Original Article

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Internal Medicine Section

Prevalence of Non Alcoholic Fatty Liver Disease and its Association with Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Non Alcoholic Fatty Liver Disease (NAFLD) and Type 2 Diabetes Mellitus (T2DM) are two common problems affecting global health as these two conditions can influence each other. There is very little information about the possible association between NAFLD and diabetic microvascular complications such as diabetic nephropathy.

Aim: The aim of this study was to evaluate the prevalence of NAFLD in patients with T2DM and to investigate the association between NAFLD and diabetic nephropathy in these patients.

Materials and Methods: This cross-sectional study was conducted on 255 patients with T2DM, with minimum age being 30 years. Hepatic ultrasonography using a 3.5 MHz probe was performed in all subjects. Fatty liver based on standard criteria was diagnosed with liver brightness, contrast between the echogenicity of the liver, kidneys and the blood vessels fading rate. Screening for microalbuminuria was performed by the preferred method, measurement of the Urine Albumin-To-Creatinine (UACR) ratio in a random spot collection.

Results: In this study, 255 patients with T2DM were enrolled of which 173 (68%) were females and 82 (32%) were males. Of these 221 subjects (86.66%) had NAFLD. Diabetic nephropathy was observed among 33% of individuals, microalbuminuria among 32% and macroalbuminuria in 10% of all individuals. Duration of diabetes, Body Mass Index (BMI), hypertriglyceridemia, and HbA1c were significantly associated with incidence of NAFLD. Also, duration of diabetes and HbA1c were significantly associated with diabetic nephropathy in patients with T2DM.

Conclusion: NAFLD in patients with T2DM is extremely common. NAFLD is not considered as a risk factor for diabetic nephropathy. To better understand the pathogenesis of NAFLD and its causal relationship with complications of diabetes such as diabetic nephropathy, prospective studies and long term follow up are needed.

Keywords: Hepatocellular carcinoma, Microvascular complications, Non alcoholic steatohepatitis

INTRODUCTION

NAFLD is defined as increased fat storage in the form of triglycerides in the liver (more than 5% of liver weight) which is not due to excess alcohol consumption or other causes of steatosis [1,2]. The spectrum of disease includes non alcoholic fatty liver, non alcoholic steatohepatitis, liver cirrhosis and hepatocellular carcinoma [3]. Natural history of NAFLD in some people is progression towards end stage liver disease. For this reason, NAFLD was the main cause of morbidity and mortality during the past 20 years and would become the first cause of liver transplant in future [4]. Recently, abundant evidence has led to this hypothesis that even mild steatosis and inflammation of the liver can progress toward fibrosis and hepatocellular carcinoma [5].

NAFLD and T2DM are considered as two common problems affecting global health. NAFLD is the most common liver disease in Western countries affecting about 35% of the general population and about 75%-90% of specific groups, such as obese and diabetic people [6,7]. The prevalence of NAFLD in parallel to obesity has increased worldwide over the past 30 years. Globally, it is estimated that a quarter of the world's adult population currently suffer from NAFLD. In Asia, according to the obesity epidemic, the prevalence of NAFLD is similar to the Western population and even slightly higher than it (27% in Asia vs 24.1% in North America, 23.2% in Europe) [8]. Similarly, more than 380 million people have diabetes around the world. The International Diabetes Federation has estimated that this amount over the next generation will reach to 592 million. Importantly, patients with NAFLD often suffer from T2DM, and vice versa. T2DM can be seen in almost a quarter of patients with NAFLD and approximately half of the patients with non alcoholic steatohepatitis. In contrast, NAFLD has been reported in 75% of patients with T2DM [9].

On the other hand, these two conditions can affect each other. NAFLD increases mortality among patients with T2DM, while, T2DM also increases progressive liver fibrosis upto three times and hepatocellular carcinoma upto two times and is an independent predictor of all cause and liver mortality in patients with NAFLD [10,11]. The link between these two diseases is resistance to insulin and NAFLD is known as liver component of metabolic syndrome. Compensatory hyperinsulinemia leads to beta cell dysfunction in T2DM and defects in lipid metabolism and hepatic triglyceride accumulation in NAFLD. This also explains why NAFLD is very common in T2DM and why patients with NAFLD are at high risk for T2DM [12,13].

