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Liver transplantation using fatty livers: Always feasible?

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Abstract

Steatotic liver grafts represent the most common type of "extended criteria" organs that have been introduced during the last two decades due to the disparity between liver transplant candidates and the number available organs. A precise definition and reliable and reproducible method for steatosis quantification is currently lacking and the potential influence of the chemical composition of hepatic lipids has not been addressed. In our view, these shortcomings appear to contribute significantly to the inconsistent results of studies reporting on graft steatosis and the outcome of liver transplantation. In this review, various definitions, prevalence and methods of quantification of liver steatosis will be covered. Ischemia/reperfusion injury of the steatotic liver and its consequences on post-transplant outcome will be discussed. Selection criteria for organ allocation and a number of emerging protective strategies are suggested.

Introduction

The lack of available organs for liver transplantation (LT) associated with the increased death rates among patients on most waiting lists for LT has triggered the use of so-called extended criteria donor (ECD) grafts, previously called "suboptimal grafts". Among the wide range of these ECD livers, hepatic steatosis is one of the most frequent disorders [1], which is mostly related to an increasing prevalence of non-alcoholic fatty liver disease (NAFLD). The decision to implant or reject a steatotic liver for LT, however, is difficult due to a risk of impaired graft function or even failure after implantation. How much and what types of fat represent a significant risk for primary non function (PNF) of the graft remains under debate. In this review, we will first highlight the relevance of NAFLD in the general population and its implication for LT. Second, we will present the various histological designations of steatosis including recent data on the validity of the assessment of steatosis through histologic assessment. Third, we will summarize the mechanisms of injury related to fat deposits in the liver and analyze the risk of implanting a steatotic graft in a LT recipient. Finally, we will attempt to summarize selection criteria for organ allocation, as well as recent protective strategies.

Prevalence and implications of NAFLD in liver transplantation

NAFLD is the most common cause of chronic liver disease, affecting up to 30% of individuals in Western countries, and 70–80% of obese individuals [2,3]. In a series of 73 patients who were scheduled for major liver resection, we found variable degrees of hepatic steatosis in approximately 50% of patients [4]. In deceased organ donors, liver steatosis has been documented in up to 30% during the 1990th [5–7]. The risk factors for NAFLD include diabetes mellitus, obesity, hypertriglyceridemia, and sedentary life style [8], and encompass a spectrum of distinct histological entities. The relevance of steatosis ranges from simple and asymptomatic fat accumulation in the hepatocytes to liver steatosis with necro-inflammatory components (non-alcoholic steatohepatitis, NASH), that may lead to fibrosis. Cirrhosis develops in up to 20% of those cases with a risk of liver failure or hepatocellular carcinoma [9]. Therefore, the increasing prevalence of NAFLD is expected to raise the number of LT candidates, and possibly become the most common indication for LT.

The first event in NAFLD genesis is liver fat accumulation induced by changes in lipid metabolism favoring excessive triglyceride accumulation in hepatocytes, as a result of insulin resistance [2,3,10]. The second step is characterized by the excessive production of reactive oxygen species (ROS), generated by mitochondria and cytochrome P-450 system in fatty hepatocytes [11].

New insights have been recently provided regarding the fat composition in steatotic livers, particularly the Ω-3 and Ω-6 fatty acids (FA) ratio [10]. In this context, Ω-3 FAs downregulate the sterol regulatory element binding protein-1; a transcription factor which enhances hepatic triglyceride accumulation via the up-regulation of lipogenic genes such as fatty acid synthase and stearoyl Co-A desaturase-1. Moreover, Ω-3 FAs upregulate peroxisomal proliferator activated receptor-α, which stimulates hepatic fatty acid oxidation and transcription of fatty acid

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Abbreviations: LT, liver transplantation; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MaS, macrosteatosis; MiS, microsteatosis; MELD, model for end stage liver disease; FA, fatty acid; ECD, extended criteria donor.

degradation genes such as mitochondrial carnitine palmitoyl transferase-1 and peroxisomal acyl-CoA oxidase. Conversely, these actions can be offset by excessive intake of Ω-6 FAs [10].

Hepatic steatosis: definition and types

Steatosis is typically characterized quantitatively and qualitatively. The quantitative evaluation is based on the percentage of hepatocytes containing cytoplasmic fat inclusions. In the clinical setting, steatosis is usually reported as mild, moderate, or severe, if, respectively less than 30%, between 30% and 60%, or more than 60% of hepatocytes contain fat vacuoles within the cytoplasm [1,12,13]. In addition, fatty infiltration is separated quantitatively into two categories, macro and microsteatosis. Macrosteatosis (MaS) is characterized by a single, bulky fat vacuole in hepatocytes, displacing the nucleus to the edge of the cell. This type is most commonly associated with obesity, diabetes, hyperlipidemia, and alcohol abuse. The underlying pathogenesis is related to an excessive triglyceride accumulation in the liver, mainly due to an increased uptake of fatty acids released from adipose tissue and/or an augmented *de novo* synthesis [1,12,13]. Additionally, a defective hepatic export, caused by reduced lipoprotein synthesis or impaired β-oxidation of fatty acids, further increases hepatic triglyceride content [14].

