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ORIGINAL ARTICLE

Evaluation of metabolic factors affecting the presence of hepatosteatosis and the effect of insulin like growth factor-1 level in overweight and obese children

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Abstract

Although previous studies related to non-alcoholic fatty liver disease (NAFLD) in childhood were predominantly ALT and uric acid level, the number of studies that have been handled in terms of insulin like growth factor-1 (IGF-1) level or IGF-1 standard deviation score (SDS) is limited. In this study, all factors that may affect NAFLD, including IGF-1 level and IGF-1 SDS, were evaluated in two groups of children who were not statistically different from each other in terms of age, gender, weight, height, body mass index and puberty. This study was a cross-sectional study. 36 children with evidence of fatty liver disease on ultrasound imaging and 38 children without it were included in the study. Anthropometric data, laboratory measurements and radiological results of all participants were evaluated. All factors that could affect NAFLD were evaluated by binary logistic regression analysis. Weight, weight SDS, body mass index (BMI) SDS, homeostasis model assessment of insulin resistance (HOMA-IR), AST, ALT, GGT, uric acid, triglyceride, HDL-cholesterol, IGF-1, IGF-1 SDS were evaluated in this model to predict NAFLD. In the statistical model, the percentage of predicting those with NAFLD, that is, the sensitivity, was 88.9%, while the detection rate of those without NAFLD, that is, the specificity, was 94.7%. IGF-1 level was found to be significantly lower in the group with NAFLD (p: 0.04), but there was no significant difference between the groups in terms of IGF-1 SDS (p: 0.10). There are conflicting results in studies examining the relationship between IGF-1 SDS and NAFLD. This may be due to ethnicity, regional differences, kit-specific laboratory reference ranges, or method of measurement. Laboratory measurements including appropriate parameters with a detailed physical examination can be used to predict the presence of NAFLD without the need for radiological examination.

Keywords: *Children, insulin like growth factor-1, non-alcholic fatty liver disease, overweight*

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Introduction

The liver is an important organ that plays a key role in glucose and lipid metabolism in the body. In addition, many proteins that are used for important functions in the body (including IGF-1) are also produced in the liver. The most common chronic liver disease in childhood is NAFLD [1]. Non-alcoholic fatty liver disease is a chronic disease that occurs with abnormal levels of triglyceride accumulation in the liver in an individual who does not consume a significant amount of alcohol. Although obesity is the most important risk factor; overweight, hypertension, insulin resistance, dyslipidemia, and other pre-atherogenic conditions have been associated with NAFLD [2-4]. Reports of study results on NAFLD prevalence in childhood are variable. The frequency varies depending on the differences in the methods used for detection. There are differences in terms of noninvasive methods (ultrasound, magnetic resonance imaging) and liver biopsy, which is seen as the gold standard in diagnosis. Reported prevalence rates range from 1.7-85% [2,5]. Because liver biopsy is a risky method, ultrasonographic imaging has become a more common method. In addition, many studies have been conducted to predict NAFLD with some parameters thought to be associated with NAFLD. Body mass index (BMI), liver function tests (ALT, AST), uric acid and HOMA-IR calculated by measuring glucose and insulin levels and IGF-1 levels are some of them [6-10]. Therefore, our primary aim in this study is to examine the relationship between IGF-1 level and IGF-1 SDS and NAFLD in overweight or obese children, and to evaluate the relationship between biochemical and hormonal parameters to predict NAFLD.

Materials and Methods

Subjects

The study was approved by the clinical research ethics committee of Afyonkarahisar Health Sciences University, where the patients were examined, with the number of 2011-KAEK-2, 2021/7. This retrospective cross-sectional study was carried out on overweight and obese children who were followed up in Afyonkarahisar Health Sciences University Pediatric Endocrinology Outpatient Clinic. A total of 74 patients with and without evidence of hepatosteatosis in ultrasonography examined between August 2020 and April 2021 were included in the study. Inclusion criteria in the study were body mass index above 1 standard deviation score according to age and gender according to CDC growth references and being between 6 and 19 years of age. The exclusion criteria from the study were; 1) use of drugs and alcohol that could affect blood pressure, liver, glucose and lipid metabolism in the last 3 months; 2) conditions causing secondary obesity (i.e. hypothyroidism, Cushing's disease), monogenic, syndromic or hypothalamic obesity; 3) primary and secondary liver diseases, including hepatitis B and hepatitis C. When cases with body mass index standard deviation score above +1 SD were divided into two groups according to the presence of NAFLD in ultrasonography; 36 cases were NAFLD patients and 38 cases were as controls. Anthropometric examinations, laboratory measurements and abdominal ultrasonography evaluation by an experienced pediatric radiologist were performed from all participants. Written informed consent was obtained from all participants and their accompanying parents. The research ethical principles were carried out in accordance with the Declaration of Helsinki.

