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Characteristics of non-alcoholic fatty liver disease in Palestinian diabetics: A cross-sectional study

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Abstract

This cross-sectional study was performed to identify the factors associated with non-alcoholic fatty liver disease (NAFLD) in type 2 diabetes mellitus (T2DM) patients in Nablus, Palestine, and decrease the burden of liver diseases. Patients with T2DM who visited primary healthcare clinics in Nablus from January to April 2022 were invited [n=508] to participate. A face-to-face interview was conducted, and medical reports were used to collect the patient's details. The hepatic steatosis index (HSI) was calculated as an indicator of the possibility of the presence of NAFLD. Ultrasound was used to diagnose fatty liver disease (FLD) as mild, moderate, and severe. 399 Patients completed participation, with a mean age of 56.1±10.4 years; 56.1% were males, 91.2% had an HSI score ≥36, and 8.8% had an HSI score of 30-36. Moreover, 3.8% were diagnosed with mild FLD, 42.1% with moderate FLD, and 3.8% with severe FLD. Compared to patients without fatty liver disease, severe FLD patients were at higher risk of having increased cholesterol levels (OR=1.047), increased HSI (OR=1.32), and diabetic retinopathy (OR=7.074). Predictors for moderate FLD have increased cholesterol levels (OR=1.023), glycated hemoglobin (HbA1c) (OR=1.06), HSI (OR=1.21), and age (OR=1.071). Predictors for mild FLD have increased cholesterol levels (OR=1.02), HbA1c (OR=1.312), HSI (OR=1.102), and age (OR=1.047). Decreased levels of low-density lipoproteins were associated with decreased risk of mild (OR=0.982), moderate (OR=0.97), and severe (OR=0.955) FLD. Diabetes treatment regimen, the number of years diagnosed with diabetes, hypertension, high-density lipoprotein, and triglycerides levels were not associated with FLD. In conclusion, the prevalence of NAFLD among Palestinian T2DM patients was higher than the reported global prevalence. Several modifiable (weight, HbA1c, HSI score, total cholesterol, and low-density lipoprotein levels) and non-modifiable (age and diabetic retinopathy) factors were associated with NAFLD. This research recommends a screening program for the early detection of NAFLD among Palestinian people with diabetes using ultrasound.

Keywords: Non-alcoholic fatty liver, Diabetes mellites, Fatty liver disease, hepatic steatosis index.

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) refers to a group of disorders characterized by an accumulation of fat in the liver without a secondary cause, such as alcohol intake, viral hepatitis, autoimmune hepatitis, steatogenic medications, and hereditary diseases (1). It is the most common cause of chronic liver disease, leading to high morbidity and mortality worldwide (2-4). This condition has a broad range of liver damage, including simple fatty liver (steatosis), non-alcoholic steatohepatitis (NASH) (1, 5)(1, 5), fibrosis, and cirrhosis (6).

NAFLD has been linked to extrahepatic diseases, including obesity, type two diabetes mellitus (T2DM), cardiovascular disease, and chronic renal disease (7, 8). Diabetes is the most potent risk factor for NAFLD-related cirrhosis (3). NAFLD and diabetes commonly co-exist and affect the development of each other (9). Insulin resistance, the main feature of T2DM, is one of the significant factors that play a role in the pathogenesis of NAFLD

(10). NAFLD also increases the risk of developing T2DM in patients who develop NAFLD and do not have diabetes (11). The two diseases act together to produce more severe adverse outcomes. NAFLD causes an increased risk of development of micro and macro-vascular diabetic complications (10), and diabetes exacerbates the progression of NAFLD (9), with higher levels of glycated hemoglobin (HbA1c) being associated with a higher risk of NAFLD development (12).