In microsteatosis (MiS), the cytoplasm of the hepatocytes contains tiny lipid vesicles without nuclear dislocation. MiS is usually encountered in mitochondrial disruption following acute viral, toxin- or drug-induced injury, sepsis, and in some metabolic disorders [15]. Importantly, other histo-pathological features should be carefully assessed in the presence of steatosis including inflammation, fibrosis, and ballooning degeneration [15,16]. MaS alone is exceptional, most often MaS and MiS present simultaneously at different degrees in the liver.

Assessment of fatty liver grafts

The assessment of donor liver fat is a difficult task for the transplant team. An initial evaluation, based on visual inspection and palpation, is first done during procurement of the graft in the donor. However, criteria such as color and texture of the graft depend solely on the experience of the explanting surgeon, and thus remain subjective. A recent German study analyzing explanted, but not transplanted livers, confirmed that neither preoperative evaluation by ultrasound nor macroscopic evaluation during harvesting were reliable in steatosis evaluation [17]. Imaging modalities like CT or MRI may help in a more objective assessment of hepatic fat, but such information is rarely available before procurement [18].

The gold standard to assess hepatic steatosis is a histological analysis by a pathologist [15,16]. Despite this general agreement, a European survey showed that liver biopsy at the time of procurement for LT is rarely performed [19]. Only 23% of liver transplant recipients in the United Network for Organ Sharing (UNOS) had a liver donor biopsy recorded. Half of the transplant surgeons in the UK never integrate a liver biopsy into their decision-making process [20]. However, several transplant programs consider a liver biopsy mandatory before discarding a potential liver graft [17,19,21]. As another strategy, 38% of liver transplant surgeons in the UK and 47% in the US proceed with the histological examination of the graft, when steatosis is suspected at inspection at the time of procurement [20].

Besides different practices regarding the biopsy procedure itself, another shortcoming is the variability in interpreting the histological assessment. Staining techniques can affect detection and grading of steatosis. Sample size errors that lead to misleading interpretation may be related to focal steatosis, hypersteatosis, or hepatic fatty sparing [16]. In this context, an autopsy study demonstrated that the addition of a second biopsy from the opposite hepatic lobe provides more accurate information, due to the heterogeneity of fat distribution within the liver. Two biopsy cores from the right and left liver were regarded to best predict overall liver histological characteristics (correlated with average findings in the liver, spearman correlation coefficient of 0.95) [22].

In addition, a recent study confirmed that H&E-stained frozen biopsy overestimates MiS but underestimates MaS, when compared with permanent sections using more specific staining modality [23]. Therefore, it can be argued that a significant bias in most studies investigating fatty livers has been the use of only H&E-stained frozen biopsy specimens [13]. Alternative methods to detect steatosis with higher sensitivity are Sudan-III, toluidine blue, and oil red O staining [12,15,16,20,24], but are rarely used in the decision process of using or not a potential graft.

The assessment of fat in biopsies by pathologists, irrespective of the staining used, bears another shortcoming. A recent study showed a significant inter-observer variability among experts for both quantitative and qualitative assessments of the histologic features of liver steatosis [16]. For instance, marked ($\geqslant$30%) steatosis was diagnosed in 22–46% of patients by various blinded pathologists. Furthermore, significant disagreement was found regarding the features and overall diagnosis of steato-hepatitis. To minimize this inter-observer variability, computerized programs have been developed to more objectively quantitate hepatic steatosis by determining the area occupied by lipid droplets in a given field of a liver section [16]. However, these quantitative methods provide information only on the total amount of fat, omitting any data on the chemical composition of hepatic lipids. Therefore, novel and objective tools, such as measurement of the Ω-6 and Ω-3 FAs and prostanoid levels in liver biopsy samples, may help prediction of the magnitude of reperfusion injury, as described below [15].

Reperfusion injury in the steatotic liver graft

Several experimental studies have shown increased reperfusion injury in a variety of models of liver steatosis [13,25,26]. For example, hepatic arterial flow and microcirculation are significantly impaired in steatotic compared with lean rats [27]. The contribution of hepatic lipid composition was recently highlighted. The metabolism of dihomo-γ-linolenic, arachidonic (Ω-6), and eicosapentaenoic Ω-3) acids result in the synthesis of vasoactive mediators impacting on liver microcirculation [10]. For example, the release of long chain fatty acids from cell membranes which is triggered by phospholipase A_2 and the further metabolism by cyclooxygenase and the lipoxygenase enzymes results in the synthesis of particular Ω-6 and Ω-3 prostanoids. Products of the cyclooxygenase pathway include prostaglandins (PGs) and thromboxanes (TXs), while leukotrienes (LTs) are synthesized through lipooxygenase-mediated reactions. Abnormally

elevated Ω-6:Ω-3 FA ratio may dramatically influence the equilibrium among those metabolites [10]. Experimental studies showed that prostaglandin E_1 (PGE_1) suppresses leukocyte adhesion to the sinusoidal endothelium of rodents and reduces the oxidative stress-induced hepatocyte injury in cultured rat hepatocytes [10]. Moreover, inhibition of PGE_2 synthesis contributes also to hepatocyte damage [10]. Inhibition of the powerful vasoactive pro-inflammatory eicosanoid TXA_2, in rats subjected to reperfusion injury by selective blockage of TXA_2 synthase or TXA_2 receptors, ameliorates liver necrosis, improves hepatic blood flow, and prolongs animal survival [28]. Likewise, intravenous administration of TXA_2 synthase inhibitor in humans intra-operatively reduces plasma TXB_2 (a downstream metabolite of TXA_2) and blunts serum transaminase levels [29] In contrast to TXA_2, PGI_2 decreases platelet aggregation and leukocyte adhesion to the endothelial surface. In rats, a PGI_2 analog significantly reduced the hepatic microcirculatory defect after reperfusion, reduced leukocyte adhesion, and improved blood flow [10]. Therefore, normalization of the Ω-6:Ω-3 FA ratio appears to be crucial for protection of the steatotic liver from reperfusion injury. In human LT, hepatic microcirculation was also significantly altered in fatty compared with lean liver grafts [30]. Impaired microcirculation at the sinusoidal level may also be a decisive factor for blood supply for the biliary tree. Accordingly, moderate to severe MaS was found to be an independent risk factor for the development of biliary complications after LT [31].

