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Investigating the relationship between fatty liver and diabetes in patients admitted to hospitals affiliated to Tehran Shahid Beheshti University of Medical Sciences

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ABSTRACT

Fatty liver is the most common chronic liver disease in Western industrialized countries. However, there is evidence on correlation between management of fatty liver risk and diabetes. In this regard, the current study was conducted to find the relationship between fatty liver and diabetes in patients admitted to hospitals affiliated to Tehran Shahid Beheshti University of Medical Sciences .This descriptive correlational study was conducted on 180 patients admitted to the hospitals of Shahid Beheshti University of Medical Sciences in Tehran. The instruments used in this study included demographic and clinical characteristics of patients such as serum levels of cholesterol, LDL, HDL, triglycerides, hemoglobin and liver horns. Results were analyzed using t-test and chi-square tests .According to ANOVA tests, significant difference was found among indicators of LDL, triglycerides, cholesterol and ALT so that with an increase in triglycerides, HbA1c level also increased (05/0> P). On the other hand, by reducing HDL, the indicator of HbA1c increased. In addition, significant relationship was found between indicators of ALP and triglycerides so that with an increase in triglyceride and ALP, FBS level also increases (P<0.05). Due to the great impact of obesity and type 2 diabetes at an increased risk of non-alcoholic fatty liver disease, regular exercise and physical activities appropriate with age, low-fat diet, weight loss and different treatments to control diabetes and hypertension are recommended to reduce nonalcoholic fatty liver disease.

Keywords: Fatty liver, diabetes, cholesterol, LDL, HDL, triglycerides, HbA1C.

INTRODUCTION

Non-alcoholic fatty liver disease [NAFLD] is the most common state including wide range of liver lesions including simple steatosis and steatosis with mild inflammation of liver cells to severe nonalcoholic steatohepatitis [1]. It is mainly associated with type 2 diabetes, obesity, and hyperlipidemia [2, 3]. The importance of this disease is due to damage to liver cells and in the case of lack of early diagnosis and appropriate treatment, it can lead to progressive and irreversible liver disease called hepatitis - cancer [4]. In fact, NAFLD includes a wide range of liver dysfunctions and tissue damage similar to alcoholic liver disease, but it occurs in people who do not drink alcohol or use only moderate amounts of alcohol [5].

Accurately diagnosis of NAFLD is based on liver biopsy and pathological examination, but ultrasound imaging methods including computed tomography and ultrasound are clinically can be used. AS biopsy is invasive and other imaging technologies are costly, clinical diagnosis of NAFLD is based on gloss liver sonographic evidence and reduced posterior attenuation in the non-alcohol people and people using low amount of alcohol [6].

The pathogenesis of this disease is multifactorial and it seems that insulin resistance is essential for fat accumulation in hepatocytes [7]. This disease is known as one of the most common liver diseases in western developed countries, so that its prevalence is 2 to 3 times more than hepatitis B and alcohol-dependent liver diseases and it is currently considered as the most common disorder of the liver tests [8 and 9]. Recent studies conducted in Eastern countries have reported that its prevalence is increasing due to changes in lifestyle [diet, low physical activity, obesity and diabetes mellitus type 2], so that only the prevalence of one form of disease, hepatic steatosis, has been estimated about 16 to 30 percent of the general population, that this rate is comparable with western countries [10].

Prevalence of NAFLD in third world countries [Asia – Pacific area] has its own limitations. Non-inclusion of it in health system screening plan, asymptomatic disease, paying more attention to viral hepatitis and religious issues [lack of asserting the using alcohol] lead a lack of information about the prevalence of the disease [10]. Urbanization, behavioral changes [reduced physical activity and diet with high-energy fat] and increased prevalence of type 2 diabetes, the prevalence of this disease is increasing has been increased in Asian regions. The incidence range of this disease has been estimated 7 to 40 percent that it has been increased from 3 to 20 times in countries like Japan over the past 20 years [11]. NAFLD patients are mainly asymptomatic. Many patients are discovered due to increased liver enzymes in the routine laboratory tests or during the examination of other conditions such as obesity, diabetes, hyperlipidaemia and high blood pressure. The symptoms od this disease are usually nonspecific. Some patients may complain of tiredness, lethargy, and abdominal pain. Due to the lack of any evidence on the relationship between fatty liver disease and type 2 diabetes, especially in Iran, this study was performed in this regard.

