Chapter

New Perspectives on the Use of Sub-Optimal Donor Livers

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Abstract

Liver transplantation is the therapy of choice for patients with end-stage liver disease. However, a shortage of donor organs remains a major obstacle to the widespread application of liver transplantation. To overcome this problem, transplant centers have developed strategies to expand the organ donor pool, including the routine use of sub-optimal donor livers. However, these have an increased risk of initial poor function or primary non-function that may cause greater risk of morbidity in the recipient. This chapter aims to describe the pathophysiological changes that may occur in sub-optimal donor livers, focusing on viral infections, since, after transplantation, infection of the graft is almost universal and can lead to chronic hepatitis, cirrhosis, and graft failure. The different experimental models as well as the clinical outcomes of the transplantation of sub-optimal donor livers with viral infections will be discussed. Such information may be useful to guide the design of better experimental models than those described to date as well as the effective use of sub-optimal livers with successful clinical application.

Keywords: liver transplantation, fibrosis, HCV, HBC, treatment

1. Introduction

End-stage liver disease is associated with high morbidity and mortality, and the only cure is orthotopic liver transplantation (LT). The number of people awaiting LT continues to increase [1] and exceeds the number of available grafts. Between 20 and 30% of patients waiting for LT will die on the waiting list or are delisted because of disease progression [2]. The large imbalance between the growing pool of potential LT recipients and the scarcity of donor organs has led to efforts to maximize the number of existing donors and identify possible new donors based on the use of liver grafts that are currently considered unsuitable for transplant due to their pathological condition [3]. To expand the potential donor pool, the clinical and scientific community is continually modifying the criteria for an acceptable liver donor and is turning to marginal or extended-criteria donors to meet waiting list demands [4]. Thus organs infected with hepatitis B (HBV) or C virus (HCV) are increasingly being used [5], although the risk to recipients of using such grafts remains unclear [6].

Over 2 billion people across the world have serological evidence of present or past infection with HBV and more than 350 million individuals are estimated to be chronically infected [7]. It is estimated that 2–15% of liver donors are anti-hepatitis B core antigen (anti-HBc) positive. The proportion of positive anti-HBc livers in donors aged 60 years or over may rise to as much as 25% [8, 9]. Acquisition of HBV remains a concern after LT because the majority of infections occur via transmission by the donor liver [10], but some donors with past exposure to HBV infection can be used selectively in some recipients [3].

HCV is the most common indication for LT, and at current it accounts for 40–50% of individuals on waiting lists [11–13]. About 5% of all potential organ donors are positive for HCV [14]. To date, one of the most controversial issues regarding extended-criteria donors has revolved around the potential positive impact of HCV-infected donors on short-term outcomes [15]. In Europe, the prevalence of anti-HBc-positive grafts reaches as much as 10% in some regions [5, 9, 16]. A multivariate analysis of the United Network for Organ Sharing database revealed that the use of anti-HBc-positive grafts is not an independent determinant of graft or patient survival [17]. There is a trend towards increasing the use of HCV-positive donors [18]. One-year patient survival rates of 97% have been reported in recipients of HCV-infected livers compared with rates of 87% for recipients of organs meeting the United Network for Organ Sharing-approved criteria, with no differences in surgical conditions including warm and cold ischemia times between the two groups [19].

A significant number of organ donors have viral infections and the effect of using such organs is an important and timely question. In this chapter we describe the pathophysiological changes in sub-optimal donor livers with viral infections. In addition, post-operative outcomes after LT using sub-optimal donor livers with viral infections will be discussed. Therefore, I/R injury, hepatic inflammation and the different treatments used in recipients of donor livers with viral infections will be reviewed. Finally, we give details of the different experimental models of LT with viral infections. All of this may be useful to guide the design of appropriate experimental models of LT that resemble clinical conditions as much as possible, together with addressing the effective use of sub-optimal livers for transplant and the development of new protective strategies in the clinical setting of LT.

