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The evaluation of liver abnormalities in IBD patients

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Abstract

Purpose of Review: Develop a clinical presentation-based approach for common liver abnormalities encountered by providers caring for patients with IBD. Develop a treatment pathway for those with nonalcoholic fatty liver disease (NAFLD) arising in IBD. Discuss recent studies of prevalence, incidence, risk factors, and prognosis NAFLD in the IBD population.

Recent Findings: The work-up for liver abnormalities should be approached systematically in IBD patients, similar to the general population, while still appreciating the differing prevalence of underlying liver diagnoses. Although immune mediated liver diseases occur commonly in patients with IBD, NAFLD is still the most common liver disease in patients with IBD paralleling its expanding prevalence in the general population. IBD is also an independent risk factor for NAFLD, developing in many patients with lower degrees of adiposity. Furthermore, the more severe histologic subtype, nonalcoholic steatohepatitis (NASH), is both more common and difficult to treat considering the lower effectiveness of weight loss interventions.

Summary: Having a standard approach to the most common liver disease presentations and care pathway for NAFLD will improve the quality of care provided and ease the medical decision making complexity for IBD patients. The early identification of these patients should prevent the development of irreversible complications like cirrhosis or hepatocellular carcinoma.

Keywords

nonalcoholic fatty liver disease (NAFLD); primary sclerosing cholangitis (PSC); drug induced liver injury (DILI); cirrhosis

Introduction:

Liver disease is a common comorbidity in patients with inflammatory bowel disease (IBD). The increased prevalence of liver disease is mirrored by an increased standardized mortality rate (SMR) for all alcohol-related and nonalcohol-related liver disease [1]. The most impactful diagnosis that increases the liver-related SMR is primary sclerosing cholangitis (PSC), but PSC does not impact IBD patients equally. For example the increased liver-related SMR in patients with ulcerative colitis (UC) is almost completely explained by PSC,

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but this signal is not present and thus cannot explain the liver-related SMR in patients with Crohn's disease (CD) [2]. Real or perceived drug induced liver injury (DILI) is the most common reason that otherwise promising IBD-pharmaceuticals do not make it to the patient bedside [3]. Furthermore, concerns for DILI are commonly cited for discontinuation of otherwise efficacious IBD-treatments in real-world clinics [4,5].

This narrative review will outline the approach to the common clinical presentations of liver disease in IBD patients: incidental hepatic steatosis and incidental abnormal liver biochemistries. Then we will outline a treatment pathway for the most common liver disease in patients with IBD, nonalcoholic fatty liver disease (NAFLD).

Approach to an incidental imaging finding of hepatic steatosis

The human liver did not evolve as a fat storing organ and thus any lipid droplet accumulation in the fasting state is technically abnormal. Despite that principal, it is widely accepted that hepatic steatosis is defined as ≥ 5% of hepatocytes having lipid droplets on biopsy. The most used imaging threshold however is ≥ 5.5% liver fat (e.g. ^{1}H MR spectroscopy) since that represents the 95th percentile of metabolically normal, lean patients in the Dallas Heart Study [6]. There is some debate if ≥ 3% liver fat should be considered the imaging threshold since that is the number that agrees with a pathologist impression of steatosis [7], but that is beyond the scope of this review.

The poor sensitivity of liver ultrasound or CT scans for mild hepatic steatosis [8] is not relevant when considering patients presenting with incidental hepatic steatosis; however, the operator dependence of liver ultrasound is [9]. In my experience it is common for inexperienced ultrasonographers to fail to distinguish the difference between coarse liver echotexture and a hyperechoic liver, which translates into miscalling hepatic fibrosis as hepatic steatosis in the radiographic impression.

