INCIDENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETIC PATIENTS

Original Article

TİP 2 DİYABETLİ HASTALARDA NON ALKOLİK YAĞLI KARACİĞER HASTALIĞININ SIKLIĞI

Sevil Ozkan

Haydarpasa Numune Education and Training Hospital, Istanbul, Turkey

Corresponding Author

Sevil Ozkan
Haydarpasa Numune Education and Training Hospital, Istanbul, Turkey
Tel: +90 530 363 39 59
Email: sevilfurkan@hotmail.com

ABSTRACT

Introduction: The objective of this study is to evaluate presence, grade and associated factors of hepatosteatosis detected in type 2 diabetic patients by liver ultrasound.

Materials and Methods: 89 type 2 diabetic patients referred to our Internal Medicine Outpatient Unit were retrospectively included into our study. Liver ultrasound examination of type 2 diabetic patients were evaluated in terms of presence and grade of hepatosteatosis and factors associated with hepatosteatosis were also investigated.

Results: Incidence of hepatosteatosis was 48% in diabetic patients included into our study. There was no statistically significant difference between patients with hepatosteatosis and without hepatosteatosis in terms of sex, age, height, weight and BMI measurements, glucose, Hemoglobin A1c (HbA1c), creatinine, Blood Urea Nitrogen (BUN), total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) levels and ALT/AST ratio (p>0,05). Mean serum triglyceride levels and mean waist circumference of patients with hepatosteatosis were statistically significantly higher relative to patients without hepatosteatosis (p=0,001). There was statistically significant 26.5% positive correlation between BMI and total cholesterol (r: 0,265; p: 0,013). In the liver ultrasound; the rate of statistically significant correlation between hepatosteatosis grade and ALT measurement, AST measurement, waist circumference, BMI measurement, total cholesterol levels, LDL cholesterol levels, triglyceride levels was respectively 32,0%(r=0,320; p=0,003; p<0,01), %33,6 (r=0,336; p=0,001; p<0,01), 36,7% (r=0,367; p=0,001; p<0,01), 21,2% (r=0,212 p=0,048; p<0,05), 28,2% (r=0,282; p=0,008; p<0,01), 23,8% (r=0,238; p=0,033; p<0,05), 40,7% (r=0,407; p=0,003; p<0,01). In the liver ultrasound examination hepatosteatosis was grade 1 in 31 patients, grade 2 in 15 patients and grade 3 in 4 patients.

Conclusion: HS is common in type 2 diabetics. The risks of non-alcoloholic fatty live diseases at the later stages requires close monitoring of patients with type 2 diabetes in terms of fatty liver disease and associated metabolic factors such as high BMI, large waist circumference and high serum triglyceride levels should be treated.

Key words: Type 2 diabetes, non-alcoholic fatty live disease

ÖZET

Amaç: Bu çalışmanın amacı tip 2 diyabetli hastalarda karaciğer ultrasonografisi ile saptanmış hepatosteatoz varlığını, derecesini ve hepatosteatoza eşlik eden faktörleri araştırmaktır.

Materyal ve Method: Hastanemiz İç Hastalıkları Polikliniğine gelen 89 tip 2 diyabetik hasta retrospektif olarak çalışmaya dahil edildi. Tip 2 diyabetli hastalar karaciğer ultrasonografisinde hepatosteatoz varlığına ve derecesine göre değerlendirilerek hepatosteatoz ile ilişkili faktörler değerlendirildi.

