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The Relationship Between Non-Alcoholic Fatty Liver Disease and Metabolic Syndrome in Children

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Abstract

Background: With respect to the increased prevalence of fatty liver and its development at young age in the Iranian population, as well as the importance of prevention and control of its related factors, the current study aimed to explore the relationship between fatty liver and metabolic syndrome in 6-18-year-old children in Birjand, Iran.

Methods: In this case-control study, thirty 6 - 18-year-old children and adolescents with metabolic syndrome were selected based on Adult Treatment Panel (ATP) III criteria by convenience sampling. Then, 46 children and adolescents not affected by this disease with the same gender and age were selected as the control group. Weight, height, waist circumference, and blood pressure of the participants were measured and recorded, and blood sugar tests, blood lipid profile (triglycerides, cholesterol, high density lipoprotein (HDL) and liver enzymes alanine aminotransferase (SGPT) and aspartate aminotransferase (SGOT) were performed. Data were analyzed by SPSS software using Chi-square test, independent T-test and logistic regression analysis at the significant level of $P < 0.05$.

Results: The mean age in the case and control groups were 13.17 ± 1.64 and 12.46 ± 2.27 years, respectively ($P = 0.14$). The relative frequency of fatty liver in the case group (86.7%) was higher than that of the control group (28.3%) ($P < 0.001$), and the chance of developing non-alcoholic fatty liver disease (NAFLD) in patients with metabolic syndrome was 5.38 times greater than healthy people. The results showed a significant relationship between gender, body mass index (BMI) and triglyceride (TG) levels and fatty liver among the participants ($P < 0.05$).

Conclusions: According to the results of the current study, it is recommended to develop some programs to modify the lifestyle and encourage children and adolescents by schools, the media and parents to keep fit.

Keywords: Fatty Liver, Metabolic Syndrome, Obesity, Children

1. Background

Fatty liver is the most important disease of the liver cells and a reversible disease created by accumulation of large amounts of fat (triglycerides) in liver cells. In fatty liver, fat constitutes more than 5% of the liver weight (1). The disease is often silent, sometimes presents elevated liver enzymes, which in the absence of early diagnosis and appropriate treatment can lead to cirrhosis (2). Fatty liver is the most common chronic liver disease in obese children (3), the prevalence of which is reported from 42.6% to 77.1% in various studies (4, 5) as well as 54.4% in the study by Adibi et al. on children with obesity in Isfahan, Iran (6).

Factors such as obesity, resistance to insulin, hyperlipidemia, hypertension, cardiovascular diseases (7, 8), age (9), genetic factors (10) and using some drugs can contribute to the development of fatty liver.

Given the increasing prevalence of overweight and obesity in children, the liver dysfunctions caused by it are a public health threat in society and attracted special attention. The adverse effects of overweight and obesity in childhood or adolescence may manifest themselves more apparently in the physical, metabolic, psychological or even economic conditions (11). In addition, obesity can be the cause of conditions such as insulin resistance, abnormal levels of blood lipid (increased triglycerides and decreased high-density lipoprotein) and high blood pressure. The term metabolic syndrome refers to the simultaneous existence of these diseases and people with metabolic syndrome are at a greater risk of developing cardiovascular diseases, type 2 diabetes, cancer and fatty liver (12).

Metabolic syndrome refers to a set of metabolic disorders including abdominal obesity, impaired glucose homeostasis, lipid disorders and high blood pressure (13). Metabolic syndrome in children and adolescents is increasing due to the progressive increase in the prevalence of obesity and overweight (14).

According to the national health and nutritional examination survey (NHANES) III criteria, about 25% of American adults and 21.9% of Iranian adults have metabolic syndrome (15). The prevalence of metabolic syndrome in Iran

is 25.6% on the basis of the definition by adult treatment panel (ATP) III, and based on the revised definition of ATPIII and international diabetes federation (IDF) this amount is 29% and 30.5% respectively, which is about one-third of the total population; statistically higher than this amount in Europe and America (16). Metabolic syndrome can also occur in children. Different studies show that children with overweight are more at risk of metabolic syndrome (17, 18).

