EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Liver transplantation using fatty livers: Always feasible?

Lucas McCormack[1,†], Philipp Dutkowski[2,†], Ashraf Mohammad El-Badry[2], Pierre-Alain Clavien[2,*]

[1]*Hepatobiliary Surgery and Liver Transplant Unit, Hospital Aleman of Buenos Aires, Buenos Aires, Argentina;* [2]*Swiss HPB (Hepato-Pancreato-Biliary) and Transplant Centers, Department of Surgery, University Hospital Zurich, Switzerland*

Abstract

Steatotic liver grafts represent the most common type of "extended criteria" organs that have been introduced during the last two decades due to the disparity between liver transplant candidates and the number available organs. A precise definition and reliable and reproducible method for steatosis quantification is currently lacking and the potential influence of the chemical composition of hepatic lipids has not been addressed. In our view, these shortcomings appear to contribute significantly to the inconsistent results of studies reporting on graft steatosis and the outcome of liver transplantation. In this review, various definitions, prevalence and methods of quantification of liver steatosis will be covered. Ischemia/reperfusion injury of the steatotic liver and its consequences on post-transplant outcome will be discussed. Selection criteria for organ allocation and a number of emerging protective strategies are suggested.

© 2010 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

The lack of available organs for liver transplantation (LT) associated with the increased death rates among patients on most waiting lists for LT has triggered the use of so-called extended criteria donor (ECD) grafts, previously called "suboptimal grafts". Among the wide range of these ECD livers, hepatic steatosis is one of the most frequent disorders [1], which is mostly related to an increasing prevalence of non-alcoholic fatty liver disease (NAFLD). The decision to implant or reject a steatotic liver for LT, however, is difficult due to a risk of impaired graft function or even failure after implantation. How much and what types of fat represent a significant risk for primary non function (PNF) of the graft remains under debate. In this review, we will first highlight the relevance of NAFLD in the general population and its implication for LT. Second, we will present the various histological designations of steatosis including recent data on the validity of the assessment of steatosis through histologic assessment. Third, we will summarize the mechanisms of injury related to fat deposits in the liver and analyze the risk of implanting a steatotic graft in a LT recipient. Finally, we will attempt to summarize selection criteria for organ allocation, as well as recent protective strategies.

Prevalence and implications of NAFLD in liver transplantation

NAFLD is the most common cause of chronic liver disease, affecting up to 30% of individuals in Western countries, and 70–80% of obese individuals [2,3]. In a series of 73 patients who were scheduled for major liver resection, we found variable degrees of hepatic steatosis in approximately 50% of patients [4]. In deceased organ donors, liver steatosis has been documented in up to 30% during the 1990th [5–7]. The risk factors for NAFLD include diabetes mellitus, obesity, hypertriglyceridemia, and sedentary life style [8], and encompass a spectrum of distinct histological entities. The relevance of steatosis ranges from simple and asymptomatic fat accumulation in the hepatocytes to liver steatosis with necro-inflammatory components (non-alcoholic steatohepatitis, NASH), that may lead to fibrosis. Cirrhosis develops in up to 20% of those cases with a risk of liver failure or hepatocellular carcinoma [9]. Therefore, the increasing prevalence of NAFLD is expected to raise the number of LT candidates, and possibly become the most common indication for LT.

The first event in NAFLD genesis is liver fat accumulation induced by changes in lipid metabolism favoring excessive triglyceride accumulation in hepatocytes, as a result of insulin resistance [2,3,10]. The second step is characterized by the excessive production of reactive oxygen species (ROS), generated by mitochondria and cytochrome P-450 system in fatty hepatocytes [11].

New insights have been recently provided regarding the fat composition in steatotic livers, particularly the Ω-3 and Ω-6 fatty acids (FA) ratio [10]. In this context, Ω-3 FAs downregulate the sterol regulatory element binding protein-1; a transcription factor which enhances hepatic triglyceride accumulation via the up-regulation of lipogenic genes such as fatty acid synthase and stearoyl Co-A desaturase-1. Moreover, Ω-3 FAs upregulate peroxisomal proliferator activated receptor-α, which stimulates hepatic fatty acid oxidation and transcription of fatty acid

Received 17 September 2010; received in revised form 18 October 2010; accepted 8 November 2010

* Corresponding author. Address: Department of Surgery, University Hospital Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland. Tel.: +41 44 255 33 00; fax: +41 44 255 44 49.

E-mail address: clavien@access.uzh.ch (P.-A. Clavien).

† These authors contributed equally.

Abbreviations: LT, liver transplantation; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MaS, macrosteatosis; MiS, microsteatosis; MELD, model for end stage liver disease; FA, fatty acid; ECD, extended criteria donor.

degradation genes such as mitochondrial carnitine palmitoyl transferase-1 and peroxisomal acyl-CoA oxidase. Conversely, these actions can be offset by excessive intake of Ω-6 FAs [10].