Impact on early post-transplant outcome

Accumulating evidence from clinical and experimental observations indicates that steatosis in liver grafts increases complications after LT [19,32] [19,31] such as prolonged ICU stay, hospital stay, the incidence of primary graft dysfunction or non-function, and cost [30,50,60]. However, while there is general agreement that mild steatosis (<30%) causes minor graft injury, studies have been inconsistent regarding the relevance of the higher degree of steatosis (>30%) or type of fat [1,12,24,33–36]. For example, the primary non function rates range between 0% and 75% in moderate graft steatosis (30–60%) after LT (Table 1).

When the total amount of hepatic steatosis is more than 60%, most transplant surgeons currently discard grafts because of an expected high risk of graft failure (Table 2). By contrast, some authors reported excellent results after transplantation using markedly steatotic liver grafts. For example, a case control study comparing 20 patients with severely steatotic grafts (median of 90% liver steatosis) with 40 matched patients without fatty grafts

Table 1. Reported data on liver transplantation using moderately steatotic (30–60%) grafts considering only the amount of macrosteatosis.

Reference	Year	Institution	Staining	Macrosteatosis (%)	No. grafts	PNF rate (%)	12 months graft survival (%)
Zamboni *et al.* [69]	2001	Molinette Hospital Turin, Italy	H&E	>25	8	75+	N/A
Verran *et al.* [7]	2003	Royal Prince Alfred Hospital, Sydney Australia	N/A	30-60	25	0	60
McCormack *et al.* [19]	2007	Swiss HPB center, Zurich, Switzerland	H&E Sudan red	30-60	6	0	100
Nickeghbalian *et al.* [70]	2007	Nemazee Hospital Shiraz, Iran	H&E	30-60	34	18 $	73
Angele *et al.* [5]	2008	Klinikum Grosshader, Munich, Germany	H&E	30-60	36	4*	77% &*
Li *et al.* [32]	2009	West China Hospital Chengdu, China	H&E	20-40	18	5.6	89.7
Frongillo *et al.* [71]	2009	Gemelli Hospidal Rome, Italy	H&E	30-60	3	33	33
Noujaim *et al.* [40]	2009	Hospital Beneficencia Portuguesa, San Paolo, Brasil	H&E	30-60 #	6	0	50
Gao *et al.* [72]	2009	Zhejiang University school of medecine Hangzhou, China	N/A	30-60	24	0	91.7
Doyle *et al.* [73]	2010	Washington University University, St Louis, US	H&E	30-60	22	0	81.5

PNF: primary graft non-function defined as death or re-transplantation in the first week after LT; H&E: hematoxylin and eosin staining technique; N/A, not assessed; $: PNF defined as death or re-transplantation within 4 months; +: PNF defined as death or re-transplantation within 1 month; *: data available only for a combined group involving moderate and severely steatotic livers; &: 4 months survival; #: predominant MaS (<10% of MiS). (See above-mentioned references for further information.)

Table 2. Reported data on liver transplantation using severely steatotic (>60%) liver grafts of mixed type.

Reference	Year	Institution	Staining	Mixed steatosis (%)	No. grafts	PNF rate (%)	12 months graft survival (%)
Todo *et al.* [74]	1989	University of Pittsburgh, Pennsylvania, US	Oil-O-red	>60	2	100	0
Adam *et al.* [75]	1991	Paul Brousse Hôpital, Villejuif, France	N/A	>60	7	14	N/A
Markin *et al.* [76]	1993	University of Nebraska Medical Center, Omaha. US	Frozen H&E Oil-O-red	>45	22	Not transplanted	-
Ploeg *et al.* [77]	1993	University of Wisconsin, Madison, US	N/A	>60	5	80	N/A
De Carli *et al.* [78]	1999	Niguarda Hospital, Milan, Italy	N/A	>60	21	66	N/A
Canelo *et al.* [79]	1999	Georg- August-Universitat, Gottingen, Germany	N/A	>60	10	40 #	N/A
McCormack *et al.* [19]	2007	Swiss HPB center, Zurich, Switzerland	H&E Sudan red	>60	20	5	84
Frongillo *et al.* [71]	2009	Gemelli Hospital, Rome, Italy	H&E	>60	3	33	0
Noujaim *et al.* [40]	2009	Hospital Beneficencia, Portuguesa, San Paolo, Brasil	H&E	>60	21	0	35

PNF: primary graft non-function defined as death or re-transplantation in the first week after LT; H&E: hematoxylin and eosin staining technique; N/A: not assessed; #: PNF defined as death or re-transplantation within 4 months. (See above-mentioned references for further information.)

