Prevalence of Non-alcoholic Fatty Liver Disease among Patients with Diabetes Mellitus Attending Primary Health Care Centers in Bahrain

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Abstract

Objectives: We aimed to identify the prevalence of non-alcoholic fatty liver disease (NAFLD) among patients with type-2 diabetes mellitus (T2DM) and to assess the possible risk factors. ***Methods:*** In this retrospective cross-sectional study, a random sample from patients receiving treatment for T2DM in the non-communicable disease clinic, primary health centers, Bahrain in 2018 was reviewed. Three-hundred eighty-two patients who underwent abdominal ultrasonography were selected for the study. Detailed patients' data were collected and statistically analyzed. Prevalence of NAFLD and its' possible risk factors were assessed. ***Results:*** The study populations were mostly females (235 (61.5%) patients). The mean age was 59±12 years. Hypertension was the most frequent associated disease (221 (57.9%) patients). Most of the patients were either overweight or obese, 103 (30.5%) and 197 (58.3%),

respectively. Elevated alanine aminotransferase (ALT) was found in 75 (21%) of 357 (93.5%) tested patients. Two-hundred sixty (68.06%) patients had fatty liver based on ultrasound imaging. In univariate analysis, female gender (p=0.013), high body mass index (BMI) (p<0.0001), high waist circumference (p=0.011) and high triglyceride levels (p=0.043) were significant risk factors for fatty liver. In binary logistic regression, BMI was the independent risk factor for fatty liver (p=0.005).

Conclusions: The prevalence of NAFLD among patients with T2DM was found to be high. However, it was comparable to what has been reported in other studies. Female gender, high BMI, waist circumference and triglyceride level are risk factors for NAFLD. BMI is the independent risk factor.

Keywords: Diabetes Mellitus; Non-alcoholic Fatty Liver Disease; Prevalence; Risk Factors; Bahrain.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of liver diseases worldwide and is emerging as the most important cause of end stage liver disease across the globe.[1] NAFLD is a spectrum of progressive liver disease ranging from simple steatosis, nonalcoholic steatohepatitis, and fibrosis to liver cirrhosis. NAFLD increases liver disease related morbidities and mortalities. Moreover, it increases risk of comorbidities like diabetes mellitus and cardiovascular diseases.[2] In patients with NAFLD, half of the deaths are related to cardiac disease and malignancies. Early identification of NAFLD can help in improving the patient outcome through prevention and proper treatment.[3]

NAFLD had been recognized as the hepatic component of metabolic syndrome.[4] It is more prevalent among obese patients and patients with type-2 diabetes mellitus (T2DM) irrespective

of degree of obesity.[5] NAFLD is associated with T2DM due to the compensatory hyperinsulinemia resulting from insulin resistance leading to progressive defective lipid metabolism and hepatic triglyceride accumulation in NAFLD or to β-cell dysfunction in T2DM.[6]

NAFLD is defined as the presence of ≥ 5% steatosis usually detected by radiological imaging in absence of any secondary causes of fat accumulation in the liver such as alcohol, drugs or autoimmunity.[2,7]

The prevalence of NAFLD is growing in developed countries with the growing of the obesity epidemic.[2] Bahrain is also facing an increase in the number of patients suffering from obesity and overweight. According to the world health organization, the number of patients with diabetes in Bahrain is projected to reach 99,000 patients in 2030.[8] As NAFLD and T2DM are common conditions that co-exist, the prevalence of NAFLD in countries like Bahrain with high diabetes prevalence is expected to be high.[9]

By reviewing the literature, NAFLD in Bahrain was understudied. The aim of this study is to assess the prevalence of NAFLD among patients with T2DM attending the primary health care services in Bahrain.

METHODS

Setting

Primary health care is the corner stone for the health care system in Bahrain with 28 health centers distributed across the country. Health care services that include caring for patients with chronic diseases are provided primarily in those health centers. Each health center has a non-communicable disease (NCD) clinic that is run by specialized nurses and family physicians.

Study design

Retrospective cross-sectional study including patients diagnosed with T2DM attending the NCD clinics in the primary health care centers in the period between January and March 2018.

