



Non invasive evaluation of liver fibrosis in paediatric patients with nonalcoholic steatohepatitis

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Abstract

AIM: To identify the independent predictors of hepatic fibrosis in 69 children with nonalcoholic steatohepatitis (NASH) due to nonalcoholic fatty liver disease (NAFLD).

METHODS: All patients with clinically suspected NASH underwent liver biopsy as a confirmatory test. The following clinical and biochemical variables at baseline were examined as likely predictors of fibrosis at histology: age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, fasting insulin, homeostatic model assessment for insulin resistance (HOMA-IR), cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST/ALT ratio, gamma glutamyl transferase (GT), platelet count, prothrombin time (PT).

RESULTS: At histology 28 (40.6%) patients had no fibrosis and 41 (59.4%) had mild to bridging fibrosis. At multivariate analysis, BMI > 26.3 was the only independent predictor of fibrosis (OR = 5.85, 95% CI = 1.6-21).

CONCLUSION: BMI helps identify children with NASH who might have fibrotic deposition in the liver.

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Key words: Nonalcoholic steatohepatitis; Obesity; Body mass index; Liver fibrosis; Non invasive diagnosis

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INTRODUCTION

With the current epidemic prevalence of obesity and diabetes mellitus in the general population^[1], nonalcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease in many countries^[2,3]. The characteristic histological features of NAFLD may range from a bland hepatic steatosis to hepatocellular damage plus inflammation with or without fibrosis known as nonalcoholic steatohepatitis (NASH)^[4,5]. Paralleling the increasing prevalence of obesity and type 2 diabetes in the pediatric population, NAFLD especially its more severe histological form-NASH, is expected to become one of the most common causes of end-stage liver disease in both children and young adults. In this population, histological confirmation remains controversial due to the cost of liver biopsy and the complications directly related to the procedure or to the sedation, reported to be higher (up to 18%) in infants than in adults^[6]. Furthermore, there is no proven therapy for NASH that could justify paired biopsies to compare histology with baseline features.

A first step for the clinician is to select children at risk of progressive liver disease from those with steatosis alone, and the secondary step is to identify in the former possibly by non invasive diagnosis of those with liver fibrosis. Raised alanine aminotransferase levels (ALT) have been shown to correlate best with a diagnosis of steatohepatitis (95% CI = 3.1-23.5, $P < 0.001$), but the other two factors, namely insuline resistance index ($IR > 5.0$, 95% CI = 3.4-26, $P < 0.001$) and hypertension ($> 140/90$, 95% CI = 2.0-13.5, $P = 0.001$), are also found to have significant independent predictive effects^[7]. The presence of at least two of the three factors provides the best combination of sensitivity (0.8) and specificity (0.89) for predicting NASH^[7].

Non invasive diagnosis of liver fibrosis has been extensively evaluated in adult population with NAFLD^[8-11]. Obesity, hypertension, male gender, hyperdyslipemia, and insulin resistance have been reported to be independent predictors of advanced fibrosis. In contrast, in paediatric population data are lacking and liver biopsy is still considered the only reliable tool for diagnosing histological

features.

The aim of this study was to identify the independent predictors of fibrosis in children with NAFLD by selecting groups of children at a higher risk of progressive liver damage (NASH population). Clinical and/or biochemical parameters routinely performed in clinical practice that can predict abnormal liver histology were tested.

MATERIALS AND METHODS

The study protocol was conformed to the ethical guidelines of the 1975 Declaration of Helsinki and performed according to the recommendations of the Ethics Committee of Children's Hospital and Research Institute Bambino Gesù in Rome, Italy. Informed consent was directly obtained from each parent or responsible guardian.

Patients

Sixty-nine untreated consecutive children (49 males and 20 females) seen at our institution from June 2001 to April 2003 were included in this study. All patients underwent evaluation for persistently elevated serum aminotransferase levels associated with diffusely echogenic liver on imaging studies suggestive of fatty infiltration. The diagnosis of NAFLD was confirmed by a percutaneous liver biopsy in all cases. Secondary causes of steatosis including alcohol abuse (≥ 140 g/wk), total parenteral nutrition, and the use of drugs known to precipitate steatosis were excluded in all cases. Hepatitis A-G, cytomegalovirus and Epstein-Barr virus infections were ruled out by appropriate tests. In all cases, autoimmune liver disease, metabolic liver disease, Wilson's disease, and α -1-antitrypsin deficiency were ruled out using standard clinical and laboratory evaluation as well as liver biopsy features. Body mass index (BMI), the weight in kilograms divided by the square of the height in meters, was calculated. To compare BMI across different ages and in both boys and girls, BMI Z score was calculated. The Z score represents the number of standard deviations above or below the considered population mean value, based on standardized tables for children^[12].

