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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.

Despite the above reported considerations according to the European data, NASH-cirrhosis seems to have the best 5-year post-LT survival (78%) among all the LT indications [14].

3. Metabolic complications after transplantation

The increase of body weight, development of insulin resistance and drug-induced dysmetabolism have been described in liver transplants and are risk factors for increased morbidity and mortality in long-term follow-up [26]. Indeed, both recurrent and *de novo* NAFLD have been reported in this population [27–33].

3.1. *NAFLD/NASH recurrence*

According to the review article by Burra et al. [34], NASH recurrence ranges between 20% and 40% depending by the methodology used for the diagnosis.

Bhagat et al. [27] reported that NASH recurred in one third of transplanted patients during the first 6 months after surgery, but its course in the vast part of cases was indolent without evolution to cirrhosis. Yalamanchili et al. [28], analysing a long post-LT follow-up, suggested that among patients transplanted for cryptogenic cirrhosis or NASH, the prevalence of hepatic steatosis was 8.2%, 13.6%, 24.9% and 32.9% at 1, 2, 5 and 10 years after LT, respectively. As in the previous study [27], authors reported that the patients' outcome was generally benign without a fibrotic evolution. Dureja et al. [29] reported that recurrent NASH was found in 39% of recipients after 5 years from LT and confirmed that the disease had not a progressive pattern. Nevertheless, these patients showed a high frequency of cardiovascular disease and higher infection-related morbidity and mortality in comparison to those without liver disease recurrence. A retrospective single-centre study [35] on LT recipients from 1997 to 2008 analyzed the characteristics of post-LT liver histology and the clinical outcome of 98 LT recipients for NASH cirrhosis compared with 686 LT recipients for non-NASH related aetiology (cholestatic disease, alcohol liver disease, hepatitis C virus, cryptogenic cirrhosis). After a mean observation time of 18 months, 70% of patients transplanted for NASH had the recurrence of NAFLD, 25% was diagnosed with NASH and 18% had a fibrosis stage greater than II. Moreover, subjects with recurrent NASH had a higher incidence of diabetes, weight gain, and dyslipidemia respect to the non-NASH counterpart, although with no cases of graft failure [35].

3.2. *NAFLD/NASH* de novo

One third of patients transplanted for a reason different from NASH, develop insulin resistance or other risk factors for NAFLD within 3 years from the LT [30–32]. Obesity, hyperlipidaemia, diabetes mellitus, arterial hypertension, tacrolimus based immunosuppression, alcoholic cirrhosis and liver graft steatosis, represent the main risk factors for the development of a *de novo* NAFLD [33]. The main metabolic complications that can arise in transplanted patients are reported in Fig. 1. In detail, the prevalence of diabetes rises from 15% before LT to 30–40% after LT [36,37]. From 45% to 69% LT recipients develop hyperlipidaemia, this latter being a significant risk factor for cardiovascular disease [38,39]. Also the obesity has been found to affect the post-LT outcome. Richards et al. [40] reported that the median weight gain at 1 and 3 years from LT was 5.1 and 9.5 kg, respectively. Notably, at 1 and 3 years, 24% and 31% of transplanted patients were obese, the greatest weight gain occurring after the first 6 months. The metabolic syndrome, which definitively groups the above-cited conditions, can be found in 48–58% of transplanted patients after six months from the surgery, and it is associated with a higher cardiac- and cerebrovascular risk [30]. Indeed, the high prevalence of metabolic diseases

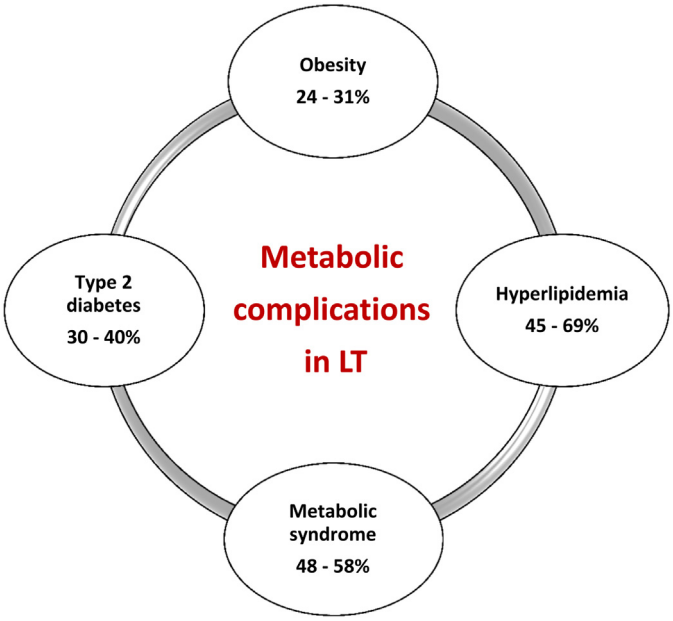

Fig. 1. Prevalence of major metabolic complications in liver transplant.

after LT makes the NASH recurrence (or the development of NASH in patients transplanted for other reason), a topic of great relevance. Finally, genetic predisposition seems to play a role in the post-LT recurrence of NAFLD. In particular, it was shown that the presence of the rs738409-G allele of the PNPLA3 gene in the LT recipients represents an independent risk factor for post-LT obesity, diabetes mellitus and steatosis [41,42].