Table 3. Reported data on liver transplantation using severely steatotic (>60%) grafts considering only the amount of microsteatosis.

Reference	Year	Institution	Staining	Macrosteatosis (%)	No. grafts	PNF rate (%)	12 months graft survival
Fishbein *et al.* [37]	1997	Mount Sinai Medical Center New York. US	N/A	>60	25	N/A	N/A
Urena *et al.* [80]	1998	University Hospital 12 de Octubre, Madrid, Spain	Sudan III	>60	2	0	N/A
Yoong *et al.* [38]	1999	Queen Elizabeth Hospital, Birmingham, UK	N/A	>66	10	100 §	0
Zamboni *et al.* [69]	2001	Molinette Hospital, Turin, Italy	H&E	>45	6	N/A	N/A
McCormack *et al.* [19]	2007	Swiss HPB center, Zurich, Switzerland	H&E Sudan red	>60	10	10	90
Noujaim *et al.* [40]	2009	Hospital Beneficencia Portuguesa, San Paolo Brasil	H&E	>60 #	10	10	60

PNF: primary graft non-function defined as death or re-transplantation in the first week after LT; H&E: hematoxylin and eosin staining technique; N/A: not assessed; #: predominant MiS (<10% of MaS); §: referred to graft failure with a median survival of 1.5 months. (See above-mentioned references for further information.)

showed comparable 60-day post-transplant mortality (5% vs. 5%) and 3-year patient survival rates (83% vs. 84%) [19]. Noteworthy, all recipients disclosed a low MELD (Model for end stage liver disease) score (median lab MELD 12 (range 6–25) (Table 2).

In addition to the controversial data available on the total amount of hepatic fat, the influence of MiS vs. MaS in liver grafts on outcome remains unclear. While some authors suggested that livers with severe MiS can be safely used for LT [37], another

study reported a 100% primary graft non-function rate when severely steatotic grafts with MiS were used for re-transplantation [38] (Table 3). A recent study showed that MiS *per se* is an independent donor factor influencing donor graft function [39]. Reports on transplanting livers with ⩾60% of predominantly MaS are scarce. Two studies showed 12 month survival of 58% [7] and 25% ($n = 5$) [40]. The lack of agreement among pathologists regarding evaluation of the type and degree of steatosis [16] may explain the discrepancies among the studies.

The most recent and largest study on post-transplant outcome of donor liver steatosis originates from the USA and refers to 5051 liver transplanted patients [21]. In this registry, the presence of more than 30% of macrosteatosis was found to be an independent risk factor associated with lower one year graft survival (relative risk 1.71). Importantly, when cold ischemia extended beyond 11 h, also lower degrees of macrosteatosis (20%, 25%, and 30%) were associated with an increased risk of graft loss (relative risk 1.51). The data additionally suggested that donor livers with >30% MaS may be successfully used, if other donor risk factors are eliminated (e.g., donor age <40y, cold ischemia <5 h, no donation after cardiac death) [21].

There are currently no guidelines for an optimal allocation of steatotic liver grafts [35,41,42]. Most centers advocate the concept that steatotic grafts should be directed only to candidates in relatively good clinical condition but higher need of LT (e.g., cirrhotic patients with hepatocarcinoma having MELD <25), and avoid using them for recipients with fulminant liver failure or re-transplantation [19,43,44]. This strategy is based on the rationale that healthier recipients could better tolerate a poor initial graft function or major post-operative complications [33,45,46]. However, caution must be taken in using low quality organs for less urgent patients with questionable survival benefit of LT since they could eventually wait longer for a better organ [47]. In conclusion, an appropriate balance between donor age, graft MaS, graft ischemia time, and also recipient MELD appears decisive for outcome after liver transplantation [21].

While these results are valid for deceased donor liver transplantation, the experience of using fatty liver grafts for living donor liver transplantation is scarce and hepatic steatosis is usually regarded as a contraindication for living donation in most centers [48]. However, the regeneration ability of the fatty liver is controversially discussed [49,50]. Whether potential donors with mild steatosis should be completely denied from live donation depends, therefore, also on graft volume and donor age. In cases with no other risk factors, a steatosis degree up to 15% appears acceptable.

Impact of graft steatosis on long-term outcome after LT

Recipients receiving a fatty liver, show a dramatic decrease in fatty infiltration shortly after LT [6,19,32]. The mechanism of this phenomenon remains elusive, but may have important consequences for the long-term outcome. Independent factors that negatively affect this reversal of steatosis were donor age (>50 years) and prolonged cold ischemia time (>12 h) [32]. Corresponding to the fat changes in transplanted liver grafts, the presence of moderate to severe MaS before LT did not affect long-term organ survival [5].

Besides these results, LT recipients are particularly at risk for *de novo* development of NAFLD as they cumulate several risk factors. For example, cyclosporine has been associated with a high incidence of hypertension and hyperlipemia, and tacrolimus or sirolimus may cause a variety of adverse effects, including diabetes mellitus [51,52]. Moreover, LT recipients are subject to major changes in nutritional status, especially those with history of alcoholic disease, which may contribute to some metabolic dysfunctions [9]. The grafts itself may contribute to the pathogenesis of NAFLD, as its own personal history and genetic predisposition may influence its response to the new and different environment provided by the recipient. In this scenario, weight management, prevention and treatment of post-LT obesity, correction of metabolic syndrome, and long-term close monitoring might help minimizing the risk of occurrence of post-transplant steatosis [53].

