

The Overweight Donor: Pre and Post Operative Considerations

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Objectives



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

Terminology

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

Obesity- BMI >30

Relevance

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):

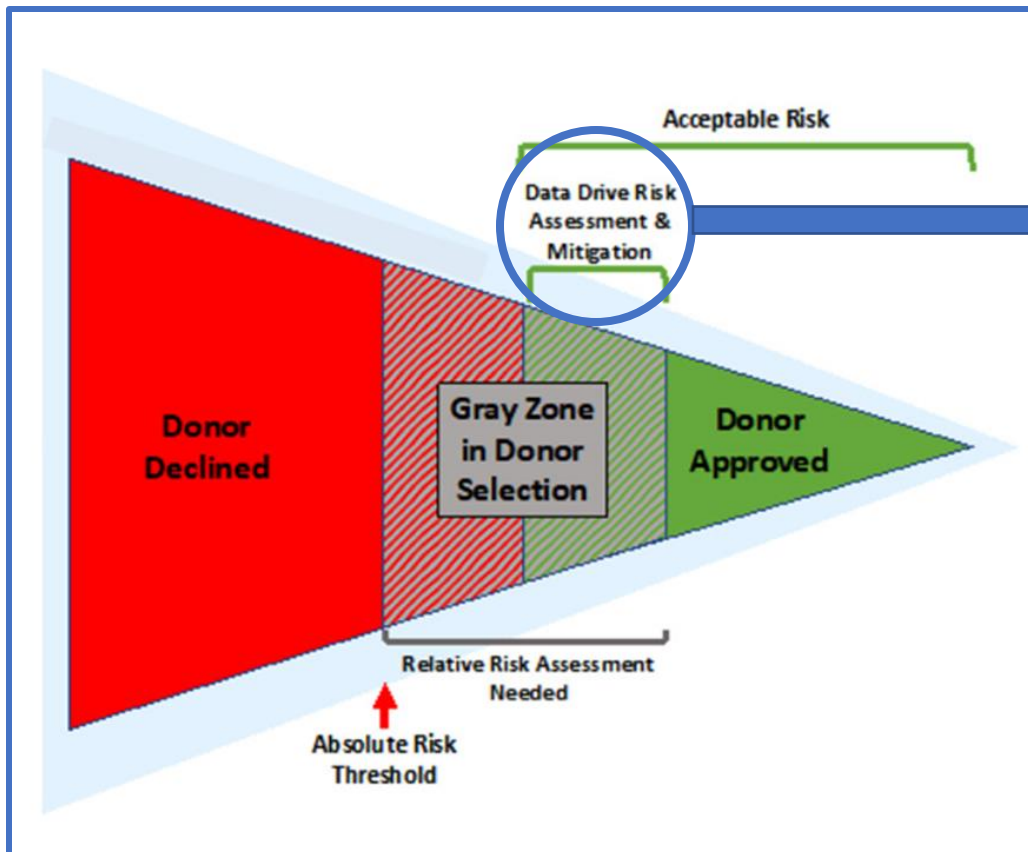
What we want to know.....



- 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



<https://www.invensislearning.com/blog/risk-management-process-steps/>

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

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

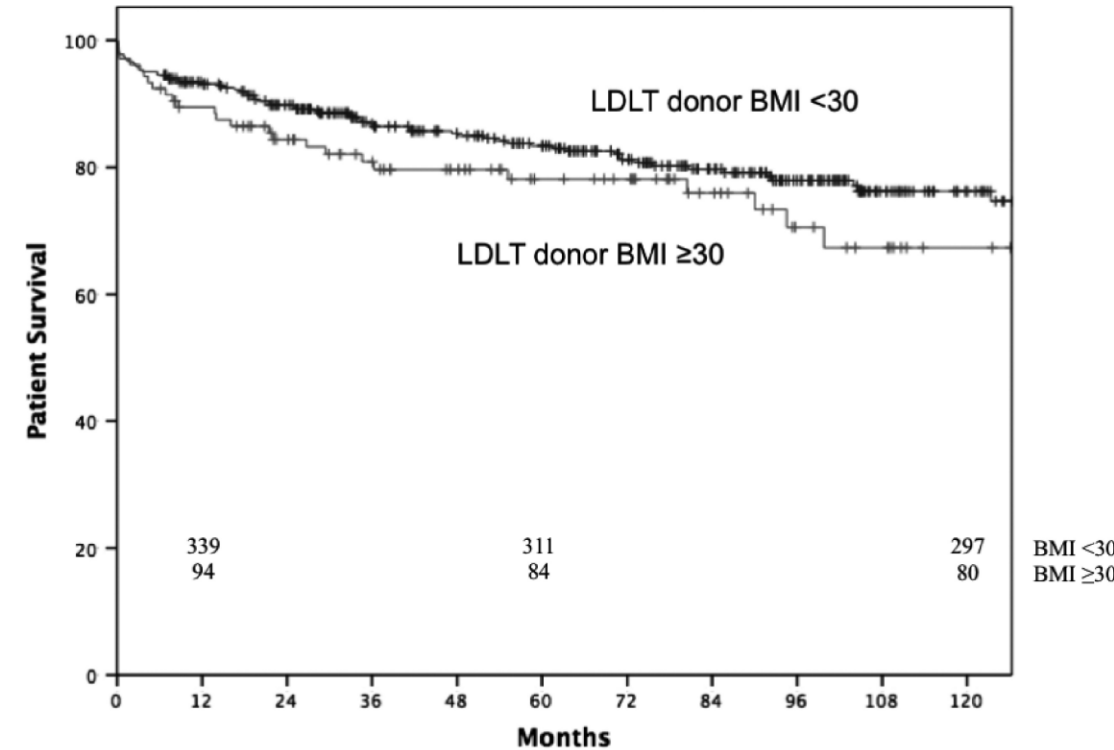
Dindo D, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. Lancet. 2003 Jun 14;361(9374):2032-5.

