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Study of Non-Alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus

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Original Article

Summary

***Background** : Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of chronic liver disease globally and it is more prevalent in patients with type 2 diabetes mellitus (T2DM). European Association for the Study of the Liver (EASL)- European Association for the Study of the Diabetes (EASD)- European Association for the Study of the Obesity (EASO) guidelines recommend screening of all patients with T2DM for NAFLD.*

***Objectives**: To assess the effect of T2DM on prevalence and severity of NAFLD, in patients with type 2 diabetes in comparison to non-diabetic patients in Erbil city, using non-invasive biomarkers.*

***Patients and methods**: A case-control study included 100 patients with type 2 diabetes and 100 non-diabetic subjects as control group, who attended the consultation department of Laila Qasm diabetes center in Erbil city were enrolled in this study. NAFLD diagnosed by Ultrasound (U/S) or Hepatic Steatosis index (HSI) >36, and risk of advanced fibrosis determined by using NAFLD Fibrosis Score (NFS) and Fibrosis-4 Index (FIB-4).*

***Results**: The prevalence of Hepatic steatosis was more common in diabetic versus non-diabetic population (76% vs.47%; p <0.05). Higher risk of advanced fibrosis reported in diabetic cases compared to controls, 22% vs. 6% , respectively, (P <0.05) by using NFS, same for FIB-4 which is 14% to 7% respectively (p <0.05).*

***Conclusion**:*

The prevalence of hepatic steatosis and high risk of advanced hepatic fibrosis are more common in type 2 diabetic patients than non-diabetic subjects.

***Keywords:** Non-Alcoholic Fatty Liver Disease, Type two Diabetes Mellitus.*

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1. INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming the leading cause of chronic liver disease globally (1). NAFL is histologically defined as the presence of ≥5% hepatic steatosis without evidence of hepatocellular injury, and nonalcoholic steatohepatitis (NASH) is defined as the presence of ≥5% hepatic steatosis and inflammation with hepatocyte injury (e.g., ballooning), with or without fibrosis (2). NASH is the most common reason for liver transplantation in women, patients over 54 years, and Medicare recipients in the United States (3). Currently, NAFLD affects more than 60% of type 2 diabetic patients and 25% of the global population (4). According to Studies determining the prevalence of NASH, it may affect as many as 37% of patients with T2D and between 1.5% and 6.5% of the overall population (4). NASH will occur in at least 20%–30% of NAFLD patients and may progress to cirrhosis and hepatocellular carcinoma (HCC) (2), NAFLD is frequently linked to worse insulin resistance (5), Dyslipidemia (6), diabetes mellites (7), and cardiovascular disease (CVD) (8). T2DM increases risk of developing NAFLD/NASH (9), and conversely, NAFLD increases risk of T2DM (10). Liver fibrosis (not fatty liver) is associated with an increased risk of mortality from its complications, so real target of screening is liver fibrosis (8,11). Type 2 diabetic patients with hepatic steatosis or elevated plasma alanine aminotransferase are particularly susceptible for developing steatohepatitis with severe liver fibrosis (12).

The diagnosis of NAFLD is usually based on history and serum biomarker scores that combine patients' clinical characteristics with laboratory investigations, followed by imaging (elastography) and liver biopsy (11,12). A meta-analysis depends largely on liver ultrasonography reported a global prevalence of NAFLD in ~55% of type 2 diabetic patients (13). The fibrosis-4 index (FIB-4) and NAFLD fibrosis score (NFS) are the two biomarker scores that are most commonly used to determine the degree of fibrosis, because they can anticipate liver-related mortality in patients with NASH (11,12,14). However, their use in type 2 diabetic patients has suffered from heterogeneous study design, small sample size and populations that diabetic and non-diabetic patients were analyzed together (9,15). NAFLD is currently one of the most difficult public health issues in the world due to the contradiction that it is a highly prevalent disease but that only a small percentage of cases advance to serious disease. There is a need for population-wide policies to efficiently recognize, refer, and manage those patients (16), therefore, detecting patients with, or at higher risk