Population and sample

The sample was randomly selected from the patients' lists of diabetic patients seen in NCD clinics in all primary health care centers during the study period which had 6730 patients. The sample size was calculated at 95% confidence interval with 5% confidence level. As the prevalence of fatty liver is unknown, the proportion was set at 50%. The sample size was calculated to be around 382 patients. The patients' names were listed in an excel file and a random number was generated for each record. Only patients with abdominal ultrasonography (USG) were included in the study. Total number of records reviewed was 2500 to reach the required sample size.

Data collection

Sociodemographic data related to age, sex and nationality were collected. Patient's abdominal ultrasound reports were gathered with anthropometric data such as weight, height and body mass index (BMI). Laboratory data related to patient's diabetes such as the last fasting blood sugar, last glycosylated hemoglobin (HbA1c), last lipids profile, the last liver function profile and viral hepatitis B and C serology were collected. Liver biopsy results were reviewed.

Specific excel sheet was created to collect the data and then data were transferred to SPSS program version 21 (SPSS Inc., Chicago, IL, USA) for statistical analysis.

Data analysis

Descriptive statistics for social-demographic data were calculated. Numerical variables were presented as mean and standard deviation (SD) or median and range. The number and percentage

for sex and nationality was calculated. The patients were segregated into four groups based on their BMI (underweight, normal, overweight and obese) then their number and percentage were calculated. Patients were considered to have a metabolic syndrome if, in addition to T2DM, they had at least two of the following: blood pressure ≥ 130/85 mmHg or on antihypertensive treatment; triglycerides ≥ 1.7 mmol/L or receiving a fibrate; HDL cholesterol <1.04 mmol/L for men or 1.29 mmol/L for women; waist circumference >102 cm for men or 88 cm for women according to Adult Treatment Panel III criteria (ATP III).[10]

Abdominal ultrasound reports were grouped into normal, with hepatomegaly alone, with combined fatty liver and hepatomegaly, and fatty liver alone; then the number and percentage of each group were reported. In addition, fatty liver was graded using certain characteristics found in ultrasound such as greater echogenicity of the liver parenchyma relative to the cortex of the right kidney along with the diaphragm and hepatic veins' interface visibility and sharpness. [11]Accordingly, the severity of hepatic steatosis was classified into three grades: Grade 0, no steatosis: liver and renal cortex of the same echogenicity; Grade 1, mild steatosis: slightly brighter liver as compared to the renal cortex, clear diaphragm visualization, and interface of hepatic veins with sharp contours; Grade 2, moderate steatosis: brighter liver with attenuated ultrasound beam at deeper parts of the liver, diaphragm, and hepatic veins still visible but with blunted contours; Grade 3, severe steatosis: very bright liver, severe ultrasound beam attenuation, diaphragm, or hepatic veins not visible.[11] Patients who developed hepatic fibrosis, cirrhosis and malignancy were also reported.

The laboratory data like lipids and blood sugar levels were grouped into controlled or uncontrolled according to the diabetes guideline followed up in primary health care centers. The liver enzymes were grouped into normal or abnormal (elevated).

Univariate analysis was used to study the relationships between different factors or associations (demographic, anthropometric, laboratory factors, use of lipid lowering agents, tobacco smoking, adherence to dietary advice (diet of five fruit/vegetable portions per day) and physical activities recommendations (physical activity of 30 minutes per day, five days per week)) and the presence or absence of fatty liver. Student's t test, Fisher's exact test and Mann-Whitney U test were used. Risk factors found to be significant in the univariate analysis and have no multicollinearity using a variation inflation factor (VIF) > 8 were included in a binary logistic regression to find the independent risk factors of fatty liver. The level of significance was set at 0.05.

RESULTS

During the study period, medical records of 382 patients with T2DM were reviewed. Patients' demographic data are shown in Table 1. Most of the patients (362 (94.8%) patients) were Bahraini while 20 (5.2%) patients were non-Bahraini (five from Pakistan, four from India, two from Egypt, two from Syria, one patient from Iraq, Saudi Arabia, Philippine and Bangladesh each; and three patients were from other non-specified countries). The study populations were mostly females (235 (61.5%) patients). The mean (SD) age at the time of study was 59 ± 12 years.

Table 1: Demographic data of the study population.