Bulgular: Çalışmamızda tip 2 diyabetli hastalarda hepatosteatoz sıklığı %48 olarak saptandı. Hepatosteatoz olan hastalarla olmayan hastaların cinsiyet, yaş, boy, kilo ve VKI ölçümleri, glukoz, Hemoglobin A1c (HbA1c), kreatinin, Kan üre azotu (BUN), Total kolesterol, yüksek yoğunluklu lipoprotein kolesterol (HDL), düşük yoğunluklu lipoprotein kolesterol (LDL), Alanin aminotransferaz (ALT), Aspartat aminotransferaz (AST), ALT/AST oranı ölçüm değeri ortalamaları arasında istatistiksel olarak anlamlı fark saptanmadı (p>0,05). Hepatosteatoz olan hastaların serum trigliserid ölçümleri ortalaması, bel çevresi ölçümü ortalaması, hepatosteatoz olmayan hastaların ortalamasına göre istatistiksel olarak anlamlı yüksekti (p=0,001). VKI ile total kolesterol ölçümleri arasında pozitif yönde %26,5 düzeyinde istatistiksel olarak anlamlı ilişki saptandı (r: 0,265; p: 0,013). Karaciğer Ultrasonografisinde; hepatosteatoz derecesi ile ALT ölçüm değeri arasındaki %32,0 düzeyinde (r=0,320; p=0,003; p<0,01), AST ölçüm değeri arasındaki %33,6 düzeyinde (r=0,336; p=0,001; p<0,01), bel çevresi arasında %36,7 düzeyinde (r=0,367; p=0,001; p<0,01), VKİ ölçüm değeri arasında %21,2 düzeyinde (r=0,212 p=0,048; p<0,05), Total Kolesterol ölçümleri arasında %28,2 düzeyinde (r=0,282; p=0,008; p<0,01), LDL Kolesterol ölçümleri arasında %23,8 düzeyinde (r=0,238; p=0,033; p<0,05), Trigliserid ölçüm değeri arasında %40,7 düzeyinde (r=0,407; p=0,003; p<0,01) istatistiksel olarak anlamlı ilişki bulundu. Karaciğer ultrasonografi incelemesinde; 31 hastada hepatosteatoz derecesi grade 1, 15 hastada hepatosteatoz derecesi grade 2 ve 4 hastada hepatosteatoz derecesi grade 3 olarak tespit edildi.

Sonuç: HS, tip 2 diyabetli hastalarda sık rastlanmaktadır. Non alkolik yağlı karaciğer hastalığının ileri dönem riskleri göz önüne alındığında, tip 2 diyabetli hastalar yağlı karaciger hastalığı yönünden yakından takip edilmeli ve VKI, bel çevrsinde artış ve hipertrigliseridemi gibi eşlik eden metabolik faktörler tedavi edilmelidir.

Anahtar kelimeler: Tip 2 diyabet, non alkolik yağlı karaciğer, ultrasonografi

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has been described firstly in 1980 by Ludwig et al. (1) in a group of women who use no alcohol or less than 140 alcohol in a week as an entity concordant with pathological features of alcoholic liver disease. NAFLD is closely associated with insulin resistance and genetic predisposition and it occurs in liver due to metabolic stress injury. Despite pathological alterations observed in NAFLD are similar to findings observed in alcoholic liver disease there is no history of alcohol use. NAFLD usually consists of a wide clinical spectrum varying from non-alcoholic simple fatty liver (hepatosteatosis) to steatohepatitis associated with liver cirrhosis or hepatocellular carcinoma (2-4). NAFLD is the most common liver disease in developed countries (5,6).

NAFLD is associated with cardiovascular risk factors such as obesity, dyslipidemia and diabetes (7). Pathogenesis of NAFLD is not clear yet. However, the main pathological mechanisms are insulin resistance and oxidative stress (8). Insulin resistance suppresses synthesis of Apolipoprotein B-100 carrying triglycerides and cholesterol esters from hepatocytes to periphery and leads to de novo lipogenesis in hepatocytes (9). Grade and duration and of obesity and presence of abdominal obesity increases risk of type 2 diabetes. Most of the type 2 diabetic patients are also obese (10). It's assumed that in obesity high serum leptin levels and adipocytokines may

lead to oxidative stress and endotoxemia and this in turn may cause hepatocellular inflammation and fibrosis and thus may contribute to hepatosteatosis (11).

The most effective non-invasive imaging technique showing the presence of hepatosteatosis and determining its extent is magnetic resonance imaging (MRI). However, ultrasound (USG) is the most important and most commonly used specific diagnostic method, because MRG assessment is more difficult due economic and practical setbacks (12).

