Editorial

Liver transplantation in the era of non-alcoholic fatty liver disease/metabolic (dysfunction) associated fatty liver disease: the dilemma of the steatotic liver graft on transplantation and recipient survival

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Liver transplantation remains the only curative therapy for end-stage liver disease and there is a well-established shortage of transplantable deceased donor organs to meet the growing demand of waitlisted patients. Steatotic liver grafts represent the most common type of so-called extended criteria donor (ECD) grafts aimed at ameliorating this disparity. However, steatotic grafts are associated with increased post-transplant complications and graft failure (1). Hepatic graft steatosis is strongly correlated with the high prevalence of non-alcoholic fatty liver disease (NAFLD) and metabolic (dysfunction) associated fatty liver disease (MAFLD) in the general population. NAFLD and MAFLD are related, but not equivalent, liver disorders that are linked with obesity and diabetes (2). Global prevalence of NAFLD is estimated at ~25% and rising (3). Models predict that NAFLD prevalence will increase by 21% to affect 100.9 million persons worldwide by 2030 (4). As more donors have NAFLD, the steatotic liver graft will continue to be a challenge for liver transplantation. But, promising efforts (e.g., organ pump with defatting agents) are under way, aimed at expanding the donor pool in the coming years. Herein, we briefly summarize approaches for assessment of hepatic steatosis, describe recipient outcomes associated with the use of steatotic liver grafts, and highlight strategies that may be used to mitigate risk considering the ongoing NAFLD/MAFLD epidemic.

Hepatic steatosis, or fat >5–10% of the liver parenchyma, is characterized by both the pattern and the amount of fatty infiltration in tissue sections. The two major histologic patterns are macrovesicular and microvesicular steatosis. Macrovesicular steatosis involves one or a few large, intracytoplasmic fat vacuoles that displace the nucleus to the edge of the cell with underlying pathogenesis related to excessive triglyceride accumulation in hepatocytes through a variety of mechanisms. In contrast, microvesicular steatosis is characterized by accumulation of tiny lipid vesicles in the hepatocyte cytoplasm without displacement of the nucleus whose pathogenesis is related to mitochondrial injury. These histologic patterns are not mutually exclusive and most often present simultaneously at different degrees in the liver. Importantly, other histologic features should be carefully assessed in the presence of steatosis including inflammation, fibrosis and ballooning degeneration which are indicative of significant liver injury (e.g., nonalcoholic steatohepatitis/NASH). Quantitatively, steatosis is characterized as mild (grade 1), moderate (grade 2), or severe (grade 3) if the amount of fatty infiltration is <30%, 30–60%, or >60%, respectively.

Unfortunately, a reliable and reproducible process for steatosis quantification in liver grafts is lacking. For deceased-donor liver transplantation (DDLT), assessment of the donor graft begins with visual appraisal and palpation by the procuring surgeon. Visual and tactile cues for significant steatosis include yellow discoloration, greasy or firm

texture, absence of scratch marks, and rounded liver edges. Gross examination using these parameters detects severe steatosis (usually macrovesicular) more reliably than mild or moderate steatosis but has overall low accuracy compared to microscopic assessment (5). One series reported the positive predictive value of macroscopic assessment to be 71% for severe, 46% for moderate, and 17% for mild steatosis, with 66% of steatotic livers being described as "normal" in appearance (5).

Microscopic examination of biopsy specimens by a pathologist remains the gold standard for steatosis assessment. However, there is variability in detection and grading of steatosis even among experts based on differences in timing of biopsy, tissue procurement (core needle or wedge), biopsy site, processing (e.g., frozen section *vs.* paraffin-embedded permanent section), and staining performed (6). Computerized image analysis using machine learning algorithms is showing some very promising early results to mitigate some of these issues but at this time has not been widely adopted (7). Despite data supporting histologic analysis as the gold standard, biopsy of deceased donor grafts is not a routine practice, and parameters that prompt biopsy differ widely by institution and surgeon (5). For example, only 23% of liver transplant recipients in the United Network for Organ Sharing (UNOS) have a liver donor biopsy recorded (5).

Other non-invasive modalities for hepatic fat quantification include biomarkers (e.g., lipid accumulation product), clinical decision-making scoring tools (e.g., fatty liver index), and an array of imaging tests (3). These tools are particularly relevant for initial evaluation of the donor graft in living-donor liver transplantation (LDLT). Common and accessible tests such as liver ultrasonography and computed tomography (CT) are limited by poor sensitivity, only detecting fat when >20–33% of the liver parenchyma is involved (sensitivity/specificity 66–94%/66–97% and 85/100%, respectively) (3). More sensitive imaging modalities that allow for accurate quantification of steatosis include magnetic resonance (MR) spectroscopy and MR proton density fat fraction (PDFF) and are widely used in LDLT. Although MR-PDFF can accurately quantify steatosis, the availability, cost, and logistics of this technique are prohibitive to transplant procurement in DDLT, particularly in small community hospitals. Transient elastography-based controlled attenuation parameter (CAP) is a point-of-care ultrasound-based imaging tool that can be used to detect hepatic steatosis with reasonable accuracy (AUC 0.86–0.89) (8). CAP has some advantages over other methods of measurement such as being nonionizing, inexpensive, and easy to perform. Therefore, CAP may be useful to exclude hepatic steatosis in both living and deceased donors with preoperative percutaneous liver biopsies reserved only for those with detectable steatosis (8,9). Importantly, none of the aforementioned methods provide insight to the morphologic pattern of fatty infiltration (micro- *vs.* macrovesicular).

