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Graft steatosis - where to stop?

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ABSTRACT

The gap between the availability of livers from organ donors and the increased demand has led many centers to apply strategies to reduce this deficit. Splitting of cadaveric organs for use in 2 recipients; domino transplantation; and organs from living donors, non–heartbeating donors, and extended-criteria donors (ECDs) are all currently used in expanding the liver graft availability for orthotopic liver transplantation (OLT). Fatty changes in the donor liver are a risk factor for poor function after OLT, especially for primary non-function; however, the presence of steatosis, frequently present in livers from ECDs, does not exclude the use of these organs. The aims were to study the steatosis as a cause of nonacceptance of a liver for transplantation after exploration by the donor surgical team. All donor harvesting procedures performed by our unit from 2008 to 2014 were retrospectively studied. Donors were divided in those accepted and harvested and those discarded by the donor surgical team. Donor characteristics of accepted and used liver grafts were compared with those rejected due to steatosis. Five hundred sixty-one donor liver procurements were performed, out of which 60 (10.6%) demonstrated on liver biopsy macroscopic steatosis. Out of these 44 had mild steatosis (>30% but <60%) and 16 had severe steatosis (>60%). The main indication for biopsy was macroscopic doubt about the degree of steatosis. The main indication for discarding the liver was macrovesicular steatosis above 60%.

Key words: liver transplantat, steatosis, marginal donors

INTRODUCTION

Excellent results have been achieved with orthotopic liver transplantation (OLT) owing to improved surgical techniques and instruments, optimized anesthesia, better postoperative care, and new immunosuppressive drugs (1). In contrast, an increasing number of patients are dying while on the organ waiting list, which justifies the use of grafts from donors that were once considered marginal (2). Extending the donor pool remains a critical concern in OLT. The definition of extended-criteria donors continues to evolve; currently, we

identify the following ECD donor characteristics as pertinent: age older than 60 years (3), prolonged intensive care unit length of stay, peak serum sodium concentration over 165 mmol/L, alanine aminotransferase (ALT) or aspartate aminotrasferase (AST) over three times the normal range, previous drug abuse, history of cancer, positive findings at serology (anti-HBc or HBsAg positivity), bilirubin level over 3 mg/dL, and presence of steatosis (4,5,6).

In developed countries, increased liver steatosis is noted in all age groups and is usually associated with obesity, alcohol abuse, or type 2 diabetes mellitus. Steatosis, recently termed nonalcoholic fatty liver disease (NAFLD), shows a prevalence of 10% to 30% in the general population. It involves a large part of the donor pool, ranging from the less severe forms through many stages from a benign condition to severe non-alcoholic steatohepatitis (NASH).

MATERIAL AND METHOD

Since January 2008 until December 2014, all referred livers were considered potentially transplantable. All livers suspected of being moderate to mild steatotic before harvesting at ultrasonograpy or CT scan or at physical inspection at the time of procurement were studied after wedge biopsy.

We performed 60 wedge biopsies of the left lobe, obtaining 1 to 2 cm^3 of tissue. The biopsy specimens were cut in a cryostat after being freezed. Steatosis was defined as the presence of fat droplets in more than 5% of hepatocytes, MaS as a single vacuole larger than and usually displacing the nucleus to the cell membrane, microscopic (MiS) as multiple small vacuoles around a centrally located nucleus.

RESULTS

Out of 561 referred livers, 195 (34.75%) showed some degree of macroscopic steatosis at macroscopic inspection made by the procurement team. Out of those 59 had macroscopic minor steatosis and did not required biopsy and the liver has harvested. 76 had severe macroscopic steatosis (*figure 1*), did not required biopsy, and the liver was not harvested, and the remaining 60 grafts were biopsied. Grafts characteristics are given in *table 1*.

Out of the 60 biopsies, 44 grafts had a degree of steatosis between 30% and 60%, and were harvested and 16 had a degree of steatosis greater than 60% and were rejected (*figure 2*). The degree of steatosis at biopsy is shown in *table 2*.