In this study, type 2 diabetic patients were evaluated by liver ultrasound in terms of presence, grade and associated factors of hepatosteatosis.

MATERIALS AND METHODS

89 patients with type diabetes referred to Haydarpasa Numune Training and Research Hospital Internal Medicine Outpatients Unit between April 2015 and September 2015 and had liver USG examination were retrospectively included into our study. Detailed history of patients were sought. Patients with history of alcohol use (> 20 gr/day), diagnosis of malignancy, thyroid disease, history of hepatitis, cardiac insufficiency and autoimmune or genetic liver diseases (hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency) weren't included into the study. Weight, height and waist circumference measurements were done in addition to routine physical examination. Body mass index (BMI) was calculated as weight (kg)/height (m2). If BMI was 25-29.9 kg/m² the patients were considered overweight and if > 30 kg/m² they were considered obese. Waist circumference was measured at the midpoint between lower rib margin and anterior superior iliac crest. Systolic and diastolic blood pressures were recorded by calculating the average of last 2 of 3 measurements done in 2 min intervals. Serum glucose (mg/dl), BUN (mg/dl), creatinine (mg/dl), total cholesterol (mg/dl), triglyceride (mg/dl), HDL cholesterol (mg/dl), LDL cholesterol (mg/dl), aspartate aminotransferase (AST) (U/L) alanine aminotransferase (ALT) (U/L) and HbA1c (%) levels were measured after 10 hours of overnight fasting. For diagnosis of hepatosteatosis ultrasound examination was preferred instead of liver biopsy, since the former is an invasive method and the patients were reluctant about undergoing liver biopsy. After excluding other chronic liver diseases and establishing hepatosteatosis findings by USG the patients were followed up as NAFLD cases. Liver ultrasound (ToshibaXario US, Town, Japon) was done by 3,5 MHz convex probe. Grade of hepatosteatosis was defined as follows according to USG findings: Grade 1 if slight increase in echogenicity was present and appearance of diaphragm and intrahepatic vessel walls were normal. Grade 2 if there was moderate increase in echogenicity and slight indistinction of diaphragm and intrahepatic vessel walls. Grade 3 if echogenicity was very much increased and indistinction of diaphragm and intrahepatic vessel walls were prominent and liver right lobe posterior image was indistinct (13,14).

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. For evaluation of statistical data descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Percentage, Minimum, Maximum) were used and also for comparison of quantitative data Student t Test was used for normally distributed parameters in two group comparison and Mann Whitney U test was used for non-normally distributed parameters in two group comparison. Pearson Chi-Square test and Fisher-Freeman-Halton test were used in comparison of qualitative data. Correlation between parameters was evaluated by using Spearman's Correlation Analysis. $p<0.01$ and $p<0.05$ were considered significant.

Logistic regression analysis was used for the multi-variate assessment of the risk factors with an impact on hepatosteatosis.

RESULTS

Of 89 type 2 diabetic patients included into the study 61,7% (n=55) were female and 38,3% (n=34) were male and mean age was 54,6±7,17 years. Height (Mean ±SD) was 163,79±7,89 (cm), weight (Mean ±SD) was 84,1±12,02 (kg), BMI (Mean ±SD) was 24,17-44,06 (kg/m2), waist circumference (Mean ±SD) was 102,51±11,154 (cm). Hepatosteatosis was observed in 57.5% of patients. 62% of those were female and 38% were male. There was no difference statistically between patients with hepatosteatosis or without hepatosteatosis in terms of sex, age, height, weight and BMI (p>0,05). Mean waist circumference of patients with hepatosteatosis was statistically significantly higher than patients without hepatosteatosis (p=0,001) (Table-1). There was no difference statistically between patients with hepatosteatosis or without hepatosteatosis in terms of mean blood glucose, HbA1c, creatinine, BUN, total cholesterol, HDL cholesterol, LDL cholesterol, ALT levels and ALT/AST ratio (p>0,05). There were no significant differences between patients with or without hepatosteatosis with respect to mean glucose (mean ±SD 168.49±42.03 mg/dl and 186.32±63.58 mg/dl, respectively; p=0.255) and HbA1c (%) (mean±SD 7.75±1.22 and 8.12±1.71, respectively; p=0.343) levels (p>0.05).

