Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Obesity increases mortality in liver transplantation – the Danish experience

Jens G. Hillingsø, André Wettergren, Masanobu Hyoudo and Preben Kirkegaard

Department of Surgical, Gastroenterology, and Liver Transplantation, Center of Abdominal Disease, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Keywords
body mass index, mortality, obesity, orthotopic liver transplantation, survival analysis.

Correspondence
Jens G. Hillingsø MD, PhD, Department of Surgical Gastroenterology and Liver Transplantation, Center of Abdominal Disease, Rigshospitalet, Blegdamsvej 7–9, DK 2100 Copenhagen Ø, Denmark. Tel.: (45) 35452320; fax: (45) 35452183; e-mail: jenshillingsoe@dadlnet.dk

Received: 8 November 2004
Revision requested: 14 April 2005
Accepted: 13 July 2005

doi:10.1111/j.1432-2277.2005.00206.x

Summary

Obesity is increasing in the western world at an epidemic rate. The USA results in obese patients undergoing orthotopic liver transplantation (OLT) are divergent, and so far no European experience has been reported. This study was designed to determine if obesity is a risk factor for mortality and morbidity in OLT in a medium-size European center. In a retrospective study of the records of 365 consecutive patients who had undergone OLT from 1990 to 2003, 20 obese patients [body mass index (BMI) > 30 kg/m^2] were identified. Their data were compared with those of the nonobese (BMI < 30 kg/m^2) patients operated immediately before. There were no differences in demographic data, diagnosis leading to OLT, United Network of Organ Sharing (UNOS) classification, Child-Pugh score, or preoperative morbidity. The groups were also comparable concerning donor data, duration of operation, use of blood products, intensive care unit (ICU), or hospital admission. Mortality was, however, significantly increased in the obese group ($P = 0.01$). Our study clearly demonstrates an increased mortality in obese patients undergoing OLT and the relative scarcity of organs taken into account, it seems reasonable to consider obesity as a relative contraindication to OLT.

Introduction

Obesity is increasing in the western world at an epidemic rate and is considered one of the most serious health issues in the USA causing an estimated 300 000 deaths and more than a $100 billion direct and indirect costs annually [1]. Obesity is considered as a major cardiovascular risk factor by American Heart Association [2] and is an established risk factor for type 2 diabetes mellitus (DM), stroke hypertension, dyslipidemia, premature death to mention a few [1,3]. Relatively few studies have evaluated elective abdominal surgery in obese patients [4–6]. A quite recent study describes impact of obesity on surgical outcome after elective colorectal surgery [6]. It showed increased use of blood-products, duration of operations, number of anastomotic leakages and mortality in the obese group.

In studies after orthotopic liver transplantation (OLT) results have been divergent. Braunfeld *et al.* [7] found no differences in morbidity and mortality in the morbidly obese compared with controls. Sawyer *et al.* and Nair *et al.* [8,9] demonstrated increased morbidity and early mortality with the same long-term survival, whereas a larger database study found increased morbidity and mortality [10]. So far no studies, to our knowledge, have been carried out outside the USA and we therefore decided to do a retrospective study to evaluate short-term and long-term survival and morbidity in obese patients (body mass index (BMI) > 30 kg/m^2) undergoing OLT compared with matched lean controls (BMI < 30 kg/m^2).

Materials and methods

Between the October 1, 1990 and the December 31, 2001, 365 patients had 421 OLTs performed. In a retrospective study of the medical records of the primary OLTs we identified 20 obese (BMI > 30 kg/m^2) patients and compared them with the lean patients (BMI < 30 kg/m^2)

undergoing liver transplantation immediately before provided that this was not a re-transplantation or a child (age: <16 years). Obesity was defined as BMI > 30 kg/m^2 using the World Health Organization's (WHO) classification for obesity, where BMI is the weight in kg divided by the height in m^2 (underweight BMI < 20 kg/m^2, overweight BMI 25–30 kg/m^2, obesity BMI 30–40 kg/m^2, and morbidly obese BMI > 40 kg/m^2).

