The Overweight Donor: Pre and Post Operative Considerations

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Medical Director Living Donor Liver Transplant
# Objectives

<table>
<thead>
<tr>
<th>Data</th>
<th>Review data/experience regarding overweight persons as living liver donors</th>
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<tbody>
<tr>
<td>Triage</td>
<td>Outline a suggested triage guidance for the consideration of such donors</td>
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<tr>
<td>Care Pathway</td>
<td>Present a care pathway for risk mitigation peri-operatively and long-term</td>
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Terminology

Overweight - Body mass index (BMI) 25.0 to <30

Obesity - BMI >30
World-wide center specific reports of living liver donor assessments cite 5-38% of potential donors declines due to obesity/liver steatosis.

In A2ALL (2007):
What we want to know….

• Which obese donors are suitable for donation?

• How might we “push the envelope” without increasing short and long-term risk?

• What clinical scenario would create the “perfect storm”?……
Considerations
Evaluation and Triage

Jesse, MT, Jackson, WE, Liapakis, AM et al. Living donor liver transplant candidate and donor selection and engagement: Meeting report from the living donor liver transplant consensus conference. Clin Transplant. 2023;e14954

https://www.invensislearning.com/blog/risk-management-process-steps/
Screening & Evaluation

Identify potential risks

BMI determination, weight classification

• attention to ethnic variation
Evaluation: What are centers currently doing?

2019

• Worldwide survey of 24 centers CT scan was the most used noninvasive method to assess steatosis (75%), followed by MRI (17%) and US (8%)
  • 23/24 centers considered steatosis on imaging an indication for liver biopsy
  • 11/24 centers considered BMI >25-20 an indication for liver biopsy
  • In 7/24 metabolic syndrome, 5/24 raised triglycerides, 4/24 diabetes mellitus were considered indications for liver biopsy

• Survey of 9 North American centers, 33% utilized MR elastography

• Combination of MR fat fraction and elastography proposed by Yoon et. al., to identify donors with >10% steatosis and >/= F1 fibrosis

Evaluation: What are centers currently doing?

2022

• US survey of all 53 LDLT centers with 100% response
  • 90% routine assessment of liver steatosis with imaging
    • MRI 95.8%
    • CT 60.4%
    • Elastography 45.8%

• Of 36 centers that used imaging as indication for biopsy, 50% used threshold of 10% steatosis; 8.3% 15% steatosis, 13.9% 20% steatosis, 27.8% any steatosis
Risk Assessment: Green Zone Data

- **Obesity alone** is not a risk factor for postoperative complications in surgery. However, an increased incidence of wound infections in open surgery is noted.

- Obesity in liver surgery prolongs operative time & might be a risk for certain complications depending on the procedure, though it is possible that obesity doesn’t adversely impact long-term surgical outcomes. (assessment of mixed studies)

- Obesity withOUT liver steatosis (<10%) withOUT metabolic syndrome is:
  - not associated with a reduction in recipient graft or patient survival in LDLT.
  - not associated with a reduction in recipient graft function in LDLT
  - not associated with an increased rate of recipient complications in LDLT.
  - not associated with an increased rate of donor complications or hospital length of stay in LDLT

- Visceral fat area not BMI is an independent risk factor for significant hepatic steatosis.


“Healthy Obese”

- Donors with BMI <30 (n 364) versus donors with BMI ≥30 (n 105) 4/2000 to 5/2014
- Liver steatosis >10% was excluded in all donors with BMI >30 by imaging and liver biopsies. No comorbidities.
- Similar postoperative complication rates (Dindo-Clavien ≥3b: 2% vs. 3%; p = 0.71)
- Same lengths of hospital stay (LOS) (6 vs. 6 days; p = 0.13).
- Recipient graft function (peak serum bilirubin and international normalized Ratio) was identical.
- No difference was observed in recipient complication rates (Dindo-Clavien ≥3b: 25% vs. 20%; p = 0.3) or lengths of hospital stay.

Risk Assessment: Red Zone Data

- **Hyperglycemia** causes an increase in oxidative stress & inflammatory response.
- **Diabetes mellitus** (DM) compromises liver regeneration & is associated with poor prognosis after ischemia-reperfusion injury.
- Insulin dependent DM is a risk factor for major complications in liver resection.
- **Obesity + metabolic syndrome** increase risk of peri-operative complications in liver resection.
- Patients with obesity + metabolic syndrome have a greater than 2-fold increased risk of death after liver resection.
- **NASH with fibrosis** risks progression to cirrhosis. There is no LDLT specific data.


