Challenges in the hepatic histopathology in non-alcoholic fatty liver disease

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Bedossa *et al*[1] present a cross-sectional clinicopathological correlation study of 798 consecutively prospectively obtained liver biopsies from patients who underwent bariatric surgery for severe obesity (body mass index >40 or >35 kg/m^2 in whom at least one obesity-related comorbidity existed). Clinical phenotyping included body weight and composition by dual-emission X-ray absorptiometry (DXA), relative and total body fat mass, limb fat measurements and fasting venous samples for liver, glucose and insulin tests. Diabetes and metabolic syndrome were defined according to international criteria, and 84% of subjects also had abdominal subcutaneous fat needle aspiration biopsies. The latter were analysed for adipocyte size and volume by published methods.[2]

As expected, the majority of subjects were women (78%), and Caucasian (73.5%). A range of liver histology was found, including 141 (18%) with 'no' (grade 0) steatosis (0%–5%) and no other lesions, and 38 (5%) with grade 0 steatosis, but with either inflammation, ballooning or mild fibrosis. Thus, 77.5% of subjects in the study had some form of non-alcoholic fatty liver disease (NAFLD), and the authors detailed the findings according to the Fatty Liver Inhibition of Progression (FLIP) European Consortium scoring system[3 4] further discussed below.

Several interesting findings resulted from this careful study. In spite of similar durations of obesity, younger individuals had less severe liver disease (most were categorised as 'presumably normal') compared with their older counterparts (whose biopsies showed the full spectrum of fatty liver including non-alcoholic steatohepatitis (NASH) and cirrhosis). The younger cohort was more often female (92% vs 73%), but less often Caucasian (40% vs 81%). Unfortunately, there was no breakdown of race and ethnicity of these non-Caucasian patients, which could have been valuable information, as it has been noted in the USA that while African-Americans have a significant rate of obesity, there is a low rate of fatty liver disease.

The authors also demonstrated variation in body fat distribution in relation to histology. As the overall fat mass measured by DXA decreased, both hepatic steatosis grade and disease severity worsened. In contrast, an increased trunk:limb ratio of fat was associated with increased steatosis grade. Finally, adipocyte size and volume from the abdominal wall biopsies showed linear correlation with increased severity of histological diagnosis of NAFLD, but only in the women. For unclear reasons this did not hold true in the men, and is an area worth further evaluation.

The primary goal of this study was to evaluate and correlate the hepatic histological changes in bariatric surgery patients found in a single surgically obtained, contemporaneous liver biopsy; as no prior biopsies were reviewed, this study cannot be considered a true natural history study. The biopsies, all from the left lobe, were nonetheless arguably not ideal as they were 'wedge' biopsies, which may contain liver capsule and subcapsular fibrosis. Intraoperative liver biopsies provide additional difficulties due to clusters of neutrophils that accumulate after anaesthesia and liver manipulation. When one is 'counting' inflammatory foci, these add to the difficulty of interpretation.[5]

The biopsies in the current study were interpreted by a recognised expert hepatic pathologist who used the FLIP European Consortium system, referred to by abbreviations for the lesions semi-quantitatively reported: S (steatosis) A (activity) F (fibrosis). In this algorithm, each lesion is followed by the numeric for severity, and thus, as an example, S2A2F2 indicates grade 2 (of 3) steatosis, grade 2 (of 4) activity (which is the sum of ballooning and lobular inflammation scores), and stage 2 (of 4) fibrosis. The final values of each of these lesions were used to separate the biopsies into five categories: 'presumably normal', 'NAFL or NAFL+', 'NASH or NASH+'. One of the study conclusions made was that the steatosis, activity and fibrosis (SAF) method could capture the heterogeneity of liver disease in severe obesity. While the methods and discussion mentioned recording values for the National Institute of Diabetes and Digestive and Kidney Diseases-sponsored NASH Consortium-based NAS (NAFLD Activity Score) system that was created for comparative measurements of activity in fatty liver disease biopsies in clinical trials,[6] no results or actual discussion of the NAS followed.

Interestingly, results of the SAF scoring (table 2)[1] raise questions of the categorisations into which some subjects were placed. Furthermore, while clinicopathological associations were statistically significant, whisker plots of some (figure 1)[1] highlighted overlaps between each category. A worrisome finding, in fact, was that of the 38 subjects with 'presumably normal liver' (grade 0 steatosis but mild lesions), 2 biopsies had shown hepatocellular ballooning, 3 biopsies had stage 2 (zone 3 perisinusoidal plus periportal) fibrosis and 2 biopsies had mild activity and mild fibrosis. These cases were combined with the S0A0F0 cases by the investigators because there were no differences in the 'clinical or biological parameters' from the other 141 S0A0F0 biopsies, however, even though the numbers were small, this subgroup may represent a significant category of patients whose livers had been previously injured and now show some resolution. Since the SAF system is limited to the evaluation of only four histological features, we would also wonder if there were other histological findings present but not recorded simply because they are not included in the scoring system, such as portal inflammation or iron deposition. Thus, the statement that '22% had histologically presumably normal liver' needs to be carefully understood in the context of the actual data and the limitations of the evaluation tool. Along the same lines, NAFL (and NASH) cases were defined as having at least grade 1 steatosis. The NAFL+ cases differed from the NAFL cases in that they had evidence of activity or fibrosis, but did not meet the SAF criteria for definite NASH.[3] Cases with some, but not all of the lesions to be diagnosed as definite NASH have been defined as 'borderline NASH' in the pattern-based classification system for diagnosis used by the NASH Clinical Research Network, which differs from the numeric NAS. Cases of borderline NASH have clinical and biological features that are intermediate between NAFL and NASH, just as shown in this study, and therefore should not be grouped with cases of pure NAFL.

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As the authors iterate, there is a spectrum of lesions in fatty liver disease. This spectrum has been well described in the literature, differs in adults and children and includes many lesions beyond steatosis, lobular inflammation, ballooning and fibrosis. Scoring systems have been developed for a variety of uses, including comparative use in clinical trials, relative 'ease' of communication of severity of disease to clinical colleagues and for teaching purposes. But the use of a scoring system, in and of itself, must be kept in the perspective for which it is being used. As was shown from a study of 976 biopsies from the NASH Clinical Research Network, a histological diagnosis is based on pattern recognition, global evaluation and relationships of the numerous lesions of a process and can be informative and correlative with clinical features of fatty liver disease, which is why diagnosis remains a separate exercise from the act of scoring selected individual lesions for us.[7] This comment is not meant to detract from any of the important and novel work represented in the current paper from Bedossa *et al*, but rather, to add perspective.

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