Preoperative data were weight, height, gender, and age. The cause of transplantation, termed diagnosis, was recorded as acute liver failure, chronic hepatocellular or cholestatic disease. Comorbidity [11], United Network of Organ Sharing (UNOS) status, Child-Pugh scores, and estimated amounts of ascites were recorded to estimate the patients' preoperative status. Donor weight, height, gender, and age was also recorded.

Perioperatively the duration of cold ischemia, length of surgery, number of units of packed red blood cells (PRBC), fresh-frozen plasma (FFP), and platelets (TC) were registered.

Postoperatively we recorded morbidity and duration of stay in intensive care unit (ICU), the surgical ward, and follow up time. The cause of death and days post-LTX was specified. The time of follow up was defined as days after primary OLT to death, re-transplantation or the March 31, 2003.

Indications of antibiotic prophylaxis and immunosuppression were as follows: ceftriaxon 2 g twice daily and ampicillin 1 g four time daily for 5 days. In the beginning of our transplant era we used cyclosporine, azathioprine, and steroids as immunosuppression. Our present regime is based on tacrolimus, mycophenolate mofetil, and steroids.

Data are expressed as medians and ranges. Because of the small number of patients and the risk of a type II error, statistical analyses were only used to a very limited extent when data were available for the entire group and for survival. Nonparametrical statistical analysis was used, because the data did not follow a normal distribution. Differences between groups were estimated using a Mann–Whitney rank sum test. Finally, data for survival were analyzed using a Kaplan–Meier plot and a log-rank test $P < 0.05$ was considered statistically significant. For statistical analysis SPSS 12.0 (Chicago, IL, USA) was used.

Results

The demographic and preoperative data are shown in Table 1. All parameters matched except for the BMI. There were no differences in diagnosis, preoperative UNOS status, and Child-Pugh scores between the groups. There was a larger degree of concomitant disease in the obese group. The term 'other' comorbidity covers polycystic kidney disease, ulcerative colitis, and medically treated myxoedema in the nonobese group and one case of α-1 antitrypsin deficiency in the obese group. In the obese group two patients had a previously diagnosed cancer; one ulcerative colitis patient was diagnosed with a cancer Dukes' type B in the resected colon specimen 12 years prior to transplantation. The other patient had an adrenal tumor that prior to the transplantation was histologically classified as an adenoma, which after transplantation turned out to be an adrenocortical carcinoma. The term hematopoietic disease covered one case of hemophilia in

Table 1. Demographic and preoperative data for obese patients and nonobese control group.

	Obese	Nonobese
Sex (male/female)	14/6	14/6
Age (years)	52 (32–61)	48 (27–73)
BMI (kg/m^2)	33.7 (30.1–46.3)*	23.8 (19.1–29.3)
Cold ischemia (min)	582.5 (469–923)	577 (337–893)
Donor sex (male/female)	13/7	8/12
Donor age (years)	52 (18–55)	48 (15–66)
Donor BMI (kg/m^2)	24.7 (21.6–30.4)	22.9 (16.4–32.3)
Diagnosis		
Acute	1	3
Cholestatic	3	3
Parenchymatic	15	11
Vascular	1	3
UNOS score		
ICU (I)	2	2
Hospitalized (II)	6	2
Home (III)	12	16
Child-Pugh score		
A ≤ 6	1	4
B = 7–9	11	9
C ≥ 9	8	7
Ascites		
None	8	8
Light	7	6
Moderate	5	6
Preoperative comorbidity		
Cardiac		
Hypertension	1	1
Angina	2	
Congestive	2	
Respiratory	1 (α-1 trypsin deficiency)	1 (fibrosis)
Nephropathy	2 (1 hemodialysis)	1 (polycystic kidney disease)
Hematopoietic	1	2
IDDM	1	2
NIDDM	1	0
Cancer	2	
Other	1	3

All data are median (range).

*$P < 0.05$ (Mann–Whitney rank sum test), all other values are NS.

BMI, body mass index; UNOS, United Network of Organ Sharing; ICU, intensive care unit; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus.

each group and a case of polycythemia in the nonobese group. The usual comorbidity in terms of sequelae to hepatic cirrhosis and sclerosing cholangitis was not reported.