It has been shown that macrovascular complications of diabetes (coronary artery disease) have a close relationship with NAFLD [14]. In contrast, there is little information about the possible association between NAFLD and microvascular complications of diabetes. Diabetic nephropathy is one of the most common microvascular complications associated with T2DM. But in the early stage of this disease there is little clinical manifestations and if there is persistent albuminuria, kidney damage is usually irreversible. So, it is critical to monitor the people with risk factors for diabetic nephropathy. Such approach could help to identify individuals with diabetic nephropathy in early stage and may improve the outcome of the disease. A number of studies have shown that NAFLD in adults has been associated with increased incidence and prevalence of chronic kidney disease [15-19]. In contrast, another study on patients with T2DM showed no association between NAFLD and progression of diabetic nephropathy [20].

Despite the known association between T2DM and NAFLD, there is little information on the prevalence of NAFLD in individuals with T2DM in Iran [21]. Although, recent studies on association between NAFLD and chronic kidney disease have shown different results, whether the NAFLD is raised as an independent risk factor for diabetic nephropathy in patients with T2DM or not, remains unclear. The purpose of this study was to evaluate the prevalence of NAFLD in population of patients with T2DM in Iran and determination of association between NAFLD and diabetic nephropathy in these patients.

MATERIALS AND METHODS

This cross-sectional study was done on patients with T2DM who referred to endocrine clinics in Zahedan, Southeastern Iran, between April 2015 and February 2016. Patients with T2DM of at least age 30 years were continuously enrolled in the study by consecutive sampling. Then, information about their age, gender, type of diabetes, duration of diabetes, incidence of other diseases, drug consumption recorded. Diagnosis of T2DM was based on American Diabetes Association (ADA) criteria [22].

The participants with evidence of viral or autoimmune hepatitis, Wilson's disease, primary biliary cirrhosis, haemochromatosis, type 1 diabetes mellitus, latent autoimmune diabetes of adults, gestational diabetes, or other special types of diabetes, acute complications associated with diabetes, infectious disease, acute renal failure, malignancies, patients with hypercortisolism (Cushing's syndrome), acromegaly, or thyroid dysfunction, history of alcohol consumption of any volume were excluded. Furthermore, individuals who had taken amiodarone, antiviral drugs, sodium valproate, corticosteroid, methotrexate, isoniazid, tamoxifen, tetracyclin in past six months were also, excluded from the study.

Body weight without shoes using a digital scale and height in standing position was measured using a stadiometer. BMI was determined using this formula: weight in kilograms divided by the square of height in meters. Systolic and diastolic blood pressures of all participants were measured after 15 minutes rest and before blood sampling in a sitting position with a manual sphygmomanometer.

Hepatic ultrasonography (Aloka Co. Ltd., Tokyo, Japan) using a 3.5-MHz probe was performed in all subjects after 12 hours fasting by a single sonologist, and fatty liver based on standard criteria was diagnosed with liver brightness, contrast between the echogenicity of the liver, kidneys and the blood vessels fading rate. Grading of diffuse hepatic steatosis on ultrasound has been used to assess the extent of fatty changes in the liver as follows; Grade I - the increased echogenicity of the liver along with visible periportal and diaphragmatic echogenicity; Grade II - the increased echogenicity of the liver along with invisible periportal echogenicity, without diaphragmatic fading; Grade III - the increased echogenicity of the liver along with invisible periportal echogenicity, with diaphragmatic fading [23].

All blood samples were collected between 8 am-9 am and after eight hours fasting. The levels of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP) were assessed by enzymatic colorimetric assays (Pars Azmoon kit, Tehran, Iran). Viral serology for hepatitis B and C, was assessed only in patients who had increased liver enzymes, in order to exclude viral causes of chronic liver disease. The abnormal ALT, AST were defined as ALT > 40 u/l, AST > 40 u/l respectively.