for advanced fibrosis among the large NAFLD population is important for the patients and challenging for the physician. With this purpose the EASL-EASD-EASO Guidelines recommend to routinely screen type 2 diabetes patients for the presence of NAFLD and to assess the presence of advanced fibrosis in high-risk individuals (17). Also, the American Diabetes Association (ADA) recommended screening for advanced fibrosis in all patients with prediabetes or DM with elevated plasma alanine aminotransferase (ALT) and/ or hepatic steatosis (18). According to current guidelines an earlier diagnosis of NAFLD would facilitate treatment with lifestyle management, vitamin E, or pioglitazone (11,12,19). Improving metabolic abnormalities in type 2 diabetic patients like glycemic control, reducing weight, and using specific drugs for treating hyperglycemia or dyslipidemia are also useful tools for NAFLD management (20, 21). The aim of our study is to show the prevalence and severity of NAFLD in type 2diabetic patients in comparison to non-diabetic patients in Erbil city by using non-invasive biomarkers according to EASL-EASD-EASO guidelines.

2. PATIENTS and METHODS

This was a case control study carried out during the period from the 1st of January to the 31st of March, 2022. A total of 100 patients with type two diabetes mellitus at the age of 35 years or older were enrolled in this study as cases group. Additionally, 100 non-diabetic participants were recruited as a control group. Patients and controls were selected from the clients who attended the consultation department of the Laila Qasm diabetes center in Erbil city. Data collected through face-to-face interview and thorough clinical examination.

Patient was excluded if he/she had an acute intercurrent illnesses, currently use medications affecting liver function tests, pregnant women patient who had known other liver diseases or high alcohol consumption (male more than 30g and female more than 20g per day).

The clinical and anthropometric characteristics include: age, sex, past medical and drug history, blood pressure. Patient's height and weight were measured using standard scales and approximated to the nearest 0.5 digit and the body mass index was calculated using the standard equation;

$BMI = weight\ (kg)/\ Height\ (m^2)$

Samples of venous blood were collected from all participants and HbA1c, glucose, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), triglyceride, total cholesterol, low-density lipoprotein

cholesterol (LDL), high-density lipoprotein cholesterol, total cholesterol, albumin, and platelets were measured. Cobas e 411 auto-analyzer was used to perform biochemical tests. Type 2 diabetic participants were already known cases of diabetes and taking care of their diabetes at Laila Qasm diabetes center. Hepatic steatosis was diagnosed by ultrasound or liver enzymes (17). Although ultrasound is a useful tool for the diagnosis of fatty liver diseases specially for the moderate and severe grades with an accuracy of >80%, but to a lesser extent for mild cases (22).

Hepatic steatosis index (HSI) = 8 × (ALT/AST) + BMI + (2, if diabetes mellitus) + (2, if female), with values < 30 ruling out and values>36 ruling in steatosis (23).

The risk of liver fibrosis is calculated by using the Fibrosis-4 (FIB-4) score (24), and NAFLD Fibrosis Score (NFS) (25).

FIB-4 = Age (years) × AST (U/L) /Platelet (× 10^9/L) × √ ALT (U/L).

Age <65: FIB-4 < 1.3 or Age >65: FIB-4 < 2 were considered as being at the lowest risk of advanced liver fibrosis

Age <65: FIB-4 ≥ 1.3 and <2.67or Age >65: FIB-4 ≥ 2 and <2.67 represent indeterminate risk of advanced liver fibrosis.

FIB-4 ≥ 2.67 were considered as having a high risk of advanced liver fibrosis.

NFS = −1.675 + 0.037 × Age (years) + 0.094 × BMI (kg/m2) + 1.13 × (Impaired Fasting Glucose or DM) + 0.99 × (AST/ALT) − 0.013 × Platelet (× 109 /L) − 0.66 × Albumin (g/dL), in which Impaired Fasting Glucose or DM had a value of 1 if the participants had impaired fasting glucose or DM and 0 if they did not.

