiffness and considers the confounding role of obesity. The widespread epidemic of obesity and type-2 diabetes is directly linked to the increasing prevalence of FLD which has emerged as the most common chronic liver disease worldwide. At the cellular level, excess lipids accumulate in cytosolic droplets that are stiffer than the aqueous cytosol and might mechanically distort the cell and alter its elasticity (Shoham et al., 2014).

In vivo, liver stiffness measurement is currently employed to determine the extent of liver steatosis and fibrosis. The present findings combining in vitro and in vivo evidence clearly indicate that an increase in liver/hepatocyte stiffness occurs as a direct consequence of the extent of steatosis and the enlarging of lipid droplets, and, in turn, is associated with body/cell dysfunction.

Being overweight and obesity are a typical consequence of excess food intake leading to hypertrophic adipose tissues and visceral fats, the first hallmark of metabolic syndrome. In this condition, the liver rapidly becomes a target for the excess circulating FAs and TGs released from adipose tissue, and it develops into a condition of hepatic steatosis whose severity may progress along with FLD pathophysiology.

A total of 90 participants were enrolled for the study. The mean age and BMI are presented in Table (3-1). Overall, FLD was present in 90 study participants. Moreover, patients having FLD with Type-2 DM were compared with patients having FLD with obesity. There was no statistically significant difference between the two groups regarding mean age. However, there was a statistically significant difference between the two groups in terms of mean BMI, Steatositis score, Stiffness, Fasting blood sugar, triglycerides, total cholesterol, and LDL increased in patient FLD with T2DM compared with obesity, and HDL level decreased in T2DM compare with obesity patients. The baseline demographic and laboratory characteristics along with the comparison of clinical and laboratory findings between the two groups of patients are presented in Tables 3 and 4, respectively.

The mean BMI of patients in this study in the FLD with T2DM group was (23.55 ± 4.30) kg/m^2 compared to the other group (29.70 ± 4.51) kg/m^2 in the FLD with obesity group. A study conducted by Targher et al. (2007) in T2DM patients revealed that patients with FLD had a mean BMI of 28.3 kg/m^2 compared to 26.5 kg/m^2 in patients with obesity FLD. These results were closely related to the mean BMI in this study. This was also observed in a study by Leite et al. (2009) who revealed that obesity and central obesity were independent predictive factors for FLD in the diabetic population.

Table 3. Comparison of baseline clinical characteristics of Type-2 DM patients and Obesity with FLD

Patient characteristic	All patients (n= 90)	DM with FLD (n=45)	OB With FLD (n=45)	*p*-value
Age (years)	55.11 ±7.85	54.52 ±7.28	54.72 ±8.92	0.2
BMI (Kg/m^2)	27.61 ±4.90	23.55 ±4.30	29.70 ±4.51	0.0001
Steatositis score UAP (dB/m)	275.49 ±36.80	271.33 ±37.44	194.64 ±13.60	0.001
Stiffness (kPa)	11.05 ±3.11	10.03 ±5.06	8.38 ±4.55	0.037

Values expressed as mean ±SD. Non-significant (*p*-value ≥ 0.05); BMI: Body mass index; DM: diabetes mellitus: OB: Obesity

The mean Steatositis score, Stiffness of patients in this study in the FLD with T2DM group was (271.33 ± 37.44), (10.03 ± 5.06) compared with (194.64 ± 13.60) (8.38 ± 4.55) in the FLD with obesity group. Stiffness in physics defines the extent to which an elastic object resists deformation in response to an applied force. The liver is a viscoelastic structure whose stiffness is affected by diet, inflammation, steatosis, cholestasis, and other pathological factors (Ding et al., 2022).

In patients with FLD, an increase in liver stiffness might precede the development of fibrosis, so the measurement of the liver viscoelastic properties by noninvasive techniques is of important diagnostic value.

