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Review

Management of Steatosis in Living Donors: Where Do We Stand?

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Abstract

With the progressive rise in rates of liver transplantation, stagnant donor pool, and social factors, living donor liver transplantation (LDLT) forms the majority of liver transplantations performed in Asian countries. As the global prevalence of metabolic-associated fatty liver disease (MAFLD) is increasing, around 17-25% of all the prospective donors turn out to be steatotic at the time of evaluation and, as such, rejected for donor hepatectomy, thereby considerably reducing the living donor pool. Steatotic grafts are a risk factor to both the recipient (primary nonfunction, delayed graft function, and mortality) and the donor (poor regeneration, higher blood loss, and prolonged hospital stay). Weight reduction and dietary optimization have been known to be associated with improvement in steatosis, and multiple interventions have been used in the past to reduce steatosis in these donors and be able to convert these donors from marginal steatotic donors to normal or low-risk donors and utilize these grafts. Most of these studies indicated the efficacy of these optimization protocols. They suggested similar outcomes in these previously steatotic donors compared to donors without steatosis at baseline, but these optimization protocols lack uniformity. This review article aims

to highlight the rising prevalence of steatosis in living liver donors, assess the literature on pre-operative management options for steatosis donors, and study the efficacy, safety, and feasibility of these management options.

Keywords
steatosis; fatty liver; living donor liver transplant; GM diet: general motor diet; donor hepatectomy; weight loss

1. Introduction

Liver Transplantation (LT) has evolved in the past 2 decades, has shown excellent results, and is now established as the standard of care for acute liver failure (ALF) and end-stage liver disease [1]. With improvements in surgical technique, perioperative management, anesthesia techniques, better immunosuppression regimens, and advances in organ procurement and preservations, the survival rates after liver transplant have improved to more than 90% at 1 year [2] and 70% at 5 years. and 60% at 10 years [3].

Deceased donor liver transplant (DDLT) is preferred to live donor liver transplant (LDLT) in countries where cadaveric organs are readily available. However, in Asian countries where the rates of organ donation are low, LDLT is more commonly performed. However, LDLT is technically more challenging and is known to be associated with surgical risks to donors [4]. LDLT offers advantages over DDLT in multiple aspects, including the availability of healthy donors, shorter cold ischemia time (CIT), lower waitlist dropout in HCC, and preoperative optimization, with a reduction in waitlist mortality being the most important [5].

Before donors undergo donor hepatectomy, they undergo a thorough evaluation, including blood investigations, contrast-enhanced computerized tomography abdomen (CECT abdomen), and magnetic resonance imaging (MRI) to assess for any anomalies. MR-fat fraction and CT-liver attenuation index (CT-LAI) are performed to evaluate liver morphology and the degree of steatosis [6]. One of the most common reasons for rejection of a live liver donor is the abnormality in the hepatic parenchyma because of steatosis and steatohepatitis, which can lead to increased risk to the donor [6]. With the increase in obesity rates, there has been a significant rise in the rates of steatosis. It is estimated that 10-50% of the general population is affected by steatosis, with the prevalence being notably higher in individuals with obesity [7, 8]. The acceptable upper limit of steatosis for live liver donors (LLD) is not well defined, but most centers reject donors with macrovesicular steatosis of >15-20% [6, 7]. Donor hepatectomy, being a purely altruistic surgery, needs particular attention, and strict measures are taken to ensure donor safety and minimize donor morbidity [9]. Live donor hepatectomy is a major surgery and is associated with major morbidity of around 2-5% and minor morbidity of around 15-20% [6]. During evaluation for LDLT, 17-25% of potential healthy donors are found to be steatotic and therefore rejected [6].

Steatosis has been recognized as a major risk factor following hepatic resections and is associated with poorer patient outcomes. Steatosis is associated with poor hepatocellular recovery due to impaired hepatic homeostasis and more hepatocellular injury because of lipid accumulation in hepatocytes [10]. Donor steatosis is associated with an increased initial poor graft function and a

higher risk of primary nonfunction in the recipient [11, 12]. In contrast, in donors, steatosis was found to be associated with impaired liver regeneration after hepatectomy [13], increased risk of intraoperative bleeding, blood transfusion requirement, morbidity, post-operative infection rates, and prolonged hospital stay [14, 15]. Steatosis was also identified as a significant risk factor for intrahepatic cholestasis and transient hyperbilirubinemia during regeneration following liver donor liver transplantation [16].