NAFLD is often asymptomatic; hence, diagnosis is typically based on the accidental detection of abnormal liver enzymes or steatosis on abdominal ultrasonography (13, 14). A liver biopsy is a gold standard for diagnosing NAFLD (15). However, it is constrained due to its cost, sampling errors, and invasiveness with the risk of pain, bleeding, and rarely death (13). Therefore, emerging studies are exploring the possibility of using imaging and serum biomarkers for liver steatosis, injury, and fibrosis assessment (16). Hepatic steatosis index (HSI) is one of the currently available biomarkers with high sensitivity (89.6%) and specificity of (95.24%) (16-19). These scoring systems can help physicians identify candidates for further imaging investigations (16). Although there are multiple emerging systems for grading hepatic steatosis on ultrasound, they lack validation (20). The currently accepted method for grading hepatic steatosis uses the ultrasound B-mode. It compares the liver echogenicity to the echogenicity of the kidney and the appearance of the intrahepatic vessels and diaphragm (20, 21). It is recommended as the first-choice imaging technique for NAFLD in the population at risk by the European guidelines for managing NAFLD (16).

The early stages of NAFLD are easily reversible with interventions such as lifestyle modifications and proper glycemic control (22, 23). Weight loss and a personalized treatment program for glycemic control in people with diabetes have improved liver steatosis (22-24). Therefore, experts recommend screening for NAFLD in T2DM patients and some other high-risk populations (11, 25), using ultrasound and liver enzyme assay as the best initial tests according to the European Association for the study of the Liver guidelines (26). Moreover, it is essential to determine the factors associated with the development of NAFLD in diabetics to reduce NAFLD and its complications which could reduce the incidence of diabetic micro and macro-vascular complications (10).

NAFLD has emerged as a new pandemic in both developed and developing countries, along with an increase in the rates of obesity and the incidence of T2DM (27, 28). Diabetes and obesity are significant health issues in Palestine. The global prevalence of NAFLD in T2DM patients (50-70%) is higher than the prevalence in the general population (24%), with the highest rate of NAFLD among the general population being in the middle east (32%) (9, 29, 30). Studies investigating the prevalence and risk factors of NAFLD among Palestinians are scarce (31). Given that T2DM and NAFLD co-exist and act synergistically to cause catastrophic health consequences, this study aimed to assess the prevalence and characterize NAFLD among diabetic patients in Nablus -Palestine in 2022 and to identify the hepatic steatosis index score that necessitates further imaging investigations. Using ultrasound imaging, this research could recommend a screening program to detect NAFLD early among high-risk diabetics.

METHODS:

Study design and setting

A cross-sectional study from January to April 2022. Recruited adult T2DM patients aged ≥18 who presented for routine follow-up in primary health care centers of the Palestinian Ministry of Health in Nablus.

Sampling technique and sample size

A systematic random sampling technique was used to ensure an unbiased random sample. Every other T2DM patient who met the inclusion criteria was invited to participate. Patients were excluded if they had a personal history of any liver disease other than NAFLD (autoimmune hepatitis, genetic liver disease, and alcoholic fatty liver disease) or a family history of genetic liver disease or alcohol consumption. Based on the number of type 2 diabetics in the city of Nablus, which was around 6000 patients according to the Palestinian ministry of health 2020 annual reports (32),

the required sample size for this study using a sample size calculator was 362 patients.

Study tool, validity, and reliability

A face-to-face interview was conducted to determine sociodemographic and background information. Data collected from patients' files were lipid profile panels, liver enzyme tests, patient medications, and disease history. Biochemistry tests reported from the patients' files were HbA1c, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, total cholesterol, aspartate aminotransferase (AST), and alanine transaminase (ALT). Patient's disease history, including complications if present and the number of years since T2DM and diabetic complications, were also reported from the patients' files. This included diabetic retinopathy diagnosed by an ophthalmologist, diabetic nephropathy, and diabetic neuropathy previously diagnosed and reported in patient files. Moreover, diabetes treatment regimens and other medications were extracted from the patient's file. Dyslipidemia is identified as a previous diagnosis of dyslipidemia based on a fasting lipid panel.