Mean triglyceride levels of patients with hepatosteatosis were statistically significantly higher compared to patients without hepatosteatosis (p=0,001; p<0,01). Statistically significant 26.5% positive correlation was found between BMI and T. cholesterol levels (T. cholesterol increases as BMI increases) (r: 0,265; p=0,013; p<0,05). There was no statistically significant correlation between BMI and triglyceride levels (p>0,05). A logistic regression analysis examining the risk factors in hepatosteatosis included uni-variables with significant or near-significant effects in the model. Waist circumference, triglycerides, total cholesterol, HDL cholesterol, ALT, and AST effects were therefore included in the logistic regression model. The general explanatory coefficient of the model was 73.6%, with a sensitivity and specificity of 82.0% and 62.2%, respectively. An assessment of the factors that could have an effect on hepatosteatosis with Backward (Conditional) Logistic regression analysis showed significant results (p=0.001, p < 0.01). Triglyceride, total cholesterol, waist circumference, and HDL cholesterol had significant effects on hepatosteatosis (p=0.041, 0.044, 0.001, and 0.043, respectively). Other variables included in the analysis lost their significance in the model, despite being significant in the univariate analysis (p > 0.05) (Table-2).

Correlation rate between hepatosteatosis grade evaluated in USG and ALT levels was 32% (r=0,320; p=0,003; p<0,01) and AST level 33,6% (r=0,336; p=0,001; p<0,01) and waist circumference 36,7% (r=0,367; p=0,001; p<0,01) and BMI 21,2% (r=0,212 p=0,048; p<0,05) and Total Cholesterol 28,2% (r=0,282; p=0,008; p<0,01) and LDL Cholesterol 23,8% (r=0,238; p=0,033; p<0,05) and Triglyceride 40,7% (r=0,407; p=0,003; p<0,01) and all these correlations were statistically significant. In USG examination liver was normal in 37 of 87 type 2 diabetic patients and there was grade 1 hepatosteatosis in 31 patients, grade 2 hepatosteatosis in 15 patients and grade 3 hepatosteatosis in 4 patients.

		HEPATOSTEATOSIS		*p*
		No	**Yes**	
Glucose (mg/dl)	*Min-Max(Median)*	122-313(160)	93-391(167,5)	[c]***0,255***
	Mean±SD	168,49±42,03	186,32±63,58	
HbA1c (%)	*Min-Max(Median)*	6,2-12,8(7,5)	6,4-15(7,85)	[c]***0,343***
	Mean±SD	7,75±1,22	8,12±1,71	
Creatinine (mg/dl)	*Min-Max(Median)*	0,61-1,1(0,9)	0,63-1,33(0,87)	[b]***0,555***
	Mean±SD	0,86±0,14	0,88±0,15	
BUN (mg/dl)	*Min-Max(Median)*	9-22(14)	10-28(14)	[b]***0,373***
	Mean±SD	14±2,92	14,68±3,87	
Total Cholesterol (mg/dl)	*Min-Max(Median)*	153-340(220)	132-380(234)	[c]***0,038****
	Mean±SD	223,65±39,41	239±41,89	
LDL Chol. (mg/dl)	*Min-Max(Median)*	81-233 (132)	78-263 (140)	[b]***0,479***
	Mean±SD	134,74±34,02	139,98±31,45	
HDL Chol. (mg/dl)	*Min-Max(Median)*	24-69(38)	24-59(37)	[b]***0,125***
	Mean±SD	40±9,48	36,48±7,17	
Triglyceride (mg/dl)	*Min-Max(Median)*	66-1420(145)	84-1420(235)	[c]***0,001****
	Mean±SD	224,92±267,27	290,06±285,96	
ALT (IU/L)	*Min-Max(Median)*	14-50(24)	9-71(24,5)	[c]***0,140***
	Mean±SD	24,73±7,01	29,08±12,68	
	Normal*n(%)*	34 (91,9)	39 (78,0)	[a]***0,081***
	High*n(%)*	3 (8,1)	11 (22,0)	
AST (IU/L)	*Min-Max(Median)*	15-33(20)	9-42(22)	[c]***0,019****
	Mean±SD	20,78±4,5	23,4±6,24	
	Normal*n(%)*	35 (94,6)	46 (92,0)	[a]***1,000***
	High*n(%)*	2 (5,4)	4 (8,0)	
ALT/AST (IU/L)	*Min-Max(Median)*	0,75-1,93 (1,17)	0,36-2,89 (1,10)	[c]***0,877***
	Mean±SD	1,2±0,25	1,24±0,42	