Low risk of advanced liver fibrosis if: Age <65: NFS <-1.455 or Age >65: NFS <0.12

Indeterminate risk of advanced liver fibrosis if: Age <65: -1.455 to 0.676 or Age >65: 0.12 to 0.676.

High risk of advanced liver fibrosis if: NFS >0.676.

Body mass index categorized as followed

Normal; BMI = 18.5 to 24.9 kg/m^2, Overweight; BMI = 25.0 – 29.9 kg/m^2, Obese; BMI = ≥ 30.0 kg/m^2. The prevalence of NAFLD and risk of fibrosis determined in each subgroup

Statistical analysis was carried out by using SPSS version 25 for Windows, to calculate the mean, SD, and compare it for continuous variables. Rate (%) and cross tabulation for nominal variables. Level of statistically significance (P. value) was set at ≤ 0.05 to be significant.

3. RESULTS

The mean age of the studied diabetic cases was 54.9 ± SD of 13.2 whereas that of the non-diabetic group was 52.6 ± SD of 12.1, nearly 50 % of the cases were male in both diabetic and non-diabetic groups, there is a statistically significant difference between the mean HbA1C of diabetic and non- diabetic groups (p. 0.003). A part from the sex parameter (P. 0.12), all other parameters show a statistically significant difference between the mean of the parameters of diabetic and non-diabetic groups (p.<0.05), Obesity, hypertension and dyslipidemia were more common among diabetic patients than non-diabetic patients, which can be regarded as significant. Prevalence of obesity and overweight in the diabetic group was 36% and 44% respectively while in the non-diabetic group was 25% and 41%. Hypertension (43%) and dyslipidemia (98%) were also higher in the diabetic group in comparison to the non-diabetic group 31% and 60%. Alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), were significantly higher and platelets significantly lower (p <0.05) in type 2 diabetic patients versus the control group.

the detailed data were shown (**Table 1**).

The prevalence of Hepatic steatosis diagnosed by either HSI >36 or ultrasound (mild, moderate and sever steatosis) was more common in diabetic versus non-diabetic population (76% vs.47%; p <0.05) (**Table 2**).

In diabetic group prevalence of fatty liver increased by increasing BMI, using either u/s or HSI. By ultrasound prevalence were 45%, 70% and 100% in normal weight, overweight and obese group respectively and same is true regarding non-diabetic group (26%, 41% and 80%). All of the patients with obesity and diabetes were had fatty liver by both ultrasound and HSI, and the number of patients with high risk for advanced fibrosis (NFS >0.676 or FIB-4 ≥ 2.67) increase from 3% and 6% respectively in non-diabetic normal weight group to 22% and 14% in diabetic obese group. High risk of advanced fibrosis is more in diabetic patients than in non-diabetic cases, 14%in diabetic patients versus 7% in non-diabetic participants (p <0.05). Using ultrasound associated with higher rate of fatty liver diagnosis in comparison to HSI in both groups (76% vs. 70% in diabetic group and 46% vs. 43% in non-diabetic group). (**Figure 1 and Figure 2**). The percentage of risk of advanced liver fibrosis depending on NFS was (22% for high risk) and (67% for indeterminate risk) in comparison to FIB-4 which was (14%

and 45% respectively) in diabetic group. on the other hand, in non-diabetic group using FIB-4 biomarker was (7% and 31% for high and indeterminate risk respectively) against NFS which was (6% and 26% respectively) (**Figure 3**).

Table 1. Comparison of different parameters of the diabetic and non- diabetic groups stratified by BMI categories.

