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Sonographic Evaluation of Mean Carotid Intima-Media Thickness of Patients with Moderate to Severe Non-Alcoholic Fatty Liver Disease

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Abstract

***Background*:** Nonalcoholic fatty liver disease is a highly prevalent condition that is strongly associated with obesity, type II diabetes, and dyslipidemia. The purpose of this study is to investigate mean common carotid artery intima-media thickness as a marker of atherosclerosis in moderate to severe nonalcoholic fatty liver patients in comparison with control group.

***Materials and Methods*:** In this study, the mean common carotid artery intima-media thickness (CCIMT) and other cardiovascular risk factors were measured in 39 nonalcoholic fatty liver patients and 39 control subjects. All were selected from general population in Zahedan. Then, the data were analyzed using χ^2 and independent *t*-tests.

***Results*:** The results showed that nonalcoholic fatty liver patients had significantly higher common carotid intima-media thickness, waist circumference, waist/hip ratio, body mass index, triglyceride, total cholesterol (p=0.001), ALT (p=0.04), ALP (p=0.048), compared with the control group.

***Conclusion*:** Nonalcoholic fatty acid liver patients are at significantly higher risk for atherosclerosis and cardiovascular diseases. Therefore, all of these patients should be evaluated for common carotid intima-media thickness and other cardiovascular risk factors.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent condition which is characterized by fatty infiltration of liver cells resembling that of alcohol-induced liver injury but occuring in patients who do not abuse alcohol [1]. The incidence of fatty liver is estimated at 14-23%. This figure is 70-90% in obese and type II diabetic people [2].

The spectrum of NAFLD ranges from fatty liver alone to steatohepatitis, which histologically is similar to alcoholic hepatitis, and may progress to end-stage liver disease and cirrhosis. That is why the fatty liver, long considered an incidental finding, has received increasing attention [3].

In terms of diagnosis, liver biopsy is the best NAFLD diagnostic test, but ethical and medical considerations may limit its use in patients [4]. Increased levels of liver enzymes is commonly observed in these patients, but these tests have low specificity. Therefore, clinical evaluation of NAFLD is usually based on a combination of ultrasonic findings and laboratory tests. The previous studies have shown that ultrasonographic results are well correlated with histological findings due to fatty infiltration [4, 5]. Therefore, ultrasonography alone can indicate the level of fatty infiltration in liver. On the other hand, NAFLD is strongly associated with obesity, type II diabetes, and dyslipidemia. In addition, the majority of these patients have central obesity and insulin resistance symptoms. Consequently, NAFLD shares many features of the metabolic syndrome, which is a highly atherogenic condition, and its presence is associated with marked cardiovascular risk [1].

It has been shown that intima-media thickness (IMT) of carotid artery, as a reliable index of subclinical atherosclerosis, is a predictor of myocardial infarction and stroke. Recently, a relationship between nonalcoholic fatty liver and atherosclerosis has been reported in healthy men, reflecting the contradictory effects of metabolic syndrome especially insulin resistance and increased visceral fat [6, 7].

In order to investigate atherosclerosis, B-mode ultrasounography enables non-invasive, direct vitalization of the arterial wall. The carotid intima-media thickness (CIMT) quantified using this technique is a reliable marker of atherosclerosis burden. Furthermore, it demonstrates greater sensitivity in detection of early atherosclerosis compared with angiography [8].

In cross-sectional studies, carotid atherosclerosis was observed in NAFLD patients. In addition, the relationship between IMT and severe liver injury has recently been recognized [9]. The results from a cohort of patients with NAFD, followed for up to 18 years, showed that mortality rates from coronary heart disease (CHD) equaled those attributable to cirrhosis [1].

Therefore, regarding the high prevalence of fatty liver in the society and the possibility of easy and noninvasive diagnosis of it by using ultrasound, the aim of this study is to investigate ultrasonic CIMT compared with control group, which is a non-invasive marker for atherosclerosis and cardiovascular risk of non-alcoholic fatty liver.