Steatotic grafts are particularly vulnerable to ischemic insults and reperfusion injury through several proposed mechanisms, including abnormal adenosine triphosphate production leading to mitochondrial oxidative injury, impaired hepatic microcirculation/sinusoidal blood flow, and Kupffer cell dysregulation accompanied by proinflammatory milieu (6). Steatosis in liver grafts increases rates of primary non-function (PNF), delayed or early allograft dysfunction, biliary complications (e.g., ischemic cholangiopathy), renal impairment, hospital/intensive care length of stay, resource utilization and decreases short- and long-term patient and graft survival (6). The steatosis pattern, grade, and other relevant donor and recipient factors strongly influence clinical outcomes associated with the use of steatotic liver grafts (*Table 1*). Interestingly, the degree of microvesicular steatosis does not seem to be associated with increased risk of PNF (1). Several gene polymorphisms that are associated with NAFLD/MAFLD development, when detected in the donor, are associated with worse post-transplant outcomes including the development of post-transplant NAFLD and NASH (10,11).

Although there is no uniform guideline regarding use of steatotic grafts, the general consensus is that mildly (<30%) steatotic livers are associated with good outcomes and that steatosis up to 50% is associated with acceptable outcomes in DDLT (12). In LDLT, this threshold is much lower (e.g., <5–10%) and is highly dependent on the transplant center. It is well-established that grafts with severe (>60%) steatosis are typically unacceptable for transplantation due to the poor clinical outcomes associated with this level of hepatic steatosis (6). However, recent data emphasize that although the use of moderately and severely steatotic livers is associated with unfavorable short-term outcomes, long-term outcomes are relatively less affected (13,14). Therefore, efforts aimed at mitigating risk for adverse short-term outcomes associated with use of moderately or severely steatotic liver grafts may effectively increase utilization of these ECD organs.

Table 1 Donor and recipient factors associated with worse clinical outcomes after transplantation with steatotic liver grafts

Donor factors
Macrovesicular > microvesicular fat
Steatosis severity
Older age
Prolonged CIT
Donation after cardiac death
Diabetes
PNPLA3 rs738409 GG
TM6SF2 c.499A allele
Recipient factors
High BMI
Hypertriglyceridemia
Diabetes
Transplant indication of NASH
Renal dysfunction

BMI, body mass index; CIT, cold ischemia time; NASH, nonalcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing 3; TM6SF2, transmembrane 6 super family 2.

Strategies to mitigate risk associated with use of moderate-severe hepatic steatosis in DDLT include minimizing ischemia time (e.g., <6 hours), de-fatting approaches (e.g., new machine perfusion) and donor-recipient matching [e.g., fatty livers in low native model for end-stage liver disease (MELD) patients]. The use of machine-based liver perfusion systems may have particular benefit. Machine perfusion systems include *in situ* warm oxygenated perfusion before harvest (normothermic concept) or *ex situ* normothermic machine perfusion (NMP) or hypothermic oxygenated machine perfusion (HOPE) after organ procurement and transfer to the transplant center. Machine perfusion may minimize both ischemia time and, in certain cases (e.g., NMP), may also allow for manipulation of lipid metabolism (15). Currently, the studies investigating defatting strategies have focused heavily upon animal models without direct translation into human models to date (16). Therefore, these methods are still highly experimental. In contrast, donor-recipient matching has been suggested as the optimal way to maximize use of steatotic liver grafts. Many centers advocate that steatotic grafts should be directed only to candidates in relatively good clinical condition but who are in higher need of liver transplantation (LT) (e.g., first-time recipients with a MELD score 15–34, without primary biliary cirrhosis, and not on life support before transplant) as they may not achieve transplantation prior to death on the waitlist (6,17). However, this must be balanced against lower post-transplant survival that is associated with the use of lower-quality organs among low-MELD patients (18). In LDLT, approaches to mitigate risk associated with graft steatosis include weight loss interventions and manipulation of the chemical composition of hepatic lipids using dietary supplementation with omega-3 fatty acids (19,20).

In conclusion, steatotic livers pose a conundrum in liver transplantation. These organs sustain greater injury but form an ever-increasing proportion of the donor pool that is expected to rise in parallel to the NAFLD/MAFLD epidemic. In more recent years, it appears that outcomes using moderately and severely macrosteatotic grafts have improved as strategies to minimize short-term complications have emerged, thereby preserving long-term patient and graft survival. Machine perfusion provides a unique opportunity to improve the quality of a steatotic donor graft by acting as a vehicle for the application of pharmacological and nonpharmacological interventions, particularly regarding defatting. In living donors, lifestyle interventions through structured weight loss programs and dietary supplements may help to expand the donor pool further. The global epidemic of NAFLD/MAFLD has increased the prevalence of steatosis in organ donors, to the extent that it has become one of the main reasons for declining livers for transplantation. It is critical that as a transplant community we seek innovative approaches to improving recovery and reconditioning of these marginal livers in order to expand the donor pool.

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