The hepatic steatosis index was calculated by a scoring system based on gender, BMI, AST, ALT, and the presence of T2DM using the following formula: (HSI)= 8 x (ALT/AST ratio) + BMI (+2, if female;+2, if diabetes mellitus). For HSI, values <30 rule out NAFLD with a sensitivity of 93.1%, and values of >36 predict NAFLD with a specificity of 92.4%, with a positive likelihood ratio starting from 6.069. Scores between 30 and 36 are inconclusive (33).

NAFLD in diabetic patients was diagnosed using ultrasound B-mode in An-Najah University Hospital. It was categorized as mild, moderate, and severe NAFLD based on the echogenicity and visualization of liver parenchyma and surrounding structures (kidney, portal vein, and diaphragm). Steatosis is graded based on the following: mild when there is a slight diffuse increase in liver echogenicity with typical visualization of the diaphragm and portal vein wall; moderate, in case of a moderate increase of liver echogenicity and slightly impaired appearance of the portal vein wall and the diaphragm; and severe, in case of the marked increase of liver echogenicity with poor visualization of the portal vein wall, diaphragm, and posterior part of the right liver lobe (20). B-mode ultrasound can diagnose hepatic steatosis and stratify hepatic steatosis based on severity as mild, moderate, and severe, with a reported sensitivity of 84.8% and specificity of 93.6% (34).

Data analysis

Descriptive statistics were calculated for the prevalence of NAFLD among people with diabetes. Patients' characteristics were described using means, standard deviations, and percentages. Associations between general characteristics and outcomes were assessed using Pearson's Chi-square test. Multinomial logistic regression analysis was used to evaluate the relative risk by generating the odds ratios (OR) and 95% confidence intervals (CI) for risk factors. A p-value of less than 0.05 is considered statistically significant. Statistical Product and Service Solutions (SPSS) (version 21, IBM Corporation) was used for data entry and analysis. Kolmogorov-Smirnov test was used to test the normality of continuous variables distribution.

RESULTS

Patients diagnosed with T2DM (N=508) were recruited; 422 (83.0%) agreed to participate, 23 of whom did not complete their participation as they did not agree to do an ultrasound. The final number of participants was 399 with a mean age of 56.1±10.4 years; 56.1% were males, 57.6% lived in the city, 40.4% were from villages, 2.0% were living in refugee camps, and 31.1% were current smokers. The mean BMI was 29.3, and the majority (90%) were overweight (56.6%) or obese (23.4%) (Table 1).

Table (1): Demographics, anthropometric data, frequencies, and mean values.

A- Frequencies		**Frequency n(%)**
Gender	Male Female	224(56.1) 175(43.9)
Smoking	Yes No Ex-Smoker	124(31.1) 268(67.2) 7(1.8)
Residency	City Village Camp	230(57.6) 161(40.4) 8(2.0)
Body Mass Index category (BMI)	Normal Overweight Obese Severe obesity	40(10.0) 226(56.6) 90(22.6) 43(10.8)
B- Mean values	Mean	Standard deviation
Age (years)	56.05	10.34
Waist circumference (cm)	90.16	10.21
Body mass index (kg/m^2)	29.31	4.39
Systolic blood pressure (mmHg)	130.99	11.37
Diastolic blood pressure (mmHg)	84.05	8.47

Patient medical history, disease information, and medication regimen

Patients were diagnosed with different complications, including hypertension (51.4%), dyslipidemia (46.1%), diabetic retinopathy (26.8%), diabetic neuropathy (25.6%), and diabetic nephropathy (14.8%). The mean number of years since diagnosis with diabetes was 8.46 years, and since diagnosis with complications was 1.6 years. Most patients (77.7%) used metformin, 33.1% used insulin, 41.9% used anti-hypertensive medications, and 52.6% used statins as part of their medication regimen (Table 2).

Table (2): Patient comorbidities, medications, and laboratory test results.