Parameter	Normal weight n=54		Overweight n=85		Obese n=61		Total n=200		P value
	T2DM n=20	No T2DM n=34	T2DM n=44	No T2DM n=41	T2DM n=36	No T2DM n=25	T2DM n=100	No T2DM n=100	
Age, mean (SD)	52.5 (11.2)	51.6 (10.1)	53.4 (13.5)	50.9 (12.8)	53.7 (10.3)	52.6 (12.1)	54.9 (13.2)	52.6 (12.1)	0.021
Sex % male	16	11	18	25	17	14	51(51)	50(50)	0.12
BMI, mean (SD)	24.1(1.1)	23.2(91,5)	29.8(2.3)	27.7 (1.9)	34.1(2.8)	33.2(1.9)	30.8(2.2)	28.1 (2.2)	0.035
HbA1C, mean	7.4(0.3)	4.7(0.4)	7.6(0.3)	4.9(0.4)	8.1(0.4)	5.1(0.12)	7.9 (0.43)	4.9 (0.32)	0.003
Hypertension n (%)	12	7	16	11	15	13	43(43)	31(31)	0.023
SBP, mean (SD)	132 (1.1)	139 (2.2)	140 (1.1)	123 (2.5)	145 (4.1)	125 (3.2)	145 (4.4)	126 (3.1)	0.04
DBP mean (SD)	81 (2.2)	88 (1.2)	85 (2.4)	83 (1.8)	89 (3.3)	84.2 (2.2)	89 (3.1)	84 (2.1)	0.04
Dyslipidemia n (%)	18	17	44	24	36	19	98 (98)	60(60)	0.005
cholesterol mean (SD)	158.7(2.1)	164.7(5.5)	169.1(3.3(	169.9(2.9)	172.3(3.8)	176.2(4.9)	171.3 (4.2)	174.4(5.6)	0.039
LDL, mean (SD)	103.7(2.6)	105.6(2.90	104.6(4.4)	107.7(5.3)	106.9(6.1)	109.2(6.3)	107.4 (3.7)	108.7 (6.3)	0.048
HDL, mean (SD)	35.2(1.3)	36.1 (1.4)	36.2(1.9)	35.1 (1.3)	37.9(1.7)	38.9 (1.5)	37.2(1.8)	38.7 (1.4)	0.041
TG, mean (SD)	201.9(7.6)	196.2(5.3)	198.9(7.2)	196.9(5.7)	200.9(6.4)	199.7(5.9)	203.9(7.7)	198.9(5.9)	0.045
Creatinine, mean (SD)	1.01 (0.01)	0.92 (0.02)	1.01(0.0009)	0.94 (0.02)	1.01 (0.01)	0.96 (0.02)	1.01 (0.01)	0.95 (0.02)	0.038
ALT, mean (SD)	39.9 (1.5)	32.2(1.2)	40.4 (1.4)	32.5(1.3)	41.3 (1.7)	33.9(1.6)	41.9 (1.6)	33.4(1.4)	0.016
AST, mean (SD)	32.1 (1.2)	39.(1.3)	31.4 (1.8)	40.(1.7)	32.4 (1.5)	42.(1.8)	33.4 (1.4)	41.(1.9)	0.028
ALP, mean (SD)	79.8.(2.1)	62.1(2.5)	80.1(2.1)	63.(91.3)	80.9(3.3)	64.1(2.3)	80.6(3.1)	65.1(2.2)	0.032
GGT, mean (SD)	33.8(1.9)	31.7(2.5)	34.8(1.6)	32.7(2.1)	35.9(1.7)	33.9(2.9)	35.8(1.8)	33.7(2.8)	0.044
Albumin, mean (SD)	3.5(0.03)	3.7(0.3)	3.6(0.03)	3.8(0.4)	4.08(0.03)	4.1(0.3)	4.02(0.03)	3.9(0.3)	0.054
Platelet, mean	241.7(6.3)	280.5(7.5)	245.97(6.5)	281.9(5.7)	243.7(5.8)	281.6(8.9)	244.7(6.8)	282.9(7.9)	0.037

Table 2. The prevalence of NAFLD and degree of severity of hepatic fibrosis among participants