Steatosis is reversible and has been the target of prehabilitation prior to donor hepatectomy. Multiple methods have been described in living liver donors for improving hepatic parenchymal quality and reversal of hepatic steatosis, including dietary optimization, weight reduction, enhanced physical activity, and medication intake. However, still, there is no consensus, and the optimum method and duration to reduce steatosis are yet to be elucidated [17-25].

2. Dietary Optimization

The study by Hwang *et al*. [22] was the first scientific study to evaluate the efficacy of dietary optimization on steatotic LLDs. 9 potential liver donors with steatosis were enrolled and started on a balanced diet with low-calorie (25-30 calories × ideal body weight [Kg] per day) along with increased physical activity and alcohol abstinence for around 3 months. Pre, and post-intervention and intraoperative liver biopsies, along with CT assessment of steatosis, were done. All 9 donors had a significant reduction in BMI ((~1.6 kg/m^2) (25.3 ± 3.8 to 23.7 ± 3.4, $P = 0.0001$)) and in steatosis ((~28%%) (48.9% ± 25.6% to 20.0% ± 16.2%, $p = 0.006$)) and underwent donor hepatectomy with no difference in outcomes as compared to normal donors without steatosis. They concluded that dietary optimization could help reduce steatosis and help increase the donor pool, with results similar to those of normal donors without steatosis. (Table 1).

Table 1 Previous studies on dietary optimization for steatosis reduction in donors.

S No	Reference	Country	No.	Type of intervention	Duration (months)	BMI reduction	Steatosis reduction (%)	Liver donation	**Outcomes**
1	Hwang et al., 2004 Liver transplantation [22]	Seoul, South Korea	9 (Steatosis 10-30%)	Diet (25-30 calories x ideal body weight) + Exercise	~3 Months	2 (P = 0.0001)	28.9 (P = 0.006)	9	No different from the control group
2	Oshita et al., 2012 Transplantation [21]	Hiroshima, Japan	42 (Steatosis 10-30%)	800 to 1400 kcal/d diet + 100 to 400 kcal/d exercise	~2.9 Months	0.90 (P < 0.0001)	-	41 (1 had stage 2 fibrosis)	No different from the control group
3	Doyle et al., 2016 Liver transplantation [18]	Toronto, Canada	16 (steatosis > 10%)	Optifast VLCD: 1000 kcal/d	~7.3 weeks	2.3 (P < 0.001)	24.55 (P < 0.001)	14 (1 low volume, 1 fibrosis)	No different from the control group
4	Pamecha et al., 2022 Langenbeck's archives of surgery [26]	Delhi, India	13 Biopsy-proven NASH	1200 to 1600 kcal/d diet (<30% fat; 40-50% carbohydrate, 50-60 g protein/day) + 40-60 minutes of exercise/day.	60-110 days	Wt loss - ~7.5 ± 2.7kg	Reversal of NASH in 6 donors.	6	Higher bilirubin levels and a longer time to normalization of bilirubin. Rest same.

5	Gupta Anish et al., 2023, RCT, Annals of surgery [23]	Delhi, India	Dietary optimization in 28 non-Steatotic donors (34 controls)	Low-calorie diet (equalling basal requirement) + exercise	14 days	Wt loss (~2 kg), BMI reduction by 1.6	-	100%	Better liver regeneration in donors and lesser EGD in recipients.
6	Anish Gupta [27]	Delhi, India	51 donors with steatosis	General Motors diet (low-calorie diet)	7 days	Wt loss (3.5 kg), BMI reduction by 1.2	3.8% (MR fat fraction)	100%	No difference in outcomes.

(Table adapted from Gupta A et al., [28]).

Similar studies by Oshita et al. and Doyle et al. also suggested marked weight reduction and improvement in steatosis by dietary optimization, leading to good donor and recipient outcomes [18, 21].

The study by Pamecha et al. was the first study that described the resolution of steatohepatitis in donors following dietary optimization. Finally, it resulted in successful and safe donor hepatectomy in donors previously with steatohepatitis [26]. They enrolled 13 potential donors with biopsy-proven steatohepatitis. They started them on a low-calorie diet (1200-1600 kcal/day) comprising 50-60 grams of protein/day, <30% fat, 40-50% carbohydrate, and 45-60 minutes of daily exercise for 60-110 days. Following this intervention, there was a reversal of NASH in 6 out of the 13 donors, and they could safely undergo donor hepatectomy with no major difference in donor or recipient outcomes. (Table 1).