A-Comorbidities	**n(%)**
Diabetic Retinopathy	107(26.8)
Diabetic Nephropathy	59(14.8)
Diabetic Neuropathy	102(25.6)
Hypertension	205(51.4)
Dyslipidemia	184((46.1)
Mean(SD)	
Years since diagnosis with DM (years)	8.46 (6.78)
Years with complications (years)	1.63 (2.522)
B-Medication use (Yes)	
Anti-hypertensive	167(41.9)
Statin	210(52.6)
Metformin	310(77.7)
Insulin	132(33.1)
Sitagliptin	59(14.8)
Dapagliflozin	23(5.8)
Glimepiride	97(24.3)

A-Comorbidities	n(%)
C- Lab test results	**Mean(SD)**
Hemoglobin A1c (%)	8.33 (1.42)
Low-Density Lipoprotein (mg/dL)	118.45(24.1)
High-Density Lipoprotein (mg/dL)	45.35(9.22)
Triglycerides (mg/dL)	156.19(50.23)
Total cholesterol (mg/dL)	180.80(27.24)
Aspartate Aminotransferase (AST) (U/L)	18.47(7.51)
Alanine Transaminase (ALT) (U/L)	21.07(8.84)
Hepatic steatosis Index (HSI)	41.4784(5.13)

mg/dl: Milligram per discilliter, SD: Standard deviation, U/L: Unit per liter.

Hepatic steatosis index scores and liver ultrasound reports

Based on the HSI scores, the mean HSI score was 41.47. The majority of the patients (91.2%) had an HSI score ≥36, and (8.8%) with HSI score of 30-36. None of the patients had HSI score <30. Based on B-mode ultrasound diagnosis, the majority of the patients (79.7%) were diagnosed with NAFLD; (33.8%) mild, (42.1%) moderate, and (3.8%) severe NAFLD. Most of the patients (82.4%) with HSI scores ≥36 and 51.4% of patients with HSI scores (30-36) were diagnosed with NAFLD based on ultrasound. (Table 3).

Table (3): HSI categories and NAFLD based on liver ultrasound results.

Hepatic steatosis features	Category	n(%)
Hepatic steatosis index (HSI)	HSI≥36	364(91.2)
	HSI 30-35.99	35(8.8)
Liver Ultrasound result	No NAFLD	81(20.3)
	Mild NAFLD	135(33.8)
	Moderate NAFLD	168(42.1)
	Severe NAFLD	15(3.8)
NALFD based on the HSI category		
HSI results	**Liver ultrasound results**	
	Yes NAFLD	**No NAFLD**
HSI≥36	300(82.4)	64 (17.6)
HSI 30-36	18(51.4)	17(48.6)
Total	318(79.7)	81(20.3)

HSI: Hepatic steatosis index, NAFLD: Non-alcoholic fatty liver disease.

The distribution of NAFLD severity based on HSI values

Based on ultrasound results, 17.6% of the patients with HSI ≥36 were diagnosed free of NAFLD, 34.6% with mild, 44.0% with moderate, and 3.8% with severe NAFLD. Patients with HSI values 30-36 were free of NAFLD (48.6%), 25.7% mild, 22.9% moderate, and 2.9% severe NALFD. None of the patients had an HSI score of <32 (Table 4).

Table (4): Non-alcoholic fatty liver severity based on hepatic steatosis index.

		Liver Ultrasound Result n(%)				Total n
		no NAFLD	mild NAFLD	moderate NAFLD	severe NAFLD	
HSI category	HSI≥36	64(17.6)	126(34.6)	160(44.0)	14(3.8)	364
	HSI 30-36	17(48.6)	9(25.7)	8(22.9)	1(2.9)	35
Total		81(20.3)	135(33.8)	168(42.1)	15(3.8)	399

HSI: Hepatic steatosis index, NAFLD: Non-alcoholic fatty liver disease.