Table 4. Comparison of laboratory parameters of Type-2 DM and Obesity patients with FLD

Lab parameter	All patients (n=90)	DM with FLD (n=45)	OB With FLD (n=45)	*p*-value
FBS (mg/dl)	184.17 ±73.31	198.36 ±76.14	161.53 ±62.40	<0.0001
TC (mg/dl)	175.12 ±116.55	198.26 ±140.82	144.38 ±30.80	<0.0001
TG (mg/dl)	215.90 ±109.63	253.51 ±97.63	135.20 ±44.28	<0.0001
LDL-C (mg/dl)	95.46 ±36.62	111.12 ±35.29	81.11 ±22.46	<0.0001
HDL-C (mg/dl)	31.70 ±9.47	28.33 ±9.71	35.06 ±11.84	<0.0001

Values expressed as mean ±SD. Highly significant (p-value < 0.001); DM: diabetes mellitus: OB: Obesity; FBG: Fasting blood glucose; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides

Lomonaco et al. (2021) reported a prevalence of steatosis of 70% and advanced fibrosis of 9% (liver stiffness measure ≥ 9.7 kPa) in 561 participants with T2DM. In a cohort of patients from the NHANES III undergoing VCTE screening, Ciardullo et al. (2021) reported, in 825 patients with T2DM, a prevalence of steatosis of 74% and advanced fibrosis (liver stiffness measure ≥ 9.7 kPa) of 15.4%. The prevalence of steatosis in the T2DM group in the current study (70.8% by USFLI) was comparable with the aforementioned results in Table 3. It is known that the relatively low sensitivity and PPV of blood-based testing is a limitation of blood-based approaches that call for complementary strategies for patients at high risk of advanced liver disease (such as individuals with obesity, metabolic syndrome, and/or T2DM).

The current results in Table 4 showed a significant increase ($p<0.0001$) in TC, TG, and LDL levels, and a significant decrease ($p<0.001$) in HDL levels, in patients compared with the control group.

T2DM shows hyperinsulinemia, hyperglycemia, and hypertriglyceridemia. In people without diabetes, nutrition raises blood sugar and this stimulates pancreatic insulin secretion, which leads to increased synthesis of triglycerides, glycogen and fatty acids within the liver and inhibits gluconeogenesis. IR is associated with failure to inhibit gluconeogenesis but is associated with hypertriglyceridemia, rather than impaired TG synthesis (Ciardullo et al., 2021).

A condition known as hyperlipidemia is connected to metabolic syndrome and excessive blood fat levels. Several risk factors, including abdominal obesity, insulin resistance, atherogenic dyslipidemia, and hypertension, are associated with metabolic disease (Czech, 2017).

Adult metabolic syndrome increases the risk factors for cardiovascular disease and includes hypertension, dyslipidemia, and obesity (Tomeleri et al., 2015). In patients who are obese, abnormalities in lipid metabolism are frequently seen. Dyslipidemia affects 60 to 70 percent of obese persons. High dyslipidemia is typically experienced as having high levels of triglycerides, LDL-C, and HDL-C. These aberrations are caused by a confluence of elevated free fatty acid supply to the liver, increased general and instinctive adiposity, insulin resistance, and pro-inflammatory conditions brought on by macrophage-sensitive fat tissue (Flegal et al., 2016).

The findings of the Algayed et al. (2017) study showed that patient levels of TC, triglycerides, and LDL were higher, but that patient levels of HDL were lower in diabetic obese patients than in non-obese subjects and patient levels of HDL were lower than in controls, are supported by the findings of the current study.

In diabetic obese, healthy obese, and control subjects, Elsaid et al. measured serum total cholesterol, LDL, VLDL, HDL, and TG. They discovered that diabetic obese individuals compared to healthy controls had significantly higher total cholesterol, TG, and LDL values as well as lower blood HDL-C levels. The current findings support this study (Elsaid et al., 2018).