*[a]Pearson Chi-square Test [b]Student t Test [c]Mann Whitney U Test *p<0,05 **p<0,01*

Table 1. Comparison of laboratory results of patients with hepatosteatosis and without hepatosteatosis

	p	ODDS	95% C.I.for ODDS	
			Lower	**Upper**
Triglyceride	0,041*	1,082	1,080	1,102
Total Cholesterol	0,044*	1,015	1,009	1,052
Waist circumference	0,001**	1,090	1,035	1,148
HDL Cholesterol	0,043*	0,928	0,863	0,998

a. Variable(s) entered on step 1: Triglyceride , Total Cholesterol, Waist circumference, HDL Cholesterol

Table 2. Logistic regression analysis of the risk factors with an effect on hepatosteatosis

DISCUSSION

NAFLD is a very common disease globally and its prevalence is consistently increasing. Hepatosteatosis which is included in NAFLD and first grade steatohepatitis is very common within the general population.

NAFLD is more prevalent in obesity, diabetes and hypertriglyceridemia. In general population, the prevalence of steatosis is 10-24% and prevalence of non-alcoholic steatohepatitis (NASH) 5% but in obesity/type 2 diabetes prevalence of steatosis is 55-74% and prevalence of NASH is 25-75% (15). Hepatic steatosis and steatohepatitis may be associated with several diseases affecting liver such as Hepatitis A, B, C, autoimmune hepatitis, hemochromatosis and hypothyroidism. In obese type 2 diabetic adult's prevalence of NAFLD is >70% (16). In our study, hepatosteatosis rate was 57.5% in type 2 diabetics which is in line with literature.

Pathogenesis of NAFLD is not clear yet. However, insulin resistance is the most important factor. Excessive calorie intake and progressive obesity increase lipid deposits in the body and this increase alters lipid metabolism via inflammation of the ectopic fat depositions and fat tissue causing insulin resistance secondary to post-receptor abnormalities in insulin signaling pathway (17). Increasing free fatty acid in the circulation leads to a decrease in suppression of lipolysis in the fat tissue via insulin and this in turn increases accumulation of free fatty acids in the liver. Excessive triglyceride synthesis in the liver increases further the impairment of hepatic fatty acid oxidation secondary to insulin resistance and thus steaotosis of liver increases and more fatty acid provided. Increase in glucose level provides more substrate for triglyceride synthesis. Impaired secretion of very low density lipoprotein (VLDL) occurs more frequently in insulin resistance. This also contributes to hepatic lipid deposition. As it was shown by a euglycemic insulin clamp study, insulin resistance is a cause for obesity and diabetes and also the underlying mechanism of NAFLD observed in non-obese, non-diabetic individuals. Development and progression of NAFDL is associated with both insulin resistance and excessive calorie intake (18). Obesity, type 2 DM and hyperlipidemia are conditions frequently accompanying NAFLD.