A recent randomized control trial evaluated the role of a customized low-calorie diet (based on each donor's basal metabolic requirement) and exercise for 2 weeks before surgery in normal, healthy live liver donors without steatosis [23]. The study found a significant reduction in weight, lesser intraoperative blood loss, earlier normalization of liver function tests, and lesser peak AST and ALT levels post-donor hepatectomy in the intervention group. They also described improvement in liver regeneration in the donors based on CT volumetry following this optimization protocol along with decreased rates of early graft dysfunction in the recipient, thereby emphasizing the role of short-term dietary optimization even in healthy donors without steatosis to improve both donors as well as the recipient outcomes. (Table 1).

A recent study by our group evaluated the efficacy of ultra-short dietary optimization following the General Motors diet (GM diet) for 1 week in steatotic donors before surgery [27]. 51 LLDs with BMI over 30 kg/m^2, CT-LAI < 0 HU, and MR fat-fraction >10% were advised on a GM diet for 1 week. Following a week of GM diet initiation, there was an average improvement of 6.7 (±3.7) HU in CT LAI, 3.8% (±2.7) in fat fraction, and 3.46 (±2.1) kg weight loss. All these LLDs successfully underwent donor hepatectomy after a week of GM diet with an average post-op ICU and hospital stay of 2.86 (±0.8) days and 6.82 (±0.81) days, respectively. On intraoperative Tru-cut biopsy, none of the donors had >10% steatosis and had similar post-operative outcomes compared to donors without prior steatosis. It was concluded that the GM diet is safe and effective in reducing steatosis and increasing the pool of healthy LLDs without compromising the safety of the donors or the recipients. (Table 1).

3. Medications

Nakamuta et al. subjected steatotic liver donors with a combination of short-term weight loss intervention along with exercise and medications. 11 potential donors with ≤30% combined microvesicular and macrovesicular steatosis were enrolled. All 11 patients underwent pre and post-intervention liver biopsy. They employed a low-calorie, low-fat diet with calorie intake ranging from 1000 to 1400 kcal/day and exercise (600 kcal per day (200 kcal × 3 exercise sessions)). These donors were also started on Bezafibrate (400 mg/day) and continued till the day of surgery. Following this optimization protocol, they found a significant reduction in steatosis (18%; P = 0.0028) and BMI (2.3 kg/m^2; P = 0.0033). There was an improvement in liver function tests and lipid profile in all donors post-intervention, and 7 donors underwent LDLT with good outcomes in both the donors and recipients [20] (Table 2).

Table 2 Previous studies on steatosis reduction using medications in donors.

S No	Reference	Country	No.	Type of intervention	Duration (months)	BMI reduction	Steatosis reduction (%)	Liver donation	**Outcomes**
1	Nakamuta et al., 2005 Transplantation [13]	Fukuoka, Japan	11 (Steatosis 10-30%)	1000 kcal/d diet + exercise (600 kcal/d) + Bezafibrate	~37.8 ± 4.6 days	4.4 (P = 0.0033)	18 (P = 0.0028)	7 (2 recipient deaths, 1 low GRWR)	No different from the control group
2	Fujii et al., 2020 Annals of Transplant [17]	Sapporo, Japan	8 (steatosis > 10%)	<1600 Kcal/d + exercise 20 min × 3/wk. ± statins	~58 days	2.6 (P = 0.0009)	Yes (P = 0.0006)	8	No different from the control group
3	El Badry et al., [28]	Zurich, Switzerland	3 (Steatosis > 30%)	Omega 3 fatty acids	1 month	-	-	3	Not available.

(Table adapted from Gupta A et al., [28]).

Fujii *et al.* evaluated 8 potential donors with steatosis (hepatic attenuation of <55 HU on Non-Contrast CT or liver-to-spleen attenuation ratio of <1.1). Donors were subjected to a low-calorie diet (<1600 Kcal/day along with exercise for 20 min for 3 days a week in addition to statin administration till the day of surgery. Donors were taken up for donor hepatectomy when macrovesicular steatosis was <10% on liver biopsy. They found a significant reduction in BMI and steatosis, and all 8 could undergo successful donor hepatectomy with no significant difference in either donor or recipient complication and similar graft functions (Table 2).

In a study by El Badry et al. 2010, the role of Omega 3 fatty acid supplementation in 3 steatotic live liver donors was assessed. Oral Omega 3 fatty acid supplementation was continued for 1 month in these donors, leading to steatosis reduction and successful surgery [28].

