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Comparison of non-invasive imaging methods and laboratory findings on non-alcoholic fatty liver disease (NAFLD) in childhood

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ABSTRACT

Aim: Diagnosis and follow-up of non-alcoholic fatty liver disease in children with practical and non-invasive methods have been researched for many years. Ultrasonography (USG), Shear wave elastography (SWE), and Magnetic Resonance (MR) are thought to help demonstrate the impairment which is also displayed in liver function tests. This study aims to identify the most effective imaging method among liver scanning methods in exhibiting the fatty condition of the liver and laboratory tests.

Material and Method: This study was carried out on a population of 84 children who applied to the clinic. The relationship between the diagnostic performances of three different noninvasive methods [USG, MR, and SWE] and liver function tests in children with suspected NAFLD was analyzed. Age, BMI (body mass index), waist circumference, gender, liver function tests, total cholesterol, triglyceride, and Homeostasis Model Assesment-Insulin Rezistance (HOMA-IR) parameters of NAFLD and control group were put into comparison and their relationship with USG, MR, and SWE imaging methods were also analyzed.

Results: There is no statistically significant relationship between hepatosteatosis grade and the mean SWE ($p>0.05$) while there is a positive and statistically significant relationship between waist circumference and liver long axis values at 33.3% level (p: 0.036; $p<0.05$). On the other hand, there is no statistically significant difference in laboratory values between those with and without NAFLD based on MR and SWE examinations ($p>0.05$).

Conclusion: Abdominal USG, SWE, and dynamic MR examinations are very essential to demonstrate liver functions and liver pathology in children with non-invasive methods. It is also useful in patient follow-up. In this study, no difference was detected between SWE and MR findings, and we think that the SWE examination will be more suitable in estimating liver functions in follow-up as opposed to costly MR examination.

Keywords: Fatty liver disease, elastography, scanning method, ultrasound

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) can range from simple steatosis to non-alcoholic steatohepatitis (NASH); it is an illness that can lead to cirrhosis and liver failure as a result of the progression of fibrosis (1). NAFLD is the most common chronic liver disease in the world today. There is a marked increased risk of cardiovascular mortality in NAFLD (especially in the more severe form of NASH) (2). The clinical significance of fatty liver disease is increasingly better understood. Especially in the last two decades, many scientists have focused on distinguishing the subtypes of this disease. Because, unlike simple steatosis, NASH is a progressive form of the disease. Although it is now accepted that simple steatosis and NASH are two histological subtypes of the NAFLD spectrum, these two conditions are probably completely different not only in terms of clinical results but also in terms of histological and pathophysiology (3). Fibrosis is not expected to accompany simple steatosis. NASH can be accompanied by fibrosis and cause cirrhosis. Advanced stage fibrosis is detected in 20% of patients with NASH, and this is directly related to the prognosis of the disease (4). Therefore, it is recommended to consider these issues in noninvasive diagnostic studies.

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Liver biopsy is considered to be the gold standard in distinguishing simple steatosis from NASH in patients with NAFLD. However, it is an invasive procedure that may have serious clinical complications and it is not easily accepted by the parents of pediatric patients. It is highly ineffective for follow-up and unsuitable for a large screening of patients at risk (such as obesity, type 2 DM, hyperlipidemia). Due to the increasing prevalence of obesity and diabetes, economic, simple, and easily accessible screening tests are required instead of costly, invasive, and specialized methods. Furthermore, insufficient material, sampling errors, and human mistake may be a problem in the pathological examination. Therefore, a non-invasive method is needed. Besides, there is no single ideal method for NAFLD. Moreover, the use of models (panels) or scoring systems belonging to different pathophysiological mechanisms can raise diagnostic accuracy (5).

Our objective in this study is to compare the diagnostic performances of 3 different noninvasive methods [USG, MR, and SWE] in the analysis of liver functions in individuals with NAFLD. SWE is an ultrasonic medical device that predicts fibrosis by measuring liver stiffness with the help of a sort of elastic wave (6). Until now, studies adopting USG, MR, and SWE together in the Turkish population are limited. In many patients with suspected NAFLD, the reliable detection of fibrosis by only taking blood and/or performing SWE without the need for an invasive procedure in outpatient and clinical conditions can help us identify patients who need a liver biopsy.