Materials and Methods

In this case-control study, mean CIMT of 78 subjects, divided into two groups, one with sonographically moderate to severe degree of fatty liver subjects and the other with non-fatty liver controls. The study population was chosen from people over 25 years old within Zahedan city. In addition, age and sex-matched controls were selected from the same area. These people underwent ultrasound examination of the liver, using Aloka SSD-3500 ProSound, and right common carotid artery intima-media thickness evaluation, by only one ultrasonologist.

All the subjects signed informed consent before inclusion of them into the study. Demographic information of all subjects including age, gender, ethnicity, marital status, smoking or passive smoking, and alcohol consumption were recorded. Moreover, blood pressure measurements were carried out in two time intervals of 30 minutes, using mercury thermometer. Height and weight (to calculate body mass index), waist circumference at the midpoint between the lowest rib cage and the iliac crest post-exhalation, hip circumference at the widest point between hip and bottom, and waist/hip ratio were measured. In addition, a series of examinations including fasting venous blood glucose samples, triglycerides, total cholesterol, HDL, LDL, and liver enzymes such as AST, ALT, and ALP were carried out by accredited laboratories.

Ineligible people for inclusion were: 1) those with a history of known liver disease, 2) those who consume more than 20 g alcohol daily or abuse alcohol, and 3) those with ultrasonic-proven liver disease other than fatty liver.

Non-alcoholic fatty liver diagnosis depends on two factors: 1) proof of fatty liver or steato-hepatitis presence, and 2) proof of non-alcoholic nature of the disease.

The definitive diagnosis of fatty liver is based on histologic examination of liver biopsy samples. However, ethical considerations as well as inherent risks associated with this procedure limit its widespread applicability as a screening method. In terms of laboratory parameters, increased liver enzyme levels are seen frequently in patients with fatty liver, but these tests have low specificity [4].

Radiological imaging with ultrasonography, CT scan, and MRI, alone or together, have adequate threshold for diagnosis of fatty infiltration of liver. Ultrasonography is the most accessible and cheapest of these methods [10].

Abdominal ultrasonic criterion for fatty liver was set based on literature and examination with 3.5 MHz probe as follow [11]:

-Grade I (mild) is slight increase in liver echogenicity, but normally visualized diaphragram and intrahepatic vessels.

-Grade II moderate increase in liver echogenicity with slight impairment of visualization of the intrahepatic vessels.

-Grade III marked increase in liver echogenicity with poor or no visualization of the diaphragm, intrahepatic vessels, and posterior part of the right lobe of the liver.

In order to calculate mean CIMT using 7.5-MHz ultrasound probe, mean IMT in the right common carotid artery, proximal to the bulb and the wall of the artery distal to the probe, was measured (Fig. 1). Then, these two groups were analyzed using SPSS-16, independent *t*-test, and χ^2 test.

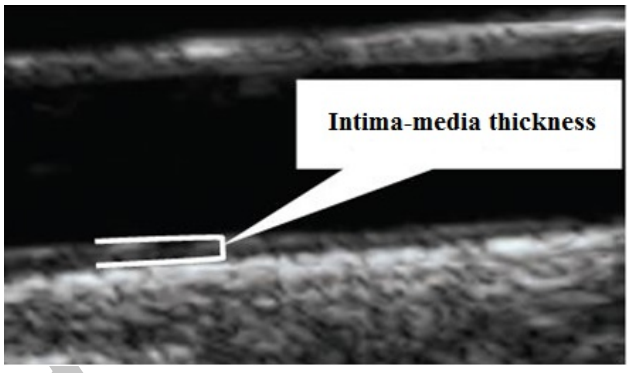

Figure 1. Carotid artery intima-media thickness measurement

Results

In this study, 39 patients with moderate to severe fatty liver disease and 39 age and sex matched healthy controls were investigated. Forty six percent of the subjects were men and 54% were women, and mean age of fatty liver group (57±10) was almost equal with that of control group (57±8) (Table 1).