Ri M, Aikou S, Seto Y. Obesity as a surgical risk factor. Ann Gastroenterol Surg. 2017 Oct 28;2(1):13-21.

Knaak M, Goldaracena N, Doyle A, et al. Donor BMI >30 Is Not a Contraindication for Live Liver Donation. Am J Transplant. 2017 Mar;17(3):754-760.

“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.



BMI, body mass index; LDLT, living donor liver transplantation





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.

Mendes-Braz M, Martins JO. Diabetes Mellitus and Liver Surgery: The Effect of Diabetes on Oxidative Stress and Inflammation. *Mediators Inflamm.* 2018 May 8;2018:2456579.

M. G. Wiggans, J. T. Lordan, G. Shahtahmasebi, S. Aroori, M. J. Bowles, D. A. Stell, "The Interaction between Diabetes, Body Mass Index, Hepatic Steatosis, and Risk of Liver Resection: Insulin Dependent Diabetes Is the Greatest Risk for Major Complications", *HPB Surgery*, vol. 2014, Article ID 586159, 10 pages, 2014.

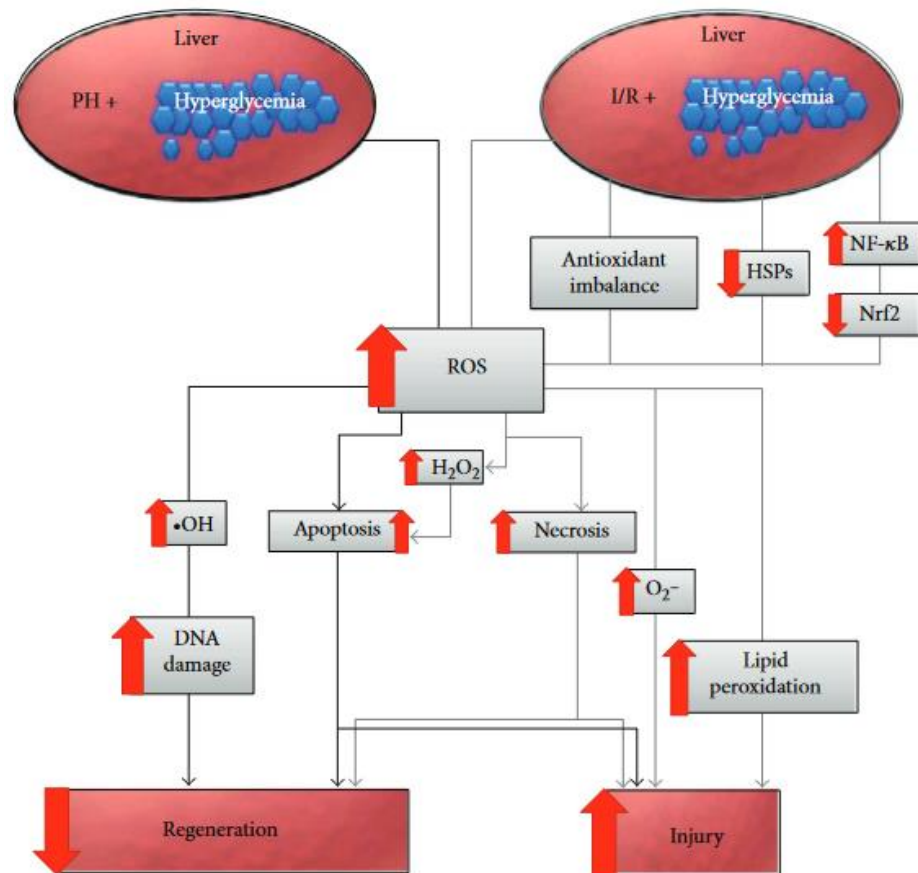
Bhayani NH, Hyder O, Frederick W, et al. Effect of metabolic syndrome on perioperative outcomes after liver surgery: A National Surgical Quality Improvement Program (NSQIP) analysis, *Surgery*, 2012 Vol 152(2): 218-226,

Sheka AC, Adeyi O, Thompson J, et al.. Nonalcoholic Steatohepatitis: A Review. *JAMA.* 2020 Mar 24;323(12):1175-1183.