MATERIAL AND METHOD

The study was carried out with the permission of Taksim Training and Research Hospital Ethics Committee (Date: 26/06/2019, Decision No: 81). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

The patients, or their parents or guardians, signed written statements of informed consent. Included in this study were obese patients who applied to Gaziosmanpaşa Training and Research Hospital and diagnosed with NAFLD, and a control group consisting of children with similar age and gender.

Patients with viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary stenosis, alpha-1 antitrypsin deficiency, myocarditis/myopathy, congenital heart disease, cerebrovascular disease, and malignancy were excluded from the study. Moreover; patients with a history of drug use that may cause NAFLD (such as anti-epileptic drugs), patients on insulin therapy for diabetes, those with iron deficiency anemia or acute severe inflammatory disease, and those with rheumatological and autoinflammatory diseases were also left out.

Clinical and Biochemical Analysis

Physical examination, anthropometric and biochemical measurements were performed on all cases. Blood samples were taken from all patients in the study who fasted overnight. Serum samples were taken from patients, before the study and adjusted according to the quantities to be used once for each ELISA test. Patients' liver function tests (ALT, AST, albumin, GGT), serum lipid profile (triglyceride, LDL, HDL), insulin, and fasting blood glucose were measured and HOMA-IR was calculated.

Abdominal USG and Shear wave Elastography (SWE)

Abdominal USG was performed on the patients following a fasting period of 6 hours. Since ultrasound is among the first preferred medical imaging methods.

The diagnosis of liver steatosis was made based on increased echogenicity of the liver parenchyma compared to the right renal cortex in USG. Visibility and sharpness of the diaphragm and hepatic vessel walls were also analyzed. Based on these 3 parameters, steatosis was classified into 3 distinct grades: Grade 0, no steatosis (liver and renal cortex with the same echogenicity); Grade 1, mild steatosis: liver slightly more echogenic than the renal cortex, clear visualization of the diaphragm, and sharply contoured hepatic veins; Grade 2, moderate steatosis: more echogenic liver and diaphragm while hepatic veins still being visible with debilitated USG beam in the deeper parts of the liver, albeit with blunt contours; Grade 3, severe steatosis: advanced echogenic liver, severe USG beam attenuation, neither diaphragm nor hepatic veins visible (7).

SWE values of all NAFLD patient groups were measured with fibroscan instrument using suitable probes on the patients. Shear Wave Elastography method is used on the liver. SWE results of the patients were obtained by examining their existing records. The fact that at least 10 valid measurements were taken from the patients was accepted as a reliable measurement. During and just prior the measurements, the patient was requested neither to breathe nor to take a deep breath.

Dynamic Magnetic Resonance Imaging

MR imaging was performed with a 1.5-T device (Intera, software version 8.1; Philips Medical Systems, Eindhoven, The Netherlands) using a phased-array coil. Multi-stage contrast-enhanced dynamic series were obtained just before and after intravenous rapid bolus administration of 0.1 mmol of gadopentetate dimeglumine per kilogram body weight to patients while in the magnetic cylinder. Imaging timings of the dynamic series included precontrast, arterial, portal and stabilization phases. Processing of multiphase, contrast, dynamic images was done automatically by the MR imaging device. The software that was used made it possible to extract precontrast images separately from those images taken during arterial, portal, and equilibration stages on each patient.

Statistical Analysis

IBM SPSS Statistics 22 software package was used for evaluating the findings of the study. The normality assumption of the parameters was checked with Shapiro-Wilks test. While evaluating the study data, besides descriptive statistical methods (mean, standard deviation, frequency), Student t-test was used for comparing normally distributed parameters between two groups, whereas Mann Whitney U test was deployed for comparisons of non-normally distributed parameters between two groups. Fisher Freeman Halton test and Continuity (Yates) Correction were used for comparing qualitative data. Pearson correlation analysis was used to examine the relationships between parameters that are suitable for normal distribution, and Spearman's rho correlation analysis was used to examine the relationships between parameters not compatible with normal distribution. Significance was checked at the p <0.05 level.

RESULTS

The study was conducted between 2018 and 2019 with a total of 84 children, 55 (65.5%) girls and 29 (34.5%) boys, aged between 4 and 17. The average age of the children is 12.23±3.47. The study was examined under 2 groups, 40 of which are NAFLD (47.6%) and 44 (52.4%) as control. NAFLD and the control group were similar in age and gender. The liver function tests ALT and GGT were higher in the NAFLD group than in the control group (**Table 1**). 35% of the patients in the NAFLD group had Grade 1 hepatosteatosis while 55% of them had Grade 2 and 10% Grade 3 hepatosteatosis, respectively. Liver long axis values and elastography average were significantly higher than the control group (p:0.000; p<0.05). Hemoglobin and insulin levels of the NAFLD group were significantly higher than the control group (p: 0.006; p<0.05). HDL level was found to be low in the NAFLD group as expected (**Table 2**). There is no statistically significant difference between the groups in terms of LDL and blood glucose levels (p>0.05) (**Table 2**).