Variable		**Number (%)**
Nationality	Bahraini	362 (94.8)
	Non-Bahraini	20 (5.2)
Age, year, mean ± standard deviation		59 ± 12
Gender	Female	235 (61.5)

	Male	147 (38.5)
Associated diseases	Hypertension	221 (57.9)
	Hypothyroidism	35 (9.2)
	Others*	39 (10.2)
Current medications	Hypoglycemic drugs	342 (89.5)
	Anti-hyperlipidemia medications including statin	295 (77.2)
	Antihypertensive medications	221 (57.9)
	Insulin	54 (14.1)
	Aspirin	49 (12.8)
Lifestyle	Tobacco smoking	41 (10.7)
	Diet (5 fruit/vegetable portions per day)	166 (43.5)
	Physical activity (30 minutes per day, 5 day per week)	98 (25.7)
Cardiovascular risk	Not calculated	189 (49.5)
	< 10%	118 (30.9)
	11 - <20%	45 (11.8)
	21 - <30%	15 (3.9)
	31 - <40%	3.0 (0.8)
	≥40%	12 (3.1)
Family history of cardiovascular death		259 (67.8)

**seven patients had sickle cell disease, five had breast cancer, five had hyperuricemia, three had rheumatoid arthritis, two had osteoporosis, two had benign prostatic hypertrophy, two had gastritis, while dust allergy, anemia, kidney stone, migraine, psoriasis, Parkinson disease, pancreatitis, epilepsy, coronary artery bypass grafting, sickle cell trait, thyroid cancer, psychiatric disease, and bronchial asthma each in one patient.*

Hypertension and hypothyroidism were the most frequent associated diseases which were found in 221 (57.9%) and 35 (9.2%); respectively. Forty patients (10.5%) had other associated diseases (seven had sickle cell disease, five had breast cancer (two underwent mastectomy, two

received chemotherapy and one received radiotherapy), five had hyperuricemia, three had rheumatoid arthritis, two had osteoporosis, two had benign prostatic hypertrophy, two had gastritis, while dust allergy, anemia, angiography, kidney stone, migraine, psoriasis, Parkinson disease, pancreatitis, epilepsy, coronary artery bypass grafting, sickle cell trait, thyroid cancer, psychiatric disease, and bronchial asthma each in one patient).

Out of 382 patients, 212 (55.5%) were adherent to their medications. One hundred ninety-one (50%) patients received foot care advice. Counselling on diet and tobacco use were received in 291 (76.2%) and 24 (6.3%) patients; respectively. Symptomatic hypoglycemia was reported in 36 (9.4%) patients. No patient had a history of alcohol consumption. One patient had a family history of dyslipidemia.

Anthropometric parameters, blood pressure and laboratory findings are shown in Table 2. Out of the 382 patients, 338 (88.5%) patients had BMI available. Most of the patients were either overweight or obese, 103 (30.5%) and 197 (58.3%); respectively. Only 37 (10.9%) had normal BMI and only one patient was underweight. Two hundred-sixteen (56.5%) patients were fitting the criteria for the metabolic syndrome. Based on HbA1c level (222 (58.1%) patients had HbA1c reading), the blood sugar was controlled in 120 (54.1%) and uncontrolled in 102 (45.9%). Fasting blood sugar was available in 315 (82.5%) patients, 159 (50.5%) were uncontrolled while 156 (49.5%) were controlled. ALT results were available in 357 (93.5%). Elevated ALT was found in 75 (21%) patients while 282 (79%) had normal ALT (normal range <33U/L in females and <41U/L in males). Out of the 91(23.8%) patients tested for hepatitis B and 89 (23.3%) patients for hepatitis C, two patients were tested positive from each.

Table 2: Anthropometric parameters, blood pressure and laboratory findings of the 382 patients.