2. Sub-optimal donor and fibrosis progression

Many studies have reported the transmission of HBV from liver allografts of hepatitis B surface antigen (HBsAg)-negative, anti-HBc-positive donors [10, 20–28]. HBV within hepatocytes and passenger leukocytes in the anti-HBc allograft can be the source of infection in the HBsAg recipient [29]. It has been shown that employing liver grafts from these donors can transmit HBV infections to HBsAg-negative recipients and result in de novo hepatitis B at rates that are estimated to vary from 33 to 78% after LT in the absence of antiviral prophylaxis [8, 10, 21]. Similarly, there are many reports of the presence of occult HBV infection in HBsAg/anti-HBc donors. Meanwhile, detectable quantities of HBV DNA have been found to be present in only 5–10% of anti-HBc immunocompetent patients, irrespective of their anti-HBs status [30]. The replication capacity of HBV in the anti-HBc liver allograft is significantly increased after LT when recipients are administered high-dose steroids [29]. Several molecular mechanisms have been proposed to explain increased HBV replication in these patients: (1) a glucocorticoid-responsive element in the HBV genome and stimulation of HBV-dependent transcription by glucocorticoids [31]; (2) immunosuppression after LT suppresses virus-specific immune responses whereby after LT wild-type HBV is more frequently re-selected and this can result in better replication

fitness of the virus; (3) mutations selected in the HBV preS region result in a cytotoxic HBV strain, which is associated with cholestatic hepatitis [32–34]. HBV infection leads to graft damage in most cases [8]. It has been speculated that a liver that already hosts occult HBV infection, as is the case in the majority of HBcAb-positive donors [35], is particularly liable to suffer rapidly progressive damage when infected by HCV when it encounters immunosuppression for LT [36]. Some studies found that the survival of recipients of anti-HBc livers was significantly reduced 4 years after LT compared with recipients of anti-HBc-negative livers [8, 10]. With a post-LT follow-up of 2–4 years, a minority of transplant recipients developed fibrosing cholestatic hepatitis or cirrhosis leading to allograft failure [37].

Recurrence rates of hepatitis C, manifested by mild chronic hepatitis, fibrosis or cirrhosis, have been reported to be 54.55% in HCV-positive donor grafts when compared with 41.74% in HCV-negative grafts [38]. Marroquin [39] showed that patient survival at 2 years was significantly higher in HCV-positive recipients of HCV-positive grafts than in HCV-positive recipients of HCV-negative grafts (90 vs. 70%). In contrast, other studies indicated that in patients with HCV-related liver disease, there was no significant difference in survival between patients who received an HCV-negative graft and those who received an HCV-negative graft [40]. Khapra et al. [41] suggested that patients receiving HCV-positive donor organs develop more fibrosis over time than those receiving HCV-negative grafts. Wang et al. [42] reported that recipients show progression in liver inflammation grade or fibrosis stage regardless of the HCV status of the donors, although a higher stage of liver inflammation and fibrosis was found in HCV-positive graft recipients at follow-up. Although histological injury in the allograft owing to HCV is exceedingly common, progression of HCV is variable: some individuals experience indolent disease, whereas others progress rapidly to cirrhosis and liver failure [43]. Recently, donor age has been recognized to play an important role after LT with HCV-positive grafts. Khapra et al. [41] reported that HCV-positive grafts aged ≥50 years showed higher rates of graft failure and death among HCV-positive recipients compared to HCV-negative grafts from donors of the same ages. In addition, HCV-positive grafts from advanced-age donors showed more advanced fibrosis than those from younger donors [44].

3. I/R injury and organ dysfunction

Ischemia-reperfusion (I/R) injury, a phenomenon in which cellular damage in a hypoxic organ is accentuated following the restoration of oxygen delivery [45–47], is a multifactorial process associated with organ dysfunction of liver failure after LT. Early graft dysfunction affects up to 22% of liver allografts, with up to 6% of patients developing primary graft non-function and requiring retransplantation [48]. The association of I/R injury with the severity of HCV has been reported by several authors but with conflicting results, since I/R may or may not influence virus recurrence [49]. Although I/R injury is the underlying cause of graft dysfunction in marginal organs [4], it remains an unexplored issue in HBV and HCV grafts from donors.