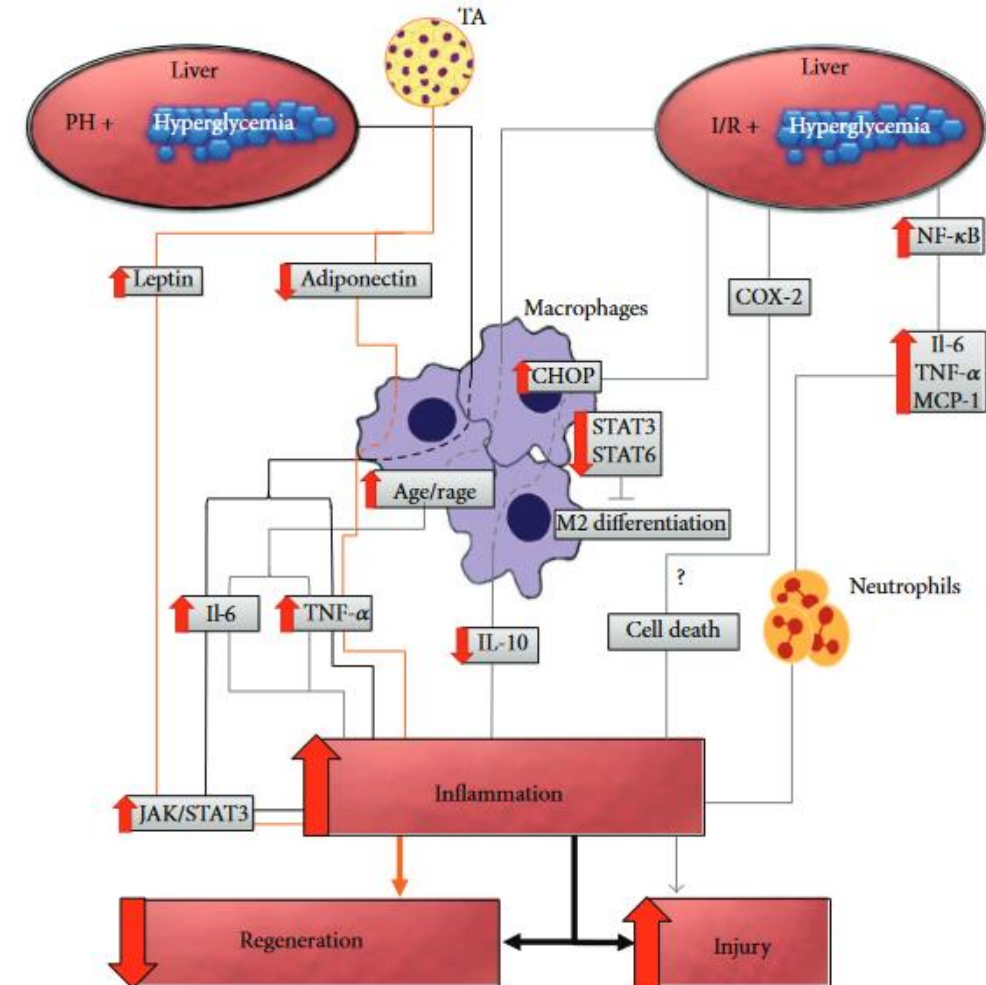
Risk: Diabetes



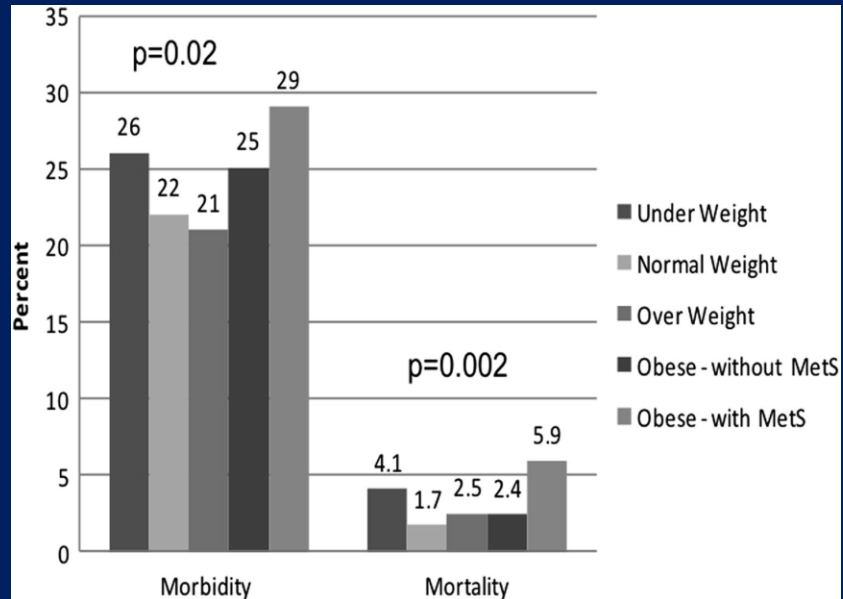
Oxidative Stress after liver resection



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)



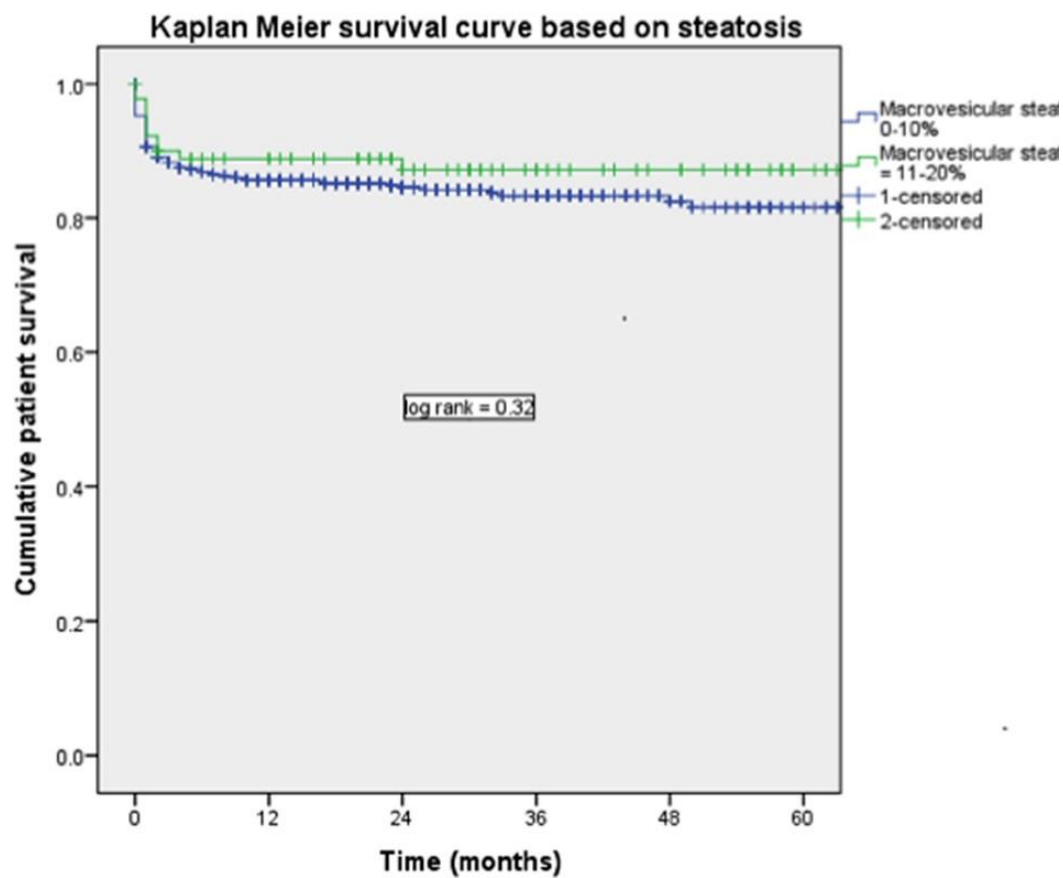
Risk Assessment Grey Zone: Hepatic Steatosis