Evaluation of glucose metabolism and insulin sensitivity

All patients underwent a 2-h oral glucose tolerance test (OGTT) with the standard 1.75 g of glucose per kg, or a maximum of 75 g. Glucose tolerance status was determined according to the recently revised American Diabetes Association classification^[14] in which a fasting plasma glucose (FPG) level up to 99 mg/dL is considered normal, impaired fasting glucose (IFG) is defined by a FPG of 100-125 mg/dL, impaired glucose tolerance (IGT) is defined by a 2-h plasma glucose of 140-199 mg/dL, diabetes mellitus is defined by a FPG ≥ 126 mg/dL, or a 2-h plasma glucose ≥ 200 mg/dL. IFG and IGT are officially termed "pre-diabetes".

The degree of insulin sensitivity/resistance was determined by the homeostatic model assessment insulin resistance (HOMA-IR) using the formula: $IR = (\text{insulin} \times \text{glucose}) / 22.5^{[13]}$, and by the insulin sensitivity index (ISI-comp) derived from OGTT using the formula: $ISI = (10\,000 / \text{square root of } [\text{fasting glucose} \times \text{fasting insulin}]$

$\times [\text{mean glucose} \times \text{mean insulin during OGTT}]^{[13]}$. Both HOMA-IR and the OGTT-derived ISI have a significant correlation with the 'gold standard' euglycemic hyperinsulinemic glucose clamp technique. A HOMA-IR value > 2 and/or ISI-comp value < 6 were considered an indication of insulin resistance.

Liver histology

Biopsies were performed in all children using an automatic core biopsy device (Biopince, Amedic, Sweden) with an 18-G needle (150 mm long), which is able to cut tissue with lengths up to 33 mm with extreme precision^[6]. Liver biopsies were at least 15 mm in length and read by a single liver pathologist who was unaware of the patient's clinical and laboratory data. Biopsies were routinely processed (formalin-fixed, paraffin-embedded) and analysed in sections stained with (1) hematoxylin and eosin for overall assessment of parenchymal architecture, hepatocyte abnormalities and inflammatory infiltrates; (2) Van Gieson for assessment of fibrosis and architectural changes; (3) PAS-D after diastase predigestion to highlight debris in portal macrophages and Kupffer cells as well as eosinophilic globules in periportal hepatocytes (characteristic of endoplasmic reticulum storage disease, namely α -1 antitrypsin); and (4) Perl's (Prussian blue) stain for estimation of iron storage in hepatocytes and sinusoidal lining cells. Additionally, immunoistochemical staining with α -1 antitrypsin was used to exclude α -1 antitrypsin-associated liver disease.

The main histological features commonly described in NALFD/NASH including steatosis, inflammation (portal and lobular), hepatocyte ballooning, and fibrosis, were scored according to the scoring system for NAFLD, recently developed and validated by the NIH-sponsored NASH Clinical Research Network^[14]. Briefly, steatosis was graded on a 4-point scale: grade 0 = steatosis involving $< 5\%$ of hepatocytes; grade 1 = steatosis involving up to 33% of hepatocytes; grade 2 = steatosis involving 33%-66% of hepatocytes; and grade 3 = steatosis involving $> 66\%$ of hepatocytes. **Lobular inflammation** was graded on a 4-point scale: grade 0 = no foci; grade 1 = less than 2 foci per 200 \times field; grade 2 = 2-4 foci per 200 \times field; grade 3 = more than 4 foci per 200 \times field. Hepatocyte ballooning was graded from 0 to 2: 0 = none, 1 = few balloon cells, 2 = many/prominent balloon cells. Stage of fibrosis was quantified in a 4-point scale: stage 0 = no fibrosis; stage 1 = perisinusoidal or periportal fibrosis (1a = mild, zone 3, perisinusoidal; 1b = moderate, zone 3, perisinusoidal; 1c = portal/periportal); stage 2 = perisinusoidal and portal/periportal fibrosis; stage 3 = bridging fibrosis; and stage 4 = cirrhosis. Other features, such as zonal distribution of steatosis, presence of microvesicular steatosis, glycogenated nuclei, lipogranulomas, PAS-D cells, acidophil bodies and Mallory bodies, also were recorded. Portal tract inflammation was graded from 0 to 3 (0 = none, 1 = mild, 2 = moderate and 3 = severe).

