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Alcohol use and smoking after liver transplantation; complications and prevention

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A B S T R A C T

The last thirty years have been very prosperous in the field of liver transplantation (LT), with great advances in organ conservation, surgical techniques, peri-operative management and long-term immunosuppression, resulting in improved patient and graft survival rates as well as quality of life. However, substance addiction after LT, namely alcohol and tobacco, results in short term morbidity together with medium and long-term mortality. The main consequences can be vascular (increased risk of hepatic artery thrombosis in smokers), hepatic (recurrent alcoholic cirrhosis in alcohol relapsers) and oncological (increased risk of malignancy in patients consuming tobacco and/or alcohol after LT). This issue has thus drawn attention in the field of LT research. The management of these two at-risk behaviors addictions need the implication of hepatologists and addiction specialists, before and after LT. This review will summarize our current knowledge in alcohol use and cigarette smoking in the setting of LT, give practical tools for identification of high risk patients and treatment options.

Introduction

Liver transplantation (LT) is the most efficient treatment for end-stage liver disease and small hepatocellular carcinoma (HCC), with excellent and constantly improving survival rates [1]. As long term survival has become commonplace, physicians have been confronted to new issues such as relapse to substance addiction. This review will summarize our current knowledge in alcohol use and cigarette smoking in the setting of LT, focusing on the consequences of such behavior and the importance of a combined management with an addiction specialist.

Is cigarette smoking before LT commonplace?

The prevalence of cigarette consumption among patients suffering from chronic liver disease has never been studied, while data are more abundant regarding tobacco use in the setting of LT. In Western countries, where the most common liver cirrhosis etiologies are hepatitis C virus (HCV), alcoholic liver disease (ALD) and, more recently, NASH, studies in transplant candidates [2] or recipients [3–5] showed incidences between 42% and 60% of any cigarette smoking, with 10%–23% actively smoking at the time of LT [3–5]. Those figures might vary depending on the predominant chronic liver disease in each center, since alcohol and tobacco use are closely related, with reports revealing that up to 90% of alcohol abusers smoke [6]. For example, in our ALD-dominant center, a prospective evaluation of 173 candidates showed that barely a quarter had never smoked, while 42.2% were active smokers (data unpublished).

Interestingly, most of these studies show methodological limits, since smoking habits were only self-reported and this can be considered as a bias since some patients might lie about addictive behavior fearing that candor could result in non-listing. To our knowledge, only one study focused on the reliability of self-reported smoking using a biological method (serum cotinine levels) in LT candidates. After evaluating 171 patients, authors found that 11% of those denying tobacco use had cotinine (a nicotine metabolite) levels consistent with active smoking behavior [7].

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Besides, only one study evaluated nicotine addiction using a validated scale such as Fagerström test [8].

When active smoking is detected in a LT candidate, cessation ought to be advised, although there is no data regarding potential benefit on success rates from smoking cessation therapies. Whether active smoking should represent a contraindication is debatable. A survey in the United States on smoking policies in 51 LT centers showed that cessation was mandatory before LT in 63% of them [9]. Professional societies remain vague, with AASLD stating that "all patients considered for liver transplantation should be encouraged to undergo efforts to abstain from smoking" [10], while EASL recommends that "smoking cessation should be mandatory in all transplant candidates" [11].

Irrespective of the consequences of smoking on LT outcomes, beneficial effects of smoking cessation on the liver function are expected. Indeed, it is well established that cigarette smoking participates in the progression of the fibrosis and disease severity in chronic hepatitis C [12,13], primary biliary cholangitis (PBC) [14] and ALD [15]. Moreover, there is mounting evidence linking tobacco exposure and HCC development [16,17].

The influence of donor smoking before transplantation was assessed in one German study of livers transplanted with extended donor criteria and showed that any smoking in the donor was associated with an increased risk of death after LT of 1.249 (95% CI, 1.011–1.544; P = 0.04), although there was no repercussion on graft survival [18].

Alcohol use before LT

In general, complete alcohol abstinence is mandatory before performing LT in patients having alcoholic liver disease (ALD) as primary indication [11]. The main objective of this rule is to allow roughly two thirds of the patients having a Child-Pugh C score to recover within the 3 months-period after a first episode of decompensation and thus avoid LT [19]. The duration of this abstinence period has been surrounded with great controversy [20], and nowadays it is recognized that the use of a "6-month rule" alone is not evidence-based and it can hinder some low-risk relapse candidates from getting a life-saving LT. The assessment of the risk of relapse after LT is a thorny issue, and the data are abundant and often contradictory. The most common risk factors associated with relapse are sobriety pre-LT <6 months [21–23]; family history of alcoholism [24]; psychiatric comorbidities, including other substance abuse [23–25]; diagnosis of alcohol dependence [25]; prior alcohol rehabilitation [25]; and female gender [26].