Studies have shown oral O-3 fatty acids supplementation to be associated with reduced total hepatic lipid content, with the conversion of the predominant macrosteatosis into microvesicular steatosis, improved sinusoidal perfusion, and decreased hepatocellular damage after reperfusion [28-30]. There is also evidence of resolution of biochemical and ultrasonographic features of fatty liver on prolonged oral Omega-3 fatty acid supplementation [31]. Omega-3 fatty acids mainly act via eicosanoid derivatives, which help in counteracting the proinflammatory Omega-6 eicosanoids [28] (Table 2). One of the biggest drawbacks of the drug-based management of steatotic donors is the longer duration of treatment needed to obtain significant results. Also, donors would need further studies to ascertain the efficacy and safety of these drugs.

4. Future Strategies

4.1 Silymarin

An extract from the dried seeds and fruits of the milk thistle plant (Sylibun marianum) is a known free radical scavenger, decreases oxidative stress and consequent cytotoxicity, and modulates enzymes associated with the development of cellular damage and protects liver cells from oxidative stress [32-34]. No study has yet been done on silymarin to assess the effect on steatotic donors.

4.2 Curcumin

(Curcuma longa) is an active compound from the curcuminoids family and is a known antioxidant and anti-inflammatory agent. Studies have shown a reduction in steatosis, hepatic enzymes, and inflammatory markers, including tumor necrosis factor-α (TNF-α) and nuclear factor-kappa-β activity (NF-κβ) following long-term curcumin supplementation along with dietary modification in patients with NAFLD. No study has yet been performed on steatotic donors [35-37].

4.3 Resveratrol

Resveratrol (3,5,4-trihydroxy-trans-stilbene) is a phytoestrogen naturally derived from skins of red grapes and blueberries. Studies have shown the efficacy of resveratrol in increasing fatty acid oxidation and reducing lipogenesis, leading to a decrease in hepatic steatosis [38, 39]. The efficacy of resveratrol is yet to be established in steatotic donors.

4.4 Liraglutide

It is a glucagon-like peptide-1 (GLP-1) analog known to reduce hepatic steatosis, concentrations of liver enzymes, and peripheral insulin resistance. A study by Armstrong et al. established the efficacy of liraglutide in steatohepatitis resolution in patients with NASH, but the efficacy in steatotic donors is yet to be established [40].

4.5 Pioglitazone

It is a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist for managing type 2 diabetes (T2DM). The study by Sathyanarayana et al. established the efficacy of pioglitazone in reducing hepatic steatosis in addition to reducing fasting plasma glucose (FPG), fasting free fatty [41, 42] acid (FFA), decreasing plasma adiponectin concentration, and body weight. These drugs have been studied and are known to decrease steatosis in patients with NAFLD. However, there is not yet enough data to support their use in steatotic donors, and further studies would be needed to evaluate their safety and efficacy in steatotic donors.

4.6 Bariatric Surgery

Though the idea is still in its infancy, there have been reports of donor hepatectomy after bariatric surgery, which leads to loss of weight and improved steatosis leading to donor hepatectomy [43-45].

Obed et al. described the case of a liver donor who had undergone laparoscopic sleeve gastrectomy 4 years back and had lost weight before successful donor hepatectomy while Garcia et al. described a case series of 4 donors who had earlier undergone bariatric surgery procedure for resolution of obesity. 2 donors had undergone laparoscopic sleeve gastrectomy while 2 underwent Roux-en-Y gastric bypass. No complications were observed in either donors or the recipients, and there was 100% graft survival with no added morbidity.

These small studies suggested that utilization of selected donors with previous bariatric surgery appears to be a safe option and increases the donor pool. However, larger studies would be needed to confirm these benefits.

5. Impact of Hepatic Steatosis in Liver Surgery

Steatosis is known to occur in two forms: macrovesicular and microvesicular. With mild steatosis, fat droplets have a zone 3 pericentral pattern, preserved periportal areas, and fat globules centered around the central vein [46, 47]. Steatosis, in turn, causes microcirculation impairment and decreased resistance to ischemic damage after liver resection, thereby leading to poor regeneration [48].

Berhns et al. reported that steatosis was associated with longer operative times, higher postoperative bilirubin and AST levels, and higher blood transfusion requirements. Various studies established steatosis to be associated with higher rates of hepatobiliary complications and wound-related complications after hepatic resection [14]. Kooby et al. also reported a similar increase in rates of hepatobiliary complications after liver surgery in steatotic patients [15]. Sultana et al. and Fagenson et al. reviewed outcomes after surgery on steatotic livers and found higher rates of liver

failure after hepatectomy and higher rates of hepatobiliary and pulmonary complications, respectively [49, 50].