A common misconception is that imaging of hepatic steatosis with otherwise normal liver biochemistries is a benign condition. Not only do liver biochemistries do a poor job predicting histologic severity in NAFLD [10, 11], but even hepatic steatosis at its lowest relevance is a modifiable biomarker for developing diabetes mellitus [12]. Anecdotally, our liver transplant clinic averages one patient per week that has developed hepatocellular carcinoma (HCC) despite following with their primary care doctor who has told them for decades that they had a fatty liver, but because their liver enzymes were always "good", nothing was done about it.

As outlined in Figure 1, the initial steps for incidental hepatic steatosis is to determine the pre-test probability that the patient has NAFLD and to perform a quality MD-directed alcohol use assessment to determine if a therapeutic trial of 100% alcohol cessation should be considered.

One strategy to clarify the pre-test probability of NAFLD is with the Dallas Steatosis Index [13], which is an improvement over other clinical prediction tools by only using routine clinical variables and it predicts NAFLD as would be determined on MR ^{1}H spectroscopy

rather than liver ultrasound. A CD-specific clinical prediction tools also exist [14] but has not yet been validated in a UC population.

The standardized Alcohol Use Disorder Inventor Test (AUDIT-c) can be a helpful resource to screen for greater than moderate alcohol use [15]. If there is concern that this is alcohol-related liver disease despite a reassuring alcohol use assessment, a phosphatidyl ethanol (PETH) concentration can be obtained. I counsel patients when I am checking a PETH that I do it because there is variability in ethanol metabolism [16] and evidence that patients using only moderate alcohol consumption but whom still have a PETH >30 ng/ml will have higher risk of hepatic fibrosis [17] and thus need to stop all alcohol consumption rather than just moderate their use. Sometimes this gets a more accurate history from the patient, but more importantly it usually avoids a confrontation that may poison a therapeutic relationship.

Many IBD-relevant medications are associated with hepatic steatosis (e.g. corticosteroids); however, these generally only modify the amount of adiposity required to develop NAFLD by promoting adipose tissue insulin resistance, rather than dramatically change the pathophysiology and thus treatment approach. In other words, simply discontinuing the medication is rarely associated with resolution of hepatic steatosis in the absence of a reduction in adipose tissue. The exception is when there is mitochondrial toxicity mechanism for a drug-induced liver injury (e.g. high dose methotrexate), but this will be discussed in the section regarding abnormal liver biochemistries.

If the pre-test probability for NAFLD is low (e.g. lean BMI, no dyslipidemia, no insulin resistance) and the alcohol use assessment is reassuring, then critical appraisal of the imaging finding of hepatic steatosis is warranted. In lieu of immediate hepatology consultation, an MRI with proton density fat fraction (PDFF) mapping (+/− elastography protocol if available) can confirm if there is truly hepatic steatosis with accuracy nearly identical to a liver biopsy [18].

Approach to abnormal liver biochemistries (AST, ALT, ALP)

The phrase liver function test (LFT) is almost always used incorrectly, although I acknowledge LFT is a useful shorthand. The word “transaminitis” however is never appropriate and should be avoided in all cases despite it having an ICD code. The preferred terminology is to assess the pattern of the liver biochemistries (i.e. liver enzymes) and separately assess the hepatic synthetic function (e.g. bilirubin, INR). This specificity in our medical terminology is helpful because it simplifies the differential diagnosis and the urgency of the work-up. The below approach is consistent with the American College of Gastroenterology guidelines [19].

The first step when there is an abnormal AST, ALT, or ALP is to determine the R value. This is objectively defined as the relative fold increase in ALT compared to the relative fold increase in ALP, and online calculators exist (e.g. https://www.mdcalc.com/calc/4064/r-factor-liver-injury). The R value classifies patients as having a hepatocellular (R >5), cholestatic (R <2), or mixed liver injury pattern. Patients without hepatic synthetic dysfunction (i.e. normal bilirubin, normal INR) can then be routinely evaluated as outlined

in Figure 2. The caveat is that there should be early consideration of hepatology consultation for IBD patients if the ALT >3x upper limit of normal (ULN) and/or ALP is >2x ULN if you are not comfortable with a complete expedited liver-disease work-up.