MATERIALS AND METHODS

This study is descriptive-correlational study in terms of the objectives and nature of the study. The study population included all patients admitted to hospitals of Tajrish Shohada, Imam Hussein (AS), Luqman, and Zaim, who had fatty liver disease. Due to extensiveness of work and time constraints, educational hospitals were considered as research environments. Sample of study was selected and included in the study in two-stage sampling (first stratified sampling and then simple randomly sampling within classes) based on statistical formula. In this cross-sectional study, 180 patients admitted to the hospitals of Shahid Beheshti Universities of Medical Sciences in Tehran were studied.

To estimate the sample size, the following formula was used:

$$n \geq \frac{\left(z_1 - \frac{\alpha}{2}\right)\sigma^2}{d^2}$$

As standard deviation of 0.4, confidence coefficient of 0.95, and error percentage of 0.065 were considered in previous studies, sample size was obtained to be180 people. Thus, the researcher included NAFLD patients admitted to Shahid Beheshti Universities, who met the criteria of inclusion and willing to participate in the study. Sampling was continued up to achieve the determined sample size, that was 180 people. Researcher referred to relevant departments in various days of the week and selected the people who met the criteria to be included in the study. He also interviewed with them to complete the questionnaire up to achieve the considered sample size by providing necessary explanations on objectives of the study and giving answer for the questions of the questionnaire and obtaining their written consent.

Inclusion criteria of patients included a diagnosis of NAFLD by doctors, ultrasound and testing in the patient's medical file, lack of type 2 diabetes and written consent of subjects. Exclusion criteria of patients included a past or recent use of alcohol by subjects, no finding showing evidence on cirrhosis (clinical, biochemical and ultrasonographic findings), hepatitis (viral, autoimmune, pharmaceutical), history of using hepatotoxic drugs and a history of known cause of secondary fatty liver (jejunoileal bypass surgery, small bowel resection surgery, surgery for obesity and intensive loss of weight).

In this study, to determine the parameters and investigation of hypotheses, designed form was used. This form includes demographic and clinical characteristics of patient such as sex, age, weight, marital status, waist circumference, height, blood pressure, serum levels of total cholesterol, LDL, HDL, triglycerides, fasting blood glucose, glycosylated hemoglobin, total number of blood cells , hepatic transaminases, and alkaline phosphatase. After receiving a letter of introduction and presenting it to the hospitals' management, researcher received a license to conduct this study. Then, figures of files of patients with fatty liver were received from medical documents, patients' files were studied, and form related to each patient was completed. The validity of the used form was investigated based on literature review of previous studies and opinions of professors, experts, and doctors.

Data were analyzed using descriptive statistics and analytical test of Pearson correlation coefficients, t-test, and ANOVA.

Table 1: Frequency and percentage of studied patients in demographic variables

Variable	Type	frequency	Percentage
Gender	Male	119	66.1
	Female	61	33.9
Age gap	31-40	21	11.7
	41-50	56	31.1
	51-60	49	27.2
	61-70	40	22.2
	71-80	14	7.8
Marital status	Married	164	91.1
	Single	16	8.9
Weight	60-70	10	5.6
	71-80	42	23.3
	81-90	46	25.6
	91-100	64	36.1
	101-110	17	9.4
Height	150-170	68	37.8
	171-180	89	49.4
	181-190	23	12.8
Waist circumference	60-80	57	31.7
	81-100	99	55
	101-120	24	13.3
Abdominal circumference	70-90	65	36.1
	91-110	99	55
	111-113	16	8.9
Hip circumference	70-90	88	48.9
	91-110	86	47.8
	111-113	6	3.3
	Total	180	100