The process of organ harvesting, cold storage and reperfusion is itself damaging, causing significant oxidative injury that can result in primary nonfunction or increase immunogenicity, prejudicing long-term graft survival [50, 51]. The duration of ischemic rewarming during implantation surgery is a risk factor for the severity of recurrent HCV disease after LT. In patients with hepatitis submitted to LT, the calculated risk for recurrent HCV disease post-LT is 19% if the ischemic time is 30 min versus 65% if this time extends to 90 min [52]. Rewarming ischemic injury appears to cause severe injury that enhances reinfection of the allograft with HCV after reperfusion, eventually leading to hepatic fibrosis and cirrhosis in some patients. Conversely,

it has also been reported that cold ischemia time was not a significant risk factor for recurrent HCV infection after LT [53]. Indeed, the authors indicated that rewarming duration during implantation of <10 min was associated with minimal recurrence, whereas a duration of >70 min was associated with moderate to severe recurrent hepatitis. This finding was supported by Velidedeoglu et al. [54] in a United Network for Organ Sharing database study that showed that a warm ischemia time of >90 min was associated with decreased graft survival in HCV-positive individuals [53].

The ischemia-reperfusion procedure itself causes apoptosis, so-called programmed cell death, in the first stages after LT [55], and it can be exacerbated by immunosuppressive drugs used in LT [56]. Balliardini et al. [56] mentioned that both hepatocellular apoptosis and cell proliferation are correlated with HCV infection. Sung et al. [57] suggested that HCV may also stimulate cell growth to counter the apoptosis and thus complete the replication cycle of HCV and produce infectious viral particles. Because the primary target cell for HCV replication in vivo is thought to be the hepatocyte, events that lead to hepatocyte proliferation may enhance HCV replication. Alternatively, HCV core proteins have been shown to interact with cellular promoters and regulators of cell growth, which may affect liver regeneration [58]. All these data suggest that liver regeneration associated with the processes associated with living related LT might affect HCV recurrence. Similarly, I/R injury associated with LT from brain dead donors is associated with apoptosis, whereas HCV is able to counteract apoptosis to increase hepatocyte proliferation. Further studies will be required to elucidate the effect of I/R on HCV recurrence as well as the effects of HCV on hepatic I/R injury associated with LT.

4. Hepatic donor inflammation in response to viral infection

The relationship between hepatocellular injury, hepatic regeneration, viral replicative activity, HCV antigen expression, and the pathologic host response remains unproven. Increased allograft damage is related to enhanced levels of known immune modulators, including interleukines 6 and 10. These cytokines are released in the milieu of injured or proliferating cells and it is known that they participate in the pathogenesis of HCV via increased viral activity, exaggerated host response, or both [59, 60]. Recurrent HCV is characterized by hepatocellular damage, infiltration of inflammatory cells into the liver, and tissue remodeling that ultimately results in progressive fibrosis and cirrhosis. Infiltrating inflammatory cells at the sites of liver injury secrete chemokines that stimulate hepatic stellate cells, these in turn proliferate and produce extracellular matrix proteins. These stellate cells are key players in recurrent HCV and can be activated by a number of stimuli in the liver transplant setting: production of ROS, secretion of cytokines by immune cells (acute rejection, CMV infection), hyperglycemia, and chronic cholestasis (biliary complications). The combination of a variety of factors explains the accelerated progression of fibrosis in HCV-infected liver transplant recipients [61]. Meanwhile, it should also be considered that the factors mentioned above are all generated as a consequence of hepatic I/R. Thus, it can be hypothesized that the mechanisms involved in hepatic I/R may exacerbate the negative post-operative outcomes induced by virus infection.

