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Assessment of Hepatic Steatosis and Fibrosis in Egyptian Patients with Type 2 Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To assess hepatic steatosis and fibrosis in patients of type 2 diabetes mellitus (T2DM), their possible risk factors and their association with metabolic syndrome and micro or macro-albuminuria.
Study Design: Cross sectional study.
Place and Duration of Study: Outpatient Clinic of Diabetes, Metabolism and Endocrinology Unit in internal medicine department, Tanta University, Egypt in a period between September 2019 to March 2020.
Methodology: We included 200 patients had a diagnosis of T2DM according to American Diabetes Association criteria. Then patients were assessed for presence of hepatic steatosis and fibrosis using fibroscan and we used liver stiffness measurements (LSMs, as a measure of fibrosis) and controlled attenuation parameter (CAP, as a measure of steatosis) and routine laboratory data were done to rule out possible risk factors.
Results: 98.5% of participants had hepatic steatosis and 53.5% of participants had hepatic fibrosis. Those patients had longer duration of DM, higher BMI, bad control of T2DM, higher lipid profile values, association with metabolic syndrome, micro and macro-albuminuria and non-significantly elevated liver enzymes.
Conclusion: Hepatic steatosis and fibrosis are highly prevalent in patients with T2DM, incidence

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of hepatic steatosis and fibrosis is positively correlated with longer duration of DM, higher BMI, bad control of DM, dyslipidemia, presence of metabolic syndrome, diabetic nephropathy, weakly correlated with liver enzymes. TE is an accurate and non-invasive tool to be used in screening for hepatic steatosis and fibrosis ,so we recommend screening for hepatic steatosis and fibrosis using fibroscan to help in early management and prevent its progression into liver cirrhosis.

Keywords: Type 2 diabetes mellitus; Hepatic steatosis; Hepatic fibrosis; fibroscan.

1. INTRODUCTION

Diabetes mellitus (DM) is a major health problem worldwide as globally, the number of people with diabetes mellitus has quadrupled in the past three decades [1]. About 1 in 11 adults worldwide have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM) [2].

Complications of DM account for increased morbidity, disability, and mortality and represent a threat for the economies of all countries, especially the developing ones [3].

For a long time, diabetologists focused only on the micro and macro-vascular complications of DM but in the last years, a great attention was directed towards the severity of liver affection mainly nonalcoholic fatty liver disease (NAFLD) in patients with type 2 DM [4].

The liver is one of the main organs that control metabolic homeostasis. Metabolic diseases such as obesity, insulin resistance (IR), T2DM, dyslipidaemia, and NAFLD which are connected through molecular-biochemical, and complex immune mechanism [5].

NAFLD is characterized by a wide spectrum of liver diseases that vary from simple fat accumulation (benign steatosis), to inflammation (nonalcoholic steatohepatitis (NASH)), fibrosis, cirrhosis, liver failure, and finally to hepatocellular carcinoma (HCC) in the absence of excessive alcohol consumption, medications or viral etiology [6].

Patients with T2DM are at a greater risk of NAFLD and have a higher rate of progression to cirrhosis than non-diabetic individuals [7].

Therefore, screening for NAFLD and evaluating liver fibrosis in the diabetic population is extremely essential for early detection and management, preventing the progression to advanced fibrosis, cirrhosis and HCC [8].

Our study proposed to estimate the prevalence of controlled attenuation parameter (CAP) defined hepatic steatosis and the severity of liver fibrosis by transient elastography (TE) performance in T2DM patients.

2. MATERIALS AND METHODS

The study included 200 patients with T2DM according to the American Diabetes Association criteria [9] were selected from the Outpatient Clinic of Diabetes, Metabolism and Endocrinology Unit of Tanta university Hospitals, Egypt, according to inclusion and exclusion criteria.

2.1 Inclusion Criteria

- Patients had a diagnosis of T2DM according to the American Diabetes Association criteria.

2.2 Exclusion Criteria

- Chronic liver diseases (viral hepatitis, autoimmune hepatitis, hemochromatosis, primary biliary cirrhosis, Wilson's disease, sclerosing cholangitis, biliary obstruction, alpha-1 antitrypsin deficiency).
- Hepatic malignancies and other malignancies.
- Type 1 diabetes mellitus.
- Heart failure (New York Heart Association class III-IV).
- Pregnant females.
- Alcohol intake >20 g/day in women and >30 g/day in men.
- Use of steatogenic drugs (e.g estrogens, amiodarone, steroids, and tamoxifen).
- Patients with other endocrinal disorders.
- Measurement failure or unreliable measurements on TE.