The lower threshold of hepatology consultation is because an important consideration for IBD patients is a drug-induced liver injury (DILI) from a critical IBD medication. Because most DILI are usually idiosyncratic, quasi-immunologic phenomena (e.g. anti-TNF) rather than a direct hepatotoxicity (e.g. high dose methotrexate), the timing is generally not immediately after the medication was started. Because the liver is an immunologically tolerant organ [20], a true DILI can still resolve spontaneously despite continuing the offending medication. This is a process termed hepatic accommodation and justifies tolerating lower levels of liver biochemistry abnormalities when there is an important therapeutic role.

Therefore, as long as the liver biochemistries are only borderline/mildly abnormal (i.e. < 3x ULN for ALT, <2x ULN for ALP) and there is no concern for hepatic synthetic dysfunction, the IBD medications can be continued while the liver-related work-up is initiated and liver biochemistries monitored for stability or spontaneous improvement. Patients presenting with hepatic synthetic dysfunction (i.e. elevated direct bilirubin, prolonged INR) should be triaged for expedited work-up to a hepatologist, or if necessary, an emergency room to exclude developing acute liver failure or biliary obstruction. These ALT/ALP thresholds and the importance of bilirubin as a prognostic marker is referred to as Hy's law [21].

It is also important to recognize that many elevations in total bilirubin (generally < 3 mg/dl) reflect an isolated indirect bilirubin. This is a benign condition called Gilbert syndrome (i.e. UDP-glucuronsyltransferase gene variant) [22] and can be diagnosed by fractionating the bilirubin and excluding a source of exogenous heme (e.g. hemolysis, myopathy) without genetic testing. Because Gilbert's allele frequency approximates 10% of the population [22], the bilirubin should be fractionated whenever there is an abnormality. Interestingly, Gilbert syndrome is not considered a disease since it is associated with less than half the overall mortality rate ratio compared to the general population without evidence of Gilbert syndrome [23]. This powerful protective effect is felt to reflect the antioxidant properties of bilirubin in adults [24].

Treatment paradigm for NAFLD in the IBD clinic

Many physicians confuse the terms NAFLD and NASH, using them interchangeably. This is not only incorrect but promotes unneeded anxiety and confusion for our patients. NASH refers to the less common histologic subtype of NAFLD characterized by hepatocellular necroinflammation [25], which is the primary driver in the pathogenesis of progressive hepatic fibrosis and hepatocellular carcinoma [26]. NASH is in comparison to simple hepatic steatosis, which is the more common subtype where there is no necroinflammation.

There is ongoing debate regarding if we should adopt new terminology to replace NAFLD and NASH. I strongly disagree with replacing simple steatosis with nonalcoholic fatty liver (NAFL) because of the implication that it is not a disease. I am also skeptical adopting the

terminology of metabolic associated fatty liver disease (MAFLD) due to the near universal inclusion of both alcohol-related fatty liver and NAFLD implying that an alcohol use assessment is not as relevant [27]. This debate is beyond the scope of this review, but I have personally adopted the descriptor “nonalcohol-related” rather than “nonalcoholic” for my patient-facing clinical documentation to avoid the pejorative connotation of “alcoholic”. Luckily this keeps my abbreviations of NAFLD and NASH the same.

It is unclear if NASH rates are higher for UC patients with NAFLD compared to the general population, but CD patients with NAFLD are more likely to have NASH compared to the general population [28]. Despite much work into developing noninvasive approaches to differentiate NASH from simple steatosis, the only reliable method remains a liver biopsy. Fortunately, the distinction between NASH and simple steatosis usually does not change clinical management, so a liver biopsy is not part of the initial counselling, work-up, and treatment of most patients with NAFLD as shown in Figure 3.

