Frontiers in Liver Transplantation

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

Biomarkers to assess graft quality during conventional and machine preservation in liver transplantation

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Summary

A global rising organ shortage necessitates the use of extended criteria donors (ECD) for liver transplantation (LT). However, poor preservation and extensive ischemic injury of ECD grafts have been recognized as important factors associated with primary non-function, early allograft dysfunction, and biliary complications after LT. In order to prevent for these ischemia-related complications, machine perfusion (MP) has gained interest as a technique to optimize preservation of grafts and to provide the opportunity to assess graft quality by screening for extensive ischemic injury. For this purpose, however, objective surrogate biomarkers are required which can be easily determined at time of graft preservation and the various techniques of MP. This review provides an overview and evaluation of biomarkers that have been investigated for the assessment of graft quality and viability testing during different types of MP. Moreover, studies regarding conventional graft preservation by static cold storage (SCS) were screened to identify biomarkers that correlated with either allograft dysfunction or biliary complications after LT and which could potentially be applied as predictive markers during MP. The pros and cons of the different biomaterials that are available for biomarker research during graft preservation are discussed, accompanied with suggestions for future research. Though many studies are currently still in the experimental setting or of low evidence level due to small cohort sizes, the biomarkers presented in this review provide a useful handle to monitor recovery of ECD grafts during clinical MP in the near future.

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Keywords: Graft dysfunction; Marker; Prediction; Biliary complications; Viability testing.

Received 29 November 2013; received in revised form 11 April 2014; accepted 24 April 2014

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Abbreviations: LT, liver transplantation; ECD, extended criteria donors; PNF, primary non-function; EAD, early allograft dysfunction; ITBL, ischemic-type biliary lesions; DBD, donation after brain death; DCD, donation after circulatory death; MELD, model for end-stage liver disease; MP, machine perfusion; SCS, static cold storage; HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated machine perfusion; SNP, subnormothermic machine perfusion; NMP, normothermic machine perfusion; COR, controlled oxygenated rewarming; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ATP, adenosine triphosphate; HA, hyaluronic acid; (s)TM, (soluble) thrombomodulin; TNF-α, tumor necrosis factor alpha; PVB, portal vein branch; miRNAs, microRNAs; HDmiRs, hepatocyte-derived miRNAs; CDmiRs, cholangiocyte-derived miRNAs; UW, University of Wisconsin solution; HTK, histidine tryptophan ketoglutarate.

Introduction

Graft quality at time of liver transplantation (LT) is a major determinant of early graft performance and thereby strongly influencing graft survival and morbidity during recipient follow-up [1]. Over the last decade, grafts from extended criteria donors (ECD) had to be used increasingly for LT due to organ shortage. The quality of these grafts has been shown to be variable [2,3]. Although some ECD liver grafts turn out to function properly in recipients, their use has also been associated with impaired graft survival due to primary non function (PNF), early allograft dysfunction (EAD) and severe biliary complications like ischemic-type biliary lesions (ITBL, Fig. 1) [4,5].

Though pathophysiology between PNF, EAD, and biliary complications is assumed to differ, extensive ischemic- and preservation injury has been recognized as a shared risk factor in these entities [1,6]. Primary non-function occurs in up to 5–8% of LT's and necessitates immediate re-transplantation in all cases. Though PNF may be caused by technical failure resulting in inadequate blood flow through the graft [7], the association between unfavourable donor risk factors and PNF suggests that its cause is likely multifactorial [8]. Early allograft dysfunction is typically characterized by increased serum transaminase levels in recipients during the first postoperative week [9], but unlike PNF, liver grafts showing EAD do not always need immediate re-transplantation [10]. The most common complication associated with ischemic- and preservation injury are biliary complications. Dependent on the type of graft (donation after brain death; DBD *vs.* donation after circulatory death; DCD), up to 50% of recipients develop complications due to bile leakage, anastomotic strictures, ITBL, bile duct necrosis, and cast formation [11,12]. The various times of onset and different nature of biliary

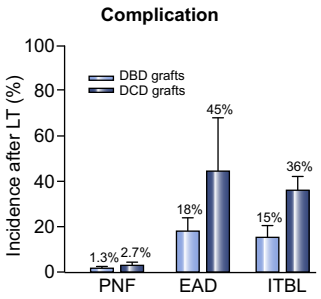

Fig. 1. Incidence of ischemia/preservation related complications after LT. Estimation of the incidence of PNF, EAD, and ITBL in separate DBD and DCD grafts, based on cohort- and case-matched studies [5,9–11,76,86,110]. Percentages represent the mean incidence ± standard error. Studies used to calculate the incidence of EAD maintained the criteria formulated by Olthoff *et al.* [9,10]. Definitions on PNF and ITBL can be found in the Supplementary data.

complications suggest that they are caused by different underlying mechanisms, including surgical trauma, DCD, high donor age, prolonged ischemia time, cytotoxicity of bile salts and immune factors [6,11].

