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Association between Non-Alcoholic Fatty Liver Disease and Carotid Intima-Media Thickness in Overweight and Obese Children

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ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is the most prevalent diagnosed liver disease in developed societies, which is known as a disorder in liver function. In this regard, the measurement of the thickness of carotid intima-media layer is the most important marker for measuring atherosclerosis. The aim of this study was to investigate the relationship between non-alcoholic fatty liver and thickness of carotid artery in children and adolescents with overweight and obesity. This study was conducted as sectional and case control study in children between the ages 6-13 with overweight and obesity in Tehran, who were not suffering from other liver and kidney diseases. The presence or absence of fatty liver disease was diagnosed in patients under ultrasound imaging. After implementing ultrasonography, the samples were divided into two groups: fatty liver (n=126) and non-fatty liver (n=232). Using ultrasound test, the thickness of the carotid artery layer was measured. Cholesterol, triglyceride, LDL-C and HDL-C levels were measured in mg/dL based on blood tests. Systolic and diastolic blood pressure was also measured and recorded. The mean weight, the measure of waist circumference, body mass index, body fat percentage, FFM value, insulin levels and blood glucose levels in the patients group were significantly higher than those of healthy participants (P< 0.05). Also, the mean of high dense lipoprotein (HDL) was significantly lower in patients than in healthy participants. The presence of systolic blood pressure in patients with fatty liver was lower than healthy participants and diastolic blood pressure in patients with fatty liver was lower than in healthy participants. These differences were not statistically significant. There were also significant correlations between fatty liver and overweight. However, our results failed to confirm the association between fatty liver disease and carotid artery thickness increase in adolescents. There was a relationship between fatty liver disease and carotid artery thickness increase in adolescents, but other metabolic disorders may be effective in relation between fatty liver and atherosclerosis.

Key words: Non-Alcoholic Fatty Liver, Carotid Artery Thickness, Obesity

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INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is characterized by fat accumulation in the liver parashism tissue of more than 5% of the liver's weight in patients who have no history of alcohol consumption. NAFLD includes a wide range of disorders from liver steatosis to cirrhosis [1]. The disease is associated with a wide range of metabolic abnormalities including abdominal obesity, type 2 diabetes, dyslipidemia, high blood pressure and metabolic syndrome [2, 3]. The prevalence of non-alcoholic fatty liver has been increasing sharply over the last decade, and in fat adults, 80-90% in patients with insulin resistance is estimated to be 30-35% and in hyperlipidemia patients are 90% [4]. Evidence suggests that the environmental context of the advancement and

development of the NAFLD dates back to the early years of life, and the main source of fatty liver is formed in childhood [5]. The prevalence of NAFLD in children in a recent meta-analysis study was 6.7% and in obese children was estimated to be 34.2% [6]. Recently, studies of NAFLD relationship with carotid artery atherosclerosis have been investigated using Intima-media thickness (CIMT) of carotid artery [7-12]. cIMT is a well-known marker for primary atherosclerosis and its progression, and is an indicator for predicting cardiovascular disease [13]. Recently, the association of non-alcoholic fatty liver with cIMT was investigated in a meta-analysis study in two groups of studies whose target population was adults and children, and in both populations of NAFLD patients were significantly at higher risk of cIMT [9]. Although in the past, in Iran, the relationship between non-alcoholic fatty liver and cIMT was investigated in a limited study and there was a direct relationship between the two [14]. However, adequate studies in this regard have not been conducted for Iranian children. Considering the high prevalence of obesity and overweight and subsequently non-alcoholic fatty liver in society, especially in the population of children and adolescents, on the one hand, and on the other hand, the high importance of cardiovascular disease as the first cause of death in the world and entered the high cost that due to young people's disability on the community and the high cost of treatment for the health care system requires that the association of chronic diseases, such as NAFLD with atherosclerosis at an early age be investigated so that, if necessary, basic preventive measures It is thought to be effective in developing cardiovascular disease. The aim of this study was to investigate the relationship between NAFLD and cIMT in children and adolescents with overweight and obesity.