The univariate analysis to determine the association between NAFLD and other factors

Table 5 represents the univariate analysis of the factors associated with NAFLD categories. The multiple logistic regression included any independent variable with a p-value ≤0.25 in the univariate analysis (Table 5).

Table (5): Univariate analysis of different factors and the association with NAFLD.

Independent variables	NAFLD category [a]	Odds ratio	95% Confidence interval	p-value
Hemoglobin A1c [c]	Mild	1.317	1.037 - 1.672	0.024 [b]
	Moderate	1.631	1.293 - 2.058	<0.001 [b]
	Severe	1.684	1.145 - 2.477	0.008 [b]
Waist circumference [c]	Mild	1.027	0.995 - 1.061	0.104
	Moderate	1.039	1.008 - 1.072	0.015 [b]
	Severe	1.078	1.032 - 1.126	0.001 [b]
Body mass index [c]	Mild	1.128	1.040 - 1.224	0.004 [b]
	Moderate	1.186	1.095 - 1.284	<0.001 [b]
	Severe	1.283	1.144 - 1.439	<0.001 [b]
Aspartate aminotransferase [c]	Mild	0.969	0.930 - 1.009	0.127
	Moderate	1.009	0.972 - 1.046	0.649
	Severe	1.022	1.022 - 1.143	0.006 [b]
Alanine transaminase [c]	Mild	0.975	0.940 - 1.011	0.176
	Moderate	1.021	0.989 - 1.055	0.202
	Severe	1.113	1.058 - 1.170	<0.001 [b]
Age [c]	Mild	1.019	0.991 - 1.049	0.188
	Moderate	1.056	1.027 - 1.086	<0.001 [b]
	Severe	1.106	1.047 - 1.168	<0.001 [b]
Hepatic steatosis index [c]	Mild	1.094	1.021 - 1.172	0.011 [b]
	Moderate	1.162	1.087 - 1.243	<0.001 [b]
	Severe	1.256	1.136 - 1.388	<0.001 [b]
Number of years since diagnosis [c]	Mild	0.977	0.932 - 1.025	0.342
	Moderate	1.041	0.998 - 1.086	0.065
	Severe	1.138	1.065 - 1.216	<0.001 [b]
Diabetic retinopathy (Yes)[d]	Mild	1.199	0.591 - 2.432	0.616
	Moderate	0.492	0.261 - 0.928	0.028 [b]
	Severe	0.062	0.016 - 0.244	<0.001 [b]
Diabetic nephropathy (Yes)[d]	Mild	1.217	0.514 - 2.885	0.655
	Moderate	0.675	0.311 - 1.463	0.319
	Severe	0.211	0.062 - 0.721	0.013 [b]
Diabetic neuropathy (Yes)[d]	Mild	0.675	0.341 - 1.335	0.259
	Moderate	0.603	0.313 - 1.161	0.130
	Severe	0.260	0.082 - 0.828	0.023 [b]
Insulin use (Yes) [d]	Mild	0.807	0.431 - 1.511	0.503
	Moderate	0.533	0.294 - 0.964	0.038 [b]
	Severe	0.219	0.069 - 0.690	0.010 [b]

[a] The reference category is No NAFLD, [b] Significant p-value <0.05, [c] Continuous independent variables, [d] The reference category for the independent variable is No

Adjusted multinomial logistic regression analysis results for the association between NAFLD and different factors