The only independent risk factor for liver-related events is the baseline fibrosis stage [29, 30], with the caveat that NASH and the severity of ballooning degeneration are significant predictors in univariable analysis. It is unclear if this paradox represents our misunderstanding of the mechanism of progressive hepatic fibrosis in NAFLD, variability in histology findings over time, and/or a form of lead-time bias from “burning out” steatohepatitis. Regardless once NAFLD is diagnosed, the first step is to noninvasively assess the risk the patient already has advanced stages of hepatic fibrosis (i.e. bridging fibrosis or frank cirrhosis).

The Fibrosis-4 score [31] and a NAFLD fibrosis score [32] use routine clinical variables and are readily available as online calculators. Unfortunately, they have not been validated or calibrated in the IBD population, and there is cause to question their validity in IBD because they rely on measurements that change in response to systemic inflammation (albumin, platelets). Therefore, a point of care transient elastography (e.g. Fibroscan™) is a very helpful triage tool. A liver stiffness < 8 kPa) [33] is highly sensitive to exclude advanced-stage hepatic fibrosis. It is unknown if there will be a higher false-positive rate of transient elastography in IBD patients considering the increased likelihood of prior IBD-related abdominal surgeries.

If the risk of advanced-stage hepatic fibrosis is low and the diagnosis of NAFLD is confident, these patients can safely be managed in the IBD (or primary care, endocrine, weight management) clinic without hepatology input. Regardless of if there is biopsy proven steatohepatitis (NASH) or biopsy proven simple hepatic steatosis, the first line treatment is at least a 5% total body weight loss [34] to resolve the hepatic steatosis. Weight loss counselling can be assisted by consulting with a dietician considering many IBD-relevant dietary restrictions are at odds with weight loss (e.g. low residue diet, increased simple carbohydrates).

Screening for cardiometabolic complications is also important because early identification allows early intervention. Furthermore, there is the consideration to use “on-FDA label” treatments, while also utilizing one that has clinical trial support for “off-FDA label”

treatment for NAFLD. Examples include treating hypertriglyceridemia with omega-3 supplementation [35] or diabetes mellitus II with GLP-1 agonists [36. 37]. Although the data for omega-3 supplementation is weaker, it is also more readily available, cheaper, and has fewer side effects compared to GLP-1 agonists. Omega-3 supplementation may be most beneficial in subjects who have been shown to be deficient in circulating essential fatty acids.

Of particular importance, statin therapy for cardiovascular risk prevention is associated with lower risk of progressive fibrosis in NAFLD [38]; the need to avoid statins in patients with liver disease is a stubbornly persistent misconception. Although vitamin E is appropriate in subsets of patients under the direction of hepatologist [39], reflexively starting vitamin E in all patients with NAFLD is inappropriate due to associations with higher overall mortality and hemorrhagic stroke.

Repeat imaging to determine if weight loss has successfully resolved the hepatic steatosis is generally not needed any more frequently than 12 months when there was no concern for advanced-stage fibrosis. Once there is resolution of hepatic steatosis, the goal is to maintain the weight loss since it is common for weight to wax and wane. Although it is unknown how much weight can safely fluctuate before hepatic steatosis recurs, I provide the goal of staying within 2 kg because that is the threshold that increases the incidence of progressive fibrosis in NAFLD [40].

A unique subset of NAFLD patients are those that are characterized as “lean” NAFLD (i.e. BMI < 25 kg/m2). This is not synonymous with non-metabolic dysfunction associated fatty liver disease (non-MAFLD NAFLD), since most of these patients will still have some degree of insulin resistance or dyslipidemia when tested. These patients require hepatology consultation because the treatment decisions are highly dependent on the histology, and it is generally inappropriate to tell these patients to lose weight. Furthermore, micronutrient deficiencies in the setting of severe malnutrition and rapid weight loss may need to be addressed [41] and are felt to be form of mitochondrial toxicity [42]. Luckily this form of NAFLD is now quite rare considering the development of more efficacious therapeutic paradigms for the underlying intestinal inflammation that defines IBD.