Liver ultrasonography

The presence of hepatosteatosis in ultrasonographic imaging was predicted according to the presence of either diffuse increase in liver echogenicity, increased liver echogenicity compared to kidneys, and decreased visual visualization in the intrahepatic vessels or diaphragm. Ultrasonographic examination was performed by the same operator in all participants after 12 hours of fasting. Ultrasonic scanning of the liver was performed using a high quality abdominal and superficial tissue transducer in the range of 7.5-13.5 MHz, and liver imaging was performed with Canon Medical Systems USA, Inc.

Anthropometric measurements

As anthropometric examinations; weight, height, body mass index and standard deviation scores were calculated using a comprehensive online calculation program (www.childmetrics.org) [11]. It was evaluated according to CDC's age and gender specific references. Physical examination and evaluation of puberty of all patients were performed. According to Tanner staging, the absence of breast development in girls and testicular volume less than 4 ml in boys were considered prepubertal period. The onset of breast development in girls and a testicular volume of 4 ml or more in boys were considered to be puberty or postpubertal, regardless of the presence or absence of pubic hair growth. Blood pressures of all children in the study and control group were within normal ranges according to age and gender.

Laboratory measurements

Blood samples were obtained for biochemical and hormonal measurements in the early morning after 8 hours of overnight fasting. Liver function tests, lipid status and uric acid were measured using an automated biochemical analyser (Cobas 8000 c502-c702 and Cobas 6000 c501-e601, Roche Diagnostics, Mannheim, Germany). Plasma glycosylated hemoglobin A1c (HbA1c), insulin, cortisol, TSH, free T4 and insulin-like growth factor-1 (IGF-1) were measured by electrochemiluminescence immunological method (ECLIA) on the Cobas 8000 e602 analyzer (Roche Diagnostics, Mannheim, Germany). Glucose was measured by hexokinase method and insulin was measured by ECLIA. The HOMA-IR method [glucose (mmol/L) X insulin (mIU/mL) / 22.5] was used to assess insulin resistance [12]. IGF-1 SDS was calculated according to age and gender specific reference data [13].

Statistical analysis

SPSS version 24.0 (IBM Corporation, Armonk, NY, USA) software program was used for all statistical analyzes. Mean and standard deviation values of numerical variables were calculated. Categorical variables were shown as frequency and percentage. Shapiro Wilk test was used to evaluate the normal distribution of variables. In addition, the data with kurtosis and skewness values within the range of -2, +2 were accepted as showing normal distribution. When comparing the means of two independent variables, Student's T test was used if the data showed a normal distribution, and the Mann Whitney U test was used if it did not comply with the normal distribution. Chi-square analysis was used to compare categorical variables. Pearson and spearman correlation analyzes were used to evaluate the degree and direction of the relationship between variables. Binary logistic regression analysis was used to evaluate the effect of independent variables to predict the presence of fatty liver in ultrasonography. A p value of <0.05 was considered statistically significant.

Results

The study was conducted in children aged 6-19 years with a body mass index standard deviation score of 1 SD or above. Participants were divided into two groups consisting of 36 individuals with hepatosteatosis on ultrasonography and 38 controls without radiological findings. Age, anthropometric and laboratory measurements of both groups were summarized in Table 1.