Variable	ean	D	edian	N nimum	Mi	M aximum	Tested patients (%)
Body mass index (kg/m^2)	2.4	.1	1.3	3 7	17. 8	67.	341 (89.3)
Waist circumference (cm)	06.9	7.0	05.0	1 0	50. 0.0	20	209 (54.7)
Systolic blood pressure (mmHg)	33.9	6.5	33.4	1 0	94. 6.0	20	370 (96.9)
Diastolic blood pressure (mmHg)	3.4	0.1	4.0	7 0	52. 8.0	10	370 (96.9)
Hemoglobin level (g/dl)	2.4	.0	2.6	1	5.5 0	19.	107 (28)
Fasting blood sugar (mmol/L)	.7	.6	.1	7	3.2 6	19.	315 (82.5)
Hemoglobin A1c (mmol/mol)	5.4	7.9	2	5 1	13. 0.0	13	222 (58.1)
Cholesterol level (mmol/L)	.4	.0	.3	4	1.3	8.5	301 (78.8)
Low density lipoprotein level (mmol/L)	.4	.9	.3	2	0.6	7.1	270 (70.7)
High density lipoprotein level (mmol/L)	.2	.4	.1	1	0.3	2.9	283 (74.1)
Triglyceride level (mmol/L)	.7	.0	.5	1	0.5	9.9	291 (76.2)
Total serum protein (g/L)	3		3	7	40	86	362 (94.8)

	Serum albumin (g/L)				4			
						21	52	370 (96.9)
		3		3				
	Serum globulin (g/L)				3			
						8	48	363 (95)
		0		0				
	Total bilirubin (µmol/L)						12	
					8	0		351 (91.9)
		1	1				0	
	Alkaline phosphatase (U/L)				7		64	
						0		356 (93.2)
		3	8	7			2	
	Alanine aminotransferase				2		59	
						7		357 (93.5)
(U/L)		0	1	1			1	
	Gamma glutamyl transferase				3		15	
						0		367 (96.1)
(U/L)		0	09	0			12	

SD: Standard deviation

Of the study population, 260 (68.1%) had fatty liver on abdominal ultrasound imaging (105 (39.9%) of them had an associated hepatomegaly). Nine (2.36%) patients had an isolated hepatomegaly, three (0.8%) patients had hepatic hemangioma, one (0.26%) had liver cirrhosis secondary to hepatitis C infection, one (0.26%) had liver metastasis secondary to breast cancer and one (0.26%) had small hepatic cyst. The remaining 107 (28%) patients had a totally normal liver. No patient had hepatic fibrosis or hepatocellular carcinoma on USG. Upon classifying the patients according to ultrasonographic grading of hepatic steatosis, 122 (31.9%) patients had no hepatic steatosis on USG (grade 0), 26 (6.8%) had mild steatosis (grade 1), two (0.5%) had moderate steatosis (grade 2), 38 (10%) had severe steatosis (grade 3) while the remaining 194 (50.8%) patients had fatty liver of unspecified grades. For the two patients with hepatitis B, one had diffuse fatty liver; and one had normal liver ultrasound while both patients with hepatitis C had fatty liver.

Fifty-eight (15.2%) patients had computed tomography (CT) (one of them had magnetic resonant imaging scan (MRI)) that confirmed the ultrasound findings.

Elevated ALT was found in 67 (27.8%) out of 241 patients with fatty liver compared to only eight (6.9%) out of 116 patients without fatty liver (p<0.0001). One of the patients with hepatitis B had high ALT and liver biopsy performed in the secondary healthcare which showed hepatic fibrosis and cirrhosis. She was on regular antiviral medication (Tenofovir 300 mg daily).

Results of univariate analysis of possible risk factors of fatty liver are shown in Table 3. Female gender (p=0.013), high BMI (p<0.0001), high waist circumference (p=0.011) and high triglyceride level (p=0.043) were significant risk factors for fatty liver. High ALT (p<0.0001) and gamma-glutamyl transferase (GGT) (p <0.0001) were found to be significant associations with fatty liver. The significant risk factors were tested for multicollinearity (VIF >8) between each other and were put into a logistic regression model. Accordingly, BMI was found to be the independent risk factor for fatty liver (p=0.005) [Table 4].

Table 3: Univariate analysis of possible risk factors of fatty liver in the 382 diabetic patients.