Hepatic steatosis: definition and types

Steatosis is typically characterized quantitatively and qualitatively. The quantitative evaluation is based on the percentage of hepatocytes containing cytoplasmic fat inclusions. In the clinical setting, steatosis is usually reported as mild, moderate, or severe, if, respectively less than 30%, between 30% and 60%, or more than 60% of hepatocytes contain fat vacuoles within the cytoplasm [1,12,13]. In addition, fatty infiltration is separated quantitatively into two categories, macro and microsteatosis. Macrosteatosis (MaS) is characterized by a single, bulky fat vacuole in hepatocytes, displacing the nucleus to the edge of the cell. This type is most commonly associated with obesity, diabetes, hyperlipidemia, and alcohol abuse. The underlying pathogenesis is related to an excessive triglyceride accumulation in the liver, mainly due to an increased uptake of fatty acids released from adipose tissue and/or an augmented *de novo* synthesis [1,12,13]. Additionally, a defective hepatic export, caused by reduced lipoprotein synthesis or impaired β-oxidation of fatty acids, further increases hepatic triglyceride content [14].

In microsteatosis (MiS), the cytoplasm of the hepatocytes contains tiny lipid vesicles without nuclear dislocation. MiS is usually encountered in mitochondrial disruption following acute viral, toxin- or drug-induced injury, sepsis, and in some metabolic disorders [15]. Importantly, other histo-pathological features should be carefully assessed in the presence of steatosis including inflammation, fibrosis, and ballooning degeneration [15,16]. MaS alone is exceptional, most often MaS and MiS present simultaneously at different degrees in the liver.

Assessment of fatty liver grafts

The assessment of donor liver fat is a difficult task for the transplant team. An initial evaluation, based on visual inspection and palpation, is first done during procurement of the graft in the donor. However, criteria such as color and texture of the graft depend solely on the experience of the explanting surgeon, and thus remain subjective. A recent German study analyzing explanted, but not transplanted livers, confirmed that neither preoperative evaluation by ultrasound nor macroscopic evaluation during harvesting were reliable in steatosis evaluation [17]. Imaging modalities like CT or MRI may help in a more objective assessment of hepatic fat, but such information is rarely available before procurement [18].

The gold standard to assess hepatic steatosis is a histological analysis by a pathologist [15,16]. Despite this general agreement, a European survey showed that liver biopsy at the time of procurement for LT is rarely performed [19]. Only 23% of liver transplant recipients in the United Network for Organ Sharing (UNOS) had a liver donor biopsy recorded. Half of the transplant surgeons in the UK never integrate a liver biopsy into their decision-making process [20]. However, several transplant programs consider a liver biopsy mandatory before discarding a potential liver graft [17,19,21]. As another strategy, 38% of liver transplant surgeons in the UK and 47% in the US proceed with the histological examination of the graft, when steatosis is suspected at inspection at the time of procurement [20].

Besides different practices regarding the biopsy procedure itself, another shortcoming is the variability in interpreting the histological assessment. Staining techniques can affect detection and grading of steatosis. Sample size errors that lead to misleading interpretation may be related to focal steatosis, hypersteatosis, or hepatic fatty sparing [16]. In this context, an autopsy study demonstrated that the addition of a second biopsy from the opposite hepatic lobe provides more accurate information, due to the heterogeneity of fat distribution within the liver. Two biopsy cores from the right and left liver were regarded to best predict overall liver histological characteristics (correlated with average findings in the liver, spearman correlation coefficient of 0.95) [22].

In addition, a recent study confirmed that H&E-stained frozen biopsy overestimates MiS but underestimates MaS, when compared with permanent sections using more specific staining modality [23]. Therefore, it can be argued that a significant bias in most studies investigating fatty livers has been the use of only H&E-stained frozen biopsy specimens [13]. Alternative methods to detect steatosis with higher sensitivity are Sudan-III, toluidine blue, and oil red O staining [12,15,16,20,24], but are rarely used in the decision process of using or not a potential graft.

The assessment of fat in biopsies by pathologists, irrespective of the staining used, bears another shortcoming. A recent study showed a significant inter-observer variability among experts for both quantitative and qualitative assessments of the histologic features of liver steatosis [16]. For instance, marked ($\geqslant$30%) steatosis was diagnosed in 22–46% of patients by various blinded pathologists. Furthermore, significant disagreement was found regarding the features and overall diagnosis of steato-hepatitis. To minimize this inter-observer variability, computerized programs have been developed to more objectively quantitate hepatic steatosis by determining the area occupied by lipid droplets in a given field of a liver section [16]. However, these quantitative methods provide information only on the total amount of fat, omitting any data on the chemical composition of hepatic lipids. Therefore, novel and objective tools, such as measurement of the Ω-6 and Ω-3 FAs and prostanoid levels in liver biopsy samples, may help prediction of the magnitude of reperfusion injury, as described below [15].

Reperfusion injury in the steatotic liver graft

Several experimental studies have shown increased reperfusion injury in a variety of models of liver steatosis [13,25,26]. For example, hepatic arterial flow and microcirculation are significantly impaired in steatotic compared with lean rats [27]. The contribution of hepatic lipid composition was recently highlighted. The metabolism of dihomo-γ-linolenic, arachidonic (Ω-6), and eicosapentaenoic Ω-3) acids result in the synthesis of vasoactive mediators impacting on liver microcirculation [10]. For example, the release of long chain fatty acids from cell membranes which is triggered by phospholipase A_2 and the further metabolism by cyclooxygenase and the lipoxygenase enzymes results in the synthesis of particular Ω-6 and Ω-3 prostanoids. Products of the cyclooxygenase pathway include prostaglandins (PGs) and thromboxanes (TXs), while leukotrienes (LTs) are synthesized through lipooxygenase-mediated reactions. Abnormally

Download English Version:

https://daneshyari.com/en/article/6108352

Download Persian Version:

https://daneshyari.com/article/6108352

Daneshyari.com