Glucose was measured with glucose oxidase technique (Pars Iran test). HbA1c was measured by high performance liquid chromatography using an automatic analyzer. For lipid measurements, total cholesterol and triglyceride kits (Pars Azmoon, Tehran, Iran) were used. Total cholesterol was measured using enzymatic colorimetric tests with cholesterol esterase and cholesterol oxidase and triglycerides also were measured with the same method and using glycerol phosphate oxidase. High Density Lipoprotein-Cholesterol (HDL-C) was measured after the deposition of lipoproteins containing apolipoprotein B by phosphotungstic acid. Everyday standard (C.f.a.s., Boehringer Mannheim, Germany; Cat. No. 759350) was used for calibration of selectra 2 auto-analyzer for laboratory analyses. If the internal quality control had acceptable standards, then samples were analyzed. Interassay and intra-assay coefficients of variation were 2% and 0.5% for total cholesterol and 1.6% and 0.6% for triglycerides respectively.

Serum creatinine (Cr) was measured by an enzymatic method (Pars Azmoon). Screening for microalbuminuria was performed by the preferred method, measurement of the UACR in a random spot collection [24]. Normal UACR was defined as <30 µg/mg Cr, microalbuminuria as 30 µg/mg-299 µg/mg and macroalbuminuria ≥300 µg/mg Cr [22]. For the measurement of albuminuria exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension were ruled out. The Glomerular Filtration Rate (GFR) was estimated by using the simplified MDRD equation: GFR [ml/(min 1.73 m^2)] = 186 × (S Cr) - 1.154 × (age) 0.203 × 0.742 (female) [25].

NAFLD diagnosis was done according to the 2012 statement of the American Gastroenterological Association [26]: 1) Hepatic steatosis based on imaging or histology ;2) Lack of high consumption of alcohol; 3) Lack of another reason for hepatic steatosis; and 4) Lack of another synchronic reason for the chronic liver disease.

Diabetic nephropathy was diagnosed by a positive persistent albuminuria for at least three consecutive readings within the study, or GFR <60 ml/min [27].

STATISTICAL ANALYSIS

Continuous variables were presented as mean values and standard deviation and categorical variables as absolute number and percentages. An independent sample t-test or a Mann–Whitney U-test was used to assess significance of differences for continuous variables and a chi-square test for categorical baseline variables. Multiple logistic regression analysis was used to estimate the odds ratios and 95% confidence intervals of the different components in development of NAFLD and diabetic nephropathy. All the analyses were performed by software STATA version 12.0 (Stata Corporation, College Station, TX). Written informed consent was obtained from all subjects. The study was approved by Ethics Committee of Zahedan University of Medical Sciences (Ethical Code Number: IR.ZAUMS.REC.1392.911).

RESULTS

In this study, 255 patients with T2DM were enrolled and among them 173 (68%) subjects were females and 82 (32%) subjects were males. Of the total of 255, 221 (86.66%) individuals had NAFLD. In patients with NAFLD, 119 (53.84%) patients had Grade I, 96 (43.43%) with Grade II and 6 (2.71%) patients with Grade III steatosis on sonography. Women in Grade 0 (normal) accounted for 19 (55.88%), 86 (72.26%) in Grade I, 67 (69.79%) in Grade II and 1 (16.66%) in Grade III. In patients with NAFLD, liver enzymes were increased in 34 (39.15%) patients and 187 (61.84%) patients had normal liver enzymes. In normal subjects (n = 34), no case of elevated liver enzymes was observed.

As shown in [Table/Fig-1], the majority of patients with NAFLD were in Grade I. Basic clinical and laboratory features between the two groups; normal and mild fatty liver (Grade 0 and 1) were compared with more advanced fatty liver (Grade II and III). Patients with Grade II and Grade III NAFLD had higher BMI, fasting plasma glucose, HbA1c, triglycerides, LDL and duration of diabetes, in comparison with subjects with milder NAFLD or normal subjects, but other variables had no significant differences between the two groups.

Diabetic nephropathy was observed among 33% of participants, microalbuminuria among 32% and macroalbuminuria in 10% of all participants and there was no significant difference between the two groups. Also, GFR lower than 60 ml/min was observed among 3.5% of participants and this amount in patients with advanced

NAFLD as compared to patients with grade one or normal subjects was not different.

As shown in [Table/Fig-2], in multiple logistic regression analysis the duration of diabetes, BMI, triglyceride level was significantly associated with incidence of NAFLD in patients with T2DM while gender, hypertension and hepatic enzymes had no clear association with NAFLD.