2.3 Methods

Full history taking, clinical examination including blood pressure measurement, chest, cardiac examination to exclude any abnormalities,

anthropometric measurements, laboratory investigations including Fasting and 2 hour postprandial blood glucose level, Hemoglobin A1c, Liver functions tests (ALT, AST), Lipid profile (triglycerides level, total cholesterol, HDL, LDL), urinary Albumin creatinine ratio(UACR) and radiological assessment using fibroscan (echosens- France) 502 using (M) probe or (XL) probe for measurement of Liver stiffness measurement (LSM) as a measure for hepatic fibrosis with F0: 2-2.8 kPa, F1: 2.9-7 kPa, F2: 7.1-10 kPa, F3: 10.1-14 kPa, F4: >14 kPa and controlled attenuation parameter (CAP) as a measure for hepatic steatosis with S0: ≤ 238 dB/m, S1: 239-260 dB/m, S2: 261-290 dB/m, S3: start at 291 dB/m.

2.4 Statistical Analysis of the Data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. We used Chi-square test for categorical variables, to compare between different groups, Monte Carlo correction test used for chi-square when more than 20% of the cells have expected count less than 5. We used Student t-test for normally distributed quantitative variables, to compare between two studied groups, ANOVA with repeated measures for normally distributed quantitative variables, to compare between more than two studied groups. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups, Friedman test for abnormally distributed quantitative variables, to compare between more than two groups. Multivariate regression analysis to detect the most independent affecting factor.

3. RESULTS

3.1 Base-line Characteristics of Studied Group

3.1.1 Demographic and clinical data

Males were represented by 53.5% and females by 46.5% in our study, our patients age ranged between 29 to 74 years with mean ± SD 52.41 ± 10.96 years, duration of DM in our selected group ranged from 1 to 28 years with mean ± SD 12.67 ± 8.39 years, clinical examination data of studied group shown in (Table 1), laboratory data of participants in (Table 2) patients were classified regarding presence of metabolic syndrome,57.5% had metabolic syndrome (Table 3) and patients were classified according to presence of albuminuria depending on urinary albumin creatinine ratio (uACR) as in (Table 4).

3.1.2 Correlations between hepatic steatosis and fibrosis with possible risk factors

There was significant positive correlation between longer duration of DM (more than 10 years) and prevalence, degree of hepatic steatosis and fibrosis in diabetic patients with P value = 0.001, 0.001 respectively (Table 7).

BMI, waist circumference and hip circumference were of significantly positive correlation with the incidence and degree of hepatic steatosis and fibrosis in our study patients with P value = 0.001, 0.002, 0.001, 0.001, 0.003, 0.001 respectively.

Laboratory data of patients showed significant positive correlation between HbA1c level and prevalence, severity of hepatic steatosis and fibrosis with P value = 0.001,0.001 respectively, while liver enzymes (ALT&AST) not significantly correlated with TE proven hepatic steatosis and fibrosis patients with P value 0.149, 0.331, 0.078, 0.290 respectively (Table 7).

Table 1. Distribution of study participants regarding age, duration of DM and clinical data

Gender		**Males**	**53.5%**	**Females**	**46.5%**
	N	**Range**		**Mean**	S. D
Age (years)	200	29-74		52.41	10.96
Duration of DM (years)	200	1-28		12.67	8.39
BMI (kg/m$^{2)}$	200	23.5-40		30.92	3.45
Waist circumference (cm)	200	79-136		104.03	11.72
Hip circumference (cm)	200	90-150		110.18	11.34
SBP (mmHg)	200	90-170		131.25	16.08
DBP (mmHg)	200	60-100		79.95	9.38

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 2. Laboratory data of studied group

	N	Range	Mean	S. D
Fasting Bl glucose (mg/dl)	200	75-241	134.47	38.21
2h pp Bl glucose (mg/dl)	200	150-416	245.01	52.00
HbA1c (%)	200	6.5-13	8.52	1.33
ALT (IU/L)	200	18-112	42.29	14.59
AST (IU/L)	200	16-86	41.54	12.09
Total cholesterol (mg/dl)	200	160-339	213.38	37.65
TGs (mg/dl)	200	130-245	172.38	24.06
HDL (mg/dl)	200	35-76	51.16	8.05
LDL (mg/dl)	200	98-231	154.49	26.03

HbA1c: glycosylated haemoglobin
ALT: alanine aminotransferase
AST: aspartate aminotransferase
TGs: triglycerides
HDL: high density lipoprotein
LDL: low density lipoprotein

Table 3. Classification of studied group regarding presence of metabolic syndrome depending on International Diabetes Federation criteria

Metabolic syndrome	N	%
Yes	115	57.5
No	85	42.5
Total	200	100

Table 4. Classification of our studied group regarding presence of albuminuria

UACR	N	%
Normal	25	12.5
Micro-albuminuria	147	73.5
Macro-albuminuria	28	14.0
Total	200	100