In fatty liver and control groups, 5 and 3% of the subjects were, in turn, smoker, and 17 and 8% were passive smoker, respectively, indicating no significant difference between two groups. With respect to carotid intima-media thickness, IMT was 0.74±0.14 and 0.53±0.1 mm in fatty liver and control groups, respectively, showing a significant difference (p=0.001). That is, fatty liver group had significantly higher IMT than control group. Regarding other clinical variables, following results were obtained: Fatty liver group had significantly higher BMI than control group (30.7±5.7 versus 25.7±4.3; p=0.001); significant differences (p=0.001) were observed regarding waist circumference and waist/hip ratio between fatty liver and control groups (103±11 versus 89±10, and 0.93±0.04 versus 0.88±0.04, respectively).

However, no difference was observed between the groups with respect to systolic and diastolic blood pressure, ethnicity, and marital status variables. Regarding systolic and diastolic blood pressure, no difference was observed between fatty liver and control groups (138±30 versus 84±12 mmHg, and 138±17 versus 80±8 mmHg, respectively). In terms of ethnicity, no significant difference was observed between fatty liver and control groups (20 versus 22 Iranian, and 10 versus 17 Afghans). All subjects, except one in the control

group, were married. In terms of laboratory analysis, despite higher levels of fasting blood glucose and AST in fatty liver group than control group (105±38 versus 97±44 mg/dL, and 28±18 versus 24±10 IU/L, respectively), the differences were not statistically significant.

However, the levels of total cholesterol, triglycerides, ALT, and ALP were significantly higher in fatty liver group (207±47 versus 174±38 mg/DL, p=0.001; 190±105 versus 111±52 mg/dL, p=0.001; 36±26 versus 26±15 IU/L, p=0.04; and 244±78 versus 214±51 IU/L, p=0.048)

Discussion

In this study, we compared carotid intima-media thickness (IMT) in patients with moderate to severe fatty liver and control group. According to the results, the level of IMT was significantly higher in fatty liver group. This is in consistent with studies which associate NAFLD with increased IMT, indicating early generalized atherosclerosis [12-14]. In fact, these patients are at higher risk for early atherosclerosis, and also at higher risk for cardiovascular complications.

As mentioned earlier, ultrasound is a cost-efficient and easily accessible method of screening. Regarding that diagnosis of mild fatty disease (grade I) requires more skill and experience, and there might be more disagreement in reporting grade I of fatty liver [15], therefore in this study moderate and severe fatty liver cases (grade II and III) were included in fatty liver group.

Non-alcoholic fatty liver disease is presented in up to one-third of the general population and is observed in the majority of patients with cardio-metabolic risk factors such as abdominal obesity, type II diabetes, and other metabolic syndrome (MetS) components. Currently, the importance of NAFLD and its relationship with MetS is being increasingly recognized, and this has got increased attention to the possible role of NAFLD in developing cardiovascular diseases [12].

Additionally, we know that metabolic syndrome includes a group of risk factors such as: abdominal obesity, dyslipidemia, high blood pressure, insulin resistance or glucose intolerance, prothrombotic condition or proinflammatory states.

According to the obtained results, waist circumference, waist/hip ratio, BMI, triglyceride, and total cholesterol values were significantly higher in fatty liver group. In addition, a significant difference was observed in ALT and ALP values between two groups. In this regard, higher value of ALT, in particular, can indicate a liver inflammatory process in NAFLD. However the mean diastolic blood pressure and fasting glucose were higher in the control group, but the difference was not significant.

Therefore, in investigating comorbidities in these patients, regarding the higher ratio of WHR in fatty liver group, more incidence of central obesity is observed. In addition, regarding higher lipid profile, i.e. triglyceride and total cholesterol, these patients are at higher risk for cardiovascular diseases. However, no significant difference was seen between two groups in terms of blood pressure or diabetes. That is, regarding the easy diagnosis of fatty liver by ultrasound examination, and its relationship with some of the metabolic syndrome components such as central obesity, triglyceride, and high cholesterol, it is necessary to examine the patients with fatty liver for carotid IMT and other metabolic syndrome components. So, early diagnosis and treatment can prevent its cardiovascular complications.

Based on this study, the researchers recommend evaluation of carotid artery IMT as a part of normal examination routine in NAFLD patients or those with metabolic syndrome symptoms.

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Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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