Although an increased BMI is associated with negative IBD-related outcomes [43], it is not clear if this reflects the impact of increased adiposity, insulin resistance, and/or NAFLD, per se. Our group has recently shown that CD patients with NAFLD have an increased incidence of abnormal liver biochemistries and IBD-related compared to CD patients with normal liver fat after starting on thiopurine therapy [44]. This is despite having similar baseline thiopurine doses, thiopurine metabolite concentrations, and after adjusting for the baseline BMI. More studies are needed if the presence of NAFLD should inform specific IBD therapy choices.

Conclusion

The liver is a ubiquitous source of concern for patients with IBD, ranging from the false positive alkaline phosphatase due to an intestinal source of inflammation to the life-

threatening acute liver failure from anti-TNF drug induced liver injury. The standardized approaches presented here will provide a reliable roadmap for navigating these often-vexing clinical scenarios.

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Key Points

Liver disease is of ubiquitous concern for patients with IBD since drug-induced liver injury is a common reason for the failure of promising, novel therapeutics to make it to clinics.

The treatment of NAFLD involves a structured approach starting with weight loss, fibrosis risk assessment, and cardiometabolic risk reduction without need for early hepatology consultation.

A low threshold for hepatology referral is required with abnormal liver biochemistries are >3x upper limit of normal if a hepatocellular pattern (i.e. ALT) and/or >2x upper limit of normal if a cholestatic pattern (ALP).

The development of jaundice without radiographic obstruction is an ominous sign and any new IBD-related medications should be discontinued, and urgent hepatology consultation obtained.