Table 5. Classification of participants regarding hepatic fibrosis

Fibrosis (LSM)	Range	Mean ± SD	N	%
F0 (kPa)	2.2-2.8	2.46 ± 0.17	45	22.5
F1 (kPa)	2.9-7	4.90 ± 1.14	48	24.0
F2 (kPa)	7.1-10	8.72 ± 0.69	56	28.0
F3 (kPa)	10.1-14	12.63 ± 1.19	36	18.0
F4 (kPa)	14.1-25.1	20.07 ± 3.07	15	7.5

Table 6. Classification of participants regarding hepatic steatosis

Steatosis (CAP)	Range	Mean ± SD	N	%
S0 (dB/m)	184-238	211 ± 27	3	1.5
S1 (dB/m)	239-260	247.8 ± 5.45	20	10.0
S2 (dB/m)	261-290	274.77 ± 8.81	78	39.0
S3 (dB/m)	291-400	331.05 ± 27.05	99	49.5

There was significant positive correlation between high lipid profile (Total cholesterol, TGs, HDL, LDL), prevalence of hepatic steatosis and fibrosis and their severity in our studied group with P value = 0.002, 0.001,0.001, 0.001, 0.001, 0.001, 0.001, 0.001 respectively (Table 7).

Also, presence of metabolic syndrome and TE proven hepatic steatosis & fibrosis showed significant positive association between metabolic syndrome and prevalence of hepatic fibrosis and its degree with p value = 0.001,0.001 respectively (Table 8).

Table 7. Correlations between hepatic steatosis and fibrosis with possible risk factors

	Fibrosis LSM)		Steatosis (CAP)	
	R	P	r	P
Age (years)	0.080	0.263	0.085	0.233
Duration of DM (years)	0.484	0.001*	0.373	0.001*
BMI (kg/m^2)	0.311	0.001*	0.387	0.001*
Waist circumference (cm)	0.210	0.003*	0.241	0.001*
Hip circumference (cm)	0.238	0.001*	0.257	0.001*
Systolic BP (mmHg)	0.059	0.409	0.020	0.781
Distolic BP (mmHg)	0.109	0.123	0.039	0.585
Fasting Bl glucose (mg/dl)	0.135	0.057	-0.042	0.558
2h pp Bl glucose (mg/dl)	0.125	0.077	0.007	0.927
HbA1c (%)	0.630	0.001*	0.447	0.001*
ALT (IU/L)	0.102	0.149	0.069	0.331
AST (IU/L)	0.125	0.078	0.075	0.290
Total cholesterol (mg/dl)	0.281	0.001*	0.306	0.001*
TGs (mg/dl)	0.340	0.001*	0.340	0.001*
HDL (mg/dl)	-0.467	0.001*	-0.366	0.001*
LDL (mg/dl)	0.486	0.001*	0.449	0.001*

Significant (P < 0.05)
r= Pearson's correlation coefficient

Table 8. Presence of metabolic syndrome and incident hepatic fibrosis and steatosis in study participants

Fibrosis (LSM)	Metabolic syndrome	
	Yes	No
Range	2.20 – 25.10	2.20 – 9.20
Mean ± SD	10.93 ± 4.60	3.93 ± 1.86
T. test	13.251	
P. value	0.001*	
Steatosis (CAP)	**Metabolic syndrome**	
	Yes	**No**
Range	211 – 400	184 – 362
Mean ± SD	318.17 ± 36.23	273.01 ± 25.25
T. test	9.854	
P. value	0.001*	

Table 9. Relation between presence of albuminuria and hepatic fibrosis, steatosis

Fibrosis (LSM)	Albuminuria(ACR)		
	Normal	Micro-albuminuria	Macro-albuminuria
Range	2.20 – 8.50	2.20 – 25.10	2.9 – 21.4
Mean ± SD	3.66 ± 2.0	8.38 ± 5.11	9.56 ± 4.83
F. test	12.138		
P. value	0.001*		
Steatosis (CAP)	**Albuminuria(uACR)**		
	Normal	**Micro-albuminuria**	**Macro-albuminuria**
Range	238 – 358	184 – 394	264 – 400
Mean ± SD	272.64 ± 25.75	301.07 ± 39.65	311.50 ± 35.99
F. test	7.858		
P. value	0.001*		

Albuminuria either micro or macro was highly prevalent in the majority of TE proven fibrosis & steatosis cases representing 175 of 200 participants which were 87.5% of the study patients indicating significant positive association between presence of albuminuria and incidence of hepatic fibrosis & steatosis with p value= 0.001, 0.001 respectively (Table 9)

4. DISCUSSION

Increased morbidity and mortality in patients with type 2 diabetes (T2DM) is associated with high prevalence of atherosclerosis, cardiovascular diseases and chronic kidney disease, but also a wide spectrum of chronic hepatic diseases ultimately able to lead to hepatic cirrhosis and hepatocellular carcinoma (HCC) in those patients [10].

