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Correlation between Non-Alcoholic Fatty Liver Disease and Carotid Intima-Media Thickness in Patient with Type II Diabetes

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ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is a very prevalent condition determined by the infiltration of fat of liver cells. This study was conducted to evaluate the correlation between NAFLD and Carotid Intima-Media Thickness (CIMT) in patient with type II diabetes. This case-control study included three groups, including those with type II diabetes without NAFLD (n = 85), those with type II diabetes and NAFLD (n = 85) and non-diabetic individuals with only NAFLD (n = 85). The CIMT and the grading of the NAFLD were determined using an ultrasound B-mode. There was no significant difference between the case and control groups in term of overall mean of age (57±10 years vs. 56.9±8 years, respectively). Considering the two factors (diabetes and NAFLD) effect, with adjustment for age and gender as a confounding effect of diabetes ($p = 0.01$) and NAFLD ($p = 0.022$) on CIMT was significant. The mean right CIMT, left CIMT and overall CIMT in three different study groups of diabetic patients, according to various NAFLD grading showed no significant difference. Our findings showed a considerable association between NAFLD and increased CIMT, in which this association is not affected by the severity of fatty liver. So, immediate ultrasound screening and treatment for the patients with NAFLD are recommended to prevent CVD complications such as atherosclerosis considering early stages of fatty liver disease.

Key words: Atherosclerosis, carotid Arteries, diabetes mellitus, fatty liver

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a very prevalent condition determined by the infiltration of fat of liver cells (Babb, 2002; Marignani and Angeletti, 2002). NAFLD occurs in patients who do not abuse alcohol (Ables, 2012; Lewis and Mohanty, 2010; Liu *et al*., 2013; McCullough, 2002; Tilg and Moschen, 2010). The prevalence of fatty liver ranges from 14-23% of the population that reaches to 70-90% in obese and type 2 diabetic populations. The spectrum of NAFLD varies from a histological appearance similar to alcoholic hepatitis includes fatty liver alone to steatohepatitis and may progress to end-stage liver disease and cirrhosis (Younossi *et al*.,

2002). Liver biopsy is the best diagnostic test for NAFLD but medical and ethical considerations limit its use in patients (Leite *et al*., 2014). Laboratory tests results such as elevated liver enzymes are commonly found in patients with NAFLD but these tests usually have low specificity. It was reported that sonographic features unique to NAFLD are existed and used to aid in diagnosis, which made ultrasound as an accurate technique with acceptable diagnostic accuracy (Khov *et al*., 2014; Lin *et al*., 2014; Mishra and Younossi, 2007; Noureddin *et al*., 2014). Thus, NAFLD medical assessment is therefore a combination of ultrasound findings and laboratory tests.

The NAFLD is associated with several characteristics of metabolic syndrome such as obesity, type II diabetes and dyslipidemia that are known as conventional risk factors increasing Cardio-Vascular Diseases (CVD) (Ballestri *et al*., 2014; Bhatia *et al*., 2012; Brea and Puzo, 2013; Guleria *et al*., 2013; Hurjui *et al*., 2012; Mikolasevic *et al*., 2014). Besides, NAFLD are associated with risk factors known to cause atherosclerosis (National Cholesterol Education Program, 2001). Carotid Intima-Media Thickness (CIMT) has been shown to be a reliable parameter for sub-clinical atherosclerosis, a predictor of myocardial infarction and stroke (Coll and Alonso-Villaverde, 2005). Moreover, CIMT is currently a connection between NAFLD and atherosclerosis in healthy people, which reflects the contradictory effects of insulin resistance and metabolic syndrome, especially visceral fat (Aygun *et al*., 2008; Caserta *et al*., 2010; Demircioglu *et al*., 2008; Fracanzani *et al*., 2008; Pacifico *et al*., 2014).

The B-mode ultrasonography enables direct and non-invasive evaluation of atherosclerotic arterial wall. So that CIMT measured with this technique is considered as a reliable marker of atherosclerosis and shows the greater sensitivity in the early detection of atherosclerosis compared with angiography (Bots and Grobbee, 2002).

This study was conducted to evaluate the correlation between NAFLD and CIMT in patient with type II diabetes.

MATERIALS AND METHODS

Study design and population: In this case-control study, the mean CIMT in 200 patients with type II diabetes and moderate to severe NAFLD were studied by ultrasound. Patients were included three groups, including those with type II diabetes without NAFLD (n = 85), those with type II diabetes and NAFLD (n = 85) and non-diabetic individuals with only NAFLD (n = 85). This study was approved by Ahvaz Jundishapur University of Medical Sciences Ethical Committee and all participants signed informed consent prior the enrollment.