Variables		**Total (%)**	**Abdominal ultrasound finding**				***p*-value (95% CI)**
			Without fatty liver=122 (31.9%)		**With fatty liver=260 (68.1%)**		
			n (%)	**Mean (SD)**	**n (%)**	**Mean (SD)**	
Age		382 (100)	122 (31.9)	60 (13)	260 (68.1)	58 (11)	0.094[a] (-0.4-5.1)
Gender	Female	235 (61.5)	64 (52.5)	-	171 (65.8)	-	0.013[b*]
	Male	147 (38.5)	58 (47.5)	-	89 (34.2)	-	-
Body mass index (kg/m^2)		341 (89.3)	105 (30.8)	30.2 (6.4)	236 (69.2)	33.4 (7.2)	<0.0001[c*]
Waist circumference (cm)		209 (54.7)	69 (33)	103.4 (20.5)	140 (67)	108.6 (14.7)	0.011[c*]
Resting systolic blood pressure (mmHg)		370 (96.9)	117 (31.6)	134.1 (19.5)	253 (68.4)	133.9 (14.9)	0.622[c]
Resting diastolic blood pressure (mmHg)		370 (96.9)	117 (31.6)	72.9 (10.3)	253 (68.4)	73.6 (9.9)	0.434[c]
Hemoglobin level (g/dl)		107 (28)	39 (36.4)	12.6 (1.6)	68 (63.6)	12.4 (2.2)	0.53 (-0.55-1.1)[a]
Fasting blood sugar (mmol/L)		315 (82.5)	101 (32.1)	7.5 (2.9)	214 (67.9)	7.8 (2.5)	0.068[c]

Hemoglobin A1C (mmol/mol)		222 (58.1)	69 (30.1)	52.2 (18.9)	153 (68.9)	56.9 (17.3)	0.052[c]
Cholesterol level (mmol/L)		301 (78.8)	96 (31.9)	4.3 (1.0)	205 (68.1)	4.4 (1.1)	0.632[c]
Low density lipoprotein level (mmol/L)		270 (70.7)	86 (31.9)	2.2 (0.7)	184 (68.1)	2.5 (0.9)	0.057[c]
High density lipoprotein level (mmol/L)		283 (74.1)	93 (32.9)	1.2 (0.4)	190 (67.1)	1.2 (0.3)	0.460[c]
Triglyceride level (mmol/L)		291 (76.2)	90 (30.9)	1.7 (1.4)	201 (69.1)	1.7 (0.8)	0.043[c*]
Metabolic syndrome	Yes	216 (56.5)	68 (31.5)	-	148 (68.5)	-	0.826[b]
	No	166 (43.5)	54 (32.5)	-	112 (67.5)	-	
Total serum protein (g/L)		362 (94.8)	115 (30.1)	73 (5)	247 (64.7)	74 (5)	0.094[c]
Serum albumin (g/L)		370 (96.9)	118 (30.9)	43 (3)	252 (66)	43 (3)	0.236[c]
Serum globulin (g/L)		363 (95)	116 (30.4)	30 (4)	247 (64.7)	31 (5)	0.211[c]
Total bilirubin (µmol/L)		351 (91.9)	111 (29.1)	10 (8)	240 (62.8)	11 (12)	0.876[c]
Alkaline phosphatase (U/L)		356 (93.2)	115 (30.1)	77 (31)	241 (63.1)	86 (54)	0.074[c]
Alanine aminotransferase (U/L)		357 (93.5)	116 (30.4)	21 (10)	241 (63.1)	34 (49)	<0.0001[c*]
Gamma glutamyl transferase (U/L)		367 (96.1)	119 (31.2)	37 (40)	248 (64.9)	71 (128)	<0.0001[c*]
Lipid lowering agents	Yes	295 (77.2)	95 (32.2)	-	200 (67.8)	-	0.896[b]
	No	87 (22.8)	27 (31)	-	60 (69)	-	
Tobacco smoking	Yes	41 (11.1)	18 (43.9)	-	23 (56.1)	-	0.111[b]
	No	327 (88.9)	101 (30.9)	-	226 (69.1)	-	
Following dietary advice	Yes	166 (45.5)	58 (34.9)	-	108 (65.1)	-	0.260[b]
	No	199 (54.5)	58 (29.1)	-	141 (70.9)	-	
Following physical activity advice	Yes	98 (26.6)	31 (31.6)	-	67 (68.4)	-	1.000[b]
	No	270 (73.4)	86 (31.9)	-	184 (68.1)	-	

SD: standard deviation; CI: confidence interval.