Statistical analysis

Continuous variables were expressed as mean \pm SD, while categorical variables were expressed as absolute and percentage frequency. Mann-Whitney rank-sum test and Yates

Table 1 Anthropometric, clinical and biochemical characteristics of patients (*n* = 69)

| Variables characteristics | mean \pm SD | Range |
|-------------------------------|------------------|-----------|
| Age (mo) | 145.7 \pm 39.5 | 44-226 |
| BMI (kg/m ²) | 26.3 \pm 4.1 | 15.2-38.3 |
| BMI Z score | 2.0 \pm 0.79 | 0.8-5.0 |
| Type II diabetes <i>n</i> (%) | 2 (2.3) | |
| Hypertension <i>n</i> (%) | 2 (2.3) | |
| AST (IU/L) | 42 \pm 16 | 19-90 |
| ALT (IU/L) | 60 \pm 31 | 10-192 |
| GT (IU/L) | 23 \pm 20 | 10-130 |
| Cholesterol (mg/dL) | 152 \pm 32 | 75-222 |
| Triglyceride (mg/dL) | 86 \pm 44.5 | 28-348 |
| Fasting glucose (mg/dL) | 82 \pm 11 | 60-138 |
| Fasting insulin (mU/L) | 12.5 \pm 6.4 | 3.5-30.7 |
| HOMA-IR | 2.55 \pm 1.39 | 0.67-6.29 |
| ISI-comp | 4.4 \pm 2.0 | 1.26-9.16 |

BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine Aminotransferase; γ GT: gamma-glutamyl transpeptidase; HOMA-IR: homeostatic model assessment-insulin resistance; ISI: insulin sensitivity index.

corrected χ^2 were used when appropriate, at the univariate analysis in which several proposed indices for the assessment of fibrosis were assessed with consideration of the following clinical and biochemical parameters, such as glycemia, BMI, body mass index standard deviation score (BMI-SDS), cholesterol, thriglycerides, systolic blood pressure (SBP), dyastolic blood pressure (DBP), ALT, alanine aminotransferase (ALT), AST/ALT ratio, GT, PLT, PT, HOMA, ISI, insulin. The independent role of variables selected by univariate analysis was tested by stepwise logistic regression. Maximal likelihood method was used for entering and removing variables. For all calculations, the biomedical data processing system (BMDP dynamic version 7, University of California, Los Angeles, CA) was used.

RESULTS

Patient characteristics

Clinical details of the 69 children with NAFLD are summarized in Table 1. The median age was 147.5 \pm 39.5 (range, 44-226) mo with a male predominance (71%). The mean ALT and AST levels were 60 IU/L (normal values < 36 IU/L) and 42 IU/L (normal values < 32 IU/L) respectively. Insulin resistance, as indicated by a HOMA-IR > 2 or ISI-comp < 6, was present in 37 (53.6%) and 54 (78.2%) children, respectively. There was no significant correlation between BMI Z-score and HOMA-IR (r = 0.15, P = 0.21) or BMI Z-score and ISI-comp (r = 0.13, P = 0.27). The mean total cholesterol and triglyceride levels were 152 mg/dL and 86 mg/dL, respectively. Only 3 children had elevated triglyceride levels (i.e. > 160 mg/dL), and 7 children had hypercholesterolemia (i.e. > 200 mg/dL).

Glucose metabolism

Overall, 67 (97.1%) patients showed normal glucose metabolism on OGTT, whereas the remaining 2 patients (2.9%) showed impaired glucose metabolism, including 1 patient classified as IFG, and 1 patient as IGT. These

Table 2 Histological findings in the patients population (Biopsies scored according to Kleiner *et al*), *n* (%)

| Grade/Stage | Steatosis | Necroinflammation | Fibrosis |
|-------------|-----------|-------------------|-----------|
| 0 | - | 12 (17.4) | 28 (40.6) |
| 1 | 25 (36.2) | 52 (75.3) | 36 (52.2) |
| 2 | 27 (39.2) | 5 (7.2) | 1 (1.4) |
| 3 | 17 (24.6) | - | 4 (5.8) |
| 4 | - | - | - |

2 patients were significantly older (18.4 \pm 0.4 *vs* 10.8 \pm 4.5 years; P < 0.05) than those with normal glucose metabolism. The BMI Z-score (1.5 \pm 1.32 *vs* 1.94 \pm 0.67, P = NS) and HOMA-IR (2.35 \pm 1.75 *vs* 2.5 \pm 1.34, P = NS) were not statistically different between the two groups (no fibrosis *vs* fibrosis).

