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Review Article

Non-alcoholic steatohepatitis and liver transplantation

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ABSTRACT

Non-alcoholic steatohepatitis is a growing liver-related health problem. In Europe, non-alcoholic fatty liver disease is the most usual reason of chronic liver illness while steatohepatitis, its progressive form, affects 1% of Europeans and North Americans. In the United States steatohepatitis-related cirrhosis is one of the main indications for liver transplant. A targeted stratification for patients waiting for transplant and affected by this disease is mandatory especially because of their increased cardiovascular and cancer risk. The adequate treatment of NAFLD is crucial for the reduction of the disease related morbidity and mortality. In post-transplant setting, the recurrent or *de novo* steatosis might seriously affect the allograft short- and long-term outcome. Many conditions can represent the basis of the post-transplant steatohepatitis: obesity, hyperlipidaemia, diabetes mellitus, arterial hypertension, immunosuppressant treatment, alcoholic habit and liver graft steatosis. Today, the only consolidated therapy is represented by a deep life-style intervention since the use of drug-based alternative strategies is still limited and a very few data are available for the post-transplant period. Targeted and personalized behaviour and pharmacological interventions have to be developed for both the pre- and post-transplant phase.

1. Introduction

In the past years, the prevalence of non-alcoholic fatty liver disease (NAFLD) has persistently increased becoming the most common reason for altered liver tests worldwide [1]. The global prevalence of NAFLD ranges from 6% to 33% while the frequency of non-alcoholic steatohepatitis (NASH), which is the progressive form of NAFLD, is lower (3–5%) [2]. The growing occurrence of this disease likely mirrors the increasing incidence of obesity and type 2 diabetes mellitus, that are the main pathogenic determinants [3,4]. In 2004 [5], an estimation that 25 million of people in USA would be affected by NAFLD in 2025 was made, along with the data on increasing obesity prevalence worldwide [5,6]. The natural history of NAFLD can lead towards advanced liver damage requiring liver transplantation (LT). Finally, the transplanted liver can experience a NASH recurrence or a *de novo* NASH with possible drastic impact on graft and patient survival.

This review focuses on the current literature concerning the clinical and epidemiological features of NAFLD as an indication to LT and its possible implication in liver allograft outcomes. Pathogenic insights of the disease are not among the scopes of this review article and are only briefly mentioned.

2. Non-alcoholic steatohepatitis: a growing indication for liver transplantation

Natural history of NAFLD/NASH is not univocal [7] and is thought to depend on grade of inflammation and stage on first histological diagnosis, besides from the concomitant presence of metabolic disorders, namely type 2 diabetes mellitus and obesity. A review on liver biopsy data pooled from 10 longitudinal studies on NASH revealed that the histological patterns worsened during a 3.7 years median follow-up period in more than one third of patients with an initial diagnosis of NASH [8].

The study of data extracted from USA Scientific Registry of Transplant Recipients, relative to 35,781 LT recipients during the period 2001–2009 and including 1959 subjects whose LT indication

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Table 1
Peculiar patterns of patients with NASH waiting for LT.

Associated comorbidities [17]	Waitlist death reasons [18]	Pre-LT factors worsening post-LT outcome [23–25]	Other relevant patterns [11]
Type 2 diabetes; arterial hypertension; obesity; cardiac disease; smoking	Cardiovascular events; cancer	BMI $\geq$40 kg/m^2; type 2 diabetes	MELD lower than in alcohol-related ESLD 3-month waitlist mortality higher than in alcohol-related ESLD

NASH, non-alcoholic steatohepatitis; LT, liver transplantation; BMI, body mass index; MELD, Model for End-Stage Liver Disease; ESLD, end-stage liver disease.

was NASH, showed that the rate of patients who underwent LT for NASH increased from 1.2% in 2001 to 9.7% in 2009 [9]. The LT recipients for NASH were significantly older, more frequently women, had a higher body mass index (BMI) and had a lower rate of hepatocellular carcinoma, compared to those for indications other than NASH. Despite these differences, the survival outcomes after 1 and 3 years from LT were similar in those transplanted for NASH compared to non-NASH LT recipients [9]. Recently Su et al. [10] updated the data regarding the patterns of patients waiting for liver transplantation (LT). Data from registry in the period 2002–2014 indicated that the mean age of liver transplant registrants increased from 51.2 to 55.7 years, with a more significant rise in HCV-positive than HCV-negative candidates. Notably, authors showed that in HCV-negative patients, aging trends were caused by both increase of NASH-cirrhosis and hepatocellular carcinoma.

Wong et al. [11] examined, more specifically, NASH as indication for LT. Authors reported the North-American data from United Network for Organ Sharing and Organ Procurement and Transplantation Network registry. From 2004 to 2013, the leading etiologies of chronic liver disease among adults awaiting LT were: HCV, alcohol-related liver disease and NASH cirrhosis, accounting for 35.2%, 18.3%, and 15.8%, respectively. Authors showed that in the same period, patients affected by NASH on the waiting list increased by 170%. Indeed, according to the last available data, in 2013 NASH has become the second indication for LT in USA.