Table 1. Evaluation of age, BMI, waist circumference, gender, ALT, AST, GGT, albumin, total cholesterol, triglyceride, and HOMA-IR parameters among the groups

	NAFLD group	Control group	p
	Mean±SD	Mean±SD	
Gender n (%)			0.216[2]
Female	23 (57.5%)	32 (72.7%)	
Male	17 (42.5%)	12 (27.3%)	
Age	13.33±2.62	12.23±3.85	0.09*[1]
BMI	28.63±5.81	24.45±3.48	0.000*[1]
Waist circumference	94.51±13.06	68.41±6.91	0.000*[1]
ALT (median)	61.53±86.04 (34.5)	18.32±8.34 (16)	0.000*[3]
AST (median)	42.58±37.73 (30)	28.34±9.09 (26.5)	0.137[3]
GGT (median)	31.08±20.38 (24)	15.48±9.06 (12)	0.000*[3]
Albumin (median)	4.42±0.36 (4.5)	4.44±0.32 (4.5)	0.728[3]
Total cholestrol	169.58±38.05	162.52±34.55	0.376[1]
Trigliserid (median)	138.65±77.17 (120.5)	139.09±48.13 (147)	0.237[3]
HOMA-IR (median)	4.03±2.31 (3.4)	2.48±0.69 (2.4)	0.000*[3]

[1]Student t test, [2]Continuity (yates) correction, [3]Mann Whitney U test, *p<0.05

Table 2. Evaluation of liver long axis, liver elasto average, hepatosteatosis grade, MR, Hb, LDL, HDL, insulin and blood glucose parameters among the groups

	NAFLD group	Control group	p
	Mean±SD	Mean±SD	
Liver long axis	147.13±11.85	120.7±15.99	0.000*[1]
Liver elasto avg (median)	1.79±0.30 (1.7)	1.6±0.15 (1.6)	0.000*[2]
Hepatosteatosis n(%)			0.000*[3]
None	0	44 (100%)	
Grade 1	14 (35%)	0 (0%)	
Grade 2	22 (55%)	0 (0%)	
Grade 3	4 (10%)	0 (0%)	
MR n(%)			0.000*[4]
No	15 (37.5%)	44 (100%)	
Yes	25 (62.5%)	0 (0%)	
Hb	13.12±0.88	12.49±1.15	0.006*[1]
LDL(median)	104.03±39.66 (104.5)	104.16±27.67 (102)	0.854[2]
HDL	43.5±8.61	49.86±9.39	0.002*[1]
Insulin(median)	19±10.22 (15.7)	11.07±2.39 (11)	0.000*[2]
Blood glucose	87.85±8.09	90.11±11.4	0.301[1]

[1]Student t test, [2]Mann Whitney U test, [3]Fisher Freeman Halton test, [4]Continuity (yates) correction, *p<0.05

62.5% of the patients who were diagnosed with NAFLD based on the USG actually presented NAFLD in MR results. There is a positive and statistically significant correlation between the degree of hepatosteatosis and liver long axis values at 48.1% level (p: 0.002; p<0.05). On the other hand, there is no statistically significant correlation between liver elasto average and hepatosteatosis (p>0.05).

There is a positive, and statistically significant correlation between waist circumference and liver long axis values (p: 0.036; $p<0.05$). There is no statistically significant relationship between the mean liver elasto and waist circumference ($p>0.05$) (**Table 3**).

Table 3. Evaluation of the correlation between hepatosteatosis and waist circumference and liver long axis and liver elasto values in the patient group

	Hepatosteatosis	Waist circumference
Liver long axis		
r	0.481	0.333
p	0.002*	0.036*
Liver elasto avg		
r	0.114	-0.007
P	0.485+	0.964

Pearson correlation analysis, +Spearman Rho correlation analysis, *p<0.05

DISCUSSION

NAFLD is closely associated with obesity and is generally accepted as the liver component of metabolic syndrome. The frequency of NAFLD continues to increase in the population. In this study, BMI mean value in children with NAFLD is 28.63±5.81 kg/m². Similarly, in a study on NAFLD in children in Malaysia, the BMI average was 29.8 kg/m² (8). Although Asians have a similar BMI to Caucasians, they develop complications associated with obesity and diabetes at a lower BMI than their Western peers due to higher visceral fat accumulation in Asia (9). Although these milestone studies were primarily conducted in adults, the conclusion that Asian children had more visceral steatosis compared to western population of the same body mass index was considered as an outcome of similar studies in the pediatric population.

