Review

Living donor liver transplantation

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Practice patterns and considerations in liver transplantation from living donors with high BMI: A review

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Abstract

Living Donor Liver Transplantation (LDLT) is a valuable solution to the shortage of donor organs for patients with end-stage liver disease. However, the eligibility of obese donors for LDLT remains a subject of debate. This literature review explores global practices and perceptions of LDLT, identifies donor eligibility criteria, and discusses special considerations and ethical caveats. The review highlights the need for standardized guidelines for donor selection, considering the global distribution of Body mass index and variations in population-specific criteria. It also emphasizes the importance of non-invasive testing and pre-operative optimization of liver steatosis for select obese donors. Furthermore, the review examines the outcomes and complications associated with obese donors in LDLT. The findings of this review contribute to the ongoing discussion on the inclusion of obese donors in LDLT and provide insights for future research and guideline development.

Keywords: Hepatic steatosis; obesity; MRI-PDFF.

Introduction

Living Donor Liver Transplant (LDLT) was initially introduced by Strong et al.[1] (Australia, 1989) as a novel solution to the cadaveric organ shortage for waitlisted patients with end-stage liver disease (ESLD). It has since proven to effectively decrease the waitlist time, dropout rate, and mortality.[2] In recent years, LDLT has gained popularity due to expanding indications for transplantation, particularly in Eastern countries where cadaveric organ procurement remains limited. Given the ethical intricacies of living donation, donor suitability is a major concern, and the use of patients with suboptimal Body mass index (BMI) became an area of debate in the medical community. Obesity is an established risk factor for surgical complications and conditions affecting the liver. In this context, research to determine the impact of obesity on LDLT outcomes and optimal selection criteria has gained momentum. This literature review aims at identifying the inter-centers discrepancies, perceptions, and eligibility criteria pertaining to LDLT, and exploring additional considerations for select obese donors with concomitant mild liver steatosis, including special considerations, non-invasive testing, and pre-operative optimization.

Global Practices and Perceptions

Although Western countries (North America and Europe) lead the LT practice in terms of case volume and organ procurement rates, LDLT remains a small portion of all LT in the area.[3] It accounted for only 6% of LTs in the USA, 15.6% in Canada, 2.5% in Italy, and 1 reported case in Spain in 2021.[4] In contrast, select countries across Asia (75% of all LT in South Korea, 91% in Turkey, 84% in Saudi Arabia, 84% in Japan, and 81% in India) have heavily relied on living liver donors.[4]

Public health policies, cultural and religious attitudes, and societal perceptions toward organ donation have been proposed to explain the discrepancies in this practice.[5–8] Religious beliefs created reluctance to use cadaveric organs; laws to halt organ trafficking in the 1990s limited the practice to direct relatives, and outsourcing of LTs in many developing countries in South-East Asia created regional hubs for LDLT. For example, 25–30% of transplant patients in India are foreigners, out of 2800 reported cases in 2021.[4] An influx of trained professionals and partial outsourcing of radiology expertise has been essential to establish high standards for LDLT.[9]

In Western countries with established cadaveric organ transplantation centers, infrastructure, and expertise are more widely. However, there is pragmatism towards the implementation of LDLT. A recent survey of 90 liver transplant program directors in the U.S. assessed barriers to LDLT. Centers most commonly did not implement LDLT due to a lack of financial support or lack of surgical expertise. In centers with LDLT, donor and recipient factors (medical and socioeconomic) were cited. Interestingly, a significant number of non-LDLT centers (16%) considered the practice unnecessary. Non-directed (altruistic) donation was limited due to "ethical concerns" and "poor risk-to-benefit ratio." Disagreement was also notable on whether liver-paired exchange should be performed at an institutional or national level.[10]

Living Donor Evaluation

The U.S. Organ Procurement and Transplantation Network (OPTN) and European Association for the Study of the Liver (EASL) guidelines for medical evaluation of donors both ensure extensive workup for any underlying or transmissible disease before any type of liver transplantation. The OPTN notes special attention should be given to liver pathologies and anatomical variations on imaging for LDLT, with either CT angiogram, MRI angiogram, or angiogram deemed acceptable; a liver