4. Therapeutic approach

In the pathogenesis of NASH many events happen in parallel, all being potential therapeutic targets [43]: insulin resistance, oxidative stress, adipose tissue derived cytokines production, altered lipid metabolism, alteration of bile acids, changes in gut microbiota, systemic chronic inflammation and genetic patterns [44]. Moreover, in LT, *de novo* metabolic complications can be induced, or at least supported, by the immunosuppressive drugs. Effectively, the administration of steroids has been already indicated to correlate with NAFLD occurrence in liver allografts [16].

In Table 2 the main metabolism-related pathogenic factors implied in post-LT liver injury are depicted along with respective therapeutic strategies.

As for the obesity treatment, according to the current Italian, European, North American and Asian-Pacific guidelines the standard of care for the treatment of NASH is represented by a strong lifestyle modification [45–48]. It is widely accepted that personalized diet, physical activity and cognitive-behaviour therapy can be useful [49]. According to recent data [50,51], the main targets to significantly decrease liver fat accumulation and necroinflammation have to be a weight loss of 7% and 150-min/week of physical activity. Notably, aerobic and physical activity resistance exercise can have an independent positive effect in the decrease of liver fat, regardless of the weight loss [52,53]. Moreover, NASH is often associated with high cardiovascular hazard and physical activity can make better the cardio-respiratory fitness, decreasing this risk [54,55]. Recently, a pre-transplant protocol was described aimed at weight loss by lifestyle and diet modification or, in case of non-invasive strategy failure, by sleeve gastrectomy procedure combined to LT [56]. The authors reported a higher post-LT mean BMI in patients who had a non-invasive pre-LT weight loss.

Table 2
Factors cooperating in liver allograft injury and respective possible therapeutic targets.

	Insulin resistance/type II diabetes mellitus	Obesity	Hyperlipidemia	NASH	Bile acid and cholesterol metabolism alteration
Target	Reduce gluconeogenesis and glucose absorption Increase glucose uptake and utilization Improve insulin sensitivity Reduction of circulating lipids Hepatic insulin extraction improvement	Weight loss Reduction of hepatic features of steatosis, steatohepatitis and fibrosis Reduction of cardiovascular risk	Low-density lipoprotein level reduction Decrease of cardiovascular risk	Transaminases normalization Ultrasound improvement Histology improvement Fibrosis regression	Decrease cholesterol secretion into bile Cytoprotective role Mitochondrial function Anti-inflammatory potential

Moreover, comparing the patients who obtained pre-LT non-invasive weight loss to those treated with peri-LT sleeve gastrectomy, the rate of recurrent post-LT severe obesity was 60% *vs.* 0% and the rate of post-LT type 2 diabetes mellitus 34% *vs.* 0%, respectively [56]. However, the role of bariatric surgery of obesity in LT candidates with NASH-related cirrhosis remains to be defined.

Thus far, the pharmacological strategies for NAFLD/NASH have been mostly focused on the correction of insulin resistance [57–60], hypercholesterolemia/hypertriglyceridemia [61–64], bile acids metabolism [65–68], oxidative stress [69–72] and, specifically in LT, on immunosuppressive regimen tailoring. Still, it is crucial to understand that the majority of the pharmacological tools for treating the metabolic factors implicated in NASH pathogenesis have not been tested in post-LT setting and their use is frequently burdened by concern of adverse pharmacological effects or drug-drug interactions [64,73]. Promising innovative pharmacological approaches are in pipeline but the results of human studies are at present mostly still ongoing [74].

However, at present, the only sound therapeutic approach for NAFLD/NASH after LT is a deep lifestyle modification, as no specific NASH-targeted drug is available. The recent literature is pointing to the need for reduction of risk factors of NAFLD to improve the length and the quality of post-LT survival [75] and the diet and physical activity represent the main implement of a lifestyle-targeted therapeutic approach [49,76].

5. Conclusions

The prevalence of NAFLD and NASH is growing worldwide. As a consequence, in both United States and Europe, NASH-related cirrhosis is raising as indication for LT.

Patients with NASH have peculiar features because this liver disease arises mostly in the context of the metabolic syndrome. In NASH, the association with high BMI, diabetes, hypertension, obesity, hyperlipidaemia and cardiac diseases can be typically found and affect the overall patient's outcome. After LT, the increase of body weight, onset of insulin resistance and drug-induced hyperlipidaemia are rather common metabolic complications. Besides predisposing to both recurrence and *de novo* NASH, the development of metabolic syndrome in LT is associated with a significant cardio- and cerebrovascular risk.

A specific approach to patients with NASH waiting for LT should be developed, acting in two directions: (a) reduce the risk of cardiovascular risk and the related morbidity and mortality; (b) act on obesity and diabetes not only when associated to overt allograft disease, so to improve the post-LT outcome. After LT, all patients should be educated from the alimentary point of view and endorsed by a motivational expert psychological support, especially when a metabolic disease had been present before the LT. Given the expected continuing growth in the number of NASH patients candidates to LT worldwide, additional research is needed to improve both the waitlist survival and the post-LT outcome of NAFLD-related liver disease.

Conflict of interest
None declared.

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