Also, duration of diabetes and HbA1c were significantly associated with incidence of diabetic nephropathy in patients with T2DM while NAFLD and other variables had no clear association with diabetic nephropathy [Table/Fig-3].

DISCUSSION

This study showed that the prevalence of NAFLD in patients with T2DM is 86% and the prevalence of diabetic nephropathy is 33%. Microalbuminuria was observed in 32% and macroalbuminuria in 10% of the participants. Also, in this study, there was no association between NAFLD and diabetic nephropathy.

NAFLD is very prevalent and is strongly linked with metabolic syndrome and its components such as insulin resistance, diabetes, obesity, hypertension and hypertriglyceridemia. On the other side, T2DM as a common metabolic disease with an increased global incidence [8,9]. In recent years, several studies have emphasized on association between T2DM and NAFLD. NAFLD has been introduced as a risk factor for T2DM, hypertension and cardiovascular disease [15,28].

Variable	NAFLD (Grade=0 & 1)	NAFLD (Grade=2 & 3)	All participants	p-value
n (%)	153 (60)	102 (40)	255 (100)	<0.001
Age (years)	52.32±10.80	50.55±10.46	50.79±10.49	ns
Sex (%women)	105 (68.62)	68 (66.66)	173 (67.84)	<0.001
Duration of diabetes (years)	6.10±5.70	7.50±6.37	6.25±5.79	<0.05
BMI (kg/m^2)	29.00±5.23	31.39±5.01	30.91±5.05	<0.05
Systolic blood pressure (mmHg)	136.96±20.80	137.27±21.45	136.78±21.16	ns
Diastolic blood pressure (mmHg)	83.55±11.10	84.08±11.10	83.81±11.10	ns
High blood pressure (%)	39.60	41.90	41.29	ns
FPG (mmol/l)	8.11±2.98	8.93±2.84	8.52±2.91	<0.05
HbA1c (%)	8.63±1.79	9.38±2.77	8.73±1.96	<0.001
AST(u/l)	20.38±6.27	22.09±10.89	21.86±10.41	ns
ALT(u/l)	22.05±12.94	23.35±18.19	22.65±17.66	<0.05
Total cholesterol (mmol/l)	5.70±1.19	5.73±1.22	5.71±1.20	ns
LDL-C (mmol/l)	4.17±0.93	4.32±1.07	4.24±1.00	<0.001
HDL-C, mmol/l	1.19±0.25	1.15±0.29	1.18±0.28	ns
Triglyceride (mmol/l)	1.71±1.29	2.26±1.35	2.06±1.31	<0.001
Urinary albumin–to–creatinine ratio (mg/g Cr)	151.48±326.30	183.18±593.8	179.45±782.54	ns
Microalbuminuria (%)	49 (32.02%)	33 (32.35%)	82 (32.15)	ns
Macroalbuminuria (%)	14 (9.15%)	12 (11.76%)	26 (10.19%)	ns
Cr (mmol/ l)	63.33±13.16	64.12±11.65	63.03±11.17	ns
GFR (ml/min/1.73 m^2)	97.18±5.61	98.22±6.95	98.97±8.91	ns
GFR< 60(ml/ min/1.73 m^2)	4 (2.61%)	5 (4.90%)	9 (3.52%)	ns

[Table/Fig-1]: Clinical features and biochemical characteristics of study participants.
Data are shown as mean± SD or percentage.
Values are means ± SD; differences were assessed by the unpaired t-test (for normally distributed variables; The Mann-Whitney test (for non-normally distributed variables); and the χ^2 test (for categorical variables)

Variables	OR	95%CI	p-value
Duration of diabetes	1.09	1.04-1.15	0.01
Sex	0.98	0.95-1.02	0.70
Age	1.01	0.99-1.02	0.07
BMI	1.06	1.01-1.15	0.01
TG	1.22	1.00-1.54	0.01
HbA1c	0.84	0.71-0.99	0.03
HTN	1.03	0.94-1.13	NS
AST	1.02	0.98-1.07	NS
ALT	1.03	0.99-1.06	0.70

[Table/Fig-2]: Multivariate logistic regression analyses of factors associated with non alcoholic fatty liver disease in patients with type 2 diabetic.
BMI: body mass index, TG: triglycerides, HTN: hypertension, OR:odds ratio, CI: confidence interval