[a]student t test, [b]Fisher's exact test, [c]Mann-Whitney U test.

**p-value is statistically significant*

Table 4: Binary logistic regression analysis of the selected risk factors of fatty liver in the 382 diabetic patients.

Variables	Adjusted odd ratio	95% CI	*p*-value
Gender	1.080	0.491 to 2.376	0.848
Body mass index (kg/m^2)	1.147	1.042 to 1.263	0.005*
Waist circumference (cm)	0.996	0.964 to 1.030	0.832
Triglyceride level (mmol/L)	1.176	0.771 to 1.792	0.452

CI: confidence interval.

**p-value is statistically significant*

DISCUSSION

NAFLD is a common term used to describe a broad range of liver conditions that are characterized by excessive fat storage in liver cells in individuals who either drink little or no alcohol.[3] The fact that insulin resistance is the most common risk factor for the development of NAFLD is well-documented in literature. Both T2DM and NAFLD are sharing the same underlying mechanisms of insulin resistance, metabolic stress and liver inflammation.[7] NAFLD per se is not a cause of insulin resistance but it is proven to be a consequence for it.[5]

In this study, the prevalence of NAFLD among patients with T2DM was found to be high. Of the 382 patients, 260 (68.1%) had fatty liver based on abdominal ultrasound imaging. Similarly, studies from Italy and Saudi Arabia reported a prevalence of 59.6% and 72.8%; respectively.[6,12] However, in a study from United Kingdom that investigated the prevalence of hepatic steatosis

and NAFLD in type-2 diabetic patients, Williamson et al established a lower prevalence of NAFLD in 42.6% of 939 subjects examined.[10] Moreover, a large meta-analysis of 86 studies and 8515431 individuals from 22 countries showed a global prevalence of NAFLD of 25.24% with highest prevalence came from the Middle East and South America.[13] Yet, our result was comparable to that of the study undertaken by Mantovani et al which analyzed 19 observational studies and enrolled a total of 16000 type-2 diabetic patients. According to the study, patients with NAFLD are 79.2% more likely to develop diabetes than those without NAFLD.[14] Subsequently, the study identified NAFLD as a predictor of diabetes.[14] The results of this study also confirm the previous one reported by Targher and Byrne in which NAFLD was identified to worsen hepatic insulin resistance thereby increasing the odds of T2DM.[15] While these studies were conducted under different settings, they all demonstrated the relationship between fatty liver and T2DM, the same findings that this study revealed.

The result of this study showed the comorbidity of several other diseases among the 382 patients diagnosed with T2DM but without any history of alcohol consumption. From the examination of their electronic health records, it was established that they had other conditions that included hypertension and hypothyroidism reported in 57.9% and 9.2% of the sample. This result aligns with the previous finding reported by Talwalkar et al study, which also found the comorbidity of hypothyroidism and hypertension in patients with T2DM.[16] In Talwalkar et al study, the prevalence rate of hypertension among diabetic patients was reported to be comparable to that of this study. However, the prevalence rate of hypothyroidism was significantly higher (24.8%) than 9.2% found in this study.[16] An earlier study conducted by Kin et al reported comorbidity diseases among 20,314 subjects with T2DM to include hypertension, gastritis and duodenitis, and lipidemias.[17]

These comorbidity conditions were also associated with diabetic patients investigated in this study. Yet, this study reported other comorbidity diseases with diabetes such as anaemia, kidney stones, migraine, psoriasis, Parkinson disease, pancreatitis, sickle cell trait, thyroid cancer, rheumatoid arthritis, psychiatric disorders and bronchial asthma. These conditions were insignificant in diabetic patients studied in Kin et al. However, the study found other comorbidity diseases such as senile cataract, cerebral infarction, heart failure, and gastroesophageal reflux disease among the subjects examined.[17]