Moreover, the development of hepatocellular carcinoma, which can account as a possible *per se* LT indication, has been described even in non-cirrhotic NASH setting [12], although it has been observed uncommonly in NASH explants [13].

The European Liver Transplant Registry collected data from 1968 to 2009 on 93,634 LTs in 83,816 subjects from 26 countries. Cirrhosis was the most common indication (52%), mainly related to hepatitis C (21%), alcohol (19%) and hepatitis B (7%). NASH-cirrhosis represented the 0.1% of the indications to LT [14]. However, these data reported cryptogenic cirrhosis in 4% of cases who, at least in part, supposedly were represented by unrecognized NASH. Indeed, it was shown that the prevalence of NASH-induced end stage liver disease as indication for LT might be significantly underestimated [15,16].

Concerning the selection of candidates for LT, patients with NASH show some peculiar features (summarized in Table 1) especially because the liver disease of these subjects often arises in the context of metabolic syndrome. The association with diabetes, hypertension, obesity, and cardiac disease can be found in these patients and a history of smoking is present more frequently respect to the general population [17]. As a consequence, NASH patients have an increased cardiovascular risk and their death is more often related to cardiovascular disease and cancer rather than to the progression of liver disease [18]. It has been found that although candidates with alcohol-related cirrhosis had a higher mean Model for End-Stage Liver Disease score at the time of waitlist registration, patients with NASH-cirrhosis showed a worse 3-month waitlist survival [11].

Definitely, patients with NASH-cirrhosis, compared to other LT candidates, show a higher risk to develop cardiovascular complications which, in turn, may contraindicate LT and merit specific hazard stratification.

A very recent systematic review [19] of studies comparing the outcomes of NASH or non–NASH LT recipients for end-stage liver disease included 9 authentic, not database-extracted, not overlapping studies. The meta-analysis of pooled data highlighted a similar 1-, 3- and 5-year survival rates although certain heterogeneity between studies subsisted for 3- and 5-year outcomes. Moreover, the analysis showed a higher number of deaths due to cardiovascular disease or to sepsis in NASH patients compared to non-NASH, while the latter had more graft failure [19]. In 2012, Vanwagner et al. [20] retrospectively compared the incidence of cardiovascular events after LT between patients transplanted for NASH or alcohol-related cirrhosis. Patients in the NASH group were older, mainly women, obese, with dyslipidemia or arterial hypertension and developed more cardiovascular events compared to others. More recently, the same group [21] examined the association between NASH and cardiovascular mortality in 48,360 LTs. The authors clearly demonstrated that the long-term cardiovascular mortality was higher among NASH recipients, compared to patients with a different aetiology. The increased post-LT cardiovascular mortality can be explained by a high prevalence of cardiometabolic comorbidities in patients with NASH-cirrhosis.

Interestingly, the NASH seems also to increase the risk of post-LT renal failure. In fact, besides the pre-LT chronic kidney disease and the recipient age at the time of LT, female gender and NASH correlated with the occurrence of post-LT chronic renal disease [22].

The metabolic conditions associated to NASH, besides constituting an element which itself impacts on morbidity and mortality before LT, may negatively alter the outcome after LT. In a recent study on a large population of LT recipients, divided in two cohorts upon BMI cut-off of 40 kg/m^2, it was found that recipients with BMI $\geq$ 40 kg/m^2 were more frequently females, diabetic and with NASH-related cirrhosis showing a worse hepatic function and a longer hospitalization at the time of LT respect to those with BMI < 40 kg/m^2 [23]. Transplanted patients with BMI $\geq$ 40 kg/m^2 had a higher post-LT length of hospital stay and were less often discharged to home respect to the others [23]. Nevertheless, both cohorts of LT recipients, with BMI < and $\geq$40 kg/m^2, had a similar short-term graft and patient survival [23].

The same cohort was analyzed to estimate the role of diabetes as predictor of post-LT survival [24]. It was stated that the majority of patients affected by diabetes were transplanted for a NASH-cirrhosis. In the post-LT period, diabetic recipients had longer length of hospital stay, higher peri-LT mortality and poorer graft and patient survival.

Conzen et al. [25] confirmed the association between high BMI (>35 kg/m^2) and NASH as indication for LT. Again, a high BMI correlated with worse liver function but also with a longer time on the waiting list. Authors reported that BMI was not relevant for surgery time, hospital stay and perioperative complications. Nonetheless, candidates with BMI $\geq$40 kg/m^2 had a considerably worse 5-year graft and patient survival respect to patients with a BMI < 40 kg/m^2 (49.0% *vs.* 75.8% and 51.3% *vs.* 78.8%, respectively).

The above-cited data demonstrate that high-degree obesity and diabetes, often associated with NASH, negatively affect the morbidity and mortality in waiting list and the post-LT outcome.