Parameter	Normal weight		overweight		obese		Total		P. value
	With T2DM N=20 (%)	Without T2DM N=34 (%)	With T2DM N=44 (%)	Without T2DM N=41 (%)	With T2DM N=36 (%)	Without T2DM N=25 (%)	With T2DM N=100 (%)	Without T2DM N=100 (%)	
US (mild, moderate & severe) n=122	9 (45)	9 (26)	31(70)	17 (41)	36(100)	20(80)	76(76)	46(46)	0.0024
HSI > 36 n = 113	7 (35)	6 (17)	27 (61)	17 (41)	36 (100)	20 (80)	70 (70)	43 (43)	0.0019
Age <65: NFS <-1.455 or Age >65: NFS <0.12	4 (20)	28 (82)	5 (11)	27 (65)	2 (5)	13 (52)	11 (11)	68 (68)	0.078
Age <65: -1.455 to 0.676 or Age >65: 0.12 to 0.676	14 (70)	6 (17)	31 (70)	11 (26)	22 (61)	9 (36)	67 (67)	26 (26)	0.0033
NFS >0.676	2 (10)	1 (3)	8 (18)	2 (5)	12 (33)	3 (12)	22 (22)	6 (6)	0.0052
Age <65: FIB-4 < 1.3 Age >65: FIB-4 < 2	10 (50)	25 (73)	20 (45)	24 (58)	11 (30)	13 (52)	41 (41)	62 (62)	0.0069
Age <65: FIB-4 ≥ 1.3 and <2.67 Age >65: FIB-4 ≥ 1.3 and <2.67	8 (40)	8 (23)	18 (40)	13 (31)	19 (52)	10 (40)	45 (41)	31 (31)	0.0073
FIB-4 ≥ 2.67	2 (10)	2 (6)	6 (13)	3 (7)	6 (16)	2 (8)	14 (14)	7 (7)	0.0032

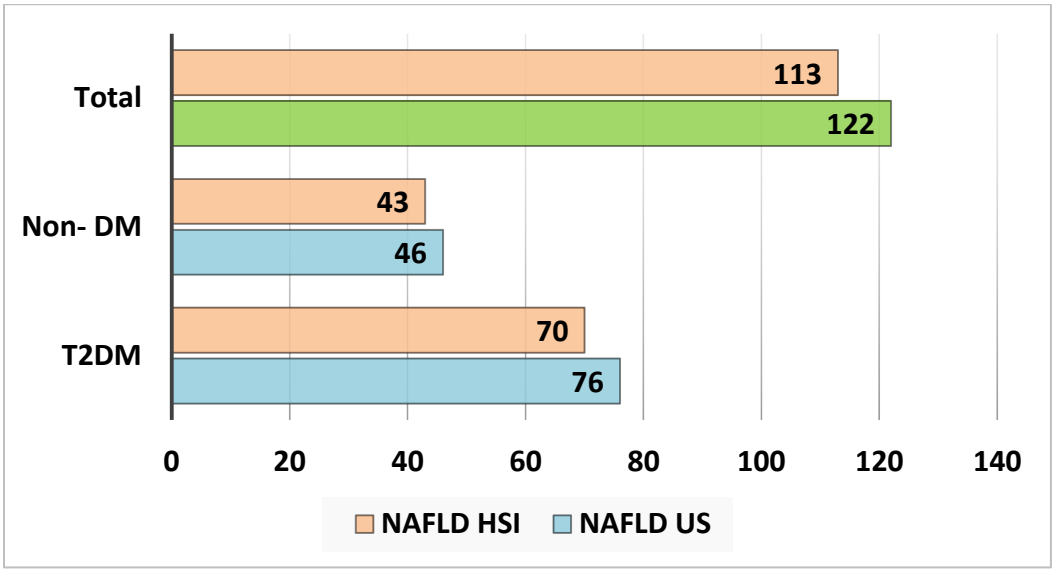

Figure 1. Frequency of NAFLD patients diagnosed by US versus HSI in both Diabetic & non-diabetic groups.