Variables	OR	95%CI	p-value
Duration of diabetes	1.08	1.03-1.14	0.01
Sex	0.89	0.89-1.08	0.70
Age	1.07	0.91-1.12	0.07
BMI	1.03	0.98-1.15	0.09
TG	1.12	0.94-1.54	0.09
HbA1c	0.93	0.83-0.98	0.03
HTN	1.15	0.78-1.11	NS
NAFLD	1.01	0.96-1.05	NS
AST	1.07	0.91-1.07	NS
ALT	1.09	0.94-1.12	0.70

[Table/Fig-3]: Multivariate logistic regression analyses of factors associated with diabetic nephropathy in patients with type 2 diabetes.
BMI: body mass index, TG: triglycerides, HTN: hypertension, OR:odds ratio, CI: confidence interval

In this study, the prevalence of NAFLD in patients with T2DM has been calculated as 86% and this amount in other similar studies varied between 21% to 75% [19,20,29-31]. Most patients with Grade I and II of NAFLD were women and this finding is in contrast to other studies, showing that NAFLD was more prevalent in men [29]. Also, in this study, BMI, fasting plasma glucose, HbA1C, triglycerides, LDL and duration of diabetes has been associated with NAFLD. Like previous studies, the increased duration of diabetes was associated with the incidence of NAFLD [31]. In some studies, shorter duration of diabetes was associated with NAFLD [29].

Diabetic nephropathy is the main complication of diabetes and about 40% of patients with T2DM make progress toward diabetic nephropathy which is the most common cause of end stage renal disease [32]. Therefore, the identification of diabetic nephropathy as a risk factor for effective prevention is important. Given the high prevalence of NAFLD in T2DM, it is important to know whether NAFLD is a risk factor for diabetic nephropathy or not. Diabetic nephropathy was observed in 33% of individuals in our study which is consistent with other studies reporting 38% to 40% ocurrance [20,33]. Microalbuminuria was observed in 32% and macroalbuminuria in 10% of participants. BMI and HbA1c also were significantly associated with diabetic nephropathy in patients with T2DM while NAFLD and other variables had no clear association with diabetic nephropathy. In this study, no significant differences in the incidence of diabetic nephropathy was observed in patients with and without NAFLD, which show that NAFLD is not considered as a risk factor for diabetic nephropathy. Of course, since histopathologic examination has not been done to reject non alcoholic steatohepatitis, the association between diabetic nephropathy and non alcoholic steatohepatitis cannot be denied and needs further studies. Several studies investigated the prevalence of diabetic nephropathy in patients with NAFLD and T2DM. In some of these studies, NAFLD has been proposed as a risk factor for diabetic nephropathy [16,34], but other studies have not reported such association [20,30,35]. The responsible mechanism for the link between NAFLD and diabetic nephropathy is not known. Inflammatory mediators released from the inflamed or steatotic liver, insulin resistance and dyslipidemia may be involved in the pathogenesis.

STRENGTH AND LIMITATION

Our study had several limitations. First, this study was a cross-sectional study, hence cannot show a causal relationship. The second limitation is the lack of a liver biopsy. Liver biopsy is the gold standard method for diagnosis of NAFLD and differentiating it from Non Alcoholic Stetohepatitis. According to the aggressiveness of liver biopsy, in this study, like most previous studies, ultrasound is used for the diagnosis of NAFLD. The sensitivity of ultrasound in detection of steatosis varies between 60% and 94%, which depends on the degree of steatosis. The strength of this study is the exact ultrasound grading by single expert operator, exclusion of other causes of liver disease and relatively sufficient sample size to assess the prevalence of NAFLD in patients with T2DM.

CONCLUSION

The results of this study showed that NAFLD is extremely common in patients with T2DM. Since, the liver fat content can be modified by lifestyle changes and medical therapy; so, the early detection programs for NAFLD should be included in patients with diabetes. Efforts toward early detection, lifestyle change, and accurate management of blood glucose, dyslipidemia and hypertension should be done to prevent and minimize incidence of NAFLD. For better understanding of the pathogenesis of NAFLD and its causal relationship to diabetes complications such as diabetic nephropathy, prospective and long term follow up studies are required.

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