Table 2 depicts technical aspects of the operation and postoperative data. There were no statistical differences in duration of operations and transfusions of blood, FFP, or platelets and postoperatively in duration of ICU or total hospital admissions. In the obese group 70% suffered from postoperative complications and 50% in the nonobese group, and we have listed the primary event. There is a degree of overlap of these diagnoses, because the technical morbidity often resulted in septicemia. The term technical covers anastomosis leakage in the Roux limb in three cases and one case of bile leakage from and 'end to end' bile duct anastomosis in the obese group and two cases of anastomosis leakage in the Roux limb, one case of portal, and one case of arterial thrombosis in the nonobese group. The term 'other' describes two cases of cancer and one case of cyclosporine-induced DM in the obese patients, whereas there is one case of bladder obstruction in the nonobese patients. Two patients in each group were re-transplanted and in both cases one was acute and the other after several years. One of the re-transplanted patients in the nonobese group died after 6 months of septicemia and one in the obese group 8 days after because of primary nonfunction.

Table 2. Operative and postoperative data including morbidity and mortality.

	Obese	Nonobese
Duration of operation (min)	375 (245–700)	355 (240–925)
Transfusions		
PRBC (290–380 ml)	16,5 (8–133)	11,5 (0–34)
FFP	20.5 (11–114)	21,5 (0–51)
TC	2 (0–24)	1 (0–4)
Postoperative morbidity		
CNS	1	
Cardiac failure	1	
Infections	8	4
Technical	4	4
Other	3	1
Re-transplantations	2	2
Death		
≤30 days	4	2
≤100 days	8	3
≤1 year	10	4
≤2 years	13	5
Admission, ICU	6 (1–96)	3.5 (1–30)
Admission, total	33 (6–156)	29 (16–218)
Follow up	173 (6–2594)*	931 (23–4153)*

*$P < 0.05$ determined by Mann–Whitney rank sum test. All data are median (range).

PRBC, packed red blood cell; FFP, fresh-frozen plasma; TC, platelets; CNS, central nervous system; ICU, intensive care unit.

Table 3. Cause of death in obese and nonobese patients.

	Obese	Nonobese
MOF	3 (7, 55, 156)	1 (30)
Septicemia	5 (23, 45, 96, 262, 245)	3 (60, 222, 3197)
Cardiac failure (AMI)	1 (6)	
CNS	2 (10, 37)	1 (23)
Lymphoma		1 (213)
Cancer	2 (401, 595)	
Liver related		
Total	13*	6

*Statistical significant difference between groups determined by a rank sum test ($P < 0.05$). Days postoperative were given in parenthesis. Statistical analysis has not been undertaken between each single cause of death due to the limited number of patients.

CNS, central nervous system.

Table 3 shows the causes of death in the two groups. Thirteen deaths in the obese group primarily because of infections (eight patients), and two cases of central nervous system (CNS)-related death because of hemorrhagic insults. One of the cases of cancer was carcinosis diagnosed at re-transplantation in the previously mentioned ulcerative colitis patient 512 days after primary OLT, whereas the other patient had a colonic cancer diagnosed 401 days after primary OLT. The patient who died of cardiac disease had had one prior myocardial infarction 16 years earlier. The patient with the adrenocortical carcinoma died of multi organ failure (MOF) 23 days after OLT.

In the control group, the causes of death were one case of lymphoma, hemorrhagic cerebral insult, and finally four deaths caused by infection. The Kaplan–Meier plot in Fig. 1 shows the difference in survival amongst the two groups. There is a statistically significant difference between the two curves determined by a log-rank test ($P = 0.013$).