The adjusted multiple logistic regression to determine the risk factors associated with NAFLD categories (severe, moderate, and mild) compared to patients free of NAFLD revealed that patients with severe NAFLD were significantly at higher risk of increased cholesterol levels (OR=1.047, p-value=0.007), HSI (OR=1.32, p-value<0.001), and diabetic retinopathy (OR=7.074, p-value=0.017). In addition, patients with moderate NAFLD were at higher risk of increased cholesterol levels (OR=1.023, p-value=0.007), HbA1c (OR=1.06, p-value=0.001), HSI (OR=1.21, p-value<0.001), and age (OR=1.071, p-value=0.001). Moreover, patients with mild NAFLD were at higher risk of increased cholesterol levels (OR=1.02, p-value=0.017), HbA1c (OR=1.312, p-value=0.046), HSI (OR=1.102, p-value=0.026), and age (OR=1.047, p-value=0.019). Decreasing LDL levels were associated with decreased risk of mild (OR=0.982, p-value=0.039), moderate (OR=0.97, p-value=0.004), and severe (OR=0.955, p-value=0.010) NAFLD. Factors that were not associated with NAFLD were diabetes treatment regimen, the number of years diagnosed with diabetes, hypertension, high-density lipoprotein levels, and triglyceride levels (Table 6).

Table (6): Adjusted multiple logistic regression for factors associated with NAFLD.

NAFLD categories [a]	Independent varibales	Odds Ratio	95% Confidence Interval	P-value
Mild NAFLD	Years since diagnosis	0.948	0.887-1.013	0.113
	Hemoglobin A1c	1.312	1.005-1.712	0.046[b]
	Low-density lipoprotein	0.982	0.965-0.999	0.039 [b]
	Total cholesterol	1.020	1.004 -1.037	0.017 [b]
	Increased age	1.047	1.008 -1.087	0.019 [b]
	Hepatic steatosis index	1.102	1.011-1.200	0.026 [b]
	Waist circumference	0.988	0.950-1.029	0.571
	Metformin use (Yes)[d]	1.294	0.613 -2.730	0.499
	Diabetic retinopathy (Yes)[d]	0.712	0.316-1.605	0.413
	Diabetic nephropathy (Yes)[d]	0.891	0.313-2.534	0.829
	Diabetic neuropathy(Yes) [d]	1.159	0.549-2.449	0.699
Moderate NAFLD	Years since diagnosis	0.982	0.922-1.045	0.560
	Hemoglobin A1c	1.604	1.228-2.096	0.001 [b]
	Low-density lipoprotein	0.974	0.957-0.992	0.004 [b]
	Total cholesterol	1.023	1.006-1.040	0.007 [b]
	Increased age	1.071	1.030-1.114	0.001 [b]
	Hepatic steatosis index	1.212	1.111-1.321	<0.001[b]
	Waist circumference	0.967	0.929-1.007	0.102
	Metformin use (Yes) [d]	1.757	0.808 -3.820	0.155
	Diabetic retinopathy (Yes)[d]	1.212	0.568-2.586	0.619
	Diabetic nephropathy (Yes)[d]	1.118	0.420-2.978	0.823
	Diabetic neuropathy(Yes) [d]	0.806	0.379 -1.714	0.576

NAFLD categories [a]	Independent varibales	Odds Ratio	95% Confidence Interval	P-value
Severe NAFLD	Years since diagnosis	1.025	0.922 -1.140	0.642
	Hemoglobin A1c	1.409	0.861-2.307	0.173
	Low-density lipoprotein	0.955	0.922-0.989	0.010 [b]
	Total cholesterol	1.047	1.012-1.082	0.007 [b]
	Increased age	1.059	0.976 -1.148	0.170
	Hepatic steatosis index	1.321	1.137-1.535	<0.001 [b]
	Waist circumference	0.983	0.923-1.047	0.588
	Metformin use (Yes)[d]	0.873	0.192-3.975	0.860
	Diabetic retinopathy (Yes)[d]	7.074	1.412-35.455	0.017 [b]
	Diabetic nephropathy (Yes)[d]	2.440	0.434-13.716	0.311
	Diabetic neuropathy(Yes)[d]	0.933	0.227 - 3.839	0.923

[a] The reference category is No NAFLD, [b] Significant p-value <0.05, [c] Continuous independent variables, [d] The reference category for the independent variable is No. NAFLD: Non-alcoholic fatty liver disease.