- **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.**

•Marsman WA, *Transplantation*. 1996 Nov;62(9):1246-1251; ·Soejima Y, *Transplantation*: July 27th, 2003 - Volume 76 - Issue 2 - p 344-348; ·Cho JY *Liver Transpl* 2005;11:210-217;

Bhangui P, Sah J, Choudhary N, Gautam D, Gupta V, Srinivasan T, et al. *Safe Use of Right Lobe Live Donor Livers With up to 20% Macrovesicular Steatosis Without Compromising Donor Safety and Recipient Outcome. Transplantation*. 2020 Feb;104(2):308-316.

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.

Bhangui P, Sah J, Choudhary N, et al. Safe Use of Right Lobe Live Donor Livers With up to 20% Macrovesicular Steatosis Without Compromising Donor Safety and Recipient Outcome. Transplantation. 2020 Feb;104(2):308-316.

Risk Assessment Grey Zone: Metabolic Abnormality



INCREASED BLOOD PRESSURE

130/85 mm Hg
or higher



HIGH TRIGLYCERIDES

150 mg/dL
or more



LARGE WAISTLINE

Men: 40" or more
Women: 35" or more



LOW HDL (GOOD) CHOLESTEROL

Men: less than 40 mg/dL
Women: less than 50 mg/dL



ELEVATED FASTING BLOOD SUGAR

100 mg/dL or higher



Source: American Heart Association

- **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

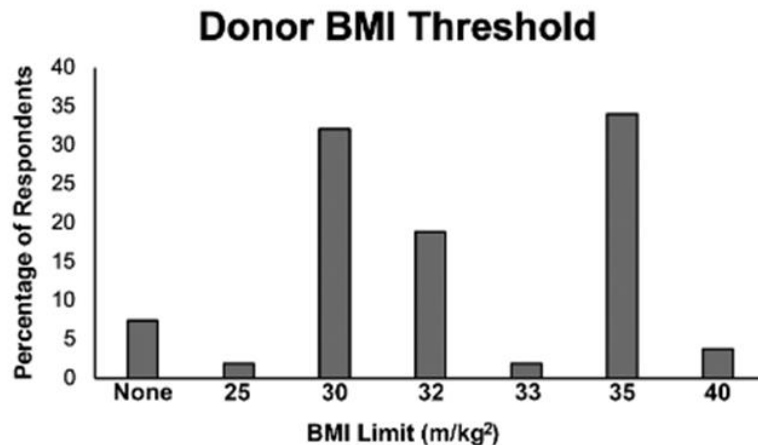


FIGURE 2 BMI limitations for living liver donors. All LDLT centers across the United States were asked if they used a BMI (m/kg²) limit as an exclusionary criterion for accepting living liver donors. All data are presented as the percentage of total respondents (N = 53).

- 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 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

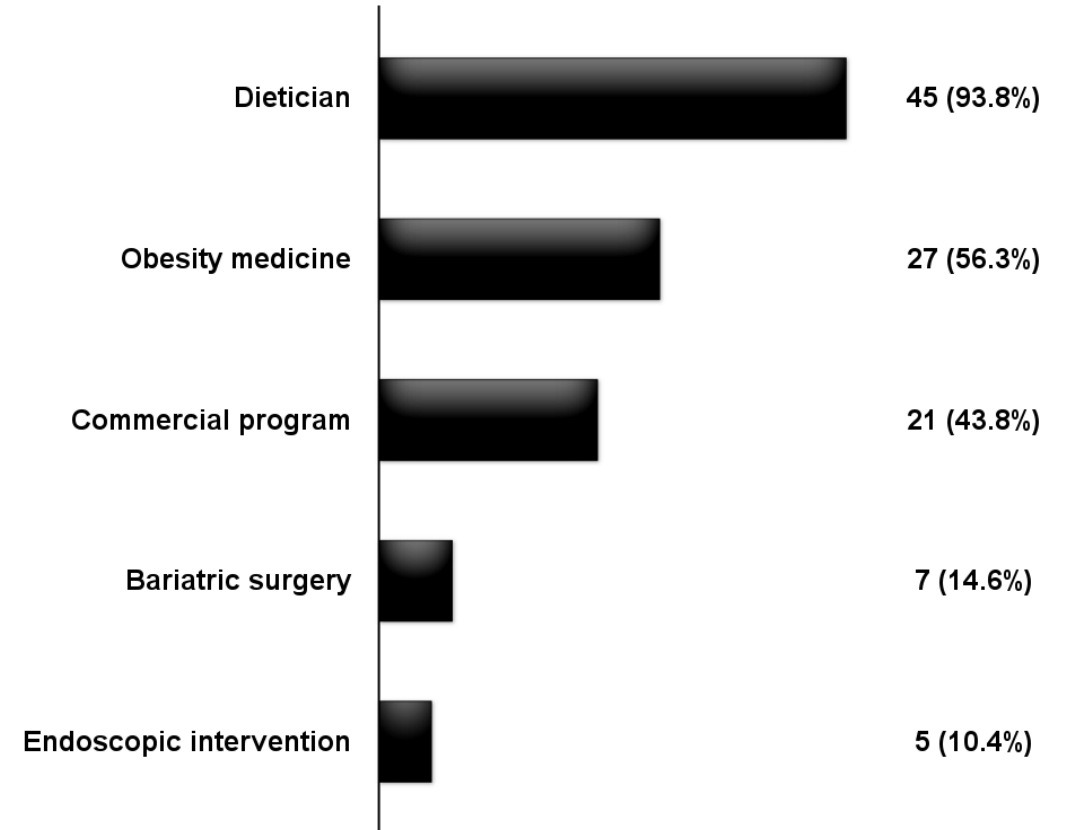
71% of respondents noted obesity was a donor exclusion