Interestingly, an Italian group recently demonstrated that transplanting livers with moderate to severe MaS is an independent risk factor for the development of biliary complications after LT [31]. Perhaps, an impaired microcirculation at the sinusoidal level could be responsible for bile duct ischemic damage, resulting in a higher risk of biliary strictures. However, this initial hypothesis needs further investigation.

Steatosis in the liver graft has been identified as a negative prognostic factor for HCV recurrence [54–56]. Donor age limitation and exclusion of moderately to severely steatotic livers were proposed to minimize the severity of HCV recurrence [57]. However, given the fact that steatosis disappears early after LT, there is no obvious mechanism by which steatosis in the liver graft synergizes HCV recurrence after LT. In contrast with previous data, a recent study suggested that steatotic grafts do not exacerbate the progression of fibrosis nor negatively affect long-term survival in HCV recipients [58]. The literature is divided on the effect of donor graft steatosis as a facilitator or stimulator of fibrosis on patients with post-LT HCV recurrence [33,54,58]. Longer follow-up studies are necessary to clarify the effect of allograft steatosis in the natural history of HCV recurrence [59].

Strategies to improve outcome after transplantation of steatotic livers

The key strategy to optimize results when using fatty liver grafts is to minimize other risk factors. In this context, cold and warm ischemia time must be shortened as much as possible. Some promising approaches preventing activation of the inflammatory cascade are under investigations in a number of experimental and clinical protocols, such as attenuation of cytokine activation (mitogen activated protein kinase, MAPK), blockade of endothelin receptors, modulation of the heme oxygenase system, or inhibition of mitochondrial dysfunction [60,61]. The use of machine-based liver perfusion systems may also offers benefits and perhaps a way to test the function of the organ prior to implantation. The new preservation concepts include *in situ* warm oxygenated perfusion before harvest (normothermic concept) [62] or hypothermic machine perfusion after organ procurement and transport to the transplantation center (hypothermic concept) [63–67]. While the perfusion system may enable to determine the viability potential of the graft, wide application of perfusion system in marginal graft such as severe steatotic livers will need long-term data after LT.

Manipulation of the chemical composition of hepatic lipids may evolve as a useful strategy to expand the donor pool and

improve the outcome after LT. We have recently treated three live liver donors with moderate degrees of steatosis by oral administration of Ω-3 FAs. All donors showed a significant reduction of hepatic fatty infiltration within one month. Subsequently, LT was carried out for three candidates with uneventful outcomes for both donors and recipients [68].

Summary

Steatosis is common in liver grafts and causes reperfusion injury, regardless of the type of steatosis. Due to large inconsistencies in the qualitative and quantitative measurement of fat deposits in the liver, new techniques of assessment of steatosis are needed. A very promising option to prevent post-transplant complications appears to be the use of a pretreatment with Ω-3 FAs. This approach is only feasible in living donation since it requires oral administration of Ω-3 FAs before organ procurement. However, machine liver perfusion of any liver graft with Ω-3 FAs before implantation may emerge as an easily applicable method to reverse an abnormal Ω-3:Ω-6 fatty acids ratio and decrease reperfusion injury. Currently, in deceased donors, the only effective strategy for the safe use of steatotic grafts is based on the concept of minimizing other donor and recipient risk factors. In this context, donor age below 40 years and a cold storage beyond 5 h were shown to be protective in combination with up to 30% of graft MaS. In addition, the general condition of the recipient is likewise the single most important factor (MELD <25). More than 60% of MaS in liver grafts bears a significant risk for decreased graft survival, regardless of other risk factors.

Key points

- While the gold standard for evaluation of hepatic fat in liver grafts remains currently histological examination, new techniques of assessment of steatosis are needed due to large inconsistencies in the qualitative and quantitative measurement of fat deposits in the liver.
- Today, the only effective and available strategy for an optimal allocation of steatotic liver grafts is an appropriate balance between donor age, graft macrosteatosis, graft ischemia time and recipient MELD score.
- A very promising option to prevent post-operative complications following live donor liver transplantation of fatty livers appears to be pretreatment with oral Ω-3 FAs to manipulate the chemical composition of donor hepatic lipids before procurement.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Nocito A, El-Badry AM, Clavien PA. When is steatosis too much for transplantation? J Hepatol 2006;45:494–499.

[2] Amarapurkar DN, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ, Goh KL. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? J Gastroenterol Hepatol 2007;22:788–793.

[3] Chitturi S, Farrell GC, Hashimoto E, Saibara T, Lau GK, Sollano JD. Non-alcoholic fatty liver disease in the Asia-Pacific region: definitions and overview of proposed guidelines. J Gastroenterol Hepatol 2007;22:778–787.

[4] Petrowsky H, McCormack L, Trujillo M, Selzner M, Jochum W, Clavien PA. A prospective, randomized, controlled trial comparing intermittent portal triad clamping versus ischemic preconditioning with continuous clamping for major liver resection. Ann Surg 2006;244:921–928, discussion 928–930.

[5] Angele MK, Rentsch M, Hartl WH, Wittmann B, Graeb C, Jauch KW, et al. Effect of graft steatosis on liver function and organ survival after liver transplantation. Am J Surg 2008;195:214–220.