Risk: Diabetes

Oxidative Stress after liver resection

Inflammation after liver resection

Risk: Metabolic Syndrome

- National Surgical Quality Improvement Program (NSQIP)
- 3,973 patients underwent hepatic resection Jan 2005 to Dec 2008
- 31.7% of patients were obese, 20% of whom had Metabolic Syndrome (MetS)
- Patients with MetS had greater risk of:
  - reintubation (OR 1.9)
  - >48hrs vent dependence (OR 2.0)
  - MI (OR 5.5)
  - surgical site infection (OR 1.7)
  - postoperative death (OR 2.7)

Risk Assessment Grey Zone: Hepatic Steatosis

• Early transplant data with deceased donors revealed that severe macrovesicular steatosis (>30%) was associated with early liver dysfunction/primary nonfunction as well as a detriment in longer term graft and patient survival.

• 2003 Soejima demonstrated that <50% steatosis could be used in LDLT if graft volume/standard liver volume was >40%, although early ischemia-reperfusion injury was often observed

• 2005 Cho demonstrated that steatosis disappeared immediately after LDLT and hepatic regeneration power was not impaired in grafts with less than 30% macrovesicular steatosis. No PNF or DGF. Major complications were like non-steatotic grafts.

• A recent analysis in Transplantation 2020 suggests that up to 20% liver steatosis is acceptable in well selected donors/livers.

Hepatic Steatosis

• Comparison of donor and recipient outcomes in 623 primary right lobe living donor liver transplantations, using grafts with (Group A; 10%–20% steatosis, n = 92) and without (Group B; <10%, n = 531) significant macrovesicular steatosis, on pre- or intraoperative biopsy.

• Use of well-selected right lobe grafts (adequate future liver remnant in donor, GRWR in recipient), with up to 20% macrovesicular steatosis, does not compromise graft function and outcomes and is safe for the donor.

Risk Assessment Grey Zone: Metabolic Abnormality

- No granular data in LDLT available
- Data emerging in LD kidney transplantation
- Metabolic parameters warrant assessment & consideration in the evaluation of potential living liver donors.

Acceptance Thresholds: What are centers currently doing?

2022
• US survey of all 53 LDLT centers with 100% response

  • Of 33 centers that reported steatosis exclusion threshold on biopsy, most used 10%. 9.1% of centers used 15% steatosis, 30.3% of centers used 20% steatosis

  • 88.5% of centers excluded donors with steatohepatitis

  • 61.5% of centers do not exclude diagnosis of diabetes alone

"The Grey Zone"

- Healthy obese
- Visceral obesity
- Metabolic Risk
  - NAFLD
  - NASH S0
- Metabolic syndrome
  - Insulin Dep Diabetes
  - NASH S1-4

Risk Management Process:
- Identify potential risks
- Monitoring & Reviewing the Risk
- Analysing the risk
- Evaluating the Risk
- Treating the Risk
Risk Mitigation- Intervention

Can we modify risk & shift Grey zone donors to the Green zone?
Weight reduction (>7%) leads to improvements in liver histology in NASH
AST LDLT Survey of US Centers

71% of respondents noted obesity was a donor exclusion

Median BMI threshold 35, range 30-45

64% refer donors to formalized weight loss programs, (don’t 23%, unsure 13%)

Variable required “maintenance” period

None 45.8%, Don’t know 20.8%, 1 month 8.3%, 3 month 22.9%, 6 months 2.1%

BMI (kg/m²)

<30
- <30 Steatosis < 17% on MRI-PDFF
  - No MetS
  - Proceed to donor surgery
- <30 Steatosis > 17% on MRI-PDFF + MetS (no DM)
  - Proceed to donor surgery

30-35
- BMI 30-33 Steatosis > 17% on MRI-PDFF
  - No MetS
  - Proceed to donor surgery
- BMI > 33
  - No steatosis
  - No MetS
  - No other donor
  - Not a candidate for donation

>35
- BMI > 35
  - No steatosis
  - No MetS
  - No other donor
  - Proceed to donor surgery
- BMI > 35 + MetS
  - Physician supervised weight loss*
  - until BMI < 33
  - Proceed to donor surgery

*Patient costs reimbursed

Unpublished data, courtesy of Abhi Humar UPMC
Donor BMI & Outcome
UPMC

Donor BMI at Time of LDLT Surgery (2009-2021, n=449)