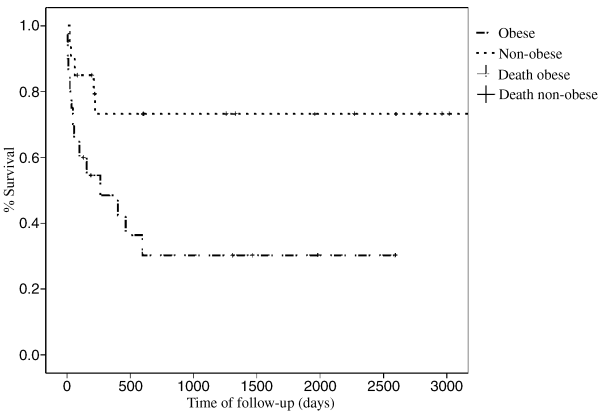

Figure 1 Percentage survival after liver transplantation in obese and nonobese. Statistical significant difference between survival curves $P = 0.013$ determined by log-rank test.

Discussion

Our results clearly demonstrate an increased mortality in the obese patients (BMI > 30 kg/m^2) operated in our transplantation program between 1991 and 2002 compared with matched nonobese controls. We chose to compare with the lean patient (BMI < 30 kg/m^2) transplanted immediately before provided that this was not a re-transplantation or a child in order to exclude differences in experience and procedural changes over time that might otherwise affect outcome.

There were no significant differences between the groups in demographic data, but there seemed to be a relatively higher preoperative morbidity in the obese group, as one would expect (11).

The duration of operation, the use of transfusions, and the stay in ICU immediately after operation was not statistically different between the groups in our material. This is contrary to the findings of others that have demonstrated increased use of transfusions [8], and duration of stay in the hospital postoperatively [9], but then again in concordance with other studies [7].

Postoperative morbidity was also quite significant and half of the control group had such complications whereas 70% in the obese group with more than half of them being due to infections (eight patients). The technical complications were quite similar, but the patients in the obese group were more prone to infections which is probably related to the perioperative tissue hypoxia, which is most pronounced in the obese patients and substantially increases their risk for developing infections [12] and postoperative nosocominal infections [13] with MOF as the best predictor of ICU-mortality [14].

Our study demonstrated a high mortality rate of 65% in the obese patients and the causes of death were in all cases related to physical ailments for which obesity is an increased risk factor [11] and took place within 2 years after primary OLT (range: 7–595 days), after which survival was comparable. Increased early mortality and morbidity has previously been described [8,9], but not reaching a level of 65%. The previously mentioned USA studies [8,9] did not demonstrate a difference in long-term survival between obese and nonobese, but Sawyer *et al.* [8] found an increased early mortality because of infection and MOF. This is pretty much in accordance with a larger study done using the UNOS network database [10], where an increased mortality was observed in morbidly obese (BMI > 40.1–50 kg/m^2) within 30 days and after 1-, 2- and 5-years and similar for the severely obese (BMI > 35.1 < 40 kg/m^2) after 5 years mostly as a result of cardiovascular events. It also demonstrated a number of independent factors for mortality after 2 years, namely morbid obesity, recipient's age, serum creatinine, diabetes, and UNOS score.

In Europe obesity is almost twice as common among the 16–24 years old as in the rest of the population [15]. The estimated, increased cost in total percentage of health costs caused by obesity is around 8% in the USA [16] compared with France, Holland, and Sweden, where it is between 1% and 3% [15]. We might become more used to handling the obese recipient, which might be why the USA surgeons only report increased mortality in severely and morbidly obese patients. As obesity in the liver transplant population is getting still more common with weight gains of 5 kg the first and 10 kg by the third year independent of immunosuppressive drugs [17], it becomes a substantial problem not only with regard to short-term morbidity and mortality, but also long-term, and measures in order to induce a weight loss should be taken probably pretransplantation and at the latest 6 months post-transplantation.

In studies of renal transplantation overweight (BMI > 25.1 < 30 kg/m^2) and obese patients (BMI > 30.1 kg/m^2) now constitute two of three patients [18]. Graft and patient survival, death censored graft survival and chronic allograft failure was significantly increased in extremes, i.e. very high and low BMI [19] in some, but not in all studies [20]. This reflects very well the difference in liver transplantation where dedicated centers might be able to reduce mortality in obese patients [8], which is not reflected in the UNOS database with its limitations in controlling data and risk of inaccurate reporting [10].