Liver histology

The histological findings are summarized in Table 2. All biopsies showed steatosis, mostly macrovesicular. The pattern of steatosis was diffuse or scattered lobular, and only showed zonal distribution in ten cases. Inflammation was present in 57 (82.6%) biopsies. The inflammatory infiltrate was mainly composed of lymphocytes and neutrophils, and when granulomas were present, mononuclear histiocytic cells and eosinophils were also present. Hepatocyte ballooning was present in 34 (49%) of the 69 biopsies, whereas apoptotic cells were noted occasionally. Glycogenated nuclei of variable dimension were present in 35 (50.7%) of the 69 cases, and this nuclear change was noted mostly in zone 1 of the hepatic lobule. No Mallory hyaline was noted in any case, and mild iron deposition was present in 3 cases.

Increased fibrosis was noted in 41 patients (59.4%), mostly of mild (stage 1) severity, one patient in stage 2, and 4 children (5.8%) were showing septal fibrosis (stage 3). Among the 36 patients with stage 1 fibrosis, 3 were 1a, 5 were 1b, and 28 were 1c. No patient showed liver cirrhosis at histology.

Table 3 shows the comparison between children with and without liver fibrosis. Children with liver fibrosis were slightly older, and had significantly higher BMI than those without fibrosis. Those with fibrosis also showed higher serum levels of cholesterol and triglycerides, although the mean values were still within the normal range, and the prevalence of hypercholesterolemia and hypertriglyceridemia was not different between the two groups. Liver enzymes or AST/ALT ratio was not different between those with and without fibrosis.

At multivariate analysis of baseline clinical and biochemical parameters in 28 patients with stage 0 fibrosis in comparison to the 41 patients with stage higher than or equal to 1, only BMI was independently associated with fibrosis (OR = 5.85, 95% IC = 1.6-21). At ROC analysis the cut off value for BMI was 26.3 (sensitivity 66%, specificity 71%). Among the 35 patients with BMI \geq 26.3, 27 (77.1%) had fibrosis stage \geq 1, whereas fibrosis stage \geq 1 was present in 14 (41.2%) out of 34 children with BMI < 26.3.

Table 3 Comparison of clinical and biochemical features according to stage of fibrosis (mean \pm SD)

| Features n (%) | No fibrosis 28 (40.6) | Fibrosis \geq 1 41 (59.4) | P |
|---------------------------|--------------------------|--------------------------------|------|
| Age (mo) | 140.3 \pm 34 | 151.4 \pm 41 | 0.2 |
| Fasting glucose (mg/dL) | 82.4 \pm 9.9 | 81.5 \pm 11.7 | 0.7 |
| BMI (kg/m ²) | 25.2 \pm 3.3 | 27.5 \pm 4.5 | 0.01 |
| BMI-SDS | 1.84 \pm 0.5 | 2.0 \pm 0.7 | 0.05 |
| Cholesterol (mg/dL) | 148.8 \pm 34.4 | 160.2 \pm 36.2 | 0.2 |
| Triglycerides (mg/dL) | 82.4 \pm 59.5 | 97.9 \pm 39.4 | 0.2 |
| Systolic pressure (mmHg) | 110.2 \pm 11.6 | 116 \pm 15 | 0.07 |
| Diastolic pressure (mmHg) | 67.0 \pm 8.2 | 67.1 \pm 8.3 | 0.9 |
| AST (U/L) | 41.6 \pm 14.6 | 49.3 \pm 32.2 | 0.18 |
| ALT (U/L) | 65.6 \pm 26 | 76.2 \pm 82.6 | 0.4 |
| AST/ALT | 0.7 \pm 0.3 | 0.9 \pm 0.5 | 0.05 |
| GT (U/L) | 25.2 \pm 25 | 23.7 \pm 16.6 | 0.7 |
| PLT (10 ³ /L) | 285 \pm 66 | 295 \pm 59 | 0.5 |
| PT | 87.9 \pm 9.3 | 90.2 \pm 7.6 | 0.3 |
| HOMA-IR | 2.7 \pm 1.5 | 2.4 \pm 1.1 | 0.4 |
| ISI | 4.0 \pm 1.7 | 4.5 \pm 1.9 | 0.4 |
| Fasting insulin (mU/L) | 13.5 \pm 6.7 | 11.6 \pm 5.8 | 0.2 |

BMI-SDS: body mass index standard deviation score; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PLT: platelets count; PT: prothrombin time; HOMA-IR: homeostatic model assessment-insulin resistance; ISI: insulin sensitivity index.