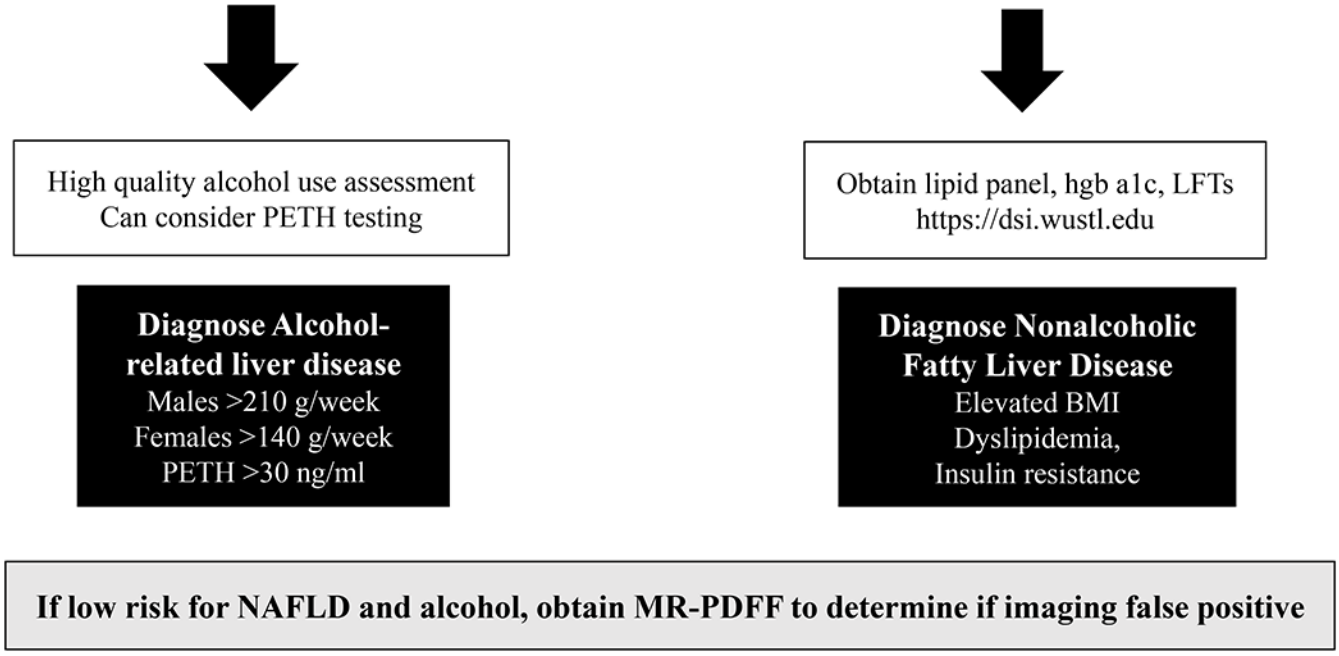

Figure 1: Hepatic steatosis appreciated on standard of care imaging

The approach to the IBD patient with incidental hepatic steatosis

Footnotes: PETH, phosphatidyl ethanol; NAFLD, nonalcoholic fatty liver disease; PDFF, proton density fat fraction. The initial step for a patient with incidental hepatic steatosis is to (1) determine if there is cause to attribute it to alcohol, (2) determine the prevalence of cardiometabolic risk factors, and (3) determine the pre-test probability that this is NAFLD. MR with PDFF protocols can address the false positive rate of hepatic steatosis on most standard of care imaging without resorting to a liver biopsy.

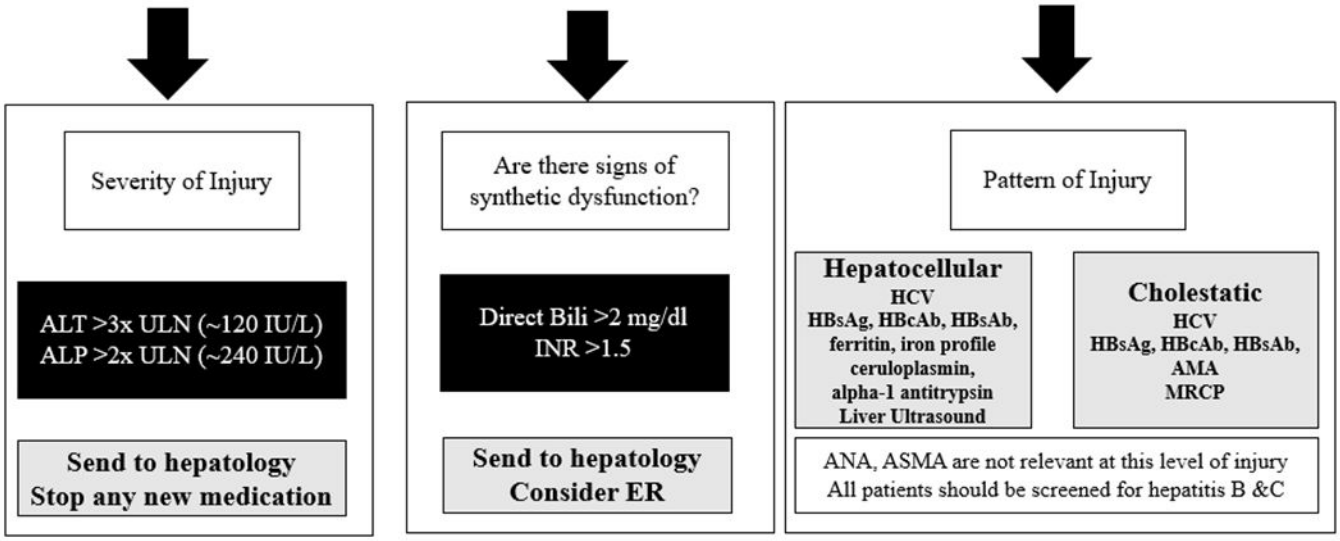

Figure 2: Abnormal Liver Biochemistries during routine/safety labs

The evaluation and indications for referral for IBD patients with abnormal liver biochemistries

Footnotes: HCV, hepatitis C virus antibody with reflex to RNA PCR; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody (total); HBsAb, hepatitis B surface antibody (total); AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, antismooth muscle antibody. The definition of a liver injury pattern (i.e. abnormalities of AST, ALT, and/or ALP) is based on the R value (relative fold increase ALT/relative fold increase ALP) with values >5 described as hepatocellular, values < 2 described as cholestatic, and values between the two as mixed hepatocellular and cholestatic patterns of injury.