In practice, the "High Risk Alcoholism Relapse" (HRAR) scale [27] can be useful to detect patients at greater risk of harmful relapse. This scale considers the daily alcohol consumption (≤9 drinks, 9–16 drinks, ≥17 drinks), length of the heavy drinking history (≤11 years, 11–24 years, ≥25 years), and previous inpatient alcoholism treatment history (none, one or ≥2), each item being graded from 0 to 2. In a French-Swiss cohort of 387 patients transplanted for ALD, an HRAR score higher than 3 was one of the independent factors associated with harmful relapse (declared alcoholic consumption level >40 g/d and the presence of physical or mental alcohol-related damage), along with a duration of abstinence <6 months and presence of psychiatric comorbidities [23].

The identification of patients at high-risk of relapse raises the question of alcohol addiction management in the pre-LT period. A randomized controlled trial conducted in 91 patients in two United States centers compared a positive reinforcement technique called Motivational Enhancement Therapy (MET), with referral to local treatment sources such as Alcoholics Anonymous. The study revealed that 25% of the patients drank alcohol before their transplant, but MET had little, if any, influence on this event [28].

Furthermore, alcohol consumption must be sought in every LT candidate, no matter what the primary indication is. Indeed, in a British single-center study, the authors evaluated lifetime alcohol consumption of 208 consecutive patients referred for LT. The assessment was conducted by a researcher completely independent of the transplant team to foster candor and they found that the referring physician had not raised the possibility of alcohol consumption as a causative factor in ten (12.5%) of the 80 patients meeting DSM-IV criteria for alcohol abuse or dependence [29]. Thus, in our center, every transplant candidate is evaluated by an independent addiction specialist. Our data revealed that up to 72% of the candidates between 2008 and 2014 have experienced excessive alcohol use at some time in their life, while merely 40% of them were labeled as "alcoholic liver disease" as the primary indication (data unpublished).

Tobacco consumption after LT

Do patients smoke after LT?

The most thorough study of smoking behavior in LT recipients for ALD examined the course of nicotine addiction through time using the Fagerström test. Authors found that smoking prevalence ranged between 39 and 58% of all LT recipients, with smokers resuming tobacco use quickly after LT and nicotine dependence increasing over time. At 9 months post-LT, 60% of smokers were dependent to nicotine according to their Fagerström test score [8]. Of interest, the incidence of "*de novo*" smoking after LT is neglectable. For example, in a single-center study of smoking patterns before and after LT of 202 recipients, 31 patients (15%) reported smoking after LT, and only one of them had not smoked before the surgery [3]. A meta-analysis of studies examining substance use after solid organ transplantation found that the average rate of cigarette smoking relapse after LT was 9.9, or approximately 10 cases per 100 PPY (persons per year) of observation (confidence intervals 2.7–17.1) [30].

What are the repercussions of smoking in LT outcomes?

Data are abundant in this regard, even though the concordance between studies is incomplete. At least two studies suggested that patient survival is hampered by cigarette smoking, assessed at the time of pre-transplant evaluation. The first study is a single-center retrospective report from Scotland that examined the outcomes of 136 consecutive liver recipients with a mean follow-up time of 8.8 years. This study found that active smokers at the time of LT had a significantly lower survival (for example, 64% vs 83% 5-year survival, p = 0.04) when compared to lifelong nonsmokers, with increased cardiovascular-specific mortality and sepsis-specific mortality but not malignancy-related mortality [5]. A more recent retrospective single-center study performed in the US, classified 1275 LT recipients in active smokers (22%), previous smokers (25%) and nonsmokers (53%) at the time of listing for LT. Cox regression analysis of post-LT patient survival showed a 10-year survival of only 57% for current smokers, significantly lower than previous smokers and nonsmokers (P < 0.01; risk of death, 1.47; 95% confidence interval [1.10–1.97]). Interestingly, authors found a dose-dependent relationship, as smokers with more than 20 pack-years tobacco exposure exhibited a lower survival than nonsmokers and smokers with less than 20 pack-years [4]. Unlike the Scottish study, cardiovascular and sepsis-related mortality were not increased in smokers, whereas HCC recurrence and non-skin *de novo* malignancy were incremented in smokers.