Median BMI threshold 35, range 30-45

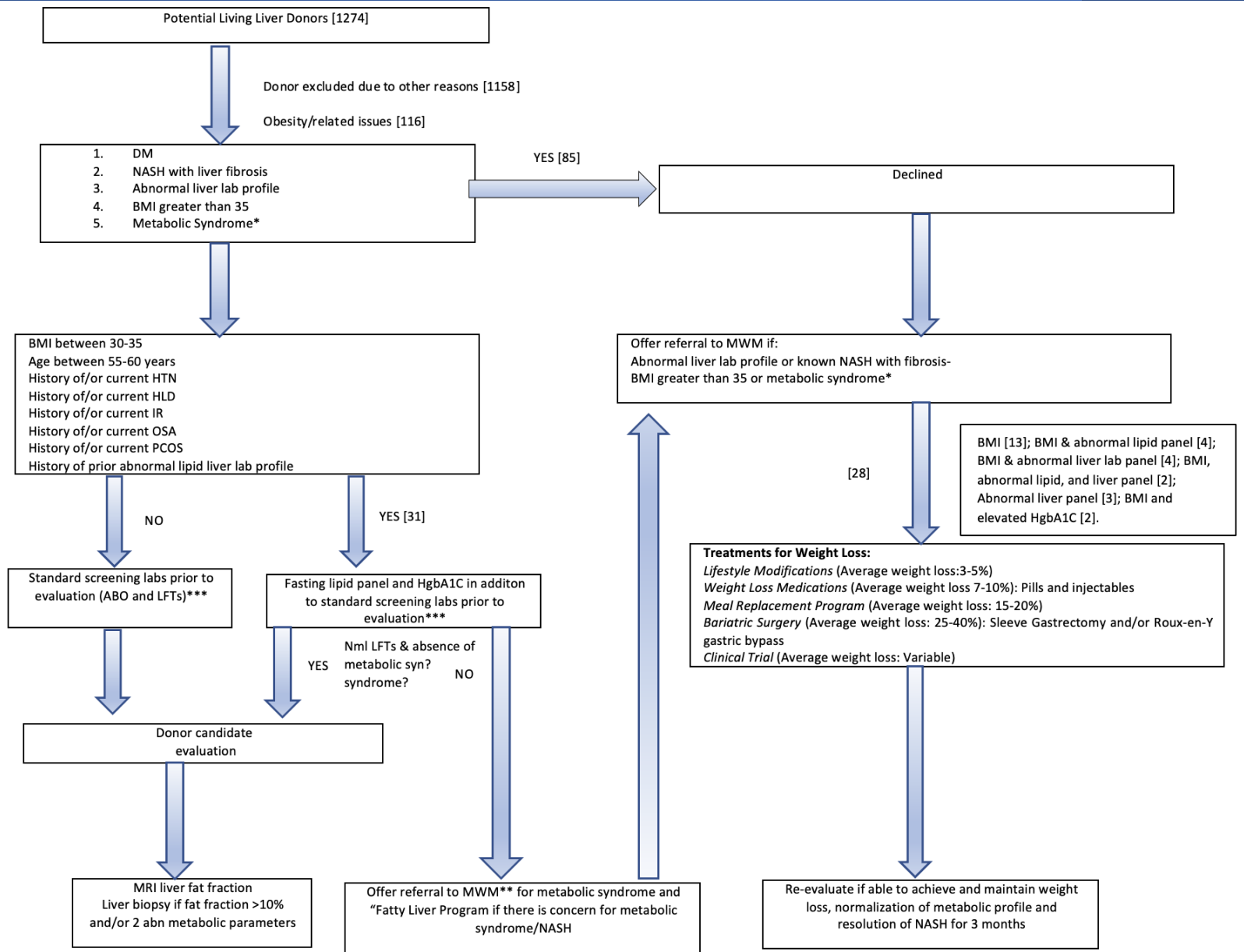
64% refer donors to formalized weight loss programs, (don't 23%, unsure 13%)