The results of the study by Nakhjavani et al. showed a meaningful relationship between increased blood lipids as triglyceride (TG), ChOL, low density lipoprotein (LDL), high density lipoprotein (HDL) and also increased blood glucose- which are mostly a consequence of metabolic syndrome-with the risk of fatty liver (19); Vajro et al. also stated that obese children are prone to fatty liver (20).

2. Objectives

The association between overweight in childhood and adolescence with overweight in adulthood and the existence of various problems to resolve the overweight problem underlies the need to prevent and control childhood weight problems more than ever. Therefore, considering the increased prevalence of fatty liver and its development at young age in Iranian society and also the importance of prevention and control of the factors related to it in childhood, the current study investigated the relationship between fatty liver and metabolic syndrome in 6-18-year-old population in Birjand, Iran.

3. Methods

The current case-control study conducted on thirty 6 - 18-year-old children and adolescents with metabolic syndrome in the master plan of metabolic syndrome from atherosclerosis and coronary artery research center at Birjand University of Medical Sciences. To recruit the subjects who met the inclusion criteria, the convenience sampling method was employed. Then, 46 children and teenagers (from the same plan) non-affected by metabolic syndrome with the same gender and age who met the inclusion criteria were selected as the control group.

Inclusion criteria included the informed consent of the individuals and their parents, lack of mental retardation, lack of chronic drug use, lack of chronic diseases or symptoms, lack of genetic syndromes or abnormal symptoms, absence of signs of liver disorder and lack of endocrine diseases symptoms, diabetes and metabolic diseases.

Using Equation 1, the sample size of 27 subjects from each group was selected based on the results of the study by Parry et al. (21); $p_1 = 0.07$ and $p_2 = 0.44$. In the current study, 30 subjects were assigned into the positive metabolic syndrome group and 46 ones into the negative metabolic syndrome group.

$$n = \frac{\left\{ z_{1-\frac{\alpha}{2}} \sqrt{2\overline{pq}} + z_{1-\beta} \sqrt{p_1 q_1 + p_2 q_2} \right\}^2}{(p_1 - p_2)^2} \quad (1)$$

First, the demographic characteristics form was completed. With a minimum weight of clothes, the weight of all individuals was measured using a Seca digital scale (Germany). Standing with bare feet, their heights were measured twice in meter, and the average of the two measures was recorded. Body mass index (BMI) was obtained by dividing weight (kg) by the square of height (m). Overweight was defined as 85th to 95th percentiles of BMI for children of the same age and gender; the obesity" was defined as a BMI over the 95th percentile for children of the same age and gender. By an inelastic meter, waist circumference was measured in its minimum diameter in the area between the lower edge of the chest and anterior superior iliac spine, and abdominal obesity was defined as waist size above the percentile 90.

Blood pressure, according to world health organization (WHO) guidelines, was measured twice by mercury sphygmomanometer with an armlet of appropriate size in a 10 - 15 minutes interval, and the mean of the two was recorded as individual's blood pressure. The first sound of Kortokov was regarded as systolic blood pressure and the fifth sound of Kortokov was considered as diastolic blood pressure. Then the individuals were introduced to the laboratory for testing the blood sugar, blood lipid profile (triglycerides, cholesterol, HDL) and elevated liver enzymes as alanine aminotransferase (ALT/SGPT) and aspartate aminotransferase (AST/SGOT).

The tests of blood sugar and blood lipid profile were performed on 10 - 12 hours fasting by enzyme linked immunosorbent assay (ELISA) method using Pars Azemoon kits (Iran). Also, AST and ALT tests were performed using the Cobas Integra kit (Roche, Germany). Sonography was performed for all the persons by the radiologist. To determine the presence of fatty liver, the increased parenchymal echogenicity in the liver was specified to the extent of echogenicity of fat and visibility of portal veins and hepatic arteries. Then, the portal vein diameter was measured in deep inspiration, and on the basis of ultrasonography, the diagnosis was confirmed. The sonographic criteria for severity of fatty liver disease are as follows:

Grade 1: The liver echogenicity increases slightly and the extents of diaphragm and intrahepatic vessels are normal.