The risk of developing T2DM (80-85%) has been attributed to obesity, which normally co-exists with NAFLD.[9] Research evidence also suggests a growing incidence of obesity and overweight in some Asian nations including Bahrain.[18] This rise of obesity and T2DM is multifactorial and essentially related to economic evolution, and the collateral shift in culture, life style, and dietary habbits.[19] Most of the patients in our study were either overweight or obese, 103 (30.5%) and 197 (58.3%), respectively. Globally, the increasing prevalence of NAFLD has been reported in the literature especially among obese and overweight people.[20] Although obesity is a definite risk factor for development of NAFLD, people with low BMI may develop NAFLD. Asian population tends to have more body fat percentage with lower BMI compared to those in Western countries.[21] Non-obese NAFLD patients are more likely to have other adiposity risk factors like increasing waist circumference, skin fold thickness and body fat percentage.[22] Sarcopenic obesity which is characterized by loss of skeletal muscle and gain of adipose tissue was found to be associated with increasing severity of NAFLD and worse outcome.[23,24] In the current study, none of the diabetic patients who had NAFLD had low BMI. However, 16 (6.9%) of the 233 patients with NAFLD had normal BMI.

In the current study, female gender was a significant risk factor of NAFLD. However, Forlani

et al from Italy reported more males than females to have the disease.[6] Yet, Williamson et al and Alsabaani et al studies reported no significant difference based on gender.[10,12]

In general population, NAFLD is associated with multiple metabolic comorbidities such as obesity, T2DM, hyperlipidemia, hypertension and metabolic syndrome.[13] In the current study, univariate analysis revealed that higher BMI, higher waist circumference and higher triglyceride levels were significant risk factors for fatty liver. Moreover, BMI was the independent risk factor for fatty liver. These findings were also supported by other studies.[6,10,12] A systematic review by Ashtari et al revealed that obesity, T2DM and metabolic syndrome are important risk factors for NAFLD in many countries including Asian countries.[18] Williamson et al study of 939 patients with T2DM found that BMI, lesser duration of diabetes, HbA1c, triglycerides, and metformin use were independent predictors of NAFLD.[10] On the other hand, Forlani et al study showed that impaired renal functions, higher albumin excretion, higher HbA1c and blood pressure, lower high density lipoprotein (HDL) cholesterol, and poor quality of care were associated with NAFLD.[6] Alsabaani et al study also found that high HDL cholesterol level was a protective risk factor for NAFLD in patients with T2DM.[12] In recent years, intestinal microbiota had emerged as a potential risk factor involved in the development of NAFLD. Gut microbiota had influence on the energy storage and lipid metabolism. It also affected choline metabolism, ethanol production, immune balance and inflammation.[25] NAFLD was associated with gut dysbiosis and changes in the gut microbiota metabolic functions. Certain types of gut microbiota were linked to the development of NAFLD such as Bacteroides which are linked to the development of early NAFLD stages, and Ruminococcus which is linked to hepatic fibrosis.[26]

In this study, high ALT and GGT were significant associations with fatty liver (p <0.0001 and p <0.0001; respectively). Elevated ALT was found in 75 (21%) of 357 (93.5%) tested patients

with a significantly higher mean levels among patients with NAFLD. Likewise, Fralani et al reported a comparable percentage of ALT elevation among patients with T2DM (20.3%).[6]

In this study, the presence of fatty liver was evaluated radiologically mainly by abdominal USG, along with CT scan or MRI in some patients. USG underestimates the incidence of hepatic steatosis and under-diagnoses NAFLD especially when hepatic steatosis is less than 20%.[27] However, USG, CT scan and MRI are the standard imaging modalities to diagnose NAFLD in clinical practice.[2] USG is easily available, cheap and can be performed even at bedside.[2] Moreover, when sonographic features specific to NAFLD are standardized and used to help in diagnosis, ultrasound can achieve a high diagnostic accuracy.[27] Accordingly, to diagnose NAFLD in this study, we depend mainly on hepatic ultrasound considering that this study was done at primary healthcare settings. This is also comparable to several previous publications as shown in Byrne and Targher review.[7,11] Patients with advanced disease were referred to the secondary healthcare facilities for further evaluations using other modalities including transient elastography or more invasive techniques such as liver biopsies. Liver biopsy is the gold standard to diagnose NAFLD. It confirms the diagnosis and evaluates the extent of disease effect on the liver.[2]