MATERIALS AND METHODS

This study was a sectional case-control study on 378 overweight and obese students aged 6-13 years in Tehran who had not had other liver and kidney diseases was conducted from June 2016 to March 2017.

After approval of the study at the ethics committee of the Shahid Beheshti University of Tehran (code of ethics: IR.SBMU.MSP.REC.1397.27), the goals and details of the plan were explained to the participants in the study and their parents, if they had a desire to participate in this research, the informed consent letter for participation in the project was completed by their parents. The considerable data were collected by a multidisciplinary questionnaire. The first part of the questionnaire included demographic data (age, sex, history of non-alcoholic fatty liver disease) and lifestyle related behaviors (physical activity, personal health, nutritional status), and the second part related to anthropometric measurements physical activity, puberty status, non-alcoholic fatty liver, thickness of intima in the medium of carotid artery, total cholesterol, LDL-C, HDL-C, triglyceride.

B-mode ultrasonography was used to determine the status of the liver in terms of fatty and non-fatty, as well as to determine the thickness of the carotid arterial artery. The ultrasound apparatus used in this study was UGEO WS80A, Medison. All ultrasound images were recorded by a technician. The device technician had no medical history or blood test results. Participants were placed in a sleepy, comfortable position for the study of double-edged cervical extrarenal carotid ultrasonography. The thickness of the antiemetic carotid artery in the distal part of the right and left joint carotid artery was calculated from the proximity of the site of its expansion. In participants with diagnosis of fatty liver, the degree of fatty liver was determined by the value of liver ecogeneticity in ultrasonography as fatty liver of 1st degree and fatty liver of 2nd degree.

Cholesterol, triglyceride, LDL-C and HDL-C levels were measured in mg/dL, with the help of the blood tests. Systolic and diastolic blood pressure of individuals were measured a mercury sphygmomanometer. The blood pressure of each person was measured 3 times and the mean was reported as blood pressure.

Individual height and weight were measured and outpatient and their BMI were calculated. As the samples were children and adolescents with overweight and obesity, all participants were given lifestyle modification recommendations.

Statistical analysis

Frequency distribution and mean ± SD were reported based on the type of variable. Chi-Square test was used to compare qualitative variables among non-alcoholic fatty liver and healthy subjects. Independent paired t-test was used for comparing the mean of quantitative variables between the two groups. For determining the

relationship between non-alcoholic liver and intima thickness in carotid artery mediation, a regression test will be used for modifying the confounding factors. Data analysis was performed in SPSS 20. In this study, P-value less than 0.05 was considered as a statistically significant level.

RESULTS

After sonography, out of 378 children, 20 were excluded from the study. Among them, 126 cases were diagnosed with fatty liver disease and 232 were not ill. In the group of patients with fatty liver, 102 cases were grade I and 14 cases were grade II fatty livers.

The mean age of the patients was 9.56±1.81 and the normal group was 9.18±1.72, with no significant differences between the two groups (P=0.054).

The mean weight of the patients in the group was 50.45±13.77 kg, which was significantly higher than the weight of healthy subjects (43.74±10.48 kg) (P<0.0001). Additionally, the mean height of the group was 142.36 ± 11.03 cm higher than the mean height of the healthy group with 138.11 ± 10.69 cm (P<0.0001). Mean BMI was significantly higher in patients with 24.47±3.72 compared to healthy subjects with 22.60±2.75 (P<0.0001). The average body fat percentage in patients was 28.58±7.04, significantly higher than that of the healthy subjects (24.92±5.87), and this had statistically significant differences (P<0.0001). The mean FFM in healthy subjects was 29.94 ± 6.63 and in patients was 31.93±7.75, which showed a significant difference (P=0.011). The mean of vitamin D in patients was 15.44 ± 9.08 and in healthy subjects was 13.59±9.22, which was not statistically significant (P=0.071). However, the mean LN_VitD in patients with 2.57±0.59 that was significantly higher than healthy subjects (2.42±0.61) (P=0.024).