In this study, there was a significant decrease in serum HDL-C in patients with T2DM when compared to control and that was in accordance with the study of Al-Tu'ma et al. (2015). This finding is noteworthy since postmenopausal women are more susceptible to dyslipidemia and increased cardiovascular mortality. Because androgen and estrogen receptors are present in visceral and subcutaneous adipocytes, endogenous sex hormones have been shown to alter the lipid profile in postmenopausal women. As a result, changes in endogenous sex hormone concentrations in middle-aged women's adipose tissues may disrupt lipid metabolism (Ko and Kim, 2020).

Correlation between Steatositis score and all study parameters in patients with FLD

The relationships of Steatositis score between them in FLD patients. The examined of the relationships of Steatositis score between them showed that Steatositis score level a significantly correlated ($p<0.05$) with BMI ($r= 0.286$, $p=0.006$) serum TG level ($r= -0.07$, $p=0.01$), while it was positive associated with TC level ($r= 0.80$, $p=0.0001$), Furthermore, that Steatositis score positively correlated with Stiffness level ($r= 0.387$, $p=0.0001$).

Table 5. The correlation of Steatositis score between patients with LFD and other Parameters

Variance		N	Pearson Correla-tion	P-value	Deci -sion
Steatositis score UAP (dB/m)	Age (Yrs.)	90	0.09	0.45	NS
	BMI (kg/m2)	90	0.286**	0.006	S
	Stiffness (kPa)	90	0.387**	0.0001	S
	TC (mg/dl)	90	0.80	0.0001*	S
	TG (mg/dl)	90	0.70-	0.01*	S
	HDL (mg/dl)	90	0.06	0.60	NS
	LDL (mg/dl)	90	0.02	0.87	NS

S/Significant (p-value <0.05); NS/Non-significant (p-value ≥0.05); BMI: body mass index; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

Our study revealed that central obesity, higher BMI, hypertriglyceridemia, and low HDL levels are associated with the presence of FLD. These results open new avenues for treatment in T2DM patients by focusing not only on glycemic control but also targeting these various cardiometabolic risk factors. Despite the previously discussed limitations, the present study offers a comprehensive view of the effect of fat accumulation alone on the biomechanical properties of the liver, demonstrating that liver stiffness increases as a function of the extent of fat accumulation, independently from possible pathologic confounders (Skinner et al., 2015; Baldini et al., 2022).

CONCLUSION

This study reported an increased frequency of FLD in our diabetic and obese population and evaluated in depth

the risk factors associated with FLD, underpinning the significance of carrying out further large-scale studies to assess the effects of lifestyle modification in the form of physical activity and dietary modifications on the status of FLD and glycemic control. Taking into account the results of this study, patients and their treating physicians should emphasize the modification of the associated factors and it is also advisable to screen diabetic patients for this condition in routine clinical practice. Well-established obese risk factors such as total cholesterol, triglycerides, LDL cholesterol, and were higher and HDL cholesterol was lower among diabetic patients. Serum LDL cholesterol was identified as an independent predictor of obesity among subjects with type 2 DM in this cohort of study. Early detection and timely management will help promote a healthy lifestyle and prevent long-term complications of the condition.

ACKNOWLEDGEMENTS

The authors express their gratitude to all the participants who agreed to take part in this study.

AUTHOR CONTRIBUTIONS

MF AL-Khakani, KA Khalel, MFM Ali and AJ Abed contributed to the design and conceptualization of the study and provided the data whereas N Toumi contributed in the execution and planning of the statistical analysis . The authors take full responsibility for the research, including addressing for regarding the accuracy or integrity of the study and conducting appropriate investigations.

CONFLICTS OF INTEREST

The author(s) declare(s) no conflicts of interest.

DECLARATION

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How to cite this article?

AL-Khakani MF, Khalel KA, Ali MFM, Abed AJ, Toumi N (2023). Exploring the role of type II diabetes mellitus and obesity as risk factors in patients afflicted with fatty liver disease. Journal of Conventional Knowledge and Holistic Health, 7(2), 237. DOI: 10.53517/JCKHH.2581-3331.722023237

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