Prediction models as the donor risk index were developed to estimate the risk of graft failure in recipients and to match high-risk grafts to suitable recipients [13]. Furthermore, earlier research on the topic of predicting graft function after LT has focussed mainly on clinical characteristics from donors and recipients, including the model for end-stage liver disease-score (MELD) [14–16]. However, models that are mainly based on such characteristics are unable to assess the degree of injury that is caused by the process of graft procurement, cold preservation, and reperfusion. Moreover, the under-utilization of grafts with unfavourable donor characteristics like advanced donor age, DCD, and African race, can lead to an undesirable diminution of the donor pool [17].

Therefore, machine perfusion (MP) is increasingly being investigated as a novel technique to improve graft preservation of particularly ECD grafts. Through MP, ischemia related complications like PNF, EAD, or ITBL can be reduced or even prevented and potentially allow for expansion of the extended criteria donor pool to be utilized for LT. Other potentially beneficial features of MP consist of the possibility to add supplements during perfusion that could further benefit graft quality [18,19], or even attempt for restoration of ischemic injury [20,21]. Beside safety and technical feasibility of MP, investigators pronounce on the need of sensitive biomarkers that can distinguish poor quality grafts from those that will function properly after implantation [22,23]. Next to other well-known risk factors for impaired graft quality as illustrated in Fig. 2, the time required for *ex vivo* MP provides the opportunity to monitor graft quality by measurement of biomarkers in perfusates and biopsies, which could be a helpful decision tool for improving the accuracy of selecting grafts for LT. This purpose however demands for objective surrogate biomarkers that are easily obtainable at time of graft preservation and is challenged by the various techniques of MP currently investigated.

In this review, we provide an overview of potentially useful biomarkers that were identified through a systematic search of the literature (Supplementary data), in order to assess graft viability testing during various techniques of MP. Because of the limited experience with clinical MP in LT, biomarker studies regarding conventional graft preservation by static cold storage (SCS) that correlated with either PNF, EAD, or biliary complications after LT and which could potentially be applied as predictive markers during MP were also included. Finally, the pros and cons of the different biomaterials are discussed, accompanied with suggestions for future research.

Key Points

- The increased use of extended criteria grafts demands for more objective and sensitive biomarkers to evaluate the large discrepancy of graft quality in liver transplantation
- Measurement of prudent biomarkers during machine preservation (MP) could be helpful in the prediction of early graft performance after LT
- During MP, surrogate biomarkers for graft quality could help select the most optimal preservation technique before implantation
- Research shows discriminative potential of a variety of biomarkers for graft injury and function, but requires robust validation in larger cohorts before applicable in the clinic
- Non-invasive evaluation of biomarkers released into perfusates during MP is an attractive alternative for invasively obtained tissue biopsies

Different machine preservation strategies

Because of easier accessible logistics and lower costs, SCS has become the standard preservation technique in clinical practice of LT to date. The low temperature during SCS delays metabolic processes in order to restrict ischemic injury. However, especially ECD grafts seem more vulnerable for prolonged ischemia, increasing morbidity and mortality in recipients after LT. Therefore, during the last ten years, various techniques by MP have been investigated in preclinical and clinical settings in order to further optimize graft quality and thus improve outcome of ECD liver transplantation. The main differences in the setup of MP are determined by pumping-temperature, the route- and pressure of recirculating preservation solution, and whether oxygen is administered (Fig. 3). As summarized in Table 1, several studies already performed MP on human liver grafts. Hypothermic MP (HMP) without the administration of oxygen comes closest to conventional preservation by SCS, but is believed to improve preservation through continuous recirculation of solution to all segments of the liver and the removal of remnant metabolites from the graft (Fig. 4). Guarrera *et al.* [24] performed the first clinical series of non-oxygenated HMP in humans (n = 20) using standard criteria donors. In this study, HMP was shown to be safe and analysis of perfusates and biopsies demonstrated an attenuation of ischemic injury markers during preservation [25–27]. Furthermore, the authors suggest that HMP could have beneficial effect on the incidence of EAD and biliary complications in recipients after LT. The feasibility of HMP was also investigated by Monbaliu *et al.* [28], who used HMP as a screening-tool to distinguish transplantable from

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