The mean of parathyroid hormone levels in the healthy group was 51.69±41.31 with a significant difference with the patient group 32.71± 46.76 (P=0.24). Similarly, the mean Ln_PTH in the two groups did not differ significantly (3.65±0.64 in healthy subjects versus 3.65±0.64 in the patient group). The mean of alkaline phosphatase enzyme in the patient group was not significantly different (P<0.05) different from that of healthy subjects (704.83±225.92) with healthy subjects (705.04±205.56). Mean HDL was significantly lower in patients (46.98 ±11.19) than that of healthy subjects (50.90±11.79) (P=0.002). However, there was no significant difference between mean lipoprotein cholesterol (LDL) and healthy subjects (95.37±24.60) and patients (27.45±100.25) (P=0.88). The mean of triglyceride in patients, 125.82 ±61.82, was significantly higher than healthy subjects (111.85±56.22) (P=0.031). The mean of blood sugar (FBS) in healthy subjects was 89.40 ± 89.80 and was significantly lower than the case group (92.07±9.07) (P=0.029). There was no significant difference between the mean cholesterol (172.39±32.32) and healthy subjects (169.87±35.12) (P=0.506). The mean of insulin in the body of the patients was 17.56±10.11, significantly higher than normal subjects (12.89±7.25) (P <0.0001). The mean of homa_ir in patients with a mean of 4.06±2.53 was significantly more than in healthy subjects 2.90±1.76 (P<0.0001). Additionally, the mean waist circumference of the patients in the group of patients was 84.35 ± 10.18 cm and was significantly higher than the healthy subjects (78.65±8.27) (P<0.0001). There was no significant difference between the mean systolic blood pressure (sbp) in the patients in the group 105.28±13.25 and in the healthy subjects 104.39±13.33 (P = 0.54). Moreover, there was no significant difference between the mean diastolic blood pressure (dBP) in the group of patients and the mean age of patients was 64.4 ± 8.47 and healthy subjects was 65.74 ± 9.29 (P = 0.241). The results of the relationship between the association of fatty liver with sex, vitamin D levels, Gr_VitD_20, Gr_VitD_8, Gr_VitD_10, Gr_VitD_15, Gr_VitD_30, high triglycerides, high HDL, high blood glucose, blood pressure, waist circumference, TV viewing; the carotid artery thickness are shown in Table 1-3.

Based on the results in Table 1 and 3, there was no correlation between fatty liver and sex (P = 0.124), vitamin D (P=0.74), Gr_VitD_20 (P=0.605), Gr_VitD_8 (P=0.328), Gr_VitD_10 (P=0.298), Gr_VitD_30 (P=0.55), high FBS (P=0.418), blood pressure (P=0.297), high WC (P=0.56) and thickness of right and left carotid artery (P=0.288, P=0.920).

Against, direct correlation was reported between the risk of fatty liver and obesity (P=0.03), Gr_VitD_15 (P=0.012), HDL (P=0.007) and watching TV (P=0.009) (Table 2).

Table 1: The factors which are not correlated with fatty liver

Group / Variables		Patients	Healthy people	P-Value
Gender	Girl	55	121	0.124
	Boy	71	111	
Gr_VitD_20	< 20	26	43	0.605
	≥ 20	99	189	
Gr_VitD_8	< 8	100	175	0.328
	≥ 8	25	57	
Gr_VitD_10	< 10	84	143	0.298
	≥ 10	41	89	
Gr_VitD_30	< 30	9	13	0.55
	≥ 30	116	219	
Triglyceride	Low & Normal	136	96	0.075
	High	61	64	
FBS	Low & Normal	102	197	0.418
	High	23	35	
BP	Low & Normal	102	173	0.217
	High	24	57	
WC	Low & Normal	5	20	0.106
	High	117	208	
Vit D	< 10	41	89	0.74
	10-20	58	100	
	20-30	17	30	
	≥ 30	9	13	

