Prevalence of Fatty Liver Disease among Type 2 Diabetes Mellitus Patients and its Relation to Insulin Resistance

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ABSTRACT

BACKGROUND

A substantial proportion of the mortality in patients with type 2 diabetes mellitus (T2DM) is related to non-alcoholic fatty liver disease (NAFLD) and its complications. Insulin resistance is a major etiologic factor for the development of fatty liver. We aimed to study the prevalence of NAFLD among T2DM patients and its relation to insulin resistance.

METHODS

Patients with T2DM that were referred to a tertiary referral center in Tehran from February 2003 to August 2005 were evaluated. Patients with characteristic findings on ultrasonography were considered as having fatty Livers. The Homeostasis Model Assistant - Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI) were calculated as measures of insulin resistance.

RESULTS

Of the 172 patients included in the study, 96 (55.8%) had evidence of fatty livers, 6 of which (3.5% of total) presented with elevated liver enzymes. BMI and triglyceride levels in the fatty liver group were significantly higher than patients with normal livers (p=0.002 and 0.036, respectively). The HOMA-IR and QUICKI indexes were not significantly different between the two groups.

CONCLUSION

Fatty liver is a common finding among T2DM patients. The degree of insulin resistance does not appear to be predictive of fatty liver among this population.

KEYWORDS

Non-alcoholic steatohepatitis; Type 2 diabetes; Insulin resistance

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common condition previously thought to be a benign disorder. Recent data, however, indicate that when steatosis is associated with inflammation the risk of progression to cirrhosis exists.[1-3] In fact, it is the most common cause of cryptogenic cirrhosis.[4] Research has shown that community-diagnosed NAFLD patients have higher mortality rates and lower survival than the

general population.[4-7] NAFLD is associated with many factors; including the presence of type 2 diabetes mellitus (T2DM) which can increase its risk and severity.[1,4,8] Peripheral insulin resistance is a central mechanism in the pathogenesis of both entities.[9,10]

Not surprisingly, 10-75% of NAFLD patients have T2DM and 21-72% of patients with diabetes are reported to have NAFLD.[1]

The mortality rate of diabetic patients due to cirrhosis is more than twice the general population and patients with both NAFLD and DM have poorer prognoses in terms of higher rates of cirrhosis and mortality.[5,11,12] Both NAFLD and T2DM are conditions highly dependent on genetic background and dietary factors. They are also quite common among the Iranian population.[13,14] Thus we designed a study to determine the prevalence of NAFLD among Iranian patients diagnosed with T2DM.

MATERIALS AND METHODS

Patients referred to a tertiary referral center in Tehran during an 18 month period from February 2003 to August 2005 were evaluated for inclusion in the study. Patients were included if they had at least a one year history of T2DM, were only on oral hypoglycemic agents and did not take insulin injections. Exclusion criteria included an alcohol intake of more than 40 g per week, history of chronic liver disease of any etiology, history of any severe disease such as malignancy, and intake of medications known to cause fatty liver disease.

A thorough medical history and physical examination were performed for each individual, which included measurements of weight and height.

BMI was calculated as a measure of obesity, whereas waist/hip ratio was measured as an index of splanchnic fat accumulation.[15,16] After an overnight fast, serum samples were obtained from all subjects for liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase), serum lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C] and low-density lipoprotein cholesterol [LDL-C]), fasting blood glucose (FBS), serum insulin level and hemoglobin A1c (HbA1c). Homeostasis Model Assistant–Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity check Index (QUICKI) were calculated as measures of insulin resistance and sensitivity using following formula:

$$\text{HOMA-IR}=[\text{fasting insulin}(\mu U/ml)\times\text{fasting glucose (mmol/l)}]/22.5$$

$$\text{QUICKI}=1/[\log(\text{fasting insulin}(\mu U/ml))\pm\log(\text{glucose (mg/dl)})]$$

All subjects underwent abdominal ultrasonography by the same radiologist for evidence of fatty liver disease. Based on ultrasonographic findings (diffuse increase in echogenicity as compared to that of the spleen or renal cortex)[17] patients were categorized as those with NALFD and those without NALFD. Data were analyzed using SPSS 13.0 (SPSS Inc, Chicago, IL, USA) statistical software package for Windows. Descriptive statistics were performed on all study parameters (mean, standard deviation and range). Statistical analysis was carried out for study parameters between the two groups (NAFLD and non-NAFLD) using student's t test. Analysis of variance (ANOVA) and the x^2 test were used for continuous and categorical data respectively.

p-values<0.05 were considered significant. The study protocol was approved by the Institutional Review Board and Ethics Committee of the Digestive Disease Research Center. All patients signed an approved informed consent prior to participating in the study.