DISCUSSION

NAFLD is a major cause of morbidity and mortality related to chronic liver diseases (2). It is related to insulin resistance and T2DM (9, 10). Therefore, this study has clinically significant findings. The prevalence of NAFLD among Palestinian T2DM was high (79.7%), Similar to the reported prevalence of NAFLD (80.4%) among diabetic patients in Jordan, a neighboring country (35). However, these results were slightly higher than the global prevalence (50-70%). Therefore, risk factors associated with the increased risk of NAFLD among Palestinians were investigated.

NAFLD and diabetes in patients increase the risk of developing micro and macro-vascular diabetic complications (10). In agreement with other studies, higher levels of HbA1c were associated with an increased risk of NAFLD (12, 36, 37). The univariate analysis revealed that insulin treatment was associated with decreased moderate and severe NAFLD risk. These results agree with previous studies of the protective effect of insulin over NAFLD (38, 39), with evidence of decreased intrahepatic fat, which was also associated with decreased HbA1c and better glycemic control (40). Thus, we recommend that diabetic patients follow an appropriate drug regimen and lifestyle modification. Compared to T2DM patients without NAFLD, moderate and severe NAFLD patients were more likely to have diabetes mellitus retinopathy (DMR). These results of HbA1c, insulin treatment, and diabetic complications support that the lack of control over diabetes increases the risk of NAFLD and its progression (41).

Previous studies showed that patients with NAFLD had higher levels of cholesterol, which is caused by impaired clearance due to hepatocyte injury (42, 43). Moreover, patients with NAFLD had high levels of LDL (42, 44, 45). This study showed that increased cholesterol levels were associated with an increased risk of NAFLD, while decreased levels of LDL were associated with decreased risk of NAFLD. Therefore, we recommend screening for NAFLD in people with diabetes who present with dyslipidemia, as they are at increased risk. We also recommend a routine evaluation and monitoring of LDL levels and keeping them under control, as well as implementing programs to increase awareness of the risk of high cholesterol and LDL to protect patients from NAFLD.

Previous studies stated that the results of AST or ALT are not a determinant of the presence of NAFLD (5, 46). In contrast, some studies indicate that the ratio of AST to ALT is more effective in identifying NAFLD than AST or ALT levels alone (33, 47, 48). The univariate analysis results indicated that high levels of AST and ALT are related to severe

NAFLD. Moreover, the mean value of the HSI score for diabetic patients was high (41.47). Most patients (91.2%) had HSI score ≥36, and 8.8% had an HSI of 30-36. None of the patients had HSI<32. Based on the ultrasound, most patients with HSI scores≥30 were predicted with liver steatosis, indicating that HSI scores can be relied on as a screening tool for NAFLD among diabetic patients if ultrasound imaging for all people with diabetes in the population is non-feasible.

Most of the diabetic patients in this study (90%) were obese, with an average BMI (of 29.3). The high mean HSI score in Palestinian diabetic patients is most likely due to high BMI values included in the HSI formula. Moreover, in agreement with other studies, the results of this study revealed that the increased BMI was associated with an increased risk for all NAFLD categories (49-51). In addition, it was documented that the severity of fatty liver in obese patients is related to impaired glycemic status (52). Studies also demonstrated that a 3-5% weight loss improved liver steatosis, while a weight loss of more than 5-7% has been shown to improve NASH, and a weight loss of more than 10% is thought to improve liver fibrosis (22, 24). Therefore, we recommend that diabetic patients follow measures to decrease their BMI and control their glycemic status to decrease their risk of developing NAFLD and its progression if they already have NAFLD. As there is no approved medication for NAFLD, the mainstay of treatment is lifestyle modification (53), including increasing physical activity and exercise (53, 54), caloric restriction (53, 55), and time-restricted feeding (56).

Different studies have shown an increase in the risk and prevalence of NAFLD in older age groups (27, 57). Studies also indicate that diabetes mellitus increases with age (58, 59). The results of this study indicated that the risk of moderate and severe NAFLD increased with age. Therefore, we recommend screening for NAFLD in people with diabetes with increasing age, monitoring them for other modifiable risk factors, and implementing interventions to keep them under control, whether medical or by increasing patient awareness and health education.