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biopsy is recommended in case of any suspicion of liver pathology, but at the discretion of each center. The guidelines also recommend cutoffs for criteria such as age (<60), BMI (<35), surgical suitability measured by Graft Body Weight Ratio and Remnant Volume (RV), and degree of hepatic steatosis (<20% in US).[11] These regional recommendations do not translate into transplant centers homogeneity. Absolute exclusion for diabetes mellitus (DM) (61.5%) and BMI>30 (88.4%) varied across centers in the U.S., and liver biopsy was selectively performed in only 60–70% of donors with abnormal liver function tests or imaging.[12]

The EASL guidelines acknowledge the LDLT practice as an Eastern practice and do not outline cutoff values for the evaluation of potential donors. It rather highlights the important considerations in partial transplantation, including of viability of grafts, donor morbidity, and donor mortality. The guidelines recommend a graft-to-recipient body weight ratio of at least 0.8% to achieve a volume that can sustain life post-transplantation, and note the technical difficulties of the procedure, resulting in significant morbidity in 38% of donors and a mortality rate of 0.18%.

Looking at the global practices, a worldwide survey of 24 centers with a cumulated 19,000 cases of LDLT including high-volume (>500 total LDLT) and low-volume (<500 total LDTL) centers recently assessed donor selection criteria around the globe. Lower limits of BMI were set by half of the centers at 16–20 kg/m^2, while the median upper limit was at 33 kg/m^2 for high-volume and 30 kg/m^2 for low-volume centers. Interestingly, age inversely influenced the median BMI in 63% of centers, and transplant centers with experience had higher proportions of obese donors deemed eligible for LT. More so, selective indications for liver biopsy commonly included elevated LFTs and at least one feature of metabolic syndrome. High-volume centers preferred MRI-specifically MR Spectroscopy-for radiological assessment of steatosis compared to CT at low-volume centers. Exclusion for macrosteatosis was set at cutoff values ranging from 10% to 40% for left lobe grafts and 10–30% for right lobe grafts. The most common practice across most centers (88%) was to reevaluate donors with hepatosteatosis after treatment and weight loss.[13]

Ethical Caveats and Special Considerations

Analysis of donor morbidity and mortality post-hepatectomy based on the European registry estimates one-third of donors will experience complications, the majority being Clavien–Dindo type I or II,[14] with notes on higher rate of type II and IIIa complications post right-lobe hepatectomy and an estimated mortality rate of 0.18% for LDLT. The guidelines particularly recognize the impact of "any donor mortality" on the "Western world mindset".[15] Worldwide mortality from LDLT is estimated at 0.2–0.5%, although likely underestimated due underreporting.[16] The decision to deem a patient fit for liver donation requires an ethical judgment of the risks on donors' health first, despite the internationally recognized need to expand the donor pool to match the number of ESLD patients requiring transplants for curative intent. Rigid discipline at centers with large volume of LDLT has shown to be effective in avoiding donor death. The largest case series of 5000 cases without donor mortality was reported by the largest Korean center by volume, with annual >300 LDLT since 2010. Pillars of success were attributed to standardized surgical techniques, protocols for donor/recipient selection, and perioperative management.[17]

However, guidelines for living donor selection largely differ across countries and centers, which influence the eligible donor pool across regions. An estimated 39% of adults worldwide (2.92 billion in 2016) are overweight or obese.[18] In the context of this obesity pandemic, adopting different BMI cutoffs, ranging from the Indian contraindication (BMI>25) to the American contraindication (absolute: BMI>40; relative >35), largely influences the potential donor pool before any further testing for comorbidities. These differing practices are partly explained by the differences in BMI distribution, with 19.7% of Indians versus 69.7% of Americans being at least overweight. Moreover, the WHO stratification of BMI for the Asian population differs in cutoffs (Normal BMI<23; Overweight 23<BMI<27.5; Obese=BMI>27.5), due to higher body fat percentages at lower weights than Western populations.[18]

Regardless of local policies, focus on donor risks, then recipient benefits should remain the principal concern for the eligibility of donors with suboptimal BMI. Although associated with an array of medical conditions, overweight (25<BMI<29) and obesity (BMI>30) status do not predict medical fitness. However, obesity has been associated with conditions affecting the liver, including hepatic steatosis and DM. Considerations in living donors should focus on non-invasive testing and management of these conditions for optimization of liver function before reevaluation for potential transplant. Strategies to avoid liver biopsy and rule out additional risks from comorbid conditions are also of relevance.