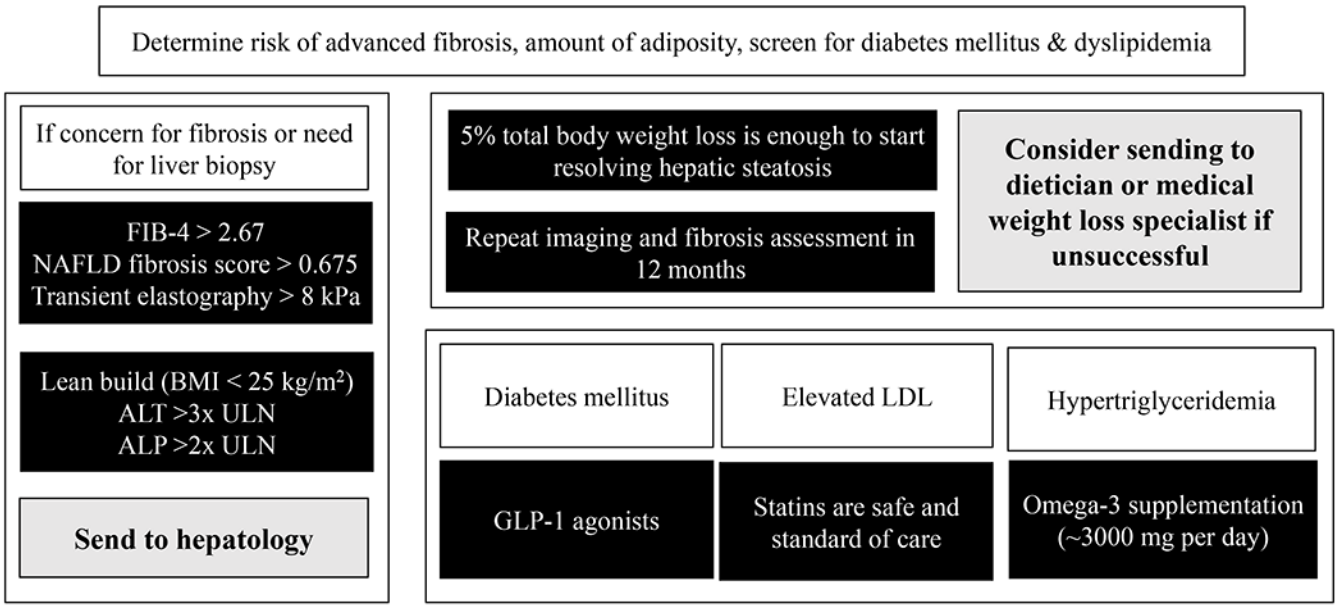

Figure 3: NAFLD has been diagnosed on clinical grounds

The management of NAFLD in the IBD clinic

Footnotes: NAFLD, nonalcoholic fatty liver disease; FIB-4, fibrosis 4 score; GLP-1, glucogon-like peptide 1. NAFLD patients without concern for at-risk hepatic fibrosis can be managed in primary care and/or the IBD clinic without hepatology consultation most of the time. In addition to weight loss and repeat imaging to document resolution of steatosis, the treatment of prevalent cardiometabolic comorbidities can be tailored to include agents that have efficacy for those with steatohepatitis. Routine use of vitamin E in the absence of a liver biopsy is discouraged and may be harmful.