Inclusion criteria: All patients with type II diabetes and underlying liver disease (primary or secondary liver cancer, cirrhosis, hepatitis, etc.), hypertension, cardiovascular disease, treated with corticosteroids, chemotherapy and consumers of alcohol.

Exclusion conditions: Patients who have problems for abdominal ultrasonography, use steroid in diseases such as bronchial asthma, rheumatoid arthritis and Intestinal Bowel Disease (IBD) and are being treated with drugs affecting laboratory results, for example, aspirin, statins, fibrates and metformin, those who have a history of liver disorders such as HBV or HCV, infection or alcohol were excluded.

Method: Ultrasound B-mode was performed using a 7 MHz transducer device GE in the common carotid artery, internal carotid and carotid bulb in each group. Demographic characteristics, including age, gender, ethnicity, marital status, smoking or passive smoking and alcohol consumption were also collected. Blood pressure was measured in two stages, with an interval of

half an hour by a mercury sphygmomanometer. Height and weight, Waist-to-Hip Ratio (WHR) were measured, as well as a series of laboratory tests, including blood samples for glucose and liver enzymes, HDL, LDL, fasting triglycerides, total cholesterol, ALP, ALT and AST was done. The diagnosis of NAFLD was based on two criteria: (1) The existence of NAFLD or steatohepatitis and (2) The non-alcoholic nature of the illness.

Liver echogenicity and size were evaluated using a 3.5 MHz transducer to determine the presence of fatty liver. The grading was done according to these criteria: grade 1 (mild), which is a slight increase in ultrasound liver echogenicity, while diaphragm and intrahepatic vessels are well visible, grade 2 (moderate), a moderate increase in liver echogenicity on ultrasound, with impaired visualization in the diaphragm and intrahepatic vessels, grade 3 (severe) a considerable increase in liver echogenicity on ultrasound, while the diaphragm, the marginal artery and the posterior portion of the right lobe of the intrahepatic vessels difficult to see or not visible at all. To measure the mean CIMT a 7.5 MHZ probe in the right common carotid artery, proximal to the bulb, on the posterior wall, was used.

Statistical analysis: After collecting the data, SPSS 15.0 statistical software was used for descriptive statistics (mean, standard deviation). Analysis of Variance (ANOVA), Chi-square test and t-test (independent t-test), were used.

RESULTS

There was no significant difference between the case and control groups in term of overall mean of age (57±10 years vs. 56.9±8 years, respectively). Baseline characteristics of four study groups are presented in Table 1.

Considering the two factors (diabetes and NAFLD) effect, with adjustment for age and gender as a confounding effect of diabetes ($p = 0.01$) and NAFLD ($p = 0.022$) on CIMT was significant. Based on the results people who have both diabetes and NAFLD had higher mean CIMT (Fig. 1).

There was no significant difference in right CIMT, left CIMT and CIMT of both groups of diabetic patients with NAFLD and without NAFLD (Table 2).

Table 1: Baseline characteristics of four study groups

Parameters	Diabetes	Diabetes and fatty liver	Normal	Fatty liver	Total	Chi-square	p-value
Sex							
Female	40 (47.1)	62 (72.9)	30 (54.5)	14 (46.7)	146 (57.3)	13.70	0.003
Male	45 (52.9)	23 (27.1)	25 (45.5)	16 (53.3)	109 (42.7)		
Age							
20-29	0 (0)	1 (1.2)	8 (14.5)	2 (6.7)	11 (4.3)	155.32	<0.001
30-39	7 (8.2)	3 (3.5)	26 (47.3)	12 (40)	48 (18.8)		
30-49	9 (10.6)	16 (18.8)	21 (38.2)	16 (53.3)	62 (24.3)		
>50	69 (81.2)	65 (76.5)	0 (0)	0 (0)	134 (52.5)		
Plaque							
yes	73 (85.9)	79 (92.9)	55 (100)	30 (100)	237 (92.9)	12.91	0.005
No	12. (14.1)	6 (7.1)	0 (0)	0 (0)	18 (7.1)		

Table 2: Relationship between NAFLD with right CIMT, left CIMT and CIMT in patients with type II diabetes by adjusting the effects of gender and weight

Groups	RIMT	LIMT	IMT
Case			
Mean	0.60060	0.64350	0.62190
Std. Deviation	0.13104	0.14939	0.12650
Control			
Mean	0.59530	0.62000	0.60760
Std. Deviation	0.12715	0.14541	0.12308
p-value	0.15100	0.19400	0.13000