[6] Marsman WA, Wiesner RH, Rodriguez L, Batts KP, Porayko MK, Hay JE, et al. Use of fatty donor liver is associated with diminished early patient and graft survival. Transplantation 1996;62:1246–1251.

[7] Verran D, Kusyk T, Painter D, Fisher J, Koorey D, Strasser S, et al. Clinical experience gained from the use of 120 steatotic donor livers for orthotopic liver transplantation. Liver Transpl 2003;9:500–505.

[8] Dumortier J, Giostra E, Belbouab S, Morard I, Guillaud O, Spahr L, et al. Non-alcoholic fatty liver disease in liver transplant recipients: another story of "seed and soil". Am J Gastroenterol 2010;105:613–620.

[9] Duvnjak M, Tomasic V, Gomercic M, Smircic Duvnjak L, Barsic N, Lerotic I. Therapy of nonalcoholic fatty liver disease: current status. J Physiol Pharmacol 2009;60 (Suppl 7):57–66.

[10] El-Badry AM, Graf R, Clavien PA. Omega 3–Omega 6: what is right for the liver? J Hepatol 2007;47:718–725.

[11] Pessayre D, Fromenty B. NASH: a mitochondrial disease. J Hepatol 2005;42:928–940.

[12] McCormack L, Clavien PA. Understanding the meaning of fat in the liver. Liver Transpl 2005;11:137–139.

[13] Selzner M, Clavien PA. Fatty liver in liver transplantation and surgery. Semin Liver Dis 2001;21:105–113.

[14] Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 2005;115:1343–1351.

[15] Silva MA. Putting objectivity into assessment of steatosis. Transplantation 2009;88:620–621.

[16] El-Badry AM, Breitenstein S, Jochum W, Washington K, Paradis V, Rubbia-Brandt L, et al. Assessment of hepatic steatosis by expert pathologists: the end of a gold standard. Ann Surg 2009;250:691–697.

[17] Rey JW, Wirges U, Dienes HP, Fries JW. Hepatic steatosis in organ donors: disparity between surgery and histology? Transplant Proc 2009;41:2557–2560.

[18] Nickkholgh A, Weitz J, Encke J, Sauer P, Mehrabi A, Buchler MW, et al. Utilization of extended donor criteria in liver transplantation: a comprehensive review of the literature. Nephrol Dial Transplant 2007;22 (Suppl 8):viii 29–viii 36.

[19] McCormack L, Petrowsky H, Jochum W, Mullhaupt B, Weber M, Clavien PA. Use of severely steatotic grafts in liver transplantation: a matched case-control study. Ann Surg 2007;246:940–946, discussion 946–948.

[20] Imber CJ, St Peter SD, Lopez I, Guiver L, Friend PJ. Current practice regarding the use of fatty livers: a trans-Atlantic survey. Liver Transpl 2002;8:545–549.

[21] Spitzer AL, Lao OB, Dick AA, Bakthavatsalam R, Halldorson JB, Yeh MM, et al. The biopsied donor liver: incorporating macrosteatosis into high-risk donor assessment. Liver Transpl 2010;16:874–884.

[22] Frankel WL, Tranovich JG, Salter L, Bumgardner G, Baker P. The optimal number of donor biopsy sites to evaluate liver histology for transplantation. Liver Transpl 2002;8:1044–1050.

[23] Lo IJ, Lefkowitch JH, Feirt N, Alkofer B, Kin C, Samstein B, et al. Utility of liver allograft biopsy obtained at procurement. Liver Transpl 2008;14:639–646.

[24] Imber CJ, St Peter SD, Handa A, Friend PJ. Hepatic steatosis and its relationship to transplantation. Liver Transpl 2002;8:415–423.

[25] Selzner N, Selzner M, Jochum W, Amann-Vesti B, Graf R, Clavien PA. Mouse livers with macrosteatosis are more susceptible to normothermic ischemic injury than those with microsteatosis. J Hepatol 2005.

[26] El-Badry AM, Moritz W, Contaldo C, Tian Y, Graf R, Clavien PA. Prevention of reperfusion injury and microcirculatory failure in macrosteatotic mouse liver by Ω-3 fatty acids. Hepatology 2007;45:855–863.