The aim of our study was to assess the prevalence of hepatic fibrosis and steatosis in patients with type 2 diabetes mellitus and the association with other possible risk factors, metabolic syndrome and diabetic nephropathy in those patients.

In our study, hepatic steatosis proved by TE was detected in the majority (98.5%) of the studied group, mild steatosis (S1) in 20 participants (10%), moderate steatosis (S2) in 78 participants (39%), severe steatosis (S3) in 99 participants (49.5%) and significant hepatic fibrosis (F2—F4) by TE was detected in approximately 53.5% of our study participants, moderate fibrosis (F2) in 56 participants (28%), severe fibrosis (F3) in 36 participants (18%), advanced cirrhosis (F4) in 15 participants (7.5%) and non-significant fibrosis (F1) was detected in 48 participants (24%) and it was in agreement with Demir et al. [11] a Turkish study that was conducted on 124 patients with T2DM, advanced fibrosis and cirrhosis were identified in 21 (16.9%) and 10 (8.0%) patients, respectively and TE-defined hepatic steatosis was detected in 117 (94.3%) patients as following: mild, moderate, and severe steatosis were identified in 0, 29, and 88 patients, respectively.

In our study, higher prevalence of hepatic steatosis, fibrosis and their severity was associated with longer duration of DM, higher BMI, higher WC, uncontrolled DM which was assessed by measuring HbA1c level, presence of dyslipidemia, associated metabolic syndrome and diabetic nephropathy either micro or macro-albuminuria measured by urinary ACR.

While, there was no statistically significance correlation between prevalence of hepatic steatosis, fibrosis, their severity and sex, age of participants, fasting, 2hour postprandial blood glucose level or liver enzymes which were only elevated in late cirrhotic cases and could not differentiate between different stages.

Almobarak, et al. [12], Zhao, et al. [13] and Dvorak et al. [14] all were supporting us in ruling out that dyslipidemia, associated metabolic syndrome are risk factors although, Almobarak, et al. [12]. found that HbA1c levels appeared to have non-significant impact on the prevalence of fatty liver. However, we depended in our results on TE which is more accurate than ultrasonography in diagnosis of hepatic steatosis and fibrosis.

But in Heidari, et al. [15] study, 255 patients with T2DM were enrolled with 86.66% of them had fatty liver on ultrasound examination and HbA1c was significantly associated with risk and severity of fatty liver in patients with T2DM.

Demir et al. [11], Lu, et al. [16], Chen, et al. [17], Portillo-Sanchez, et al. [18] and Ferreira, et al. [19] all were supporting to us as BMI, WC and longer duration of DM were the main risk factors and also ALT was not elevated in patients with cirrhosis and did not distinguish the severity of TE-identified steatosis in Demir et al. [11] study.

Given the high prevalence of NAFLD in T2DM, it is important to know whether NAFLD is a risk factor for diabetic nephropathy or not.

In our study, it was found that, 74.6% of participants with T2DM having hepatic steatosis had micro-albuminuria, 14.2% had macro-albuminuria. Furthermore, 79.4% of participants with T2DM and having hepatic fibrosis had micro-albuminuria and17.8% had macro-albuminuria showing significant correlation between diabetic nephropathy, risk of hepatic steatosis and fibrosis.

This was supported by Jia et al. [20] a Chinese retrospective study that included 465 patients, including 176 patients with fatty liver by ultrasonography and 289 patients without fatty liver to examine the association between NAFLD and diabetic nephropathy, assessed by estimated glomerular filteration rate (eGFR) and 24 h urinary albumin excretion rate in patients with T2DM and results showed that fatty liver might be a risk factor for diabetic nephropathy.

On the other hand, Zhan, et al. [21] who assessed the incidence of diabetic nephropathy in 413 type 2 diabetic patients, by testing the 24 h urinary albumin excretion rate (UAER) and there was no significant difference in the prevalence of diabetic nephropathy between patients with and without NAFLD (37.1% vs. 38.5%, p= 0.787).

5. CONCLUSION

[Hepatic steatosis and fibrosis are highly prevalent in patients with T2DM, incidence of hepatic steatosis and fibrosis is positively correlated with longer duration of DM, higher BMI, bad control of DM, dyslipidemia, presence of metabolic syndrome, diabetic nephropathy, weakly correlated with liver enzymes. TE is an accurate and non-invasive tool to be used in screening for hepatic steatosis and fibrosis].

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Informed written consent was obtained from all patients after a full explanation of the benefits and risks of the study. Privacy of all patients' data is granted by a special code number for every patient file that includes all investigations.

ETHICAL APPROVAL

The protocol was approved by the local ethics committee to conduct this study and to use the facilities in the hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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