Table 2- frequency, percentage, mean, SD of clinical indicators of patients

	Indicator	Status	frequency	percentage
Indicators related to fatty liver	LDL	Less than 130 (Normal)	42	23.3
		More than 130 (suspected)	138	76.7
		Mean and SD	138.57±14.03	
	HDL	Less than 35 (N)	13	7.2
		More than 35 (suspected)	167	92.8
		Mean and SD	43.87±6.33	
	Triglyceride	Less than 200 (Normal)	178	98.9
		More than 200 (suspected)	2	1.1
		Mean and SD	171.52±21.16	
	Cholesterol	Less than 200 (Normal)	30	16.7
		More than 200 (suspected)	150	83.3
		Mean and SD	234.97±23.27	
Indicators related to diabetes	HbA1c	3-4	85	47.2
		4-5	79	43.9
		5-6	16	8.9
		Mean and SD	4.10±0.67	
	FBS	70-80	62	34.4
		81-90	58	32.2
		91-100	60	33.3
		Mean and SD	85.35±8.84	

Findings

Out of the 180 patients studied, 66.1% were male and 91.1 percent of them were married. In the variable of age, 11.7% of them had less than 40 years old, 31.1% of them were between 41 and 50 years old, 27.2% of them were between 51 and 60 years old, and the remaining of them were over 60 years old. In variable of patients' weight, 5.6% of them had weigh less than 70 kg, 23.3% of them had weight between 70 and 80 kg; 25.6% of them had weight between 81 and 90 kg, 36.1% of them had weight between 91 to 100, and remaining patients had weight over 100 kg. in variable of height, 37.8 % of patients had height less than 170 cm, 49.4 % of them had height between 171 to 180 cm, and remaining patients had a height higher than 180 cm.In variable of waist circumference in patients, 31.7% of patients had waist circumference between 60 and 80 cm, 55% of them had waist circumference between 81 to 100 cm, and remaining patients had had waist circumference greater than 100 cm. In terms of abdominal circumference, 36.1%of patients had abdominal circumference between70 to 90 cm, 55% of them had

abdominal circumference between 91 to 110 cm, and remaining patients had abdominal circumference more than 110 cm. In in terms of hip circumference, 48.9% of patients had hip circumference between 70 and 90 cm, 47.8% of them had hip circumference between 91 to 110 cm, and remaining patients had hip circumference greater than 110 cm (Table 1).

The results showed that the majority of studied patients (76.7%) in the indicator of LDL were faced with suspected status and only 23.3 percent of patients were in the normal status. In the HDL indicator, the majority of investigated patients (92.8%) had suspected status and 7.2 percent of them were in normal status. In the triglyceride indicator, majority of investigated patients (98.9 %) had normal status, and 1.1 percent of them were in suspected status. In cholesterol indicator, the majority of studied patients (83.3 of percent) had suspected status and 16.7 % of them were in normal status. In the indicator of HbA1c, majority of patients were at the range of 3 to 5, in addition, 8.9% of them were in the range of 5 to 6. In the indicator of FBS, majority of patients (34.4%) had FBS less than 80, 32.2% of them had FBS between 81 to 90, and remaining patients had FBS higher than 90 (Table 2).

Based on ANOVA tests, significant relationship was observed between the indicators of LDL, triglycerides, cholesterol and ALT in such a way that an increase in triglycerides led to an increase in HbA1c. On the other hand, by reducing HDL, the HbA1c indicator was also increased (Table 3).