Table 2: Factors associated with fatty liver

Group / Variables		Patients	Healthy people	P-Value
HDL	Low & Normal	90	195	0.007
	High	35	37	
Weight	Overweight	31	83	0.03
	Obesity	95	149	
Gr_VitD_15	< 15	56	73	0.012
	≥ 15	69	159	
TV viewing (hours)	≤ 1	14	34	0.009
	2-3	38	102	
	≥ 4	70	92	

Table 3: The correlation between carotid artery thickness and fatty liver

Carotid artery thickness	Group	Mean±SD	P-value
Right	Healthy	0.3995±0.05841	0.288
	Patient	0.4063±0.0565	
Left	Healthy	0.4116±0.06021	0.920
	Patient	0.411±0.5826	

DISCUSSION

Based on reports of diagnostic ultrasound and because of lifestyle changes and prevalence of obesity in industrialized countries, the prevalence of fatty liver disease is reported between 20% and 60% and is increasing [15]. According to the results, the risk of fatty liver was significantly affected by weight, height and BMD of patients. In Addition, several studies demonstrated that some factors such as WC, BMD, FBS and insulin levels in patients with fatty liver were higher and they may be able to predict fatty liver [16-19]. In this regard, a combination of educational, behavioral and motivational strategies to change the lifestyle of patients is essential, which requires a team of psychologists, nutritionists and sports professionals. Increased levels of liver enzymes are associated with obesity, especially central obesity, metabolic syndrome indicators and type 2 diabetes [20]. Along with obesity and liver enzymes, liver ultrasound is an appropriate and non-invasive method for detecting non-alcoholic fatty liver among young people. Despite results of many studies, the results of present study, showed no significant difference in the thickness of carotid artery between healthy and fatty liver adolescents, similar to study of Manco et al. (2010) [21]. In another study, Fracanzani et al. (2009) showed that patients with fatty liver had lower levels of HDL and higher levels of triglyceride, glucose, and insulin resistance than healthy people [22]. In the study of Targher et al. (2004), the thickness of intima-media layer of the carotid artery with degree of steatosis was associated with inflammation rate and fibrosis in patients with fatty liver [23]. Fakharian et al. (2017) observed that the mean carotid intima-media thickness in left and right side was different in patients with fatty liver compared to healthy people [24]. Caserta et al. (2010) showed that individuals with non-alcoholic fatty liver had more atherosclerotic changes and an increase in carotid intima-media thickness compared to healthy people [25]. In a cross-sectional study, Kim et al. (2004) found that an increase in carotid intima-media thickness occurs in patients who have metabolic syndrome in addition to fatty liver [7]. According to the results of this study about the absence of a strong correlation between increased carotid artery thickness and fatty liver disease, the carotid intima-media thickness may not be able to reflect all the risk factors for cardiovascular disease [26]. On the other hand, the carotid artery thickness of children is affected by fatty liver disease when they have this disease for a long time. Several studies have shown that increasing the thickness of 0.1 mm can occur after 20 years due to liver disease and other side effects [27, 28]. In addition, genetic factors such as lipoprotein polymorphism and environmental factors, especially diet, may affect the association between fatty liver and increasing the carotid intima-media thickness and the risk of cardiovascular disease. Treatment of non-alcoholic fatty liver is considered to reduce

the risk of cardiovascular disease. In this context, changing lifestyle habits (nutritional interventions, exercise and physical activity) are the most effective approaches to treating these diseases [5].

CONCLUSION

The results of this study showed no significant relationship between fatty liver disease and increased carotid artery thickness in adolescents, and they suggested that other metabolic disorders may be effective in establishing a relationship between fatty liver and atherosclerosis.

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