Noninvasive Assessment of Nonalcoholic Fatty Liver Disease in Obese or Overweight Patients

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This article has an accompanying continuing medical education activity on page e87. Learning Objective—At the end of this activity, the successful learner will be able to select and interpret the parameters they need to assess the presence of NASH in obese patients without the need for a liver biopsy.

BACKGROUND & AIMS: Reliable noninvasive tools are needed for staging nonalcoholic fatty liver disease (NAFLD). Published scoring systems have not been validated in prospective assessments of unselected patients. We aimed to identify factors that predicted development of nonalcoholic steatohepatitis (NASH) in a large group of overweight or obese patients and compared these with established factors. **METHODS:** We performed a prospective analysis of factors associated with the development and severity of NAFLD in patients at a single obesity center. We evaluated liver involvement in 542 patients by a large set of routine and non-routine parameters, including ultrasound and genetic testing. Those suspected of having NAFLD underwent liver biopsy (57.7%). Patients were divided into design cohort (n = 200) and validation cohort (n = 113) to identify factors associated with the presence and severity of NAFLD and NASH. **RESULTS:** Factors independently associated with development of NASH included increased levels of alanine aminotransferase (ALT), fasting levels of C-peptide, and ultrasound steatosis scores (USSs), with area under the receiver operating curve (AUROC) values of 0.854 in the design cohort and 0.823 in the validation cohort. NASH activity scores also correlated with level of ALT, USS, and fasting level of C-peptide (R^2 = 0.491). Independent predictors of advanced fibrosis included waist circumference and level of aspartate aminotransferase (AUROC values of 0.839 and 0.846 for design and validation cohorts, respectively; negative predictive values of 98% and 97%, respectively, for a cutoff of −2.14). Previously published scoring systems had significantly lower AUROC values. Levels of *CK18* and *PNPLA3* polymorphisms correlated with development of NASH but did not add value. **CONCLUSIONS: Parameters routinely analyzed in assessing obese patients can be used to determine the presence of NASH and advanced fibrosis. Non-routine tests do not increase diagnostic accuracy. Previously published scores are significantly less accurate.**

Keywords: Risk Factor; Liver Disease; Complication; Genetic Test; Liver Stiffness.

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are increasingly recognized as important causes of liver-related and non–liver-related morbidity and mortality, with an increasing impact on health care resources.[1,2]

The pathophysiology of NAFLD and its related morbidities remain largely unknown. Merely on the basis of epidemiologic data, NAFLD and NASH seem to be intimately linked to (visceral) obesity, insulin resistance and diabetes, and metabolic syndrome (MS).[2] Many people are hence at risk for NAFLD and NAFLD-related complications.

The gold standard for the diagnosis of NAFLD and NASH is liver histology. Because of its inherent risks and for logistical reasons, liver biopsy cannot be applied on a large scale. Therefore, several attempts have been made to develop noninvasive tools for NAFLD and NASH diagnosis.[3–9] Because those tools are mostly designed in highly selected populations and/or are based on retrospective analysis, their diagnostic accuracy is frequently unsatisfactory when applied to randomly presenting patients.[10]

In the present study, we prospectively assessed the presence and severity of NAFLD in a population at risk by a two-step approach to avoid some identifiable mechanisms of selection bias. The patients were subsequently divided into a design cohort and a validation cohort to develop scores that must allow one to accurately and noninvasively identify the presence and severity of NAFLD and NASH in randomly presenting patients.

Methods

Metabolic Work-up

Patients presenting at the obesity clinic for a problem of overweight underwent a series of examinations including a metabolic and a liver-specific program as previously reported[11] (Supplementary Material).

Abbreviations used in this paper: ABT, aminopyrine breath test; ALT, alanine aminotransferase; APRI, AST-to-platelet index; AST, aspartate aminotransferase; CK-18, cytokeratin 18; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NAS, NASH activity score; NASH, nonalcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3; USS, ultrasound steatosis score.

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Because liver steatosis seems to be closely related to MS,[1] MS features were specifically recorded according to both the US Third Adult Treatment Panel of the National Cholesterol Education Program[12] and the International Diabetes Federation.[13]

Hepatologic Work-up

The liver-specific program, approved by the Ethics Committee of the Antwerp University Hospital, included additional blood analysis (Supplementary Material), an abdominal Doppler ultrasound, and an aminopyrine breath test (ABT) as a measure for liver metabolic reserve.[14] The ultrasound appearance of the liver parenchyma was scored by using a modification of the Saverymuttu classification[15] by making the sum of the echogenicity of the liver parenchyma compared with the renal parenchyma (no hyperechogenicity, 0; mild-to-moderate hyperechogenicity, 1; moderate-to-severe hyperechogenicity, 2) and posterior beam attenuation (absent, 0; present, 1), resulting in an ultrasound steatosis score (USS) ranging from 0 to 3.