Table 3: Investigating the relationship between LDL, HDL, triglycerides, cholesterol, ALT and ALP of patients with HbA1c indicator

Variable	HbA1c	Mean	SD	Test	Test value	Significance level
LDL	3-4	139.78	1.54	ANOVA	4.61	0.011
	4-5	139.26	1.31			
	5-6	128.62	4.87			
HDL	3-4	44.01	6.18	ANOVA	0.77	0.46
	4-5	43.39	5.89			
	5-6	45.50	8.94			
Triglyceride	3-4	171.61	19.95	ANOVA	5.004	0.008
	4-5	168.41	19.71			
	5-6	186.37	28.43			
Cholesterol	3-4	238.14	22.84	ANOVA	18.52	0.001
	4-5	237.81	18.70			
	5-6	204.06	24.50			
ALT	3-4	66.48	17.05	ANOVA	10.58	0.001
	4-5	68.00	13.22			
	5-6	47.81	23.94			
ALP	3-4	56.03	7.66	ANOVA	0.480	0.61
	4-5	56.24	6.58			
	5-6	54.31	7.76			

According to ANOVA tests, significant relationship was observed between indicators of ALP and triglycerides in such a way that by increasing the triglyceride and ALP, FBS also increased (Table 4).

Table 4: investigating the relationship between LDL, HDL, triglycerides, cholesterol, ALT and ALP of patients with FBS indicator

Variable	HbA1c	Mean	SD	Test	Test value	Significance level
LDL	70-80	138.00	13.67	ANOVA	1.52	0.22
	81-90	136.63	12.90			
	91-100	141.01	15.27			
HDL	70-80	44.04	5.86	ANOVA	0.15	0.85
	81-90	44.06	4.91			
	91-100	43.50	7.90			
Triglyceride	70-80	165.08	21.14	ANOVA	4.84	0.009
	81-90	176.34	20.60			
	91-100	173.51	20.39			
Cholesterol	70-80	240.01	20.72	ANOVA	2.39	0.09
	81-90	233.41	25.41			
	91-100	231.25	23.05			
ALT	70-80	67.35	17.70	ANOVA	1.37	0.25
	81-90	62.48	14.72			
	91-100	66.46	18.39			
ALP	70-80	54.00	5.88	ANOVA	4.91	0.008
	81-90	58.03	7.81			
	91-100	56.01	7.36			

DISCUSSION AND CONCLUSION

The results showed that the majority of studied patients (76.7%) in the indicator of LDL were faced with suspected status and only 23.3 percent of patients were in the normal status. In the HDL indicator, the majority of investigated patients (92.8%) had suspected status and 7.2 percent of them were in normal status. In the triglyceride indicator, majority of investigated patients (98.9 %) had normal status, and 1.1 percent of them were in suspected status. In cholesterol indicator, the majority of studied patients (83.3 of percent) had suspected status and 16.7 % of them were in normal status. Hyperlipidemia is among the components of metabolic syndrome associated with fatty liver disease and appropriate treatment of hyperlipidemia diminishes the damage to liver cells in fatty liver disease. In the present study, in line with previous studies, a significant correlation was found between increased levels of triglycerides, cholesterol, and LDL and reduced HDL with non-alcoholic fatty liver disease. In a study conducted by Dr. Angelico et al in 2003 on 282 patients with sonographic evidence of NAFLD in Italy, hypertriglyceridemia, and reduced HDL were reported as the main disorder in fat profile of patients with fatty liver (12). Increased liver enzymes more than 2 times than normal level and triglyceride level over 250 milligrams per deciliter of blood are also laboratory criteria indicating the fatty liver disease severity [13].

The results showed that in the indicators related to obesity, a significant correlation was found between hip circumference of patients and LDL indicator, weight with triglyceride indicator, waist circumference, hip circumference and abdominal circumference with cholesterol indicator, and weight with triglyceride indicator. The prevalence of fatty liver in society is associated with obesity prevalence [14].

