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Transient elastography to assess liver stiffness in patients with inflammatory bowel disease

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ABSTRACT

Background: Liver injury during inflammatory bowel disease (IBD) is primarily diagnosed by liver biopsy, which has a small but serious risk of severe complications. The aim of this study was to assess liver stiffness, and subsequently the prevalence and associations of liver fibrosis in IBD patients with thiopurine therapy and other clinical factors, by using transient elastography (TE).
Methods: In this prospective, international two-center study, included IBD-patients underwent TE measurements. Laboratory results and medication reports, radiology results and historical liver biopsy results were extracted from the patient charts.
Results: Transient elastography results of 168 patients were presented. Moderate and severe fibrosis were detected in 4% (7/168) and 1% (1/168) of the cohort, respectively. Factors contributing to lower liver stiffness were female gender and (historical) exposure to azathioprine. Further, there was a statistical trend towards lower liver stiffness in patients using thiopurines overall (4.7 vs. 5.2 kPa, p = 0.07). Liver stiffness correlated positively with waist circumference, liver enzyme tests, hemoglobin and 6-methylmercaptopurine concentration and negatively with platelet count.
Conclusion: Exposure to thiopurine therapy was not associated with higher liver stiffness, although no clinical difference in severity of fibrosis was detected. Further research should robustly determine the accuracy of TE as an evaluation of liver fibrosis in IBD patients.

1. Introduction

Inflammatory bowel disease (IBD) refers to both Crohn's disease (CD) and ulcerative colitis (UC), which are chronic disorders characterized by recurrent inflammation of the gastrointestinal tract [1,2]. Although the exact etiology of IBD remains unclear, it is well established that genetic and environmental factors contribute to the abnormal immune responses that underlie CD and UC [3–5].

Immunosuppressive drugs are essential to maintain remission in IBD, especially CD [6,7]. Thiopurines, consisting of the more conventionally used derivatives azathioprine (AZA) and mercaptopurine (MP) and (in some countries including The Netherlands) thioguanine (TG) [8], are immunomodulating agents used in the treatment of IBD [9,10]. Additionally, in CD patients, methotrexate (MTX), a dihydrofolate reductase, might serve as an alternative immunomodulator [11]. One of the concerns of these therapies is the associated hepatotoxicity, as both therapies are known to cause liver injury and liver enzyme abnormalities in IBD patients [12,13]. Hepatotoxicity, defined as either an elevation of liver enzymes over two times the upper limit of normal or the presence of histopathologically proven hepatic fibrosis or cirrhosis, occurs in up to 20% of IBD patients treated with conventional thiopurine derivatives [14–16] and in a fairly similar proportion of MTX users [17–19].

The gold standard of diagnosis in the management of several liver abnormalities, such as NRH or non-alcoholic fatty liver dis-

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ease (NAFLD) is, apart from detailed laboratory measurements, a histopathological examination of a liver biopsy [20–22]. However, undergoing a liver biopsy is an invasive and painful procedure with a small but evident risk of severe complications such as pain or post-procedural bleeding, occasionally resulting in death [22,23].

Therefore, there is a need for a non-invasive method to detect liver abnormalities in IBD patients. Transient elastography, which can be performed by the use of Fibroscan® (EchoSens, Paris, France), is a non-invasive procedure that is used to examine the stiffness of liver tissue [24]. Amongst a large group of patients with chronic hepatitis B or C infection, significant correlations between liver stiffness measurements (LSM) with Fibroscan and liver fibrosis diagnosed by histological evaluation of liver biopsy specimens have been found [25]. These findings were reproduced in a small number of IBD-patients [26–28]. Liver stiffness measurements are currently used to detect liver fibrosis and cirrhosis in a wide range of liver diseases, preventing patients from undergoing invasive liver biopsies [29].

Due to the lack of data assessing the role of transient elastography for diagnosing and staging liver fibrosis in IBD patients, we primarily aimed to assess liver stiffness in IBD patients and subsequently to establish the prevalence of liver fibrosis in IBD patients by the use of Fibroscan. Second, we aimed to determine whether the use of immunosuppressive agents influenced liver stiffness measurements.

2. Methods

2.1. Patient selection

All consecutive IBD patients from the VU University Medical Center (VUmc; Amsterdam, The Netherlands) and Christchurch Hospital (ChH; Christchurch, New Zealand) were asked to undergo a Fibroscan prior to their outpatient clinic appointment. Inclusion criteria for this study were: patients ≥18 years, an established diagnosis of IBD [30] and being able to give (written or digital) informed consent. Exclusion criteria were pregnancy, history of implantable cardiac device (ICD) implantation and a history of known (concomitant) liver disease (e.g. viral hepatitis, liver cancer, liver cirrhosis or liver fibrosis).