The main treatment gools of NAFLD are to improve steatosis and to prevent disease progression.[2] Unless patients with NAFLD are intervened early in the course of their disease, NAFLD can progress to decompensated liver cirrhosis, liver failure, hepatocellular carcinoma or even mortality.[7,9,28] As no single intervention can effectively cure NAFLD, modifying life style and decreasing the risk factors are the keys of disease management.[2] Considerable efforts should be made to improve healthy life style through the production of educational materials in layperson language.[19] Nutritional education is also a vital part of the treatment in patients with

T2DM and obesity.[19] Yet, education about diet and diabetes is difficult to implement.[19] Medications and surgical interventions are the second line of NAFLD managment.[2] In a recent metanalysis on antidiabetic medications, sodium glucose transporter 2 inhibitors (SGLT2Is) such as canagliflozin was found to be effective in improving liver functions among patients with T2DM.[29]

Early detection of NAFLD is essential as late intervention might lead to disease progression into decompensated liver cirrhosis and liver transplantation requirement.[28] With the rapid rise of obesity prevalence in Bahrain and worldwide, NAFLD is expected to become the main indication for liver transplantation in the future.[2,8,9,28]Although liver transplantation is curative and has been shown to enhance survival in patients with advanced liver disease of any cause, patients with NAFLD face specific challenges.[28] First, there is currently no appropriate pharmacotherapy to prevent the disease from progressing to advanced fibrosis. Second, patients with NAFLD are frequently older, obese, and have multiple comorbidities, raising the risk of mortality during and after liver transplantation. Third, increased prevalence of NAFLD in the donor population may have an adverse effect on potential liver graft availability and efficiency.[28]

Despite that this study was performed following strict scientific procedures; it has some limitations that require further explanation. Selection bias might have occurred due to a higher possibility of including exposed group with the outcome of interest.[30] Being a retrospective study, the quality of record-keeping was essential. However, this could not be assured. Another limitation of this study relates to misclassification bias, a systematic error that can occur as a result of inaccurate categorization of the subjects.[31] Misclassification error could have led to the underestimation or overestimation of the effect of NAFLD on the occurrence of T2DM.[31]

In addition, this study used a lower sample size compared to other studies.[10,14] Although the

sample was adjudged appropriate for this study, a larger sample size would have strengthened the perception about the study's validity and improve its' generalizability.

Despite limitations, the present study advances knowledge of the prevalence of NAFLD among diabetic patients. To the best knowledge of the authors, this is the first study in Bahrain that focuses on NAFLD in patients receiving treatment for T2DM from primary health care facilities in the country. The outcome of this study represents a piece of information that can guide physicians and other healthcare professions in the provision of high-quality care to diabetic patients. Moreover, the outcome of this study may reinforce the need for diabetic patients to be mandatorily screened for NAFLD and other conditions identified in this paper. The current study has revealed a significant outcome that can enrich the development of a future update to current clinical guidelines for treating T2DM. It can also serve as an impetus for early diagnosis of other comorbidity conditions, which may worsen the health status of diabetic patients. The data presented in this study will be helpful to physicians and other medical workers involved in the treatment of diabetic patients in Bahrain and around the world.

While this study provides important knowledge on this subject, additional research is needed to determine if NAFLD increases the risk of diabetes or is an indicator for other comorbidity diseases. Also, further studies are required to compare results from Bahrain to other Asian nations and non-Asian populations. Also, future studies can help determine the extent to which the onset of T2DM is linked to different stages of liver disease. Yet, the importance of this study cannot be overemphasized as its findings offer insights that could be used to develop appropriate health promotion and management strategies for reducing the incidence of this condition.

CONCLUSION

The prevalence of NAFLD among adult patients with T2DM was found to be high. It accounted for 68.06%. However, it was largely comparable to what has been reported in other related studies. Female gender, high BMI, high waist circumference and high triglyceride level are significant risk factors for fatty liver. BMI is the independent risk factor. High liver enzyme (ALT and GGT) are associated findings with NAFLD. The growing epidemic of obesity and diabetes in adult population in Bahrain may lead to high prevalence of NAFLD making it the most common cause of advanced liver diseases in the future. Further studies to assess the prevalence of NAFLD in the general population along can help in estimating the burden of the problem in the country.

Disclosure

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