RESULTS

During the 18 month period, 172 patients with T2DM were enrolled. The clinical, anthropometric, and biomedical findings of the subjects are given in Table 1. The mean duration of the diagnosis of T2DM was 10.3±7.6 years. None of the subjects had histories of alcohol consumption. Of 172 patients with T2DM, 96 (55.8%) had evidence of fatty liver disease in abdominal ultrasonography.

There were 6 subjects (3.5%) who had elevated ALT or AST (upper limit of normal: 40 IU/L), all of which also had fatty livers.

Table 1: Demographic, anthropometric, and biomedical characteristics of 172 patients with T2DM.

Parameter	No (%)		
Male	49 (28.5)		
Elevated AST	2 (1.2)		
Elevated ALT	6 (3.5)		
Elevated ALT or AST	6 (3.5)		
NALFD	96 (55.8)		
	Mean	**Range**	**SD**
Age (yr)	56.56	31-80	10.5
Duration of diabetes (yr)	10.3	4-40	7.6
BMI (kg/m^2)	28.3	16.7-45.6	4.6
FBS (mg/dl)	173.1	70-421	63.9
HbA1c (%)	8.7	1.25-16	2.2
HOMA-IR	7.17	0.02-55.6	6.4
QUIQKI	0.306	0.23-0.98	0.068
Insulin (µU/mL)	16.7	0.06-95.5	11.7
HDL (mg/dL)	46.4	20-202	18.2
LDL (mg/dL)	131.1	17-300	46.6
Cholesterol (mg/dL)	219.1	108-483	55.7
Triglycerides (mg/dL)	207.4	12.5-700	113.3
AST (IU/L)	20.4	7-57	7.5
ALT (IU/L)	22.5	7-155	14.2
AST/ALT ratio	1.02	0.13-2.33	0.37
Alkaline phosphatase (IU/L)	163.8	21-428	62.8

The prevalence of NAFLD among men was 44.8% (22/49) and among women was 60.1% (74/123) which was not statistically different (p=0.069). Study parameters were analyzed for the two groups of NAFLD and non-NAFLD patients (Table 2). BMI and triglyceride levels in the NAFLD group were significantly higher than the non-NAFLD patients (p=0.002 and 0.036, respectively). The level of serum alkaline phosphatase was significantly lower in the NAFLD group (p=0.011). None of the other parameters differed significantly between the two groups. The frequency of NAFLD within different age groups was not significant (p=0.211).

DISCUSSION

In the present study which consisted of 172 patients with T2DM, the prevalence of NAFLD based on abdominal ultrasound examination was 55.8%. This is similar to other studies which have reported the prevalence of NAFLD among DM patients at approximately 50% (range: 21-78%).[1]

In this study, there were no significant sex differences between the two groups (p= 0.69), however the prevalence of NAFLD among men and women varied in different clinical studies. In some studies, NAFLD was considered to be more common among women,[8,18] whereas it was reported to be more prevalent among men in others.[10,17,19]

However, in more recent studies, as in ours, it has been suggested that both sexes might be afflicted equally.[8] The mean age of patients in both the NAFLD and non-NAFLD groups was 58.3±10.9 and 55.1±10.1, respectively which was not statistically different (p=0.056). We also compared the frequency of NAFLD among different age groups which again did not show any significant differences (p=0.21).

Previous studies have shown that NAFLD can occur at any age,[1,5] but since its prevalence increases with age, therefore it mostly affects people in their forties to sixties.[8,17,18] The mean duration of DM was significantly lower in patients with NAFLD (8.6±6.3) as compared to patients without NAFLD (12.3±8.6; p=0.002).

Table 2: **Comparison of study parameters between diabetic patients with and without NAFLD.**

Parameter	No NAFLD	NAFLD	*P*-Value
Demographic and anthropometric			
Age (yr)	58.3±10.9	55.1±10.1	NS*
Male (%)	35	22	NS
BMI (kg/m^2)	27.1±3.9	29.2±4.9	0.002
waist/hip ratio	0.90±.06	0.88±.05	NS
Glucose metabolism			
Duration of Diabetes (yr)	12.3±8.6	8.6±6.3	0.002
FBS (mg/dL)	177±67.1	170.1±61.4	NS
HbA1c (%)	8.8±2.4	8.6±2.1	NS
HOMA-IR	7.8±8.6	6.8±5	NS
QUICKI	0.31±.10	0.30±.03	NS
Insulin level (μU/dL)	16.6±14.3	16.8±10.2	NS
Lipids			
HDL (mg/dL)	46.9±12.9	46.1±21.5	NS
LDL (mg/dL)	129.5±45.2	133.2±47.8	NS
Cholesterol (mg/dL)	212±49.5	224.7±59.8	NS
Triglycerides (mg/dL)	186.9±101.1	223.4±120.1	0.036
Liver injury and synthetic function			
AST (IU/L)	20.4±6.6	20.4±8.1	NS
ALT (IU/L)	23.3±17.7	21.9±10.8	NS
AST/ALT ratio	1.00±.33	1.03±.41	NS
Alkaline phosphatase (IU/L)	177.4±63.5	152.9±60.3	0.011