Grade 2: The echogenicity of the liver increases moderately and the extents of diaphragm and intrahepatic vessels disappear slightly.

Grade 3: The echogenicity of the liver increases significantly and the extents of diaphragm and intrahepatic vessels and the posterior segment of the right lobe of the liver eliminate or can be observed slightly (22).

The data were analyzed by SPSS statistical software using Chi-square test, independent T-test and logistic regression analysis at the significant level of 0.05.

4. Results

Of the 76 subjects, 30 (39.5%) were in the experimental group and 46 (60.5%) in the control group. Fifteen subjects (50%) of the case group and 29 of the control group (63%) were female (P = 0.26). The average age in the experimental and control groups were 13.17 ± 1.64 and 12.46 ± 2.27 years, respectively (P = 0.14).

Out of the76 children under study, 37 (47.7%) subjects were without fatty liver, and grades 1, 2 and 3 fatty liver disease observed in 30 (39.5%), 6 (7.9%) and 3(3.9%) subjects, respectively.

The result of the independent t-test showed that the mean liver enzymes AST and ALT in the two groups were not significantly different (P = 0.84 and P = 0.38, respectively) (Table 1).

Table 1. Comparison of Liver Enzymes Between Two Groups of the Study[a]

Variable	Intervention Group	Control Group	P Value
AST	23.87 ± 9.18	24.37 ± 24.37	0.84
ALT	21.07 ± 10.86	18.67 ± 12.03	0.38

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Values are expressed as standard deviation ± mean.

The relative frequency of occurrence of fatty liver instances in the case group (86.7%) was significantly higher than that of the control group (28.3%) (P < 0.001), and the result of logistic regression showed that in subjects with metabolic syndrome, the chance of developing fatty liver was on average 5.38 times greater than that of the non-affected individuals - [odd ratio (confidence interval 95%) = 5.38 (2.12 - 13.64)] (Table 2).

Based on the obtained results, the severity of fatty liver in 79% with metabolic syndrome and 76.9% without metabolic syndrome was grade 1.

To check the risk-factors of fatty liver, the logistic regression test was used in which gender, BMI and TG level, HDL, abdominal obesity, blood pressure and blood sugar were considered as independent variables, while fatty liver was considered as the dependent variable. The results indicated a significant relationship between gender (P = 0.01), BMI (P = 0.02), TG level (P = 0.005) and fatty liver occurrence. However, there was no significant relationship between HDL, abdominal obesity, blood pressure, blood sugar and fatty liver (P > 0.05) (Table 3).

Table 2. Relative Frequency of Fatty Liver in Two Groups of the Study[a]

Fatty Liver Group	Positive	Negative	P Value
Intervention	4 (13.3)	24 (86.7)	< 0.001
Control	33 (71.7)	13 (28.3)	

[a]Values are expressed as No. (%).

5. Discussion

According to the findings of the present study, the frequency of non-alcoholic fatty liver disease (NAFLD) in persons with metabolic syndrome was significantly higher compared to that of the ones without metabolic syndrome (P < 0.001) and the existence of metabolic syndrome can incr ease the chance of developing fatty liver 5.38 times, on average.

Parry et al. conducted a study on 1,112 children aged 4 - 18 years; they aimed to examine the prevalence of NAFLD and its relationship between the metabolic syndrome and obesity in the population of children in Northern India, the prevalence of fatty liver disease was 7.4% in the studied children, 44.4% in children with metabolic syndrome and 61% in children with obesity (21). The results of another study showed that the prevalence of fatty liver in children with metabolic syndrome was significantly higher than that of the children without it (23), which was consistent with the results of the current study.

Chiang et al. conducted a fixed-period study on 3,455 people to evaluate the effect of fatty liver on metabolic syndrome and found that the subjects with fatty liver were 6.6 times more at risk of metabolic syndrome than those without fatty liver (24).