The mechanism by which the identified factors exert their undesirable effect on HCV recurrence presumably involves host-viral interactions. Since HCV is not directly cytopathic, HCV damage must be mediated by the host immune response. Both CD4- and CD8-positive T-cells participate in the recognition of HCV peptide displayed by infected hepatocytes [62]. In studies using an animal model of acute hepadnavirus infection, using woodchuck HBV, Guo et al. [63] found that viral

clearance occurred following the appearance of CD4 and CD8 T-cells as well as the production of interferon gamma and tumor necrosis factor alpha within the infected liver. This was accompanied by a significant increase in apoptosis and regeneration of hepatocytes. HCV infection initiates a specific host response that is ineffective at clearing virus and results in hepatic cellular damage in a nonspecific fashion [53, 64]. The recurrence of HCV is accelerated after LT as a result of high viral loads and an exaggeration of this host response, which occurs even in the presence of exogenous immunosuppression. The alloimmune response and I/R injury may also contribute [53, 65]. Despite the limited information on inflammation and post-transplant viral recurrence, there is a need for a greater understanding of the relationship between the virus and inflammatory processes associated with either I/R or virus infection by itself. This can progress to irreversible liver damage, and is also a relevant issue for the livers of donors infected by virus (HBV and HCV), which are usually in a constant inflammatory state.

5. Viral kinetics and target treatment

Despite being widely described in the literature, viral kinetics before, during and after LT using donor grafts with viral hepatitis has never been analyzed. The subject has only been considered in healthy livers transplanted into recipients with hepatitis. Thus investigations have mainly focused on the life cycle of the viruses and the recurrence of hepatitis.

Donor	**Therapy in recipients**		**Effect**
	Before LT	**After LT**	
Anti-HBc(+) donors [76]	Vaccination with recombinant hepatitis B	Lamivudine	Prevention of de novo HBV infection.
Anti-HBc(+) donors [77]	None	HBV immune globulin plus Lamivudine	Infection successfully managed Survival 100%
Anti-HBc(+) donors [29]	HBV immune globulin	Lamivudine	Prevention of recurrent or de novo infection
Anti-HBc(+) donors [78]	None	HBV immune globulin plus Lamivudine	Prevention of HBV transmission
Anti-HBc(+) donors [79]	Lamivudine or lamivudine plus adefovir	Lamivudine	Prevention of infection development.
Anti-HBc(+) donors [80]	HBV immune globulin	HBV immune globulin plus Lamivudine	Prevention of recurrent infection
Anti-HBc(+) donors [81]	HBV immune globulin	HBV immune globulin vaccination (recombinant)	Minimize the possibility of HBV recurrence
Anti-HBc(+) donors [82]	HBV immune globulin	HBV immune globulin plus Lamivudine	De novo HBV reactivation during HBV immune globulin prophylaxis Lamivudine resulted in virus clearance
Anti-HBc(+) donors [83]	HBV immune globulin	HBV immune globulin plus Lamivudine	Prevention of HBV recurrence

Donor	Therapy in recipients		Effect
	Before LT	After LT	
Anti-HBc(+) donors [84]	HBV immune globulin	HBV immune globulin	HBsAg levels became positive
		HBV immune globulin plus Lamivudine	HBsAg-positive
		HBV immune globulin plus lamivudine plus famciclovir	HBsAg-positive
		Lamivudine plus interferon alpha	Serum HBV DNA decreased, but remained positive
		Lamivudine plus adefovir	Hepatitis B e antigen status converted to seronegative
HCV-positive [85]	None	DAA therapy	Increases in life expectancy
HCV-positive [86]	None	DAA therapy	Prevention of HBV recurrence
HCV-positive [87]	None	Ledipasvir and sofosbuvir	Prevention of HCV recurrence

LT, liver transplantation; DAA, direct-acting antivirals; HBV, hepatitis B virus; HCV, hepatitis C virus; HBc, hepatitis B core antigen (anti-HBc); HBsAg, hepatitis B surface antigen.