When the groups were compared according to gender, 14 (38.9%) of the NAFLD cases were girls, 22 (61.1%) of them were boys, while 23 (60.5%) of the non-NAFLD cases were girls and 15 (39.5%) of them were boys. When the groups were compared according to the puberty stages, 8 (22.2%) children with NAFLD were in the prepubertal period, 28 (77.8%) children were in the pubertal or postpubertal period, while 6 (15.8%) children without NAFLD were in the prepubertal period, 32 (84.2%) children were in puberty or postpubertal period. There were no significant difference between groups according to gender and puberty status, respectively (p: 0.06; p= 0.48). There was no statistically significant difference between the groups in age, gender, puberty status, weight, height, BMI and BMI SDS ($p<0.05$). Therefore, the parameters planned to be investigated in terms of metabolism could be compared in two groups similar to each other in these aspects. The linear relationship of independent variables that can affect NAFLD is shown in detail in Table 2.

Independent variables affecting NAFLD were evaluated by binary logistic regression analysis. The outputs of the model are presented in Table 3 (3a, 3b, 3c, 3d).

A statistically significant difference was found in individuals with NAFLD in terms of IGF-1 levels. IGF-1 was found to be lower in individuals with NAFLD. However, there was no statistically significant difference between the groups in terms of IGF-1 SDS.

Table 1. Clinical and laboratory parameters of the participants.

Parameter	NAFLD (n=36)	Non-NAFLD (n=38)	p value
Age (months)	148±27	149±33	0.82
Weight (kg)	80.9±19.9	75.8±18.7	0.26
Height (cm)	158±9.2	157±13.9	0.72
BMI (kg/m^2)	31.9±5	30.1±4	0.09
Weight SDS	2.53±0.59	2.28±0.41	**0.04***
Height SDS	1.03±1	0.83±1.07	0.41
BMI SDS	2.28±0.36	2.16±0.25	0.11
FPG (mg/dL)	93.3±6.5	91,7±7.9	0.35
Insulin (mIU/mL)	34.7±15.8	23.4±8.3	**<0.001***
HOMA-IR	8±3.7	5.2±2	**<0.001***
HbA1c (%)	5.4±0.3	5.1±0.2	**0.01***
AST (U/L)	26 (22-39)	21 (16-24)	**<0.001*** (Ω)
ALT (U/L) (U/L)	34 (23-53)	17 (12-25)	**<0.001*** (Ω)
GGT (U/L)	22 (14-35)	14 (11-20)	**0.001*** (Ω)
Uric acid (mg/dL)	5.5±1.1	4.9±1	**0.02***
TSH (mIU/mL)	3±1.2	2.3±1	**0.01***
Free-T4 (ng/dL)	1.25±0.16	1.29±0.14	0.31
Triglyceride (mg/dL)	128±53	117±48	0.34
Total cholesterol (mg/dL)	150 (133-177)	143 (137-173)	0.82 (Ω)
LDL-C (mg/dL)	107 (87-122)	97 (83-123)	0,74 (Ω)
HDL-C (mg/dL)	41±7	45±8	**0.02***
Cortisol (ug/L)	12.6±5.2	13±5	0.74
IGF-1 (ng/mL)	227±99	285±133	**0.04***
IGF-1 SDS	-0.20±0.82	0.14±1	0.10

* p value < 0.05 The data were presented as mean and standard deviation if they were suitable for normal distribution, and as median and interquartile ranges (Q1-Q3) if not. Data with normal distribution evaluated with Student's T test, Ω symbol used if evaluated with Mann Whitney U test.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SDS, standard deviation score; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycosylated haemoglobin A1c; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl-transferase; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IGF-1, insulin like growth factor-1.

Table 2. Linear relationship of factors affecting NAFLD.

Parameter	p value	r
Age (months)	0.82	-0.02
Sex	0.06	0.21
Weight (kg)	0.25	0.13
Height (cm)	0.72	0.04
BMI (kg/m2)	0.09	0.19
Weight SDS	**0.04**	0.23
Height SDS	0.41	0.09
BMI SDS	0.11	0.18
Pubery status	0.48	-0.08
FPG (mg/dL)	0.36	0.10
Insulin (mIU/mL)	**<0.001**	0.41
HOMA-IR	**<0.001**	0.41
HbA1c (%)	**0.01**	0.29
AST (U/L)	**<0.001**	0.42*
ALT (U/L)	**<0.001**	0.58*
GGT (U/L)	**0.001**	0.39*
Uric acid (mg/dL)	**0.02**	0.26
TSH (mIU/mL)	**0.01**	0.27
Free-T4 (ng/dL)	0.31	-0.11
Triglyceride (mg/dL)	0.34	0.11
Total cholesterol (mg/dL)	0.82	-0.02*
LDL-C (mg/dL)	0.74	0.03*
HDL-C (mg/dL)	**0.02**	-0.27
Cortisol (ug/L)	0.74	-0.03
IGF-1 (ng/mL)	0.04	-0.23
IGF-1 SDS	0.10	-0.18