[27] Ijaz S, Winslet MC, Seifalian AM. The effect of consecutively larger doses of L-arginine on hepatic microcirculation and tissue oxygenation in hepatic steatosis. Microvasc Res 2009;78:206–211.
[28] Shirabe K, Kin S, Shinagawa Y, Chen S, Payne WD, Sugimachi K. Inhibition of thromboxane A2 activity during warm ischemia of the liver. J Surg Res 1996;61:103–107.
[29] Shirabe K, Takenaka K, Yamamoto K, Kitamura M, Itasaka H, Matsumata T, et al. The role of prostanoid in hepatic damage during hepatectomy. Hepatogastroenterology 1996;43:596–601.
[30] Seifalian AM, Chidambaram V, Rolles K, Davidson BR. In vivo demonstration of impaired microcirculation in steatotic human liver grafts. Liver Transpl Surg 1998;4:71–77.
[31] Baccarani U, Isola M, Adani GL, Avellini C, Lorenzin D, Rossetto A, et al. Steatosis of the hepatic graft as a risk factor for post-transplant biliary complications. Clin Transplant 2009.
[32] Li J, Liu B, Yan LN, Zuo YX, Li B, Zeng Y, et al. Reversal of graft steatosis after liver transplantation: prospective study. Transplant Proc 2009;41: 3560–3563.
[33] Feng S. Increased donor risk: who should bear the burden? Liver Transpl 2009;15:570–573.
[34] Durand F, Renz JF, Alkofer B, Burra P, Clavien PA, Porte RJ, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. Liver Transpl 2008;14:1694–1707.
[35] Cameron A, Busuttil RW. AASLD/ILTS transplant course: is there an extended donor suitable for everyone? Liver Transpl 2005;11:S2–5.
[36] Loinaz C, Gonzalez EM. Marginal donors in liver transplantation. Hepatogastroenterology 2000;47:256–263.
[37] Fishbein TM, Fiel MI, Emre S, Cubukcu O, Guy SR, Schwartz ME, et al. Use of livers with microvesicular fat safely expands the donor pool. Transplantation 1997;64:248–251.
[38] Yoong KF, Gunson BK, Neil DA, Mirza DF, Mayer AD, Buckels JA, et al. Impact of donor liver microvesicular steatosis on the outcome of liver retransplantation. Transplant Proc 1999;31:550–551.
[39] Cieslak B, Lewandowski Z, Urban M, Ziarkiewicz-Wroblewska B, Krawczyk M. Microvesicular liver graft steatosis as a risk factor of initial poor function in relation to suboptimal donor parameters. Transplant Proc 2009;41: 2985–2988.
[40] Noujaim HM, de Goyet J, Montero EF, Ribeiro CM, Capellozzi VL, Crescentini F, et al. Expanding postmortem donor pool using steatotic liver grafts: a new look. Transplantation 2009;87:919–925.
[41] Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. Liver Transpl 2003;9:651–663.
[42] Cameron AM, Ghobrial RM, Yersiz H, Farmer DG, Lipshutz GS, Gordon SA, et al. Optimal utilization of donor grafts with extended criteria: a single-center experience in over 1000 liver transplants. Ann Surg 2006;243: 748–753, discussion 753–745.
[43] Mirza DF, Gunson BK, Da Silva RF, Mayer AD, Buckels JA, McMaster P. Policies in Europe on ''marginal quality'' donor livers. Lancet 1994;344: 1480–1483.
[44] Wiesner RH. Patient selection in an era of donor liver shortage: current US policy. Nat Clin Pract Gastroenterol Hepatol 2005;2:24–30.
[45] Axelrod DA, Koffron AJ, Baker T, Al-Saden P, Dixler I, McNatt G, et al. The economic impact of MELD on liver transplant centers. Am J Transplant 2005;5:2297–2301.
[46] Axelrod DA, Schnitzler M, Salvalaggio PR, Swindle J, Abecassis MM. The economic impact of the utilization of liver allografts with high donor risk index. Am J Transplant 2007;7:990–997.
[47] Volk ML, Lok AS, Pelletier SJ, Ubel PA, Hayward RA. Impact of the model for end-stage liver disease allocation policy on the use of high-risk organs for liver transplantation. Gastroenterology 2008;135:1568–1574.
[48] Malago M, Testa G, Frilling A, Nadalin S, Valentin-Gamazo C, Paul A, et al. Right living donor liver transplantation: an option for adult patients: single institution experience with 74 patients. Ann Surg 2003;238:853–862, discussion 862–853.
[49] Cho JY, Suh KS, Kwon CH, Yi NJ, Lee KU. Mild hepatic steatosis is not a major risk factor for hepatectomy and regenerative power is not impaired. Surgery 2006;139:508–515.
[50] Kaibori M, Ha-Kawa SK, Uchida Y, Ishizaki M, Saito T, Matsui K, et al. Liver regeneration in donors evaluated by Tc-99m-GSA scintigraphy after living donor liver transplantation. Dig Dis Sci 2008;53:850–855.
[51] Johnston O, Rose CL, Webster AC, Gill JS. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. J Am Soc Nephrol 2008;19: 1411–1418.
[52] Pagadala M, Dasarathy S, Eghtesad B, McCullough AJ. Posttransplant metabolic syndrome: an epidemic waiting to happen. Liver Transpl 2009;15:1662–1670.
[53] Nobili V, Candusso M, Torre G, de Ville de Goyet J. Steatosis and fibrosis in paediatric liver transplant: insidious graft's enemies–a call for clinical studies and research. Pediatr Transplant;14:441–444.
[54] Yilmaz N, Shiffman ML. Impact of the donor liver with steatosis in patients with hepatitis C virus: not so Fast. Liver Transpl 2009;15:4–6.
[55] Briceno J, Ciria R, Pleguezuelo M, Naranjo A, Sanchez-Hidalgo J, Ruiz-Rabelo J, et al. Contribution of marginal donors to liver transplantation for hepatitis C virus infection. Transplant Proc 2007;39:2297–2299.