Obesity is among the major diseases associated with fatty liver. However, the increase in abdominal fat measured by waist circumference to hip circumference is more important indicator for incidence of fatty liver disease [15]. Nonalcoholic fatty liver disease is among the most common liver diseases in the world. Today, with the increasing prevalence of obesity in different societies, its prevalence is growing rapidly [16]. The prevalence of nonalcoholic fatty liver disease in obese and overweight people significantly increases and more advanced stages of this disease is seen always in people with morbid obesity [17]. In obese people, fatty tissue becomes insensitive to insulin action. As a result, excessive breakdown of triglycerides and excessive circulation of free fatty acids in extreme obesity lead to development of insulin resistance [18]. It seems that increased abdominal fat is known as central obesity and it is more important indicator for fatty liver diseases compared to total body obesity [15].

By increasing the release of glycerol and free fatty acids, increased abdominal fat cause many metabolic complications in body that insulin resistance and accumulation of fat in the liver are one of the these complications [19]. In this study, the results show a significant relationship between indicators of waist circumference, hip circumference, and fatty liver. On the other hand, many studies conducted on lifestyle changes, weight loss, and increased activity have had very clear impact on improving the condition of the liver and fatty liver retrogression [20]. Giovanni et al studies also found correlation between NAFLD and central obesity [21]. Patell et al also reported in 2014 that obesity increases the risk of fatty liver [22].

The current study showed a significant relationship between obesity, overweight, and fatty liver. In a study conducted in 2003 by Bahrami et al on 53 patients with NAFLD, the average weight of patients was more than that of control group and majority of patients had higher BMI and weight greater than 11% of their ideal weight [23]. In another study conducted on blood donors with high levels of aminotransferases in Tehran, it was found that 30 percent of patients with NAFLD had overweight and 55.7 percent of them were obese [24].

In 2008, Allard et al reported high BMI, central obesity and greater body fat percentage in patients with nonalcoholic fatty liver disease [25]. A study conducted in 2013 on 317 obese children in Iran also showed that more than half of obese children have nonalcoholic fatty liver disease [26]. In addition, in a study conducted in Italy, fatty liver was observed in 42% of patients who had high body mass index [27]. The results of this study showed a significant relationship between overweight and obesity and fatty liver disease.

It seems that visceral fat leads to fat accumulation in the liver by releasing free fatty acids and different types of adipokines. Studies conducted on waist and hip circumference to estimate abdominal fat mass confirm that there is a direct correlation between abdominal fat and liver fat content [28].

According to independent t-tests, significant relationship was found between gender and LDL indicator and its mean was greater in women than that in men. Additionally, a relationship was found between the gender and indicator of triglycerides. According to independent t-tests, significant relationship was found between gender and waist circumference and cholesterol and triglycerides. In these indicators, the obtained mean for men was significantly more than that in women. Although some studies consider prevalence of fatty liver in men and women equal [29],

fatty liver was already reported greater in women, but recent studies show higher rate of it in men. Recent demographic studies in this regard have also led to contradictory results [23]. In this study, significant difference was observed in gender of patients selected consecutively. In a study conducted on adults in Shanghai, NAFLD was significantly higher in middle-aged men than that in women, and in this study, only 10 percent of patients with fatty liver were women [30]. In the study conducted by Fan et al, 77% of patients with fatty liver were men [31].

In the age indicator, results did not show a significant relationship between age of the patients and indicators associated with fatty liver. However, with increasing age at patients, rate of indicators related to fat was also increased. In a study conducted in Golestan province in 2006, the rate of fatty liver disease of 2% in the general population was reported over 18 years [14]. Age older than 50 years, obesity, diabetes and high blood pressure are clinical signs of fatty liver disease severity [32].

The results showed that the majority of studied patients [88.9%] in the indicator of AST were faced with suspected status and only 11.1 percent of patients were in the normal status. In the ALT indicator, results showed that the majority of investigated patients [88.9%] had suspected status and 11.1 percent of them were in normal status. In addition, in the ALP indicator, majority of investigated patients [99.4 %] had suspected status, and 0.6 percent of them were in normal status.