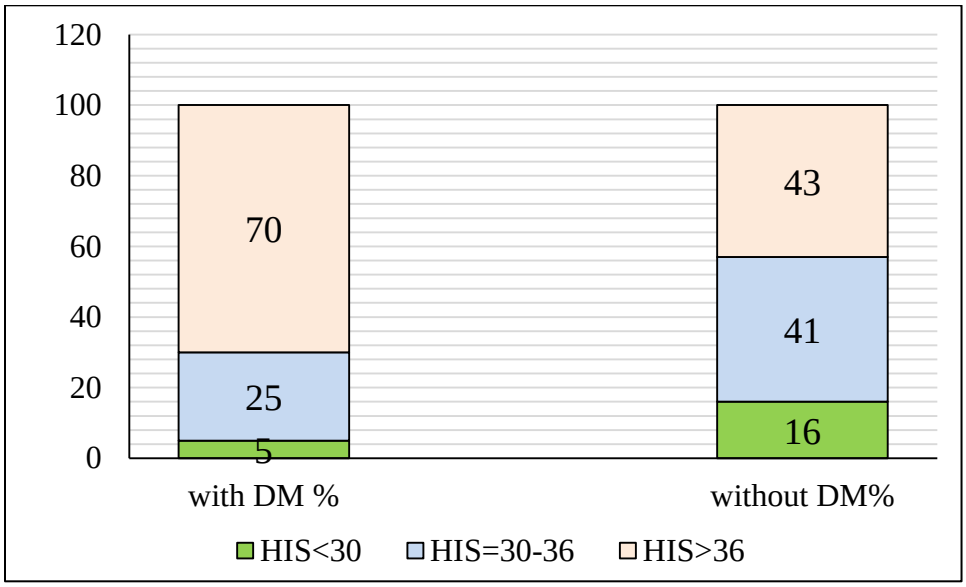

Figure 2 percentage of patients at low, indeterminate and high risk of hepatic steatosis in diabetic versus non-diabetic groups by using HSI.

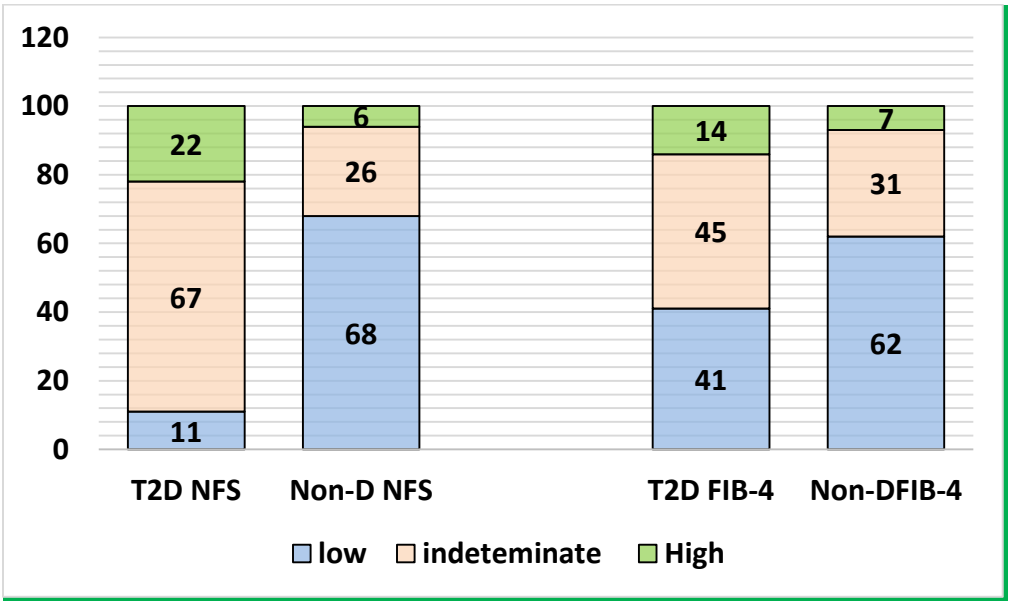

Figure 3 percentage of different level of fibrosis severity using NAFLD fibrosis score and fibrosis-4 biomarkers.