Outcomes by Donor BMI

<table>
<thead>
<tr>
<th>Summary Statistics</th>
<th>All (N=449)</th>
<th>BMI &lt;25 (N=163)</th>
<th>BMI 25-30 (N=188)</th>
<th>BMI &gt;30 (N=98)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor Length of Stay</td>
<td>Mean (sd)</td>
<td>5.27 (2.96)</td>
<td>5.13 (1.34)</td>
<td>5.41 (3.81)</td>
<td>5.24 (3.07)</td>
</tr>
<tr>
<td>BMI 1 year Post-Tx</td>
<td>Mean (sd)</td>
<td>28.31 (5.75)</td>
<td>27.11 (5.04)</td>
<td>28.91 (6.28)</td>
<td>29.13 (5.50)</td>
</tr>
<tr>
<td>Bilirubin at Discharge</td>
<td>Mean (sd)</td>
<td>1.68 (1.32)</td>
<td>1.73 (1.03)</td>
<td>1.65 (1.69)</td>
<td>1.64 (0.91)</td>
</tr>
<tr>
<td>Bilirubin 1 Month Post Discharge</td>
<td>Mean (sd)</td>
<td>1.11 (0.78)</td>
<td>1.07 (0.75)</td>
<td>1.11 (0.79)</td>
<td>1.17 (0.81)</td>
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</table>

Unpublished data, courtesy of Abhi Humar UPMC
Lose Weight to Donate: Development of a Program to Optimize Potential Donors With Hepatic Steatosis or Obesity for Living Liver Donation

John T. Rose, BS,1 Paola Vargas, MD,2 Tara Seay, RN,2 Arthur J. Pesch, MD,3 Tessa Williams, RN,2 Anita Sites, NP,2 Zachary Henry, MD,4 Patrick G. Northup, MD,4 Shawn J. Pelletier, MD,2 Jose Oberholzer, MD,2 Curtis K. Argo, MD,4 and Nicolas Golderacena, MD2

Background. Living donor liver transplantation offers an attractive option to reduce the waitlist mortality. However, in recent years, the rising prevalence of obesity and nonalcoholic fatty liver disease has posed a serious threat to the donor pool while simultaneously increasing demand for liver transplant. To our knowledge, there have been no major published studies in the United States documenting a diet and exercise intervention to expand the living donor pool. Hereby, we established a pilot program called “Lose Weight to Donate” and present our initial experience. Methods. Our center instituted a remotely monitored diet and exercise pilot program to increase eligibility for living liver donation. Potential donors with any of the following were included: body mass index >30 kg/m², hepatic steatosis >5% on screening MRI, or isolated hypertension. Results. Over 19 mo, 7 individuals enrolled in the program of remote monitoring for at least 6–8 wk. Initial and follow-up abdominal MRI was performed in 5 of these individuals to assess steatosis, anatomy, and volume. Initial steatosis was highly variable (fat signal fraction range, 8%–26%). Follow-up MRI fat signal fraction values and hepatic volume all decreased to varying degrees. Ultimately, 2 of 7 individuals donated, whereas a third was approved, but the intended recipient was transplanted in the interim. Conclusions. These results indicate the feasibility of a remotely monitored program to expand donation in light of the rising incidence of hepatic steatosis and obesity.

(Transplantation Direct 2021;7: e702; doi: 10.1097/TXD.0000000000001161. Published online 25 May, 2021.)
Risk Mitigation - Intervention

Pharmacologic Therapy within the Yale Metabolic Health & Weight Loss (MWM) Program
Pharmacologic Weight Loss Considerations

- Phentermine: a hypothalamic adrenergic agonist metabolized by the liver, risk of hepatotoxicity low

- Semaglutide: a GLP-1 agonist is metabolized by proteolytic cleavage throughout the body.