Diabetes is a chronic condition leading to various disturbances in carbohydrate, protein and lipid metabolism as a result of absolute or relative insufficiency of insulin secreted from pancreatic beta-cells or its inefficacy on target tissues. Insulin has impact on lipid mechanism as well as on glucose metabolism (19). The main reason for diabetic dyslipidemia is lack of free fatty acid uptake by peripheral tissues due to insulin resistance and return of ample amount of free fatty acid into the liver from the increased fat tissue (20). Dyslipidemia is very common in type 2 diabetic patients. In 70-97% of diabetic patients one or more lipid disorder has been reported. Interrelated lipid and lipoprotein metabolism disturbances characterized by high triglyceride levels, low HDL cholesterol level and high LDL cholesterol level have been observed in diabetes (21). As it's in the study of Gupte et al. (12) also in our study between the groups with HS or without HS T. cholesterol, LDL cholesterol and HDL cholesterol levels weren't statistically significantly different ($p<0,05$). According to National Cholesterol Education Program Adult Treatment Panel III report upper limit of normal is stated as 200 mg/dl for serum triglyceride level (22). In our study mean triglyceride level was 290,06±285,96 mg/dl. In patients with HS mean total cholesterol and mean triglyceride measurement levels were statistically significantly higher than patients without HS ($p=0,001$; $p<0,01$). In type 2 diabetes hypertriglyceridemia is the result of excessive production of triglyceride from VLDL cholesterol and impairment of clearance. It is assumed that excessive production of triglyceride from VLDL is due to increased inflow of fatty acids into the liver (23). In 70-97% of diabetic patients one or more lipid

disorder has been reported. Interrelated lipid and lipoprotein metabolism disturbances characterized by high triglyceride levels, low HDL cholesterol level and high LDL cholesterol level have been observed in diabetes (21). In our study mean total cholesterol was 232,42±41,33 mg/dl, mean HDL cholesterol was 37,98±8,37 mg/dl and mean LDL cholesterol was 137,75 ±32,46 mg/dl. Between patients with or without HS Total cholesterol, HDL cholesterol and LDL cholesterol levels weren't statistically significantly different (p>0,05); however, there was statistically significant difference between hepatosteatosis grade and total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels.

Ina study by Araz et al. (24) it has been reported that grade of steatosis in the liver increases as BMI increases and in diabetic patients BMI is the most important risk factor for development of hepatosteatosis. Wang et al. (25) have observed in their study conducted on diabetic patients that BMI is an independent risk factor for development of NAFLD. In our study mean BMI of patient groups with or without HS I (30,7±4,57 and 31,79±2,99 kg/m²) wasn't statistically different (p>0,05). This suggests that diabetes is a risk factor for HD independent from obesity. In our study, in USG statistically significant 21.2% correlation was found between HS grade and BMI (r=0,21 p=0,048; p<0,05). 59.8% of patients included into the study were obese and 39.1% were overweight. In various studies prevalence of cardiovascular disease and metabolic syndrome was observed to be increased in in type 2 diabetic patients with NAFLD compared to type 2 diabetic patients without NAFLD (26,27). In our study, in type 2 diabetic patients with HS mean waist circumference which is a component of metabolic syndrome was observed to be statistically significantly higher than type 2 diabetic patients without HS (p=0,001).

In the study conducted by Palmentieri et al. (28) sensitivity and specificity of USG in diagnosing hepatosteatosis was found to be 64% and 97% and in the study of Hamaguchi et al. (29) the rates were 91.7% and 100% respectively. Since it's a low-cost, effective, repeatable and non-invasive method we have also preferred to use USG for assessment of HS in our study. In USG examination liver was normal in 37 of 87 type 2 diabetic patients and there was grade 1 hepatosteatosis in 31 patients, grade 2 hepatosteatosis in 15 patients and grade 3 hepatosteatosis in 4 patients.

Limitations of the study: the golden standard for the diagnosis of hepatosteotosis is liver biopsy. USG may not be able to reveal hepatosteotosis before 30% of the liver is affected from steaotosis. Thus, inability to detect steatosis by liver USG can not be interpreted an absence of any steaotosis histologically. Another limitation of the study is that if more patients had been included and design of the study had been prospective the study could have been made stronger.

CONCLUSION

HS is common in type 2 diabetics. The risks of NAFLD at later stages requires close monitoring of patients with type 2 diabetes in terms of fatty liver disease and associated metabolic factors such as increase in BMI; waist circumference and serum triglycerides should be treated.

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