[56] Briceno J, Ciria R, Pleguezuelo M, de la Mata M, Muntane J, Naranjo A, et al. Impact of donor graft steatosis on overall outcome and viral recurrence after liver transplantation for hepatitis C virus cirrhosis. Liver Transpl 2009;15: 37–48.
[57] Berenguer M. Risk of extended criteria donors in hepatitis C virus-positive recipients. Liver Transpl 2008;14 (Suppl. 2):S45–50.
[58] Burra P, Loreno M, Russo FP, Germani G, Galligioni A, Senzolo M, et al. Donor livers with steatosis are safe to use in hepatitis C virus-positive recipients. Liver Transpl 2009;15:619–628.
[59] Machicao VI, Krishna M, Bonatti H, Aqel BA, Nguyen JH, Weigand SD, et al. Hepatitis C recurrence is not associated with allograft steatosis within the first year after liver transplantation. Liver Transpl 2004;10:599–606.
[60] Theruvath TP, Zhong Z, Pediaditakis P, Ramshesh VK, Currin RT, Tikunov A, et al. Minocycline and *N*-methyl-4-isoleucine cyclosporin (NIM811) mitigate storage/reperfusion injury after rat liver transplantation through suppression of the mitochondrial permeability transition. Hepatology 2008;47: 236–246.
[61] Mittler J, Pascher A, Neuhaus P, Pratschke J. The utility of extended criteria donor organs in severely ill liver transplant recipients. Transplantation 2008;86:895–896.
[62] Fondevila C, Hessheimer AJ, Ruiz A, Calatayud D, Ferrer J, Charco R, et al. Liver transplant using donors after unexpected cardiac death: novel preservation protocol and acceptance criteria. Am J Transplant 2007;7:1849–1855.
[63] de Rougemont O, Dutkowski P, Clavien PA. Biological modulation of liver ischemia-reperfusion injury. Curr Opin Organ Transplant;15:183–189.
[64] Dutkowski P, de Rougemont O, Clavien PA. Machine perfusion for 'marginal' liver grafts. Am J Transplant 2008;8:917–924.
[65] Dutkowski P, Furrer K, Tian Y, Graf R, Clavien PA. Novel short-term hypothermic oxygenated perfusion (HOPE) system prevents injury in rat liver graft from non-heart beating donor. Ann Surg 2006;244:968–976, Discussion 976–967.
[66] Dutkowski P, Graf R, Clavien PA. Rescue of the cold preserved rat liver by hypothermic oxygenated machine perfusion. Am J Transplant 2006;6: 903–912.
[67] Bessems M, Doorschodt BM, Kolkert JL, Vetelainen RL, van Vliet AK, Vreeling H, et al. Preservation of steatotic livers: a comparison between cold storage and machine perfusion preservation. Liver Transpl 2007;13: 497–504.
[68] Clavien PA, Oberkofler CE, Raptis DA, Lehmann K, Rickenbacher A, El-Badry AM. What is critical for liver surgery and partial liver transplantation: size or quality? Hepatology 2010;52:715–729.
[69] Zamboni F, Franchello A, David E, Rocca G, Ricchiuti A, Lavezzo B, et al. Effect of macrovescicular steatosis and other donor and recipient characteristics on the outcome of liver transplantation. Clin Transplant 2001;15:53–57.
[70] Nikeghbalian S, Nejatollahi SM, Salahi H, Bahador A, Sabet B, Jalaeian H, et al. Does donor's fatty liver change impact on early mortality and outcome of liver transplantation. Transplant Proc 2007;39:1181–1183.
[71] Frongillo F, Avolio AW, Nure E, Mule A, Pepe G, Magalini SC, et al. Quantification of degree of steatosis in extended criteria donor grafts with standardized histologic techniques: implications for graft survival. Transplant Proc 2009;41:1268–1272.
[72] Gao F, Xu X, Ling Q, Wu J, Zhou L, Xie HY, et al. Efficacy and safety of moderately steatotic donor liver in transplantation. Hepatobiliary Pancreat Dis Int 2009;8:29–33.
[73] Doyle MB, Vachharajani N, Wellen JR, Anderson CD, Lowell JA, Shenoy S, Brunt EM, et al. Short- and long-term outcomes after steatotic liver transplantation. Arch Surg;145:653–660.
[74] Todo S, Demetris AJ, Makowka L, Teperman L, Podesta L, Shaver T, et al. Primary nonfunction of hepatic allografts with preexisting fatty infiltration. Transplantation 1989;47:903–905.
[75] Adam R, Reynes M, Johann M, Morino M, Astarcioglu I, Kafetzis I, et al. The outcome of steatotic grafts in liver transplantation. Transplant Proc 1991;23:1538–1540.
[76] Markin RS, Wisecarver JL, Radio SJ, Stratta RJ, Langnas AN, Hirst K, et al. Frozen section evaluation of donor livers before transplantation. Transplantation 1993;56:1403–1409.

[77] Ploeg RJ, D'Alessandro AM, Knechtle SJ, Stegall MD, Pirsch JD, Hoffmann RM, et al. Risk factors for primary dysfunction after liver transplantation–a multivariate analysis. Transplantation 1993;55:807–813.
[78] De Carlis L, Colella G, Sansalone CV, Aseni P, Rondinara GF, Slim AO, et al. Marginal donors in liver transplantation: the role of donor age. Transplant Proc 1999;31:397–400.
[79] Canelo R, Braun F, Sattler B, Klinge B, Lorf T, Ramadori G, et al. Is a fatty liver dangerous for transplantation? Transplant Proc 1999;31:414–415.
[80] Urena MA, Ruiz-Delgado FC, Gonzalez EM, Segurola CL, Romero CJ, Garcia IG, et al. Assessing risk of the use of livers with macro and microsteatosis in a liver transplant program. Transplant Proc 1998;30: 3288–3291.