4. DISCUSSION

This study provides important data about prevalence of NAFLD and percentage of low, indeterminate and high risk of advanced liver fibrosis in diabetic and non-diabetic patients in Erbil city that may reflect the data of Iraq overall. As well, this study shows the great impact of type 2 diabetes mellitus and obesity on hepatic steatosis and displays the effect of diabetes to enhance advanced liver fibrosis. furthermore, demonstrates the use of ultrasound and HSI for diagnosing fatty liver and FIB-4 and NFS for assessing the risk of advanced liver fibrosis according to EASL-EASD-EASO Guidelines in type 2 diabetic patients (17). Using ultrasound associated with higher rate of fatty liver diagnosis, this may reflect the fact that about 41% in non-diabetic and 25% in diabetic group patients had HIS of indeterminate result, HSI: 30- 36 (Figure 2). Prevalence of NAFLD is significantly higher in type 2 diabetic patients which was 76% (U/S) and 70% (HSI) in comparison to non-diabetic group which was 46%(U/S) and 43%(HSI), ($p < 0.05$), so like other parts of the world it is a common finding in Erbil city and these results even higher in comparison to the general population of the world (25%), In Middle East (32%) and >60% of type 2 diabetic patients globally (4). in diabetic group mean age was higher and obesity, hypertension and dyslipidemia were more common (Table 1) and all of these risk factors are associated with increased risk of hepatic steatosis and fibrosis (9). High and indeterminate risk of advanced liver fibrosis in the diabetic group was 22% and 67% respectively by NFS as a biomarker but using FIB-4 as a biomarker will lead to a reduction of these percentages to 14% and 45%, whereas in the non-diabetic group high and indeterminate risk of advanced fibrosis using FIB-4 was 7% and 31% respectively, and these results even higher than NFS 6% and 26% and these different results may be related to the involvement of BMI and diabetes as parameter in calculating NFS. This increase in the risk of severity of liver fibrosis in diabetic population versus non-diabetic group was statistically significant ($p < 0.05$). Researches from other parts of the world determining prevalence of NASH to be about 37% in type 2 diabetic patients which were in agreement with this research result (4). In both groups' prevalence of hepatic steatosis and risk of fibrosis severity were higher with increasing BMI (Table 2). In non-diabetic group prevalence of fatty liver were 17%, 41% and 80% in normal weight, over weight and obese groups respectively and in diabetic group were 35%, 61% and 100%

respectively, as well as the risk of advanced fibrosis increased with higher BMI levels in both groups 3%, 5% and 12% in non-diabetic group and 10%, 18% and 33% in diabetic group using NFS as a biomarker, all these data support role of obesity in NAFLD prevalence and severity.

Diabetes and obesity together are associated with very high rates of hepatic steatosis and fibrosis. In the non-diabetic normal weight group prevalence of fatty liver was 17% (HSI>36), and high risk of advanced fibrosis was (NFS) 3% but in the obese diabetic group 100% and 22% respectively. Explaining the adverse synergistic effect of both T2DM and obesity on NAFLD. Patients with indeterminate risk of hepatic fibrosis need further evaluation by other means like vibration-controlled transient elastography (17). this causes a reduction in unnecessary referrals. In this research by mean of NFS in diabetic patients, 22% high risk and 67% indeterminate risk and FIB-4 14% and 45% respectively need further evaluation and referral, these results in compare to non-diabetic patients were statistically significant ($p < 0.05$), in line with the EASL-EASD-EASO guidelines. Since many patients with NAFLD develop NASH, which can lead to cirrhosis and associated complications, including hepatocellular cancer (HCC), it will be challenging for endocrinologists and diabetologists to send all of these patients with NAFLD to hepatologists for further evaluation, so determining cases that they are at higher risk of advanced hepatic fibrosis, using non-invasive biomarkers of fibrosis NFS and FIB-4 according to the EASL-EASD-EASO Guidelines will help to a better strategy regarding referral of cases to Hepatologists.