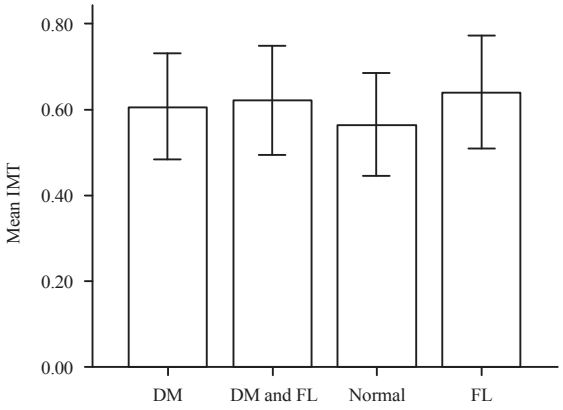

Fig. 1: Comparison of carotid intima-media thickness among study groups (0.6076 ±0.12 in diabetic group, 0.6219±0.13 in diabetic with NAFLD group, 0.6423±0.13 in NAFLD group, 0.5647±0.12 in normal control)

Table 3: Comparison of carotid intima-media thickness among patients with non-alcoholic fatty liver according to ultrasonographic grading

Grade of fatty liver	N	Mean	Std. deviation	p-value
Right CIMT				
1	55	0.6409	0.15819	0.651
2	23	0.6587	0.14511	
3	7	0.6143	0.08997	
Left CIMT				
1	55	0.6045	0.13887	0.775
2	23	0.6000	0.12060	
3	7	0.5714	0.11127	
Overall CIMT				
1	55	0.6225	0.13274	0.804
2	23	0.6291	0.12584	
3	7	0.5929	0.07868	

Table 4: Association between gender and only left CIMT and overall CIMT in type II diabetic patients with NAFLD and type II diabetic subjects without NAFLD

Groups	Sex	RIMT	LIMT	IMT
Case				
Female	Mean	0.5855	0.61850	0.60190
	Std. Deviation	0.11713	0.13742	0.11457
Male	Mean	0.6413	0.71090	0.67570
	Std. Deviation	0.15858	0.16234	0.14336
p-value		0.159	0.01400	0.03400
Control				
Female	Mean	0.5950	0.62750	0.61130
	Std. Deviation	0.13388	0.15687	0.13563
Male	Mean	0.5956	0.61330	0.60440
	Std. Deviation	0.12239	0.13585	0.11222
p-value		0.682	0.927	0.70400

The mean right CIMT, left CIMT and overall CIMT in three different study groups of diabetic patients according to various NAFLD grading showed no significant difference, so none of the indicators are related to the severity of liver disease in patients with type II diabetes (Table 3).

There was a significant association between gender and only left CIMT and overall CIMT in type II diabetic patients with NAFLD ($p<0.05$), but, no significant association was observed in type II diabetic subjects without NAFLD ($p>0.05$) (Table 4).

DISCUSSION

In this study, CIMT in type II diabetic patients with NAFLD was compared with control, which showed that mean CIMT was significantly much more than the control group. The results of our study are consistent with results of previous studies that are considered CIMT was associated with an increase in NAFLD and suggested it as the marker of early diagnosis of generalized atherosclerosis (Chiang *et al*., 2010; Guleria *et al*., 2013; Targher and Arcaro, 2007; Targher *et al*., 2008). This actually means that type II diabetic patients with NAFLD are at greater risk of premature atherosclerosis and Coronary Vessels Disease (CVD). As we stated before ultrasound screening method is a cheap and readily available. NAFLD estimates for up to one third of the total population and in the majority of patients with cardiovascular, metabolic and abdominal obesity, type II diabetes risk factors, can be seen.

Our findings revealed that the diabetes and NAFLD effect, with adjustment for age and gender, on CIMT was significant. In agreement with this finding, De Andrade *et al*. (2014) measured CIMT in a cross-sectional study on diabetes patients and showed that CIMD and CVD risk may be higher in those with a family history of type II diabetes. Besides, Nahandi *et al*. (2014) evaluated the effect of NAFLD on CIMT as a risk factor for atherosclerosis in patients with type II diabetes and reported that there is a significant association between the presence of NAFLD and CIMT and its related atherosclerosis.

Also we noticed that, there was a significant association between gender and only left CIMT and overall CIMT in type II diabetic patients with NAFLD. Similarly, Mohammadi *et al*. (2011) examined patients with confirmed NAFLD for determination of CIMT and presence of carotid atherosclerotic plaque and reported that NAFLD with type II diabetes can be associated with increased CIMT and increased risk of atherosclerosis. Moreover, Han *et al*. (2013) studied gender differences in the association between CIMT in healthy individuals and age-related increases in CIMT were correlated with a reduction in cardiac function only in women.

Our findings showed a considerable association between NAFLD and increased CIMT, in which this association is not affected by the severity of fatty liver. So, immediate ultrasound screening and treatment for the patients with NAFLD are recommended to prevent CVD complications such as atherosclerosis considering early stages of fatty liver disease.

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