DISCUSSION

Over the last decades, the prevalence of overweight and obesity among children has increased dramatically, becoming an important public health problem. The negative consequences of paediatric overweight can occur during childhood or adulthood and may result in metabolic, physical, psychosocial and economic consequences. Among these, non alcoholic fatty liver disease has become a growing clinical problem and a major cause of liver-related morbidity.

The accurate means to distinguish between simple fatty liver and steatohepatitis is a liver biopsy as NASH is diagnosed when tissue histology shows fat along with inflammation and damage to liver cells. This distinction has a prognostic relevance because whereas NAFLD is a benign nonprogressive condition, NASH can progress to cirrhosis, liver failure and hepatocellular carcinoma^[15]. However, the need for histological evaluation of NAFLD remains controversial as no efficacious treatment strategies have been yet designed. Persistent hypertransaminasemia of non-alcoholic steatohepatitis in obese children may resolve after weight reduction and high doses of vitamin E treatment, but the impact on the natural history needs to be validated by large-cohort controlled studies^[16-19]. Thereby, the search for non invasive diagnostic tests of liver fibrotic deposition should be preferred to the expensive and invasive procedure of liver biopsy, whereas the latter should be limited to those cases with uncertain diagnosis^[7].

Our previous validation study regarding non invasive diagnosis of liver fibrosis in adults with chronic hepatitis C to cirrhosis showed a significant inverse correlation between stage of fibrosis and platelet count with the

highest platelets count in patients with fibrosis 0-2, lower in those with grade 3 and lowest in those with grade 4^[20]. Also, an inverse correlation between spleen size and platelets count has been observed ($r = -0.54$, $P < 0.0001$) and thrombocytopenia presents in 71% and 23% of patients with or without splenomegaly respectively^[21]. The accuracy of platelet count was not significant in children ($P = 0.5$) as most of the children with NAFLD had stage 1 of fibrosis (52.2%), and less than 8% had a fibrotic score ≥ 2 . The amount of scar deposition that characterizes these stages of fibrosis is too low to favour hemodynamic changes with portal hypertension, altered production of thrombopoietin and enlarged spleen sequestration.

At multivariate analysis of baseline clinical and biochemical parameters in the present study, BMI was an independent predictor of fibrosis (OR = 5.85, 95% CI = 1.6-21); at the cut off value of 26.3 kg/m², the BMI evaluation showed a sensibility and specificity of 66% and 71%, respectively, in ascertaining the presence of fibrosis in children. Conceivably, the BMI evaluation may be useful in picking up those children at higher risk of disease progression. Future studies investigating the natural history and the long-term sequelae of our histological findings in children are warranted to corroborate our claim.

In conclusion, increased BMI appears to correlate with long term progression to fibrosis and cirrhosis. Reversal of obesity with a gradual weight reduction can improve laboratory abnormalities, histologic changes and liver size in children with NAFLD. BMI may be considered a good non invasive indicator of the underlying disease. Although little controversy exists about the role of liver biopsy as the best accurate method available to assess the stage of the disease, the decision to perform it should be weighed against the risk of the procedure and the impact of the information obtained. In particular, in paediatric population, the timing of biopsy should be individualized and postponed to non-invasive diagnostic tools.

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COMMENTS

Background

Interest is growing regarding the nonalcoholic steatohepatitis (NASH) in pediatric age and in the usefulness of liver biopsy for its detection.

Research frontiers

Non invasive detection of liver fibrosis may help better define new therapeutical approaches in a larger number of pediatric NASHs.

Innovations and breakthroughs

Still new diagnostic parameters for non invasive detection of liver fibrosis need to be searched and validated in paediatric population. This work proves that BMI helps identify children with NASH who might have fibrotic deposition in the liver.

Applications

BMI as one of the future criteria can be used for detection of pediatric patients with NASH-fibrosis.

Peer review

This study tested the accuracy of various clinical and biochemical parameters for the diagnosis of NASH in 69 children. The results show that only increased BMI is significantly associated with fibrosis, whereas other parameters have not been identified as predictive. This study is accurate and is of importance due to the absence of any non invasive method for the diagnosis of liver fibrosis in the paediatric population. While being interesting, this observation should be further confirmed.

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