5. CONCLUSIONS

This study concludes that obesity, hypertension and dyslipidemia were reported more in diabetic patients in comparison to non- diabetic subjects. The prevalence of NAFLD was reported more in diabetic patients in comparison to non- diabetic subjects. Liver fibrosis was reported more in diabetic patients in comparison to non- diabetic subjects. Hence, we highly recommend to screen all the type 2 diabetic patients for the presence of NAFLD and its severity by diabetologists and endocrinologists. Furthermore, the huge gap between the guidelines and clinical practice should be filled by paying more comprehensive attention to the mentioned guidelines and encouraging for more studies in this concern.

Ethical Clearance:

All ethical issues for this study were confirmed by the authors where the proposal of this study approved by the research scientific and ethical committee of the Kurdistan higher council of medical specialties. Verbal and written signed informed consent was obtained from each participants. Data collection was in accordance with the World Medical Association (WMA) declaration of Helsinki for the Ethical Principles for Medical Research Involving Human Subjects, 2013 and all information and privacy of participants were kept confidentially.

Conflict of interest: Authors declared none

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6. REFERENCES

1. *Paik JM, Golabi P, Younossi Yet al. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of nonalcoholic fatty liver disease. Hepatology 2020;72:1605–1616.*
2. *Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357.*
3. *Younossi ZM, Stepanova M, Ong J, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2021;19:580–589.*
4. *Younossi Z, Tacke F, Arrese M, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 2019;69:2672–2682.*
5. *Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. JHEP Rep. 2019;1:312-328.*
6. *Bril F, Sninsky JJ, Baca AM, et al. Hepatic steatosis and insulin resistance, but not steatohepatitis, promote atherogenic dyslipidemia in NAFLD. J Clin Endocrinol Metab.*

2016;101:644-652.

7. *Ortiz-Lopez C, Lomonaco R, Orsak B, et al. Prevalence of prediabetes and diabetes and metabolic profile of patients with nonalcoholic fatty liver disease (NAFLD). Diabetes Care. 2012;35:873-878.*
8. *Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. Gut. 2020;69:1691-1705.*
9. *Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20.*
10. *Vanni E, Marengo A, Mezzabotta L, et al. Systemic complications of nonalcoholic fatty liver disease: when the liver is not an innocent bystander. Semin Liver Dis 2015;35:236–249.*
11. *European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia. 2016;59:1121-1140.*
12. *Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328-357.*
13. *Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol. 2019;71:793-801.*
14. *Singh A, Gosai F, Siddiqui MT, et al. Accuracy of noninvasive fibrosis scores to detect advanced fibrosis in patients with type-2 diabetes with biopsy-proven nonalcoholic fatty liver disease. J Clin Gastroenterol. 2020;54:891-897.*
15. *Doycheva I, Cui J, Nguyen P, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. Aliment Pharmacol Ther. 2016;43:83-95.*
16. *Lazarus JV, Ekstedt M, Marchesini G, et al.; EASL International Liver Foundation NAFLD Policy Review Collaborators. A cross-sectional study of the public health response to non-alcoholic fatty liver disease in Europe. J Hepatol 2020;72:14-24.*

17. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–402.

18. American Diabetes Association. Comprehensive medical evaluation and assessment of comorbidities: Standards of Medical Care in Diabetes 2021. Diabetes Care. 2021;44(suppl 1):S40-S52.

19. Bril F, Cusi K. Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action. Diabetes Care. 2017;40:419-430.

20. American Gastroenterological Association. American Gastroenterological Association medical position statement: nonalcoholic fatty liver disease. Gastroenterology 2002;123:1702–1704.

21. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016;165:305–315.

22. Bril F, Ortiz-Lopez C, Lomonaco R, et al. Clinical value of liver ultrasound for the diagnosis of nonalcoholic fatty liver disease in overweight and obese patients. Liver Int 2015;35:2139–2146

23. Lee J-H, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42:503–8.

24. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/ HCV coinfection. Hepatology 2006;43:1317–25.

25. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846–54.