The obesity epidemic might influence liver transplantation program even further by reducing the number of available organs because of increased fatty infiltration (steatosis) of the donor livers, but so far one study could not demonstrate that donor BMI affected primary graft nonfunction and re-transplantation rates using whole organs [21]. In times of relative organ-scarcity we must conclude that obesity may be considered a relative contraindication to liver transplantation both on a short-term and long-term basis, although a regressive attitude in general toward elective surgery in obese patients no longer seems justified [22].

References

1. U.S. Department of Health and Human Services. *The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity*. Rockville, MD, USA: Department of Health and Human Services, 2001: 1–60.
2. Krauss RM, Winston M, Fletcher BJ, *et al.* Obesity: impact on cardiovascular disease. *Circulation* 1998; **98**: 1472.
3. Calle EE, Thun MJ, Petrelli JM, *et al.* Body-mass index and mortality in a prospective cohort of US adults. *N Engl J Med* 1999; **341**: 1097.

4. Postlethwait RW, Johnson WD. Complications following surgery for duodenal ulcers in obese patients. *Arch Surg* 1972; **105**: 438.
5. Pemberton LB, Manax WG. Relationship of obesity to postoperative complications after cholecystectomy. *Am J Surg* 1971; **121**: 87.
6. Benoist S, Panis Yalves A, Valleur P. Impact of obesity on surgical outcomes after colorectal resection. *Am J Surg* 2000; **179**: 275.
7. Braunfeld MY, Chan S, Pregler J, *et al.* Liver transplantation in the morbidly obese. *J Clin Anesth* 1996; **8**: 585.
8. Sawyer RG, Pelletier SJ, Pruett TL. Increased early morbidity and mortality with acceptable long-term function in severely obese patients undergoing liver transplantation. *Clin Transplant* 1999; **13**: 126.
9. Nair S, Cohen DB, Cohen C, Tan H, Maley W, Thuluvath PJ. Postoperative morbidity, mortality, costs and long-term survival in severely obese patients undergoing orthotopic liver transplantation. *Am J Gastroenterol* 2001; **96**: 842.
10. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. *Hepatology* 2002; **35**: 105.
11. Friedmann N, Fanning EL. Overweight and obesity: an overview of prevalence, clinical impact, and economic impact. *Dis Manag* 2004; **7**(Suppl. 1): S1.
12. Kabon B, Nagele A, Reddy D, *et al.* Obesity decreases perioperative tissue oxygenation. *Anesthesiology* 2004; **100**: 274.
13. Cantürk Z, Cantürk NZ, Certinarslan B, Utksan NZ, Tarkun I. Nosocomial infections and obesity in obese patients. *Obes Res* 2003; **11**: 769.
14. Levi D, Goodman ER, Patel M, Savransky Y. Critical care of the obese and bariatric surgical patient. *Crit Care Clin* 2003; **19**: 11.
15. Seidell JC, Deerenberg I. Obesity in Europe, prevalence and consequences for use of medical care. *Pharmacoeconomics* 1994; **5**: 38.
16. Wolf AM, Colditz GA. The cost of obesity, the US perspective. *Pharmacoeconomics* 1994; **5**: 34.
17. Richards J, Gunson B, Johnson J, Neuburger J. Weight gain and obesity after liver transplantation. *Transplant Int* 2005; **18**: 461.
18. Friedman AN, Miskulin DC, Rosenberg IH, Levey AS. Demographics and trends in overweight and obesity patients at time of kidney transplantation. *Am J Kidney Dis* 2003; **41**: 480.
19. Meier-Kriesche HU, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for craft failure and patient death. *Transplantation* 2002; **73**: 70.
20. Howard RJ, Thai VB, Patton PR, *et al.* Obesity does not portend a bad outcome for kidney transplant recipients. *Transplantation* 2002; **73**: 53.
21. Yoo HY, Molmanti E, Thuluvath PJ. The effect of donor body mass index on primary graft nonfunction, retransplantation rate, and early graft and patient survival after liver transplantation. *Liver Transpl* 2003; **9**: 72.
22. Dindo D, Muller MK, Weber M, Clavien P-A. Obesity in general surgery. *Lancet* 2003; **361**: 3032.