* NS = Not significant

We do not have any explanation for this inding. BMI was significantly higher in patients with NAFLD (29.2±4.9) than those without NAFLD (27.1±3.9; p=0.002). Obesity is the most common entity associated with NAFLD that has been reported in studies.[8]

In fact, 30 to 100% of patients diagnosed with NAFLD have been shown to be obese.[1] The prevalence of NAFLD in obese individuals is 76% as compared with 16% in non-obese individuals.[5] The greater the degree of obesity, the greater the prevalence and severity of AFLD.[8,10,17]

However, individuals with normal BMI may also be affected by NAFLD, particularly those with truncal obesity.[1,20]

In our study, the waist/hip ratio was not significantly different between the two groups (p=0.19). This ratio reflects abdominal (truncal) fat distribution and it has been shown in a previous study that there is a significant correlation between waist/hip ratio and the degree of hepatic steatosis, even in patients with normal BMI.[21]

There was no difference in HbA1c between the two groups (p=0.67). Although hyperglycemia has been reported in 20-75% of adult patients with NAFLD, we could find no statistically significant difference in serum FBS levels between the two groups (p=0.48).[8] Absence of correlation between glycemic control and NAFLD may denote to an indirect or non-casual relation between these two conditions.

Many studies have shown that insulin resistance has a critical role in the pathogenesis of NAFLD. We thus expected indicators of insulin resistance to be higher in the NAFLD group.

Somewhat surprisingly, we did not observe significant differences in insulin resistance parameters (HOMA-IR and QUICKI) between the two groups (p=0.42 and 0.34, respectively).

This inconsistency may result from the fact that all subjects in our study were diabetics and, to some degree, did have insulin resistance as well as increased insulin secretion; whereas other studies might have included healthy individuals in their control groups.

At least, in our study among T2DM patients, insulin resistance did not appear to be an important factor in the development of NAFLD. Among lipid parameters, only the mean triglyceride levels showed significant correlation with the presence of NAFLD (p=0.036). Mean cholesterol, HDL and LDL levels did not defer significantly between the two groups.

Dyslipidemias are factors commonly associated with NAFLD. Studies have shown that 20-92% of patients diagnosed with NAFLD have hyperlipidemia,[1] including hypertriglyceridemia, hypercholesterolemia or both.[8] In one study, almost 50% of the patients diagnosed with hyperlipidemia had NAFLD on ultrasound evaluations but only hypertriglyceridemia and not hypercholesterolemia, was shown to pose a risk of developing liver fatty disease.[22]

Hypertriglyceridemia along with diabetes and obesity increases the risk of NAFLD development.[4] Differences in transaminase levels were not statistically significant between the groups (p=0.98 and 0.53 for AST and ALT, respectively).

Although mild to moderate elevations of serum aminotransferase are common in NAFLD,[8] normal values can be found in up to 78% of patients at any time, even when complete histological findings are present.[5] Hence, there is a poor correlation between transaminases and disease severity.[8]

An AST to ALT ratio greater than1 might predict more severe disease[1,4,5,23] with a greater probability of fibrosis which, again, was not different between our study groups (p=0.62).

The mean serum alkaline phosphatase level was found to be significantly lower in patients with NAFLD. This finding contrasts with previous studies which showed mild increases in alkaline phosphatase levels in patients with NAFLD.[4]

NAFLD has been reported to affect nearly one third of the adult general population in the United States.[5,17] Similar reports from Iran indicate a prevalence close to 30%.[13,14]

We have used ultrasound to identify NAFLD which has a sensitivity and specificity of 89% and 93%, respectively, in detecting liver steatosis.[4] In fact, imaging tests are insensitive when the degree of steatosis is less than 33%.[10,17,20]

Therefore, our figures may be an underestimation of the true prevalence of NAFLD in T2DM patients. Our findings indicate that the prevalence of NAFLD is much higher in patients with T2DM than in the general population. Due to the significant rate of increased liver-related morbidity and mortality in T2DM patients, it is important to discover and treat this condition.

Unfortunately, with the possible exception of weight loss among obese subjects, there is no established treatment for NAFLD. Many researchers have studied insulin sensitizers, antioxidants, and other agents with various rates of success,[5,24,25] however a universally effective treatment remains to be identified.

We conclude that the prevalence of NAFLD is high amongst T2DM patients and, considering the increased liver mortality among these patients, NAFLD should be actively sought out and treated in patients with diabetes.

Insulin resistance does not seem to be correlated with the presence of NAFLD among T2DM patients. It should be emphasized that the diagnosis of NAFLD in our study was based on ultrasonography findings, not on histology.

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CONFLICT OF INTEREST

None declared.

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