Liver enzymes are available in liver cells, and by destruction of liver cells, they are entering to serum of patients. Their increase is sign of liver cell destruction [14]. An increase in liver enzymes ha d no direct relationship with the severity of the disease and it was observed in 50% of patients with fatty liver. In a study conducted based on liver biopsy, 58% of patients with histological evidence of hepatic steatosis had normal values of ALT and 76% of patients had normal values of AST [33]. In a study conducted by Dr. Yanjun et al 2001 in China, the most common abnormality in liver function tests have been reported increasing levels of ALT and AST [34]. In a study on 32 non-diabetic patients, Westerbaka et al showed significant positive correlation between ALT and AST serum levels and liver fat content measured by proton spectroscopy [35].

For example, a study conducted on 105 patients with high levels of liver enzyme, hepatic echogenicity showed a significant positive correlation with AST and ALT levels. In this study, ALT was associated not only with the intensity of accumulation of fat in liver, but also the association of ALT with visceral fat accumulation suggests the role of visceral fat as a predictor of higher levels of this enzyme in the liver disease [36]. In this study, to investigate factors associated with diabetes, HbA1c and FBS indicators were used. In the indicator of HbA1c, results showed that majority of patients were at the range of 3 to 5, in addition, 8.9% of them were in the range of 5 to 6. In the indicator of FBS, majority of patients [34.4%] had FBS less than 80, 32.2% of them had FBS between 81 to 90, and remaining patients had FBS higher than 90 [Table 2]. According to independent t-test and ANOVA tests, significant correlation was found between age and HbA1c and marital status, abdominal circumference and waist circumference and FBS indicator.

Several factors affect the progress of diabetes, including type and duration of diabetes, age, sex, blood sugar control, hypertension, smoking, high serum lipids and the presence of microalbuminuria [37]. In the study conducted by Dr. Abdullahi [38], diabetic men with more than 5 years of disease were at serious risk for retinopathy.

In addition, the most important cause of retinal complications was reported duration of diabetes. In the study conducted by Dr. Ashtari [39], age, duration of diabetes and nitrogen level of blood urea were reported as risk factors. In a study conducted in the United Arab Emirates, the age, male HTN and gender, type and duration of diabetes and microalbuminuria were reported as risk factors [40]. In some cases, duration of diabetes has been considered as a reflection of the way to control the blood sugar and other risk factors that the diabetic person was exposed to them during his diseases [41]. Despite improving health care in chronic diseases like diabetes mellitus, unfortunately, complications of this disease had become one of the most important health problems in society.

Based on ANOVA tests, significant relationship was found between the indicators of LDL, triglycerides, cholesterol and ALT and HbA1c level so that by increasing triglycerides, HbA1c level also increases. On the other hand, reducing HbA1c indicator had increased HDL. According to ANOVA tests, significant correlation was found between indicators of ALP and triglycerides in such a way that as triglyceride and ALP increase, FBS level also increases.

Insulin resistance that is a starting stage in creating diabetes mellitus [DM] is the base for the development of metabolic syndrome and it can have adverse effects on liver cells even before the onset of overt diabetes. Metabolic syndrome is a set of diseases of hypertension, hyperlipidemia, obesity and diabetes, and recent studies show that with increasing numbers of diseases of this syndrome, fatty liver disease severity increases.

People with diabetes or obesity have insulin resistance, which causes an increase in fatty acids in the liver. The accumulation of these substances in liver cells is destructive and can lead to death of liver cells [42].

Nonalcoholic fatty liver disease is one of the most common liver diseases in developed Western countries and Asia and it is recognized currently as the most common cause of disorder of liver tests. In recent years, due to change in lifestyle [diet, low physical activity and obesity], its prevalence is increasing [43]. Considering the great impact of obesity and type 2 diabetes in increased risk of non-alcoholic fatty liver disease, physical activity and regular exercise appropriate with age, low-fat diet, weight loss, as well as a variety of treatment methods to control diabetes and hypertension are recommended to reduce nonalcoholic fatty liver disease. Fatty liver patients, especially those with high liver enzymes, are in serious risk of development and progression of hepatic steatosis disease that this process ultimately leads to fibrosis.

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