Patients were excluded from further analysis in case of significant alcohol consumption (>20 g/d), history of bariatric surgery, diagnosis of another liver disease, or preexisting diabetes.

The possibility of liver involvement was defined by abnormal liver tests (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] and/or γ-glutamyl transpeptidase and/or alkaline phosphatase); liver ultrasound abnormality (steatotic liver [USS ≥1)[15]; and abnormal ABT.[14] For ALT, 3 different cutoff levels were used: the upper limit of normal set by the biochemistry laboratory (56 IU/L), the classic cutoff of 40 IU/L, and the limits proposed by Prati et al[16] (30 IU/L in men, 19 IU/L in women).

Liver Biopsy

When one or more of these criteria were met, a liver biopsy was proposed. For patients going to surgery, a liver biopsy was proposed regardless of the preset criteria. Liver biopsy was performed (after additional informed consent) percutaneously (16-gauge Menghini) or perioperatively (14-gauge Tru-Cut).

Hematoxylin-eosin stain, Sirius red stain, reticulin stain, and Perl's iron stain were routinely performed on all biopsies, which were reanalyzed by one experienced pathologist (E.V.M.) who was blinded for any clinical data. The different histologic features of NAFLD were assessed by using the NASH Clinical Research Network Scoring System.[17] The NASH Activity Score (NAS) was calculated by making the sum of the scores for steatosis, lobular inflammation, and ballooning.[17] Significant fibrosis was defined as a fibrosis score ≥2. Advanced fibrosis was defined as a fibrosis score ≥3.

Since the publication of the NASH Clinical Research Network Scoring System, the definition of NASH by a NAS ≥5 has been widely adopted. This definition is, however, slightly different from the former definition of Brunt et al,[18] and its use outside the setting of interventional studies was recently questioned.[19] We therefore used both definitions separately.

Additional Tests

Cytokeratin 18 (CK-18) has shown promising properties as a serum marker of liver fibrosis and was determined by using a two enzyme-linked immunosorbent assay (PEVIVA AB, Bromma, Sweden) according to the manufacturer's instructions.[20]

Single nucleotide polymorphisms in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) locus on chromosome 22 have recently been associated with NASH independently from metabolic factors.[21] We studied the rs738409 polymorphism, which seems to be the most important single nucleotide polymorphism.

Scoring Systems

To design and validate scores that might predict the presence and severity of NAFLD and fibrosis, patients with liver biopsy were randomly assigned to a design cohort (n = 200) or a validation cohort (n = 113) by the SPSS 18.0 (SPSS Inc, Chicago, IL) software package after all data had been obtained.

The following published scores were used for comparison: NAFLD liver fat score,[3] the fatty liver index,[4] the body mass index, AST/ALT ratio, and diabetes mellitus score,[5] the AST-to-platelet index (APRI),[6] the fibrosis test based on age, AST, ALT, and platelet count index,[7] the NAFLD fibrosis score,[8] and Forns' index[9] (Supplementary Material).

Statistical Analysis

See Supplementary Material.

Results

Main Characteristics

Between October 2005 and October 2010, 553 patients were screened. Eleven patients were excluded from further analysis because of the discovery of a formerly unknown chronic liver disease (1 primary biliary cirrhosis, 2 hemochromatosis, 1 chronic hepatitis C, 2 chronic hepatitis B, 1 autoimmune hepatitis) or because of alcohol consumption disclosed on repeated interrogation (4 patients). The main characteristics of the remaining 542 patients are listed in Table 1.

Histology

In 64 of 542 patients (11.8%), none of the criteria to propose a biopsy were present. In the other patients, at least one criterion was met. Liver biopsy was performed in 313 of 478 of those patients (65.5%, or 57.7% of the overall cohort of 542 patients). Liver biopsy was performed during bariatric surgery in 133 of 313 (42.5%).

Mean biopsy length was 18.2 ± 7.1 mm (range, 8–45), and the mean number of portal tracts was 9.6 ± 3.9 (range, 5–25). The distributions according to the grade of steatosis (Figure 1*A*), the NAS (Figure 1*B*), and the stage of fibrosis (Figure 1*C*) are shown in Figure 1. On the basis of the definition by Brunt et al,[18] 163 of 313 (52.1%) had NASH. On the basis of the definition by Kleiner et al,[17] 105 of 313 (33.5%) had NASH. Three patients had NASH on the basis of Kleiner et al but not by Brunt et al, and 61 patients had NASH according to Brunt et al, but a NAS <5. The latter 61 all had a borderline or possible NASH (NAS 3 or 4) according to Kleiner et al.

Design and Validation Cohorts

Besides a higher mean arterial blood pressure in the design cohort, no significant differences were noted (Supplementary Material).

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