Pearson correlation analysis was used to examine the relationship of the variables. * symbol used if spearman corelation analysis was used. Abbreviations: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SDS, standard deviation score; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycosylated haemoglobin A1c; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl-transferase; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IGF-1, insulin like growth factor-1.

Table 3. Effect of weight, weight SDS, BMI SDS, HOMA-IR, HbA1c, AST, ALT, GGT, uric acid, triglyceride, HDL cholesterol, IGF-1 and IGF1 SDS to predict the presence of NAFLD.

3a. Significance of the model coefficients.

		Chi square	df	Sig.
Step 1	Step	51.530	13	.000
	Block	51.530	13	.000
	Model	51.530	13	.000

Model coefficients are significant. Independent variables contribute to estimating the dependent variable.

3b. The degree of relationship between variables.

	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	51.002	.502	.669

Independent variables with dependent variable in logistic regression model the degree of the relationship between 50.2% according to Cox-Snell and 66.9% according to Nagelkerke.

3c. Classification chart of the model.

	Observed		Predicted		
			NAFLD		Percentage correct
			No	Yes	
Step 1	NAFLD	No	36	2	94.7
		Yes	4	32	88.9
		Overall percentage			91.9

As seen from the table, 94.7% of those without NAFLD and 88.9% of those with NAFLD were correctly estimated. In general, 91.9% of it was correctly estimated.

3d. Variables of the model.

		B	Sig.	Exp (B)
Step 1	Weight	-.027	.471	.973
	Weight SDS	2.326	.259	10.241
	BMI SDS	-2.038	.510	.130
	HOMA-IR	.430	.062	1.538
	HbA1c	1.032	.470	2.806
	AST	-.053	.580	.949
	ALT	.111	.110	1.117
	GGT	-.029	.710	.972
	Uric acid	.791	.079	2.206
	Triglyceride	-.001	.943	.999
	HDL cholesterol	-.129	.038	.879
	IGF-1	-.005	.510	.995
	IGF-1 SDS	-.280	.679	.756
	Constant	-5.564	.506	.004

Factors thought to be effective in NAFLD estimation were analyzed. Weight SDS, HOMA-IR, HbA1c, ALT, uric acid variables were found to be more effective.

Discussion

In this study, the relationship between NAFLD and metabolic parameters previously reported to be associated with NAFLD, including IGF-1 level and IGF-1 SDS, has been the subject of investigation. In our study, we found a positive significant correlation with NAFLD and weight SDS, AST, ALT, GGT, insulin, HOMA-IR, HbA1c, uric acid and TSH levels, and a negative significant correlation with HDL cholesterol and IGF-1 levels. There was no significant relationship with IGF-1 SDS.

Evidence-based data and long-term follow-up results suggest that NAFLD in childhood is associated with increased cardiovascular disease and mortality in adulthood [14]. Many previous studies have shown the relationship between insulin resistance and NAFLD [15,16]. The incidence of insulin resistance was found to be 95% in NAFLD cases proven by biopsy in children [17]. Insulin resistance plays an important role in hepatocyte damage and hepatosteatosis. Dietary fat, free fatty acids increased by endogenous lipolysis lead to oxidative stress and hepatic triglyceride accumulation. Detecting insulin resistance with a hyperinsulinemic euglycemic clamp gives more reliable results. However, this technique is expensive and not applicable in daily practice. For this reason, HOMA-IR was used as a simple technique. A very strong relationship was found between metabolic syndrome and NAFLD in a study conducted with overweight and obese children [18]. In another study, abdominal obesity, insulin resistance, type 2 diabetes and dyslipidemia were also closely related to NAFLD(3). As in our study, ultrasound imaging has been the preferred method to detect NAFLD in most studies, since it is a non-invasive and easily applicable technique [19,20].