NAFLD is asymptomatic mainly until the late stages of the disease, making risk factor modification and current or experimental medications ineffective unless diagnosed early (13). The treatment of NAFLD focuses on reversing risk factors such as weight loss, proper glycemic control, and lifestyle modifications (22-24). Some medications have shown promising results in treating NAFLD, such as vitamin E, metformin, statins, and ezetimibe; however, they are still experimental (22). The results of this study indicated that neither metformin nor any other oral medications taken by patients in this study (Glimepiride, Sitagliptin, Dapagliflozin, and Statins) were associated with NAFLD.

This study was limited to diabetic patients presenting to primary health care clinics in Nablus; it did not include clinics in villages. Another limitation of this study is the lack of previous studies about NAFLD in the Palestinian population and the lack of local studies on other high-risk populations for NAFLD to compare. However, this study is the first to assess the prevalence and associated risk factors of NAFLD among people with diabetes in Palestine. It is bringing attention to the fact that diabetes is a significant risk factor for NAFLD and that the prevalence of NAFLD among Palestinian diabetics is higher than that among people with diabetes in other countries. It also assessed the possibility of using the HSI as a non-invasive screening tool for NAFLD in the Palestinian diabetic population.

CONCLUSION

This study showed an alarming prevalence of NAFLD and obesity among Palestinian diabetic patients, which were higher than the global levels. Moreover, none of the patients had HSI scores<32. Modifiable risk factors associated with increased risk of NAFLD were obesity, elevated HbA1c, elevated total cholesterol levels, and higher HSI scores. Non-modifiable factors were age and the presence of diabetic retinopathy. This research could have clinical implications. It assessed the possibility of using the HSI as a non-invasive screening tool for NAFLD in the Palestinian diabetic population. This will allow for identifying diabetic patients at high risk of developing liver steatosis and enrolling them in a good screening program for early diagnosis

and application of available management options. This could decrease the burden of liver disease and the risk of hyperglycemic complications among people with diabetes. Further research is recommended on the general population and other high-risk groups.

Due to the prevalence of NAFLD among people with diabetes, we recommend implementing a screening program in Palestine using ultrasound imaging to detect NAFLD cases early to prevent progression and its complications, especially for those with significant risk factors other than diabetes, such as obese, patients with dyslipidemia or cardiovascular disease, and possible diabetics in populations other than the city of Nablus such as villages and rural areas.

Abbreviations

ANNU: An-Najah National University

AST: Aspartate Aminotransferase

ALT: Alanine Aminotransferase

BMI: Body Mass Index

BP: Blood Pressure

CI: Confidence Interval

Cm: Centimeter

FBS: Fast Blood Sugar

FLD: Fatty Liver Disease

HSI: Hepatic Steatosis Index

HA1c: Hemoglobin A 1C

HDL: High-Density Lipoprotein

KG: Kilogram

LDL: Low-Density Lipoprotein

mmHg: Millimeter of Mercury

NAFLD: Non-Alcoholic Fatty Liver Disease

NASH: Non-Alcoholic Steatohepatitis

OR: Odds Ratio

SPSS: Statistical Product and Service Solutions

T2DM: Type Two Diabetes Mellitus

WC: Waist Circumferences

Ethics approval and consent to participate: Ethical Approval was acquired from the Institution Review Board (IRB) at An-Najah National University (Approval number: Med.Oct. 2021/42). Participants were approached professionally and asked to volunteer in the study. The study's aim and objectives were explained to the patients, who were informed that they had the right to refuse or withdraw from the study at any time. Patient privacy and confidentiality were guaranteed. We obtained informed consent from all subjects involved in the study.

Availability of data and materials: Most data generated or analyzed in this study are included in this manuscript. Other data supporting this study's findings are available from the corresponding author on reasonable request.

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