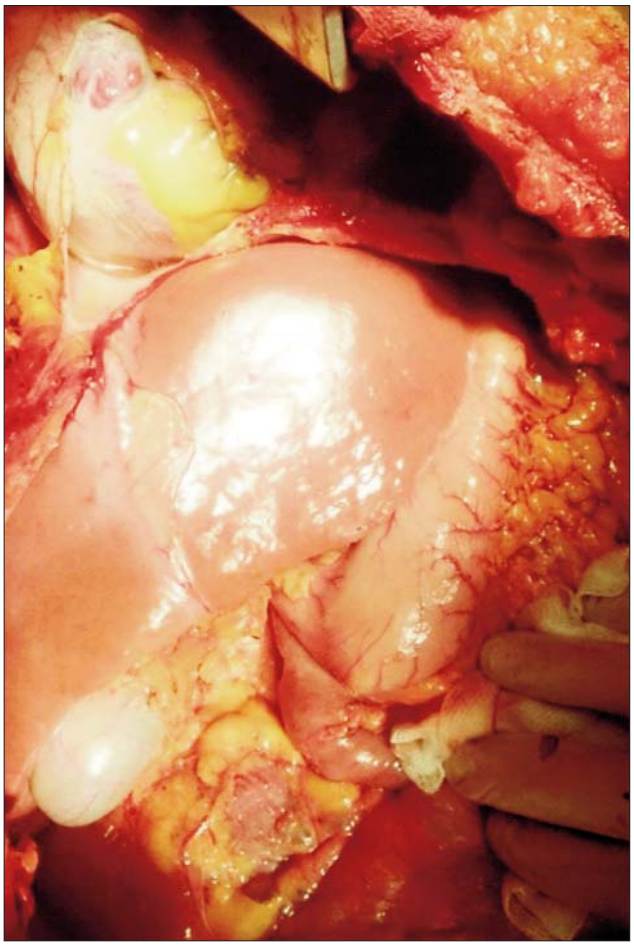

Figure 1 - Undoubtful severe macroscopic steatosis

Table 1 - Grafts characteristics regarding steatosis

Total Donors	561
Donors with some degree of steatosis	195 (b+/-)*
Donors with macroscopic minor steatosis	59 (b-)
Donors with macroscopic severe steatosis	76 (b-)
Donors with macroscopic steatosis with biopsy	60 (b+)
Donors with mild steatosis at biopsy (>30% but <60%)	44 (b+)
Donors with severe steatosis at biopsy (>60%)	16 (b+)
Total number of rejected grafts for steatosis	92 (b+/-)

*biopsy taken – b+; biopsy not taken – b-

Table 2 - Degree of steatosis at biopsy

	>30% but <60%	>60%
Microsteatosis (MiS)	11	6
Macrosteatosis (MaS)	33	10
Accepted marginal grafts	44	0

Three hundred ninety-one were harvested and transplanted including 103 with steatosis. Out of 103 transplanted steatotic grafts 59 had macroscopic minor

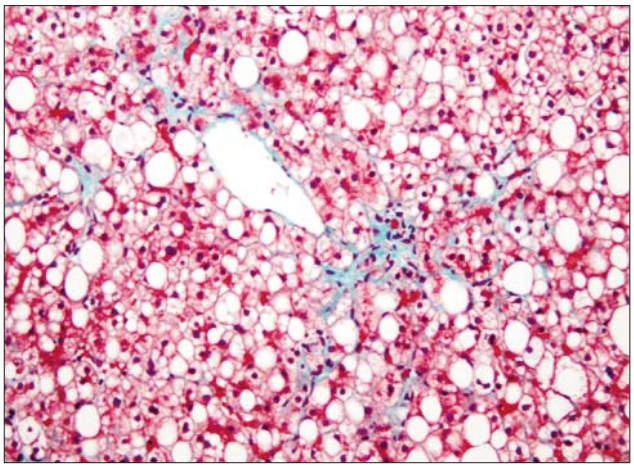

Figure 2 - Liver macrovesicular steatosis

steatosis and were considered as acceptable grafts and 44 were considered marginal grafts with a degree of steatosis between 30% and 60% documented by biopsy. Out of 195 steatotic grafts, 92 (43.19%) were discarded and 103 (52.8%) were transplanted. Of the 92 discarded grafts, 16 had severe steatosis documented by biopsy and the remaining 76 had undoubtful macroscopic severe steatosis (there was no need for a biopsy). Forty-four grafts with a degree of steatosis between 30% and 60%, considered marginal grafts were transplanted at our institution to marginal recipients. Indications of liver transplantation with marginal grafts due to steatosis are given in *table 3*.

Table 3 - Indications for transplantation of marginal grafts due to steatosis

HCC	10
HCV Cirrhosis	8
HBV + HDV Cirrhosis	8
Cirhosis – other	6
Other	5
Alcoholic cirrhosis	4
Retransplantation	2
Wilson's disease	1

DISCUSSION

Initially described by Starzl et al. (7), the evaluation of a liver allograft for transplantation is a complex algorithmin corporating clinical data, laboratory data, histological data, and organ visualization in the context of the recipient's medical necessity. Liver allograft biopsy at procurement may be uniformly applied but is typically performed "on demand" according to donor history, physiology, or features identified at organ visualization (8,9). The universal organ shortage has prompted relaxation of traditional donor criteria to increase donor supply. Extended criteria donor liver allograft provide immediate expansion of the donor pool, and steatotic livers are the most rapidly increasing type of donor organs (10,11,12). A great disparity has been reported (9%-28 %) in the prevalence of steatosis in liver donors, that may be related to different histologic techniques, donor selection, and the definition of steatosis and the overlap of MaS and MiS (13,14). Several issues should be mentioned. The definition of steatosis must be reconsidered with additional specifications, not only concerning the fundamental difference between MaS and MiS and their stratification but also the presence of fibrosis and the degree of concomitant lobular inflammationor necrosis. Steatosis in a donor without a history of significant alcohol or drug abuse (NAFDL) may be NASH, which could potentially progress to cirrhosis and hepatocellular carcinoma (HCC). The techniques adopted to diagnose such conditions include ultrasonography, computed tomography, and magnetic resonance imaging.

On the other hand different scores, like the donor risk index (15), have been described in order to assess graft quality. Although such scores seem not to predict the post liver transplant outcome (16) of both recipient and liver graft they may represent a starting point for the development of uniform criteria for graft assessment. In a recent study published by Orman ES et al. (17) they have developed a predictive model for the donor population growth. In their study they have pointed out that by the year 2030 the incidence of obesity in US donors may reach 58.2% and that these may lead to the necessity of accepting marginal liver grafts more frequently.

In conclusion, in our center liver macrovesicular steatosis is the main reason for discarding a liver graft. Careful donor selection, without additional risks to steatotic grafts, and expert management at harvesting, as well as standardization of histological techniques, and exclusion of recipients with a high MELD score (good graft-recipient pairing) seems to be important to obtain both good graft and patient survival and an acceptable risk-benefit ratio. In our opinion a MaS of 60% is the limit between a discarded graft and a marginal graft used for OLT.

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