In a study evaluating obesity and NAFLD, obesity accompanied NAFLD in one fourth of the girls and one third of the boys [21]. In previous studies examining the relationship between uric acid level and NAFLD, it was found that hyperuricemia was associated with NAFLD, and the degree of fatty liver and lobular inflammation and hyperuricemia were found to be associated with NAFLD cases proven by liver biopsy [22-24]. In some experimental studies, an increase in triglyceride level was observed with uric acid incubation with hepatocyte cells. Potential effective mechanisms and possible hypotheses were interpreted as mitochondrial stress, endoplasmic reticulum stress, increase in inflammatory response and hepatic steatosis [25,26].

In this study, while IGF-1 level was found to be low in overweight and obese children with NAFLD, there was no significant difference in IGF-1 SDS levels compared to non-NAFLD controls. It has been reported in experimental studies that fatty liver after high-calorie total parenteral nutrition is caused by a decrease in IGF-1 mRNA levels in the liver [27]. Insulin resistance causes down-regulation of IGF-1 level by acting through hepatic growth hormone (GH) receptors. IGF-1 is a polypeptide that has antioxidant and anti-inflammatory effects [7,28,29]. In one study, IGF-1 level was found to be negatively correlated with hepatic steatosis, but when IGF-1 was evaluated in terms of SDS, this degree of correlation was significantly decreased [30]. In some studies in adults, IGF-1 deficiency has also been used to evaluate tissue level progression in non-alcoholic steatohepatitis (NASH). In Japan, the use of growth hormone therapy in NASH cases has been approved in adults. There were no indications for the use of such treatment in children worldwide. Participants were divided into 3 subgroups according to the result of IGF-1 SDS level as below -1 SDS, between -1 SDS +1 SDS and above +1 SDS. There was no statistically significant difference in IGF-1 SDS levels between the groups with and without NAFLD ($p= 0.50$).

In our study, we found a close relationship between HbA1c level and NAFLD. When we look at previous studies, it is known that the relationship of NAFLD in cases where the HbA1c level is more than 5.7%, but in one study, NAFLD was reported with a rate of 29.8% in the groups where the HbA1c level was found to be less than 5.7%. Therefore, it has been stated that the HbA1c level being in the upper limit of normal may also be associated with NAFLD [31]. In some studies conducted with adults, it has been stated that HbA1c also plays a key role in the development of NAFLD in patients without diabetes mellitus and was an independent risk factor [32,33]. When we divided the groups into 3 subgroups according to the HbA1c level as below 5.3%, between 5.3% and 5.7% and above 5.7%; We found that the HbA1c level was above 5.7% in 88.9% of the NAFLD cases, and HbA1c level was above 5.3% in 42.9% of the NAFLD cases.

Our study had some limitations. The first was that the number of children in our sample was not large enough. Secondly, although age, gender and puberty status were similar in both groups in terms of evaluating IGF-1 level, reference ranges used in the evaluation of IGF-1 levels differed according to each country, ethnicity and measurement method. In addition, basal or stimulated levels of growth hormone in patients and

insulin-like growth factor binding proteins (such as IGFBP-3 level) were not evaluated. Therefore, we may not have found a significant difference between the group with NAFLD and the group without NAFLD in terms of IGF-1 SDS levels in our study. There is a need for new studies evaluating basal and stimulated GH levels in larger cohorts of NAFLD cases. Meta-analyzes using standard reference ranges and similar measurement methods to evaluate the IGF-1 level in NAFLD cases will also be enlightening.

Conclusion

Evaluation of biochemical and hormonal parameters together is as valuable as radiological diagnosis in NAFLD cases. In the clinical follow-up of the patients, the effectiveness of the treatment can be evaluated by monitoring these parameters and observing their changes. In our study, we wanted to show that HbA1c and IGF-1 levels can yield important results, as well as markers such as ALT, uric acid, and HOMA-IR, which are known to be closely related to NAFLD in previous studies. In order to make sharp and clear comments about the relationship between IGF-1 SDS and NAFLD, more studies with larger groups and standard measurement methods are needed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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