Variable required "maintenance" period

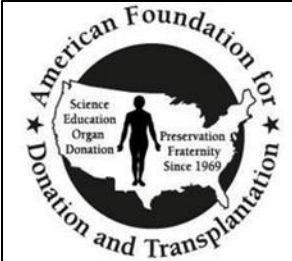
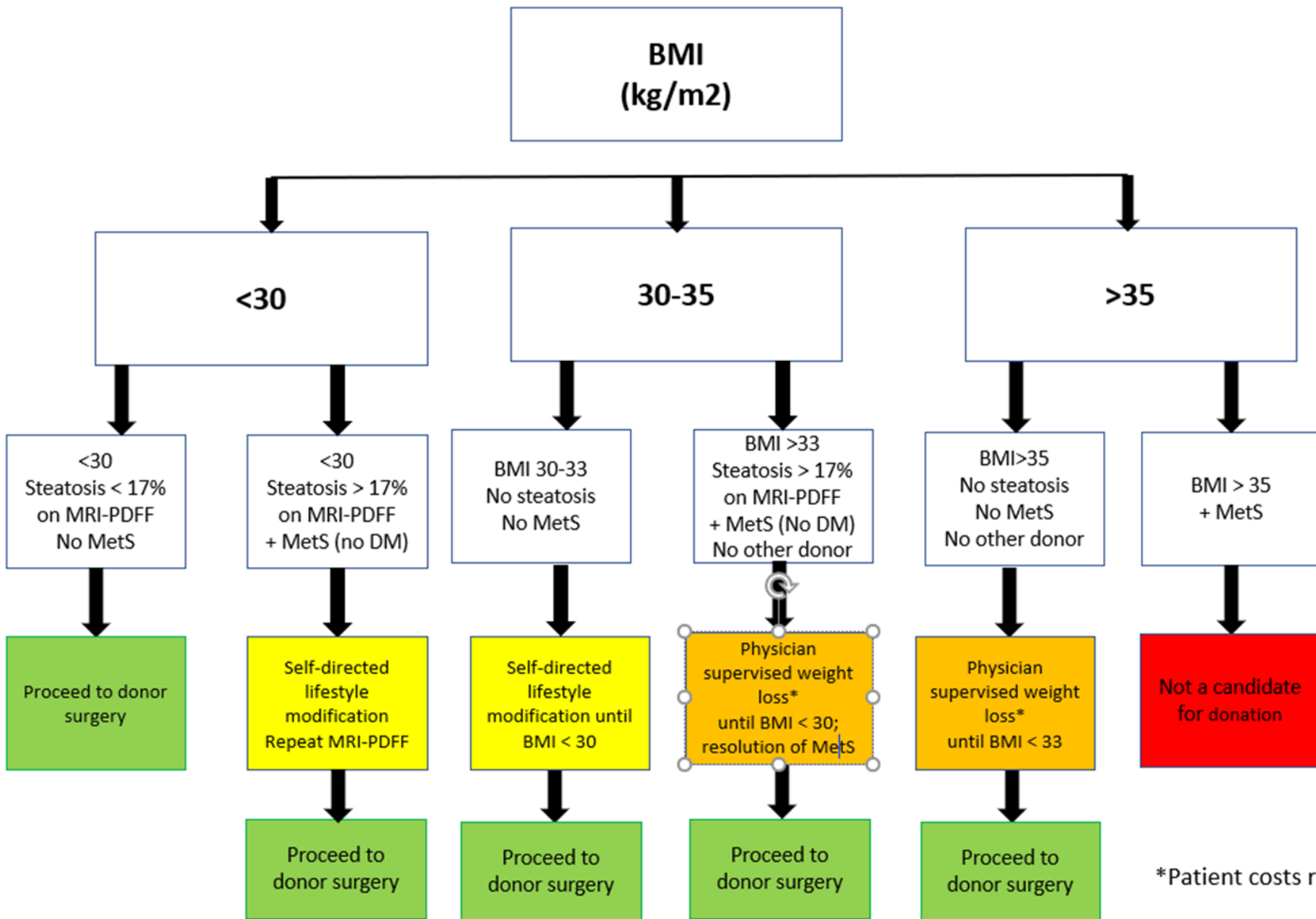
None 45.8%, Don't know 20.8%, 1 month 8.3%, 3 month 22.9%, 6 months 2.1%