Careful surgical evaluation of grafts with any degree of steatosis should be pursued since it was shown to affect hepatocyte function and weaken regeneration after hepatectomy. Rigid evaluation of suitability of graft size and RV to ensure donor safety should be followed. A case report of the first and only donor death from Japan concluded a combination of a "slight fatty liver" missed preoperatively and procurement of the right lobe with middle hepatic vein (a more extensive hepatectomy) resulted in mortality.[19] A low threshold for donor risk based on rigorous evaluation of the surgical suitability of the graft is therefore essential with any degree of steatosis.

Obese Donors' Outcomes

The debate around the exclusion of obese donors started at the turn of the millennium in concurrence with concern over the obesity epidemic. Multiple single-center retrospective studies have since compared outcomes and complications in obese (BMI>30) versus non-obese (BMI<30) donors. With respect to guidelines, all obese donors were evaluated for comorbidities before inclusion-especially hepatic steatosis-and had similar preoperative characteristics to non-obese donors in all studies. No significant differences were observed in the rate of complications at 30 days[20–22] except for wound complications.

Further weight stratification into normal (BMI<25), overweight (25<BMI<30), and obese (BMI>30) donors, with attention to similar fat percentages on MRI-PDFF between groups, also resulted in no significant differences in post-operative parameters (length of stay, emergency department visits, and readmission within 90 days) or Clavien–Dindo grade of complications within 90 days. However, wound complications were significantly higher in both overweight and obese patients, sometimes requiring antibiotics or vacuum-assisted closure.[23]

More conservative stratification into normal and overweight BMI, with longer follow-up, has also been attempted. Although associated with longer intraoperative time and higher blood loss, overweight status was not associated with a higher risk of complications or a lower liver regeneration ratio at 1-year post-operation. As for long-term outcomes, 5-year follow-up of donors showed incomplete platelet and albumin restoration unequivocally among all donors, but significantly higher gamma-glutamyl transferase in overweight patients, suggesting possible suboptimal recovery of liver function compared to normal-weight donors and warranting closer clinical surveillance.[24]

As for quality of life (QOL) of donors, a prospective cohort study 1-year post-donation assessing self-reported health-related QOL using SF-36 QOL questionnaire identified obesity (BMI>27.5; Asian population) as a risk factor for worse physical health score but not mental health score. Intriguingly, recipient outcome was the most influential factor on both mental and physical health scores of donors. This finding emphasizes the burden of caring for patients with ESLD, even post-transplantation.[25]

One prospective cohort study of 517 patients assessed long-term outcomes and predictors of self-reported mental and physical health beyond 2 years' post-donation. Donors' outcomes were comparable to the general population, except for anxiety and alcohol use disorder rates. However, obese-but not overweight-status was associated with worse clinically significant fatigue, pain interference with daily activity, poorer QOL, and more depressive symptoms.[26]

Hepatic Steatosis

Perhaps the most convincing argument for rejecting living donors with high BMI is the correlation with hepatic steatosis. The concept of disease transmission is a stringent exclusion criterion for most conditions, whether infectious, neoplastic, or hepatic pathologies. However, a more pragmatic approach is adopted by transplant centers for conditions deemed reversible, most notably non-alcoholic fatty liver disease. Factors associated with the grade of hepatic steatosis include BMI,[27,28] serum level of liver enzymes, and serum cholesterol levels.[29] BMI is also an independent predictor of degree of steatosis, with an increase of 1 kg/m^2 in BMI associated with a 58.2% higher probability of upgrading steatosis one or more grade.[29]