6. Discussion

Ensuring donor safety constitutes the most crucial aspect of LDLT, with all necessary precautions to facilitate prompt recovery and a complication-free post-operative period for the donor [51]. There have been various studies regarding steatotic donor optimization in the past. Most studies demonstrating efficacy have centered around optimizing dietary and lifestyle factors to reduce steatosis (Table 1, 2). The exact mechanism of action of these low-calorie diets is not yet known. However, it is postulated that calorie-deficit diets work by increasing insulin sensitivity, reducing glucose production, and improving intrahepatic lipolysis, leading to reduced intrahepatic triglycerides and glycogen [52].

Enhanced physical activity further helps reduce intrahepatic triglycerides and improves the overall health of the donor. Physical activity helps decrease hepatic fat content by improving insulin resistance, increasing lipolysis, and fatty acid metabolism. Improved fatty acid oxidation and decreased fatty acid synthesis further help reduce mitochondrial and hepatocellular damage by reducing the release of damage-associated molecular patterns [53].

Previous studies have shown that even after just 48 hours of calorie deficit diet consumption, there is a significant reduction in triglyceride level in the hepatic parenchyma and improved hepatic insulin sensitivity [54], indicating that even short-term dietary optimization just before transplant might be effective in reducing steatosis and improving outcomes. Marcos et al. described that each percentage increase in steatosis equals a decrease in functional graft weight by 1% [55]. This becomes significant, especially in living donors with borderline remnants where the margin of safety may improve with a reduction in steatosis. This would subsequently mean improved functional liver remnant mass and may help increase the donor pool and avoid donor rejections. Studies have shown reduced blood loss after calorie deficit low-fat diets [23, 56-58]. The exact mechanism of reduction in blood loss is not yet known, but it has been postulated to be due to reduced glycogen content in the liver. Each gram of glycogen in the liver binds to 4 g of water, thereby increasing the water content in the liver, leading to more blood loss [59].

Kirk et al. described changes in intrahepatic triglyceride levels after just 48 hours of calorie-restricted diet (1100 kcal) based on magnetic resonance spectroscopy. In addition to a decrease in hepatic triglyceride levels, they also found a decrease in glucose production rate and improved hepatic insulin sensitivity rates, hypothesizing decreased circulating insulin and increased lipolysis as the mechanism responsible for this. Under normal conditions, insulin is known to decrease lipolysis in the liver. Hence, hepatic lipolysis increases as serum insulin and glucose levels decline in the body [54].

Reeves et al. first described a decrease in hepatic steatosis and steatohepatitis based on histology after a short-term low-calorie diet. They also found that diet was an independently significant predictor for decreased steatosis and steatohepatitis rather than being dependent on weight loss and loss of BMI for causing decreased steatosis. They also found a significant decrease in intraoperative blood loss after putting the patients on a calorie-restricted diet. They recommended initiation of pre-operative lifestyle modification in all the donors, irrespective of their BMI, to

decrease steatosis and hence to decrease the complications and morbidity associated with surgery [58].

The optimization of steatotic live liver donors and their conversion to healthy liver donors is a viable option for expanding the donor pool. However, the data regarding donor and recipient outcomes is sparse in the case of such donors with a prior history of steatosis managed with dietary optimization. The goal of steatotic liver donor optimization lies in optimizing the donors for donor hepatectomy and providing for a healthy life by counseling and inculcating a healthy lifestyle, dietary optimization, and increased physical activity even after discharge after donor hepatectomy. These donors need to stay on a stringent follow-up after donor hepatectomy to assess for recurrence of steatosis in the liver remnant and for early detection of complications, if any, in the residual liver.

7. Conclusion

Severe steatosis is one of the most significant risk factors for complications after donor hepatectomy and dietary interventions; weight loss along with exercise and pharmacotherapy is safe, feasible, and effective in steatosis reduction and helps turn marginal steatotic donors into low-risk donors, thereby improving outcomes. Carefully selected steatotic diet-treated living liver donors have good donor and recipient outcomes and graft quality compared to non-steatotic donors and, therefore, may help expand the donor pool without increasing risk to the donors and recipients and also help decrease waitlist mortality. In donors with a low remnant, the safety margin can be increased. In contrast, recipients with low GRWR can decrease rates of EGD, leading to early recovery and lower morbidity and mortality.

Author Contributions

Abhideep Chaudhary, Anish Gupta, Gaurav Sood, Niteen Kumar conceived the idea; Anish Gupta, Imtiakum Jamir writing and drafting of manuscript.

Competing Interests

The authors declare that they have no conflict of interest regarding the publication of this review.

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