For NAFLD patients, it is not only common to have high BMIs, but also other parameters of metabolic syndrome at high levels (i.e., fasting blood glucose, HOMA-IR, and hypercholesterolemia) (10). In a study on adults, 60.4% of NAFLD patients diagnosed with USG were Grade 1, 33.6% Grade 2, and 5.9% Grade 3 according to the degree of liver steatosis. In these groups, blood glucose, HOMA-IR, and serum lipid values (triglyceride, LDL) rose as the USG grade increased (11). In this study, 35% of the patients in the NAFLD group had Grade 1, 55% had Grade 2, and 10% had Grade 3 hepatosteatosis, respectively. Since the number of patients in these sub-groups was insufficient, a general comparison between the patient and the control groups instead was made. Insulin levels of the NAFLD group were found to be significantly higher than the control group ($p<0.05$). HDL levels were also found to be significantly lower in NAFLD patients as expected in comparison to the control group (p:0.002; $p<0.05$). A study conducted in China indicated that increased serum HbA1c level was significantly associated with NAFLD risk. The risk is explained by two mechanisms: the HbA1c level being affected by the lifetime of erythrocytes and the "glucose permeability". Insulin resistance in NAFLD leads to an increase in hepatic glucose production and an increase in serum glucose level and hence, HbA1c in the blood. In NAFLD, it causes oxidative stress which causes changes in erythrocyte morphology by reducing the membrane fluidity of erythrocytes and facilitates its capture by liver macrophage. This increased erythrocyte destruction also increases HbA1c (12). Studies on lipid profile have shown that high triglyceride and LDL levels were the only factors that exhibited a significant relationship with the degree of liver inflammation. The inclusion of such lipid abnormalities in the etiology of NAFLD in non-diabetic patients, was found to be a significant contribution of increased BMI, triglyceride and reduced HDL in the development of NAFLD (13). In our study, however, there was no significant difference between the children with NAFLD and the control group in terms of LDL and blood glucose levels ($p>0.05$).

There was no statistically significant difference between the patients with NAFLD and the control group in terms of the levels of AST, albumin, total cholesterol, triglyceride parameters ($p>0.05$). In a cohort study carried out by Adams et al. (14) in Minnesota in 2005, biochemical parameters of NAFLD patients were not found to be statistically different from individuals in the general population. However, in this group, NAFLD ranks 13th among all causes of death in the general population, and 3rd among causes of death due to liver diseases. NAFLD is the most common cause of chronic liver disease in the United States of America (USA) (15). While the average prevalence of NAFLD in the community is 20-30%, that of NASH is around 3.5-5%. NAFLD can be seen in every gender, race and age group, including children (16). According to the estimates of the World Health Organization (WHO), more than 20 million people are expected to develop cirrhosis due to NAFLD in the coming decades, and NAFLD is expected to be the most common cause of liver transplantation in 2023 (17). Because it is such a widespread public health problem, it is evident that governments and healthcare organizations need to take measures and raise awareness for this simple but mortal disease of the liver. In another study, liver-related mortality rate was found to be 1.7% in 420 NAFLD patients who were followed up for 7 years. Hepatocellular carcinoma developed in 2 patients whereas liver transplantation was required for 1 patient. In the study, advanced age, impaired glucose tolerance and cirrhosis were associated with higher mortality risk (18).

