Editorial

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Fa(s)t assessment of the liver graft: Is it relevant?

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Non-alcoholic fatty liver disease is one of the most frequent liver parenchymal conditions in Western countries and affects 25% of adults worldwide. It is mainly related to obesity that has become endemic, affecting 14 to 34% of individuals – including organ donors – in developed countries.[1] Hepatic steatosis is the most frequent feature of non-alcoholic fatty liver disease and its presence represents the main cause of donor livers being declined, because of the risk of liver graft dysfunction.[2] Hepatic steatosis appears in 2 main types: true microvesicular steatosis (mS), which is a rare condition, and macrovesicular steatosis (MS), the most frequent form, which may appear with either small or large lipid droplets.[3] The latter is the worst type that displaces the nucleus in the periphery of the cells and narrows sinusoids. Classically, MS is graded into 3 categories according to the proportion of hepatocytes containing lipid droplets: mild ≤30%, moderate 30–60% and severe ≥60%. Moderate to severe MS of the liver graft is associated with increased recipient morbidity and mortality, especially in case of the severe form that leads to a high risk of primary liver graft non-function and poor survival after re-transplantation.[4] For obvious reasons, a fast, quantitative and reliable method of fat assessment of the liver graft is thus highly desirable in the setting of liver transplantation.

However, an estimate of liver fat content is rarely available during graft procurement. Ideally, the gold standard procedure should rely on histological semi-quantitative evaluation performed on frozen biopsy section. Scoring systems quantify fat on the basis of visible hepatic lipid droplets within hepatocytes. For logistical reasons, such procedures are rarely performed in the setting of liver transplant (LT). Furthermore, histological assessment of steatosis is subjected to sampling error and subjectivity/interobserver variation.[3]

In this setting, there is a clear need for safe non-invasive assessment modalities to estimate hepatic steatosis in the context of LT. Various techniques have been assessed and proposed as alternatives to liver biopsy for determination of liver fat content, usually in the setting of chronic liver disease evaluation. While conventional imaging techniques such as ultrasound examination or computed tomography have low sensitivity and specificity, more sophisticated approaches have been approved as reliable tools to grade liver fat such as Magnetic Resonance Spectroscopy.[5] Even more practical, Fibroscan® devices, used by physicians to estimate liver fibrosis, now have been calibrated to measure hepatic steatosis levels by using a novel Controlled Attenuation Parameter (CAP®; Echosens, Paris, France).[6] Such devices, displaying sensitivity and specificity as high as 78 and 100%, respectively, have also shown a fair correlation between different steatosis grades and are now used in routine practice.

However, these technological advances are usually neither available nor practical to use in the context of LT, and in the absence of histological examination, hepatic steatosis assessment is usually performed using the surgeon's clinical estimate, which is subject to major biases. Developing accurate tools which could be miniaturized and easy-to-use during procurement are unmet needs in the field of LT, which could overcome major caveats in the selection of liver grafts.

These challenges were met by French surgeons who designed an innovative study published in this issue of the *Journal of Hepatology*.[7] Their work aimed to assess the clinical utility of a new portable device, usually used to assess fat content in animals and food products, for the assessment of steatosis of liver grafts in the setting of LT and compared this with histological determination of hepatic fat content. The innovation lies in the determination of steatosis by means of a « user-friendly » non-invasive pocket spectrometer, which can easily be used during graft procurement. In a first phase, the authors calibrated the device in human livers and grafts, which led to the creation of specific algorithms able to correlate actual and estimated steatosis values. These algorithms were secondarily validated in 2 series of human liver grafts, which confirmed the fair sensitivity and specificity of the device to immediately detect liver grafts affected by steatosis >30%. In this setting, the authors concluded that graft LS assessed by their device is accurately correlated with histological fat content. If confirmed by large prospective multicenter efforts, such an innovative procedure could positively impact the clinical decision-making process in the setting of optimization of liver graft selection.

Even though this pocket spectrometer represents a promising tool for MS evaluation, several points still limit the clinical relevance of this study. First of all, this device has been

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calibrated to detect mild-to-moderate MS (*i.e.* <60%) and we still do not know if it can recognize the presence of severe steatosis >60%, for which the risk of primary liver graft non-function is the highest, usually leading to decline the liver graft for transplantation.[8] Second, the results given in this study have not been confirmed in an external cohort, which is needed to validate the proof-of-concept. We may hypothesize that conditions of use of this spectrometer may vary a lot in other hands according to different types of surgical light that may interact with infrared emission, or the distance between the device and liver capsule for instance. Third, the pure quantitative assessment of MS performed by this spectrometer is probably not enough to evaluate the risk of liver graft dysfunction. For instance, it cannot identify the difference between the 2 forms of MS with either small or large lipid droplets whereas the latter form is known to have the worst impact on microcirculation and liver graft function. In addition, the role of MS on early allograft dysfunction was described in the 90s, but since then the presence and consequences of other components of steatohepatitis have been described in chronic liver diseases, for instance through the SAF (Steatosis, Activity and Fibrosis) score.[9] These factors should also be taken into consideration when analyzing liver graft status. It would be risky to only evaluate the fat component of liver graft pathology and ignore the presence of inflammation and fibrosis that may also impact liver graft function but cannot be analyzed by the pocket spectrometer. These cellular alterations are best described by pathological examination, indicating that the use of frozen-section analysis will likely continue.

Despite these limitations, the study by Golse *et al.*[7] demonstrates that a pocket spectrometer may recognize the presence of mild-to-moderate MS in the liver graft during procurement with an immediate result. This method may represent a new tool that could help clinicians decide whether to transplant or discard extended criteria donor liver grafts, especially when frozen-section analysis is not available. Further studies are needed to confirm these results, demonstrate the role of this device in the most useful situation of severe MS, evaluate its role in final acceptance of liver grafts, and correlate these data with clinical outcomes.

Conflict of interest

Olivier Soubrane has no conflict of interest. Prof Nahon has received honoraria from Abbvie, Bayer, Bristol-Myers Squibb, Gilead and Ipsen.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.12.017.

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