Table 1.
Pharmacological strategies used in patient after or before the transplantation.

In patients with hepatitis undergoing LT, HCV viral load decreases during the anhepatic phase and after graft reperfusion because of a lack of virus production, blood loss, and hepatic viral clearance. Despite the decline in viral load, hepatitis C virions continue to circulate and rapidly infect the new graft. HCV replication in the liver graft begins within a few hours after LT in most patients [66], and viral load increases as early as 12 h after graft reperfusion. The rapid increase in HCV viral load indicates that viral replication is highly efficient after LT and proves the high capacity of HCV to adapt to a completely new environment. However, HCV kinetics did not follow the same pattern in all patients. Differences in the immunosuppressive regimen appeared to influence HCV kinetics immediately after LT [66]. In fact, HCV-RNA concentrations increased rapidly in patients receiving corticosteroids as part of their immunosuppressive therapy [67–69], whereas they continued to decrease in most patients who were not receiving corticosteroids. Although this observation requires confirmation in further studies, it is possible that some immunosuppressive regimens might be more appropriate in the case of early antiviral therapy to eradicate HCV [66]. Powers et al. [70] estimated that viral resurgence begins when much less than 1% of the engrafted liver's hepatocytes are infected, suggesting that antiviral therapy should begin soon after, or before, LT in order to prevent or delay reinfection.

Table 1 summarizes the pharmacological strategies used in patients before and after LT.

6. Experimental models

To the best of our knowledge, most of the current experimental models of hepatitis do not focus on LT. The only two experimental studies involving hepatitis and LT were by Dahmen et al. [71, 72], and both report severe hepatitis virus reinfection after woodchuck LT (**Table 2**). However, both studies focused on vaccines and not on the effects of I/R on viral infections after LT.

Cold ischemia	Anhepatic	Donor	Receptor	Alterations after LT
<5 h	<40 min	WHV negative	WHV positive	Vascular rejection Severe vacuolar and fatty degeneration Lymphocytic infiltrates and vacuolar degeneration in bile duct
Data not shown	Data not shown	WHV negative + vaccine	WHV positive	Cholangitis was less severe Moderate but stable jaundice Low amounts of viral particles

WHV, woodchuck hepatitis virus.

Table 2.
Experimental studies with hepatitis virus reinfection after liver transplantation.

7. Conclusion

A shortage of donor organs remains a major obstacle to the widespread application of LT in patients with end-stage liver disease [73, 74]. This shortage could be alleviated by routine use of sub-optimal donor livers including those from donors with viral infections, although infection of the graft is almost universal and can lead to chronic hepatitis, cirrhosis, and graft failure. As stated in this chapter, studies on LT using sub-optimal donor grafts with viral infections have mainly focused on survival and the recurrence rates of hepatitis. In addition, although I/R injury is the underlying cause of graft dysfunction in sub-optimal donor livers with viral infections [4], it remains an unexplored issue in recipients transplanted with HBV and HCV grafts. It should be considered that the mechanisms involved in hepatic I/R depend on the conditions used during surgery, such as the period of ischemia (ranging from minutes to days) and the subclinical condition of the graft (healthy, sub-optimal, aged, etc.). However, clinical studies that focus on the pathological effects of I/R were only performed in recipients with viral infections from healthy liver grafts. In our view, multicenter clinical studies and experimental studies of LT using grafts with viral infections are needed to identify the inflammation associated with I/R and that induced by virus infection. The clinical application of strategies designed to increase the use of sub-optimal liver grafts with virus infection will depend on the use of experimental models of LT using donors with viral infections that resemble clinical conditions as much as possible [75]. We recognize that this may be difficult; however, multidisciplinary research groups should devote additional efforts to better understand the pathophysiology of LT using donors with viral infections to ultimately develop effective therapeutic strategies aimed at improving graft viability and at significantly increasing the organ donor pool.

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Conflict of interest

The authors declare that they have no conflict of interest.

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