In this study, the liver long axis values and the mean SWE of the patient group were significantly higher than those of the control group (p: 0.000; p<0.05). In the study by Makkonen et al. (19), alcohol consumption, regular drug use, and monozygotic and dizygotic twins (n=313) without chronic liver disease were analyzed. It was observed that SWE values rose as the liver size increased in these patients. The relationship between serum ALT, fasting insulin levels and fatty liver was also investigated in the study. In both monozygotic and dizygotic twins, a strong association of high serum ALT and fasting insulin levels and liver fat content was found out. In our study, the mean age, BMI, mean waist circumference, ALT, GGT, HOMA-IR levels of the patient group were found to be significantly higher than the control group (p<0.05). In a study conducted in Malaysia, it was displayed that BMI was significantly higher in patients with steatosis compared to patients without steatosis (p=0.003). Metabolic parameters and HOMA-IR were significantly associated with fibrosis in patients with fibrosis (p<0.05). Fibrosis is three times more likely to occur in the presence of metabolic syndrome. Abdominal obesity causes a decrease in insulin sensitivity, as visceral adipose tissue is highly resistant to insulin and sensitive to lipolysis, it produces more free fatty acid than adipose tissue in other regions (20,21). The greater availability of substrate for lipogenesis, together with the relative hyperinsulinemia effect, increases hepatic lipogenesis, which leads to a vicious circle (22). This study highlighted no statistically significant difference between the groups in terms of AST, albumin, total cholesterol, triglyceride parameters levels (p>0.05). In a study conducted by Pacifico et al. (23), it was shown that insulin resistance and triglyceride: HDL-C ratio had a significant relationship with liver fibrosis in the presence of other metabolic parameters, and it was thought to explain its key role in the pathogenesis of NAFLD. In our study, there was no statistically significant difference between the children with NAFLD and the control group in terms of LDL and blood glucose levels (p>0.05).However, a study on adults highlighted a difference between LDL and blood sugar levels between NAFLD patients and the control group. In addition, liver elastography results of NAFLD patients were found to be higher than the control group (24).

There is a positive and statistically significant relationship between waist circumference and liver long axis values with a correlation coefficient of 33.3%. Waist circumference is an important indicator of central obesity and visceral fat. The decrease in body mass index with the lifestyle change of the patients, namely dietary modification and physical activity-enhancing change is the basis of real therapeutic recommendations for NAFLD. A loss of 7% in initial body mass significantly improves liver function. (25). A meta-analysis of 78 studies (38 NASH studies and 40 NAFLD studies, including liver biopsy studies) showed that a 5% reduction in baseline body weight contributed to a reduction in histological liver steatosis, but not fibrosis. A loss of 7% of initial body weight significantly improved the histological structure of the liver (p: 0.036; p<0.05). In our study, there was no statistically significant relationship between waist circumference and average SWE (p>0.05). In this case, it supports the fact that liver fibrosis is not affected (26). However, a significant relationship was noted in other studies abroad. Guidelines for non-invasive evaluation of liver disease in the adult population have been developed and these guidelines should be validated on children (27).

Based on MR results, ALT values in NAFLD patients were higher than the control group while AST values were similar between the two groups (p<0.05). However, ALT and AST values may not always reflect the state of the liver. Although elevated aminotransferase levels are common in most patients, their normalness does not exclude steatohepatitis and fibrosis. In a study carried out by Mofrad et al. (28), 51 patients with normal ALT levels were examined and bridging fibrosis was observed in 12 of them and cirrhosis was prevalent in 6 of the subjects.

There are several limitations to our study. Firstly, our sample size is relatively small and consists only of Turkish population. Secondly, the number of severe NAFLD cases in our patient population is very low. In this study, instead of finding the diagnostic performance of these three different noninvasive diagnostic methods (USG, SWE and MR), we analyzed the diagnostic performance of NAFLD groups in determining the relationship between liver function tests. The main reason for this was that we did not have enough patients for each NAFLD stage. Moreover, liver biopsy was not performed on NAFLD patients since it is invasive and it has no definite indication.

CONCLUSION

Abdominal US, SWE and MR examinations in analyzimg liver functions and NAFLD status were compared based on their effectiveness. It is highly essential to demonstrate liver functions and liver pathology in children with non-invasive methods. It is also useful in patient follow-up. In this study, no difference has been detected between SWE and MR findings, and we are of the opinion that SWE examination will be more practical in estimating liver functions in patient follow-up since MR examination is more costly.

NAFLD continues to be an increasingly common public health problem in children. It is important for patients to follow counseling from specialized dieticians, pediatric gastroenterologists and pediatric endocrinologists and of course, proper follow-up is also crucial. During this follow-up, imaging tools and tests that enable non-invasive evaluation of the liver would be very valuable.

We are of the opinion that body measurements, especially waist circumference, metabolic parameters and advanced US methods (SWE, TE) are highly relevant.

ETHICAL DECLARATIONS

Ethics committee approval: This study was approved by the Clinical Researches Ethical Committee of Taksim Training and Research Hospital (Date: 26/06/2019, Decision No: 81).

Informed consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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