- Suggest to stop 2-4 weeks before donation and resume after recovery/liver regeneration (i.e., anabolic period)
Monitoring & Reviewing Risk
<table>
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<tr>
<th>#3</th>
<th>Obesity, metabolic syndrome, and non-alcoholic fatty liver disease are highly prevalent in the U.S. population and have limited the pool of living donor candidates.</th>
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<tbody>
<tr>
<td></td>
<td>• BMI is not an adequate independent predictor of hepatic steatosis and NASH alone. Risk stratify potential living liver donors with attention to visceral fat distribution, risk factors for metabolic syndrome, quantification of hepatic steatosis, and also fibrosis as appropriate.</td>
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<tr>
<td></td>
<td>• Exclude donors with diabetes, active steatohepatitis, and/or hepatic fibrosis. Consider donors with obesity and/or risk factors for metabolic syndrome if resources allow for utilization of metabolic health and weight loss programs for risk mitigation.</td>
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<td></td>
<td>• Advocate for resources to use to explore expansion of donor metabolic health and weight loss programs and to support formalized post-donation care.</td>
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<tr>
<td>Importance</td>
<td>8.02 (1.13); 8 (8, 9)</td>
</tr>
<tr>
<td>Impact</td>
<td>7.59 (1.17); 8 (7, 9)</td>
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<tr>
<td>Feasibility</td>
<td>6.98 (1.87); 7 (6, 8)</td>
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<table>
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<tr>
<th>#6</th>
<th>Lack of long-term follow up data on donors treated in metabolic health and weight loss programs limit the ability to counsel donors regarding long term risk and health outcomes.</th>
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<tr>
<td></td>
<td>• A multicenter prospective study to collect long term follow up data in this subpopulation of donors.</td>
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<tr>
<td>Importance</td>
<td>7.63 (1.37); 8 (6.75, 9)</td>
</tr>
<tr>
<td>Impact</td>
<td>7.57 (1.47); 8 (7, 9)</td>
</tr>
<tr>
<td>Feasibility</td>
<td>6.50 (1.75); 7 (5, 8)</td>
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#5 Discussions to expand donor acceptance rates will rely on a better understanding of center-variable donor evaluation processes including testing and reasons for rule out, then follow donors both approved and declined overtime for short-term and long-term outcomes to inform attributable risk tolerance discussions. Strategies for routine follow up of the donor evaluation process, short-term and long-term living liver donor outcomes is needed.

- A living donor registry is needed to incorporate the components of the donor evaluation including testing, reasons for rule out and then to follow donors both approved and declined overtime for short-term and long-term outcomes. Any registry would need to overcome hurdles such as the burden of data entry and finances through electronic data transfer and funding. Likewise, any registry would need to make its data available to be obtained deidentified.
- National societies should endorse data collection by having an expectation of minimal data sharing.
- High volume centers should come together to combine and publish their data on reasons donors are declined for medical, anatomic and psychosocial reasons.
- Patients should be educated that different centers may have different criteria for donor approval.
- Donors with incidental findings need to be directed to appropriate follow up.

<table>
<thead>
<tr>
<th>Importance: 7.72 (1.52); 9 (7, 9)</th>
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<tbody>
<tr>
<td>Impact: 7.32 (1.84); 8 (6, 9)</td>
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<tr>
<td>Feasibility: 6.54 (1.79); 7 (5, 8)</td>
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<tr>
<td>-----------------------------</td>
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<tr>
<td>Impact: 7.30 (1.92); 8 (6, 9)</td>
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<tr>
<td>Feasibility: 7.07 (1.91); 7 (6, 9)</td>
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<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Impact: 7.63 (1.50); 8 (7, 9)</td>
</tr>
<tr>
<td>Feasibility: 6.80 (1.71); 7 (6.75, 9)</td>
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<tr>
<td>-----------------------------</td>
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<tr>
<td>Impact: 7.50 (1.56); 8 (6.75, 9)</td>
</tr>
<tr>
<td>Feasibility: 7.35 (1.58); 7.5 (6, 9)</td>
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<tr>
<td>-----------------------------</td>
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<tr>
<td>Impact: 7.20 (2.18); 8 (6, 9)</td>
</tr>
<tr>
<td>Feasibility: 7.67 (1.38); 8 (7, 9)</td>
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The Living Donor Collective

**Mission**

The mission of LDC is to expand its national living organ donor registry in which transplant programs register all living donor candidates who come to be evaluated at their center, in order to assess long-term outcomes of living donor candidates and donors.

**Vision**

LDC aims to provide living donor and candidate data analysis efforts that are accurate, clear, and timely for use by transplant programs, organ procurement organizations, living donors and transplant families, so the effects of living organ donation become widespread knowledge.
Conclusions

- Obesity and associated complications impacts potential living liver donors in the US.
- Risk assessment should include evaluation of weight, BMI, metabolic parameters, hepatic steatosis.
- Non-invasive means may be incorporated.
- Centers should develop a formalized triage algorithm and consider referral to formalized weight management programs.
- The “healthy obese” i.e., those without METs and significant hepatic steatosis may safely be considered for donation.
- Those with Diabetes, NASH, and/or hepatic fibrosis should be declined.
- Center specific thresholds for BMI, hepatic steatosis, and metabolic risk should be outlined and risk mitigation with attention to follow-up employed.
- Risk mitigation can incorporate formalized diet and exercise counseling, meal replacement, & pharmacologic therapy.
- Multi-center, long-term follow-up data are required to better inform risk.
Obese Living Liver Donors

QUESTIONS

THANK YOU
Session Survey

AnnMarie Liapakis, MD | April 20th 8:45 AM-9:30 AM