Identifying screening methods and cutoffs warranting liver biopsy is a predominant focus in LDLT. Given the procedural risk and invasive nature of liver biopsy on potential donors, centers are shying away from using BMI for screening, and new imaging techniques are replacing it. Computed Tomography - Leaf Area Index (CT LAI) <0 had a reported specificity of 100% for identifying steatosis >15% in patients with BMI<25, dropping to 76.2% and 55.6% for 25<BMI<30 and BMI>30, respectively; Positive predictive value was adequate for all groups (100%, 95.5%, 93.5%).[30] The use of CT LAI is not appropriate to rule out hepatic steatosis in overweight/obese patients but can be considered a good screening imaging for liver biopsy. Magnetic resonance spectroscopy has established itself as a reference standard for quantification of liver steatosis. A systematic review and meta-analysis identified that >30% reduction of steatosis on MRI-PPF was associated with a significant histologic response (OR 6.98) and NASH resolution (OR 5.45).[31] Danis et al.[32] proposed an algorithm to stratify patients using FIB-4<1.3 and NFS<−1.455 into low and moderate-high risk of steatosis, with MRI-PPF only for assessment of steatosis (<10% acceptable) in low risk and both MRI-PPF and MR Elastography (MRE) in moderate-high risk group. Steatosis greater than 10% and MRE>3kPa would prompt weight loss and re-evaluation, yielding a reported diagnostic accuracy of 83%, positive predictive value of 89%, and specificity of 90%.

Conceptually, hepatic steatosis is considered a reversible condition. Recipients of a liver with grade 1 or 2 hepatic steatosis should theoretically be able to downgrade with appropriate non-pharmacological and lifestyle modifications. Practicality is however of concern in ESLD patients with an initial diagnosis of NASH cirrhosis. A prospective single-center cohort study in Japan found post-operative NASH to be more common in recipients with high BMI, high body fat index, dyslipidemia, primary NASH, alcoholic cirrhosis, as well as with Everolimus use, and post-LDLT. However, only a high BMI and Everolimus use were predictive factors for the development of NASH. Of note, hepatic steatosis did not influence 5-year survival (92%).[33] Liver regenerative ability in the setting of steatosis is also of concern. Although a transient rise in ALT, AST, and bilirubin is possible, no differences were identified in liver enzymes or prothrombin levels at 30-days after the right-lobe donation of livers with <10% and 10–20% steatosis.[28]

DM and Metabolic Syndrome

The practice of including patients with DM in the donor pool is still quite unclear. This could be primarily attributed to three main factors; the first one being the increased risk of morbidity that accompanies partial hepatectomy in patients with DM;[34] the second being the increased prevalence of non-alcoholic steatohepatitis (37.3%) in DM;[35] and the third being the impaired liver regeneration due to oxidative stress in DM after partial hepatectomy as demonstrated in murine models of type 2 DM.[36] When it comes to clinical practice, DM was not an absolute exclusion criterion among 61.5% of active 53 LDTL centers in the US of which only 18.8% performed liver biopsy for steatosis evaluation before transplant.[12] A retrospective study assessing outcomes of liver transplant from donors with DM showed that post-hepatectomy hepatic artery thrombosis was significantly elevated when matched to a cohort of recipients of non-DM donors (5.8% vs 2.9% respectively). There was no difference in terms of primary nonfunction but a significantly decreased 90-day graft survival was also reported (88.4% vs. 96.4% in non-DM donor recipients).[37] Even recipients of non-DM liver donors with elevated HbA1C levels had significantly poorer allograft outcomes and patient survival.[38] Using data from the Scientific Registry of Transplant Recipient database, Zheng et al.[39] showed that recipients of DM donors had unfavorable graft survival compared to non-DM donor recipients. The 1-year survival was decreased from 85% to 81% in recipients from diabetic donor, and 5-year survival 74–67%. However, it is worth noting that baseline recipient liver disease potentiated the DM donor effect which resulted in worsened transplant outcomes.[39] Moreover, a higher risk of graft failure in recipients of DM livers was also confirmed in a recent study (HR 1.19).[40]

Metabolic syndrome in donors is becoming one of the most common reasons for donor rejections[41] with a 1.5–1.7 increase in the risk of NASH among those patients.[42] As known, metabolic syndrome is defined as a cluster of clinical characteristics which include hypertension, dyslipidemia, high fasting blood glucose, and increased abdominal circumference.[43] When considering metabolic syndrome candidates for liver donation, concerns arise regarding the outcomes of the surgery especially that it was associated with increased perioperative complications.[44] Using the NSQIP dataset, Bhayani et al.[44] investigated clinical data on patients who underwent hepatectomy and analyzed the perioperative outcomes in association with their clinical characteristics as well as comorbidities most importantly DM, BMI >30, and hypertension. Patients who had all three of the latter comorbidities were diagnosed with metabolic syndrome. Those patients were at least 2 times more likely to have peri-operative complications such as reintubation (6%), cardiovascular events (2%), and ventilator dependence lasting more than 48 h (8%). Further studies are needed to assess the safety, feasibility, and sustainability of using livers from live donors with DM and metabolic syndrome.