2.2. Data collection

Demographic information was collected at time of visit to the outpatient clinic using two questionnaires. The first questionnaire was used for the collection of medical history and demographic characteristics (e.g. age, gender, weight, height, use of medications, medical history and smoking status). The second questionnaire was used to obtain data on alcohol use based on the standardized AUDIT [31] method.

2.3. Laboratory data

Laboratory data were extracted from the medical charts and included: bilirubin (normal value <20 μmol/L), aspartate aminotransferase (AST; female <30 U/L, male <35 U/L), alanine aminotransferase (ALT; female <35 U/L, male <45 U/L), alkaline phosphatase (AP; <120 U/L), gamma glutamyl-transferase (GGT; female <40 U/L, male <55 U/L), albumin (35–52 g/L), platelet count (PC; 150–400 $\times 10^9$/L), hemoglobin concentration (Hb; female 7.5–10.0 mmol/L, male 8.5–11.0 mmol/L), white blood cell count (WBC; 4.0–10.0 $\times 10^9$/L). These results were collected at two timepoints: either at the time of IBD diagnosis or (if applicable) at initiation of thiopurine therapy, and at the time of Fibroscan (±4 weeks). Data of previous abdominal ultrasounds (US), computed tomography (CT) or magnetic resonance imaging (MRI) of the liver and histopathological liver biopsies were also extracted from the patient charts.

2.4. Thiopurine metabolite measurement

When thiopurine derivatives were used at the time of Fibroscan, thiopurine metabolites were measured using a slightly modified method by Dervieux et al. [32]. To compare the measured concentrations of 6-thioguaninenucleotide concentration (6-TGN) with the internationally used method by Lennard and Singleton [33], the measured concentrations were divided by 2.6, as demonstrated by Shipkova et al. [34]. 6-Methylmercaptopurine concentrations (6-MMP) are similar using both assays (<5700 pmol/8 $\times 10^8$ red blood cells (RBC)). The reference values used for 6-TGN in AZA/MP users were 230–450 pmol/8 $\times 10^8$ RBC [35].

2.5. Measurement of liver stiffness

Liver stiffness was evaluated by performing Fibroscan measurements in all participants. Patients were asked to be nil by mouth for at least three hours prior to participation, since blood flow and stiffness of the liver could be increased for up to 180 min after food intake [36]. The practitioners of the Fibroscan attended training in the scanning procedure. Liver stiffness measurements were performed by one practitioner per center (CvE and BM) and supervised by a specialist hepatologist (CS and DR).

As instructed by the manufacturer, the right lobe of the liver was targeted during the procedure with an ultrasound probe. The probe transducer was covered with coupling gel. A portion of the liver (at least 6 cm thick) free from large vessels was targeted by the use of ultrasound through an intercostal space. A 50-MHz wave was sent through the liver by the transducer. The shear wave velocity was measured and converted by the machine into liver stiffness, expressed in kilopascals (kPa) [37]. Patients were positioned in the dorsal decubitus position with their right arm in maximal abduction. The machine calculated the percentage of valid measurements over total measurements. Liver stiffness was expressed as the median kPa value of all valid measurements. A minimum of ten successful measurements was performed on each patient. Only measurements with a success rate of at least 60% and an interquartile range (IQR) of maximally 30% of the median value were considered reliable, as compared to earlier studies [38].

2.6. Scoring of liver fibrosis

Scoring and cut-off values for liver fibrosis and cirrhosis were based on the scoring system of a large population study that examined the accuracy of transient elastography in patients with different etiologies of chronic liver disease [25]: (METAVIR) F0/F1 (no to mild fibrosis): <7.3 kPa. F2 (moderate fibrosis): 7.3–12.5 kPa. F3 (severe fibrosis): 12.6–17.6 kPa. F4 (cirrhosis): >17.6 kPa. For patients with liver stiffness scores in stage F0/F1, no further action was undertaken. Median liver stiffness scores within stage F2 and higher were forwarded to the treating physician of these patients for further evaluation and subsequent results were documented.

2.7. Study variables

The primary outcome of this study was the variability in liver stiffness as determined by Fibroscan and its association with thiopurine therapy and other clinical factors in IBD patients. Liver stiffness was expressed in median kPa and interquartile range (IQR) of all successful measurements. The variables we analyzed in relation to liver stiffness in IBD patients were: exposure to thiopurine therapy (current/previous/none); thiopurine type (azathioprine (AZA)/mercaptopurine (MP)/thioguanine (TG)); thiopurine therapy

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