Yale Triage



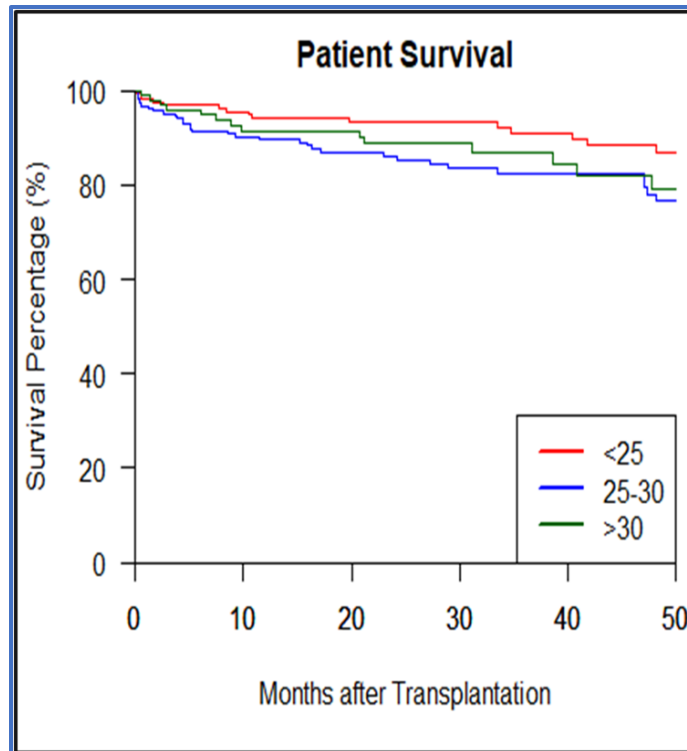
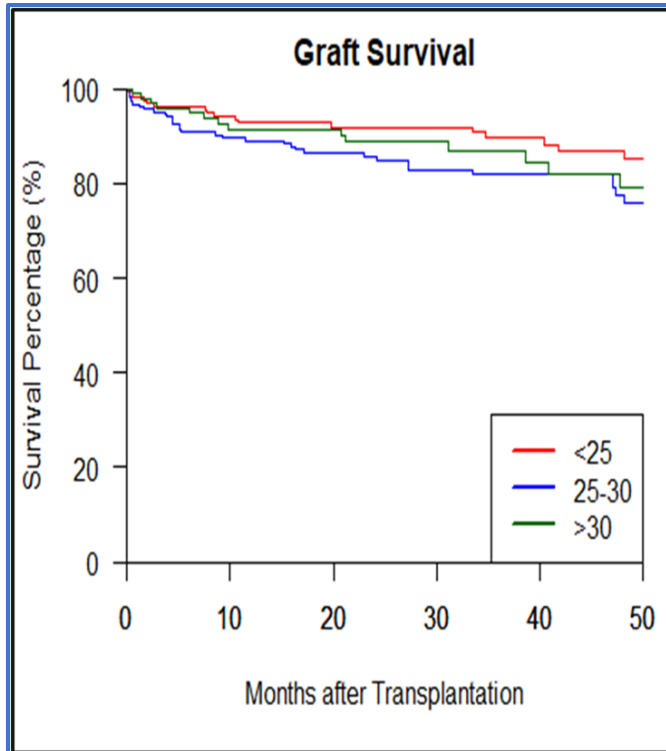
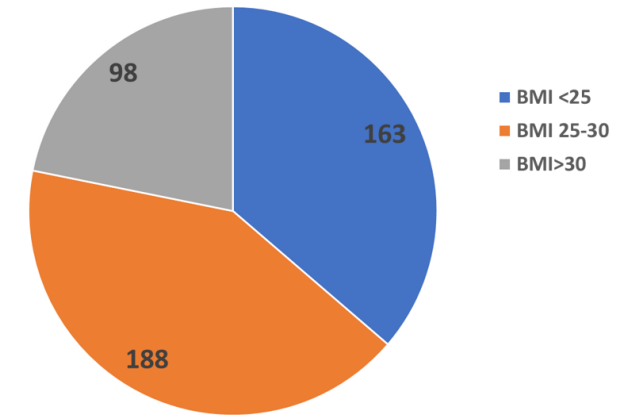
UPMC Triage



*Patient costs reimbursed

Donor BMI & Outcome UPMC

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



Outcomes by Donor BMI

Summary Statistics

	All (N=449)	BMI <25 (N=163)	BMI 25-30 (N=188)	BMI >30 (N=98)	P-value
Donor Length of Stay					
Mean (sd)	5.27 (2.96)	5.13 (1.34)	5.41 (3.81)	5.24 (3.07)	P = 0.6901
BMI 1 year Post-Tx					
Mean (sd)	28.31 (5.75)	27.11 (5.04)	28.91 (6.28)	29.13 (5.50)	P = 0.0026
Bilirubin at Discharge					
Mean (sd)	1.68 (1.32)	1.73 (1.03)	1.65 (1.69)	1.64 (0.91)	P = 0.5885
Bilirubin 1 Month Post Discharge					
Mean (sd)	1.11 (0.78)	1.07 (0.75)	1.11 (0.79)	1.17 (0.81)	P = 0.3225



Unpublished data, courtesy of Abhi Humar UPMC

Weight Loss Interventions LDLT:

Meta-Analysis



Table 1 Overview of interventions used for body mass index and steatosis reduction, and donor, recipient and graft outcomes following liver transplantation

Study number	Ref.	n	Type of intervention	Treatment duration	BMI reduction	Steatosis reduction	Liver donation	Donor, graft, recipient outcomes
1	Fujii <i>et al</i> [15], 2020	8	< 1600 Kcal/d + exercise 20 min × 3/wk ± statins	Median of 58 d	Yes (P = 0.0009)	Yes (P = 0.0006)	8	No significant difference from controls
2	Doyle <i>et al</i> [16], 2016	16	Optifast VLCD: 1000 kcal/ d	Median of 7.3 wk	Yes (P < 0.001)	Yes (P < 0.001)	14 (1 inadequate volume, 1 fibrosis)	No significant difference from controls
3	Choudhary <i>et al</i> [17], 2015	16	1200 kcal/d + 200 to 400 kcal/d exercise ± statins	Mean 28 ± 10 d	Yes (P = 0.006)	Yes (P = 0.008)	14 (2 had NASH/fibrosis)	No reported complication in perioperative period
4	Oshita <i>et al</i> [18], 2012	42	800 to 1400 kcal/d diet + 100 to 400 kcal/d exercise	Median 2.9 mo	Yes (P < 0.0001)	Yes, to < 20 %	41 (1 had stage 2 fibrosis)	No different from control group
5	Nakamuta <i>et al</i> [19], 2005	11	1000 kcal/d diet + exercise (600 kcal/d) + Bezafibrate	Mean 37.8 ± 4.6 d	Yes (P = 0.0033)	Yes (P = 0.0028)	7 (2 recipient deaths, 1 inadequate GRWR)	No different from control group
6	Hwang <i>et al</i> [20], 2004	9	Diet (25-30 calories × ideal body weight) + exercise	Median of 3 mo	Yes (P = 0.0001)	Yes (P = 0.006)	9	No different from control group

BMI: Body mass index; GRWR: Graft weight/recipient weight ratios; NASH: Nonalcoholic steatohepatitis; VLCD: Very low calorie diet.

Trakroo S, Bhardwaj N, Garg R, Modaresi Esfeh J. Weight loss interventions in living donor liver transplantation as a tool in expanding the donor pool: A systematic review and meta-analysis. *World J Gastroenterol.* 2021 Jun 28;27(24):3682-3692.