Pre-transplant BMI Optimization

Strategies to optimize donors have been proposed, most notably pre-operative weight loss. Theoretically, short-term weight loss strategies lead to the reversal of hepatic of steatosis, turning marginal donors into candidates for LDLT. However, no consensus exists on optimal weight loss programs or target BMI reduction that ensures long-term benefits. Results of subgroup analysis of pre- and post-operative parameters of obese donors with short-term weight loss-with target BMI<30 before hepatectomy – were equivocal. Findings of interest in this subgroup included higher rates of grade 1 or 2 steatosis and biliary complications.[22] A recent meta-analysis of 6 studies included 102 obese donors who achieved a mean reduction in BMI of -2.08. Results were promising, with 91.2% achieving reduction/resolution of steatosis, a mean difference of -21.2% steatosis on biopsy, and similar post-operative outcomes to the control group with no steatosis.[45]

In a recent meta-analysis, exercise training with at least 750 Metabolic Equivalents of Task min/week (or 150 min/week of brisk walking) was also associated with a significant reduction of >30% steatosis on MRI, independently of weight loss.[46] Non-pharmacological strategies to improve steatosis should therefore focus on early implementation of both weight loss and exercise training programs for potential donors.

BMI optimization was studied even further at some centers. In 2018, the first case of right-hepatectomy in a patient with a history of laparoscopic sleeve gastrostomy was reported. The 37-year-old patient had a weight loss of 74 kgs, BMI reduction from 49 kg/m^2 to 27 Kg/m^2, and less than 5% steatosis on pre-transplant liver biopsy. Although minimal adhesions were found intraoperatively, no complications and normal liver function were reported at 8 months follow-up.[47] Another case series reported right-lobe liver donation in 4 patients with a history of bariatric surgery for weight loss. In these select donors with no comorbidity, pre-transplant steatosis was evaluated by MRI-PPF and ranged from 0.1% to 3.3%. No complications, a mean operation time of 367.5 minutes, mean hospital stay of 5.8 days, and 100% graft survival were noted at 9–72 months follow-up.[48]

Conclusion

While requiring delicate consideration of potential health risks to donors, LDLT offers possibilities such as early transplantation, paired-liver exchange, and altruistic donors to relieve some of the burden of waitlisted patients. However, global practices and perceptions vary on these issues due to differences in implementation, laws, and cultural beliefs. With the obesity pandemic affecting patients globally, the use of donors with high BMI became a focal point of debate. The available evidence on "healthy donors" with BMI>30 suggests no significant difference in post-operative complications and overall survival at 1-, 3-, and 5 years, except for wound complications. Poor suggestive QOL and depression were however more frequent in common obese donors, warranting an emphasis on the mental burden and impact on QOL of a hepatectomy pre-operatively, and close monitoring with frequent follow-ups. A common finding in pre-operative evaluation of obese donors is liver steatosis, which raises concern for transmission of disease to recipients, especially those with concomitant type 2 DM. Considering donor's health risks, evidence suggests non-invasive testing with MRI can accurately detect steatosis and spare donors from the risks of liver biopsy. Treatment options such as weight loss and exercise programs were also found to significantly reverse steatosis in potential donors. Therefore, early counseling and evaluation of potential donors are essential. If detected on MRI, education on liver steatosis and provision of clear center-specific cutoffs should be given to donors along motivation interviewing and frequent follow-up to ensure the implementation of diet and exercise programs. Further research is needed to determine appropriate cutoffs of BMI and liver steatosis for donor selection while considering population-specific criteria and optimal suitability of grafts with steatosis. Another focus on donors and recipients with type 2 DM should be made given the laxity in including donors with Type 2 DM despite the higher risk of rapid progression of steatosis to NASH.

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