Although the exact course of events that leads to fatty liver is not yet known, metabolic syndrome is known through a set of cardiovascular main risk factors at the presence of insulin resistance. Insulin resistance is responsible for fat storage and lipolysis in tissues sensitive to insulin, which increases the flow of fatty acids from adipose tissue to the liver causing steatosis. In addition, insulin resistance causes lipid peroxidation which, in turn, leads to

Table 3. The Risk Factors for Fatty Liver in the Participants Under Study

Variable	No. (%)	B	SE	OR (CI 95%)	P Value
Gender					0.01
Female	44 (57.9)			1	
Male	32 (42.1)	1.78	0.71	5.90 (1.46 - 23.78)	
Body mass index					0.02
Normal	27 (35.5)			1	
Overweight	25 (32.9)	1.81	0.78	6.13 (1.32 - 28.53)	0.002
Obesity	24 (31.6)	2.51	0.83	12.35 (2.45 - 62.34)	
Triglyceride					0.005
Normal	48 (63.2)	1.96	0.70	1	
Abnormal	28 (36.8)	-2.73	0.74	7.13 (1.82 - 27.92)	
Stable	-	-2.73	0.74	0.07	< 0.001

Abbreviations: OR (CI 95%), odd ration (confidence interval 95%); SE, standard error.

activation of inflammatory cytokines and facilitates the development of simple steatosis to non-alcoholic steatohepatitis and liver fibrosis (25).

The results of the current study showed a significant correlation between gender, BMI and high level of TG with fatty liver disease in the studied subjects ($P < 0.05$), but no significant correlation was observed between HDL, abdominal obesity, blood pressure, blood sugar and fatty liver disease ($P > 0.05$).

Adibi et al. examined the frequency of fatty liver in children with overweight and obesity compared to children with normal weight and showed that the prevalence of fatty liver was significantly higher in the children with obesity than in children with normal weight or overweight (6), which is in line with the results of the current study. Based on the results of the study by Adibi et al., difference regarding the prevalence of fatty liver between two genders was insignificant ($P > 0.05$); their results are inconsistent with the results of the current study. According to a study by Shiasi et al. there is a significant relationship between fatty liver and lipid components of metabolic syndrome (HDL and triglycerides) (26), which, based on the relationship between fatty liver and triglycerides, is in line with the results of the current study; accordingly the connection between HDL and the risk of fatty liver is inconsistent with the results of the current study. Also, the highest grade of fatty liver disease was 1, similar to the current study.

Parry et al. showed a significant relationship of BMI and metabolic syndrome with fatty liver disease (21). Also, the results of different studies showed that the amount of fasting blood sugar is not significantly correlated with fatty liver disease in children, which is consistent with the results of the present study; the systolic and diastolic blood pressure in people with fatty liver was significantly higher than those of the ones without fatty liver, inconsistent with the results of the present study (26, 27).

Yunesian et al. showed a significant relationship of liver enzymes levels, weight, BMI and waist-to-hip circumference ratio; however, in the current study, no association was observed among liver enzymes, blood parameters including TG, HDL, LDL, ChOL and FBS (28). Tazhibi et al. also showed that by increasing the waist circumference, age, systolic blood pressure, diastolic blood pressure, cholesterol level and blood LDL cholesterol levels the risk of non-alcoholic fatty liver increases and by increasing the level of blood HDL cholesterol, the risk of non-alcoholic fatty liver decreases (29). Moreover high triglyceride and low HDL rates are among cardiovascular risk factors (30).

Obesity is one of the major diseases associated with fatty liver. However, the increase in abdominal fat which is measured by the index of waist to hip circumference is a more important indicator of fatty liver disease than total body obesity, however, in the current study no significant relationship was observed between abdominal obesity and incidence of fatty liver.

The increasing prevalence of NAFLD in children and adolescents and the potential for future generations to be at risk of morbidity and mortality associated with this condition are of significant concern.

Early screening of those at risk for NAFLD may also help to identify young people at risk for other chronic diseases that may potentially result in significant long-term health and economic benefits. In addition, it is important for clin-

icians working with children and adolescents consider the possibility of a diagnosing NAFLD to initiate prevention and early intervention

5.1. Conclusions

Based on the results of the current study, it is suggested to develop some programs by schools, the media and parents to modify the lifestyle of children and adolescents and encourage them to keep fit.

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