OPEN

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 Goldaracena, 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 $>30\text{kg/m}^2$, 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



HEPATOLOGY



Concise Review

Incorporating Weight Loss Medications Into Hepatology Practice for Nonalcoholic Steatohepatitis

Albert Do, Eric J. Kuszewski, Karl A. Langberg, Wajahat Z. Mehal ✉

First published: 16 April 2019 | <https://doi.org/10.1002/hep.30658> | Citations: 9

Supported by the National Institutes of Health (T32 DK00701741 to A.D.) and a VA Merit Review Award (to W.Z.M.).

Potential conflict of interest: Nothing to report.

- 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

Pertinent AST LDLT Consensus Statements



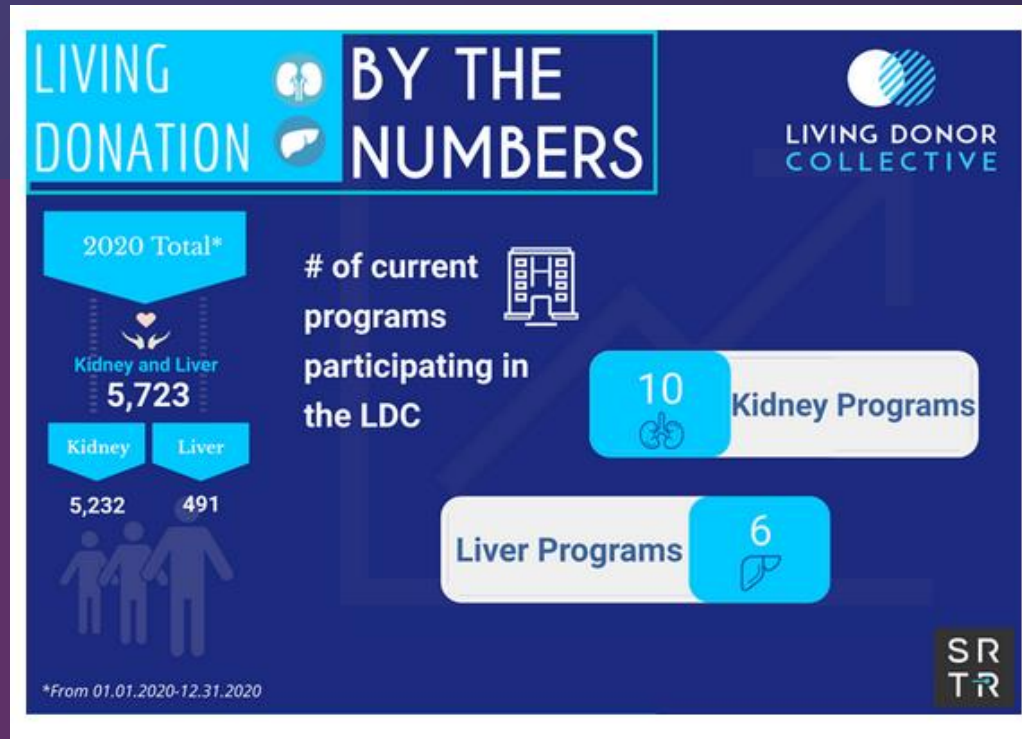
#3	Obesity, metabolic syndrome, and non-alcoholic fatty liver disease are highly prevalent in the U.S. population and have limited the pool of living donor candidates.	<i>Importance:</i>	8.02 (1.13); 8 (8, 9)
	<ul style="list-style-type: none"> BMI is not an adequate independent predictor of hepatic 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. 	<i>Impact:</i>	7.59 (1.17); 8 (7, 9)
		<i>Feasibility:</i>	6.98 (1.87); 7 (6, 8) ^a
	<ul style="list-style-type: none"> 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. 	<i>Impact:</i>	7.61 (1.32); 8 (7, 8.25) ^a
<i>Feasibility:</i>		7.21 (1.69); 7 (6, 8)	
#6	<ul style="list-style-type: none"> 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. A multicenter prospective study to collect long term follow up data in this subpopulation of donors. 	<i>Importance:</i>	7.63 (1.37); 8 (6.75, 9)
		<i>Impact:</i>	7.57 (1.47); 8 (7, 9)
		<i>Feasibility:</i>	6.50 (1.75); 7 (5, 8)

Pertinent AST LDLT Consensus Statements



#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.	<i>Importance:</i>	7.72 (1.52); 8 (7, 9)
	<ul style="list-style-type: none"> • 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. 	<i>Impact:</i>	7.32 (1.84); 8 (6, 9)
		<i>Feasibility:</i>	6.54 (1.79); 7 (5, 8) ^a
	<ul style="list-style-type: none"> • National societies should endorse data collection by having an expectation of minimal data sharing. 	<i>Impact:</i>	7.30 (1.92); 8 (6, 9)
		<i>Feasibility:</i>	7.07 (1.91); 7 (6, 9)
	<ul style="list-style-type: none"> • High volume centers should come together to combine and publish their data on reasons donors are declined for medical, anatomic and psychosocial reasons. 	<i>Impact:</i>	7.63 (1.50); 8 (7, 9)
		<i>Feasibility:</i>	6.80 (1.71); 7 (6.75, 9) ^a
	<ul style="list-style-type: none"> • Patients should be educated that different centers may have different criteria for donor approval. 	<i>Impact:</i>	7.50 (1.56); 8 (6.75, 9)
		<i>Feasibility:</i>	7.35 (1.58); 7.5 (6, 9)
	<ul style="list-style-type: none"> • Donors with incidental findings need to be directed to appropriate follow up. 	<i>Impact:</i>	7.20 (2.18); 8 (6, 9)
		<i>Feasibility:</i>	7.67 (1.38); 8 (7, 9)

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



14th Annual Living Donation Conference
Presented by the American Foundation for Donation and Transplantation