Tobacco Use Before and After Liver Transplantation: A Single Center Survey and Implications for Clinical Practice and Research

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Compared to alcohol use, and despite its potential health implications, tobacco use among candidates and recipients of orthotopic liver transplantation (OLT) has not been the focus of much attention. The purpose of the present study is to examine lifetime pre- and post-OLT prevalence rates of tobacco use, relapse rates after OLT, and comorbid use of alcohol and tobacco. Structured interviews were conducted to examine retrospective accounts of lifetime tobacco use in 202 OLT recipients. Sixty percent of OLT recipients reported a lifetime history of smoking, with 15% reporting smoking post-OLT. Of smokers who quit before OLT, 20% reported relapse to smoking post-OLT. Finally, 54% reported using both tobacco and alcohol pre-OLT. In light of these prevalence data and known health risks associated with tobacco use, there is an urgent need to examine the relationship between tobacco use and OLT outcomes. Furthermore, assessment of tobacco use and the provision of treatment for nicotine dependence should be a routine part of OLT candidacy evaluations and follow-up, based on general medical risk factors and potential relevancy to patient and graft survival. (*Liver Transpl 2004;10:412–417.*)

Tobacco is a major etiological factor in heart disease, lung disease, and cancer.[1] It is also associated with poorer surgical outcomes, including vascular thrombosis, slowed wound healing, necrosis, increased infection, worse microcirculation, and compromised bone union.[2–5] However, despite its potential relevance to morbidity and mortality, tobacco use in patients undergoing orthotopic liver transplantation (OLT) is understudied. This is especially surprising in light of recent survey data indicating that 20% of programs currently view smoking tobacco as an absolute contraindication to OLT[6] (response rate of 38% of U.S. liver transplant programs).

Pungpapong et al.[7] reported that 27% of patients were actively smoking within 2 years before their pre-OLT evaluation and that 57% of patients had a lifetime prevalence of smoking. These researchers also documented a higher rate of vascular complications (especially hepatic artery thrombosis) in OLT recipients who smoked (18%) versus those that did not (8%). Potential mechanisms of tobacco-induced injury include vasoconstriction, reduced oxygenation of the blood, impaired endothelial function, and increased platelet adhesiveness. Infections may result from a combination of tobacco-induced damage of mucoid tissues and reduced cellular immune function.[8] Separate studies, such as Hardinger et al.[9] have also documented a relationship between smoking tobacco and osteoporosis in OLT patients.

There have been several studies of tobacco use among patients who have received other types of solid organ transplants. For instance, tobacco use has been found to be associated with graft loss and mortality in renal transplant patients,[10–11] graft loss in pancreas transplant patients,[12] cardiovascular disease in renal transplant patients,[13–15] and cancer in renal,[16] lung,[17] and heart[18] transplant patients. Also noteworthy is that tobacco use has been associated with lower quality of life and lower quality of life benefit gained from surgical interventions.[19–20]

Since alcohol use is highly comorbid with tobacco use in the general population,[21] a similarly high rate of comorbidity is expected in the OLT population. Accordingly, Duvoux and colleagues[22] reported that OLT recipients with alcoholic cirrhosis smoked an average of 10 more pack-years than did patients with non-alcoholic cirrhosis. The higher incidence of squamous cell carcinoma in OLT recipients with both a history of alcoholic cirrhosis and tobacco use before OLT further highlights the need to examine tobacco use in this population.[22–23]

Based on the foregoing, the primary goal of the

Abbreviations: OLT, orthotopic liver transplantation; OR, odds ratio; CI confidence interval; PPD, packs per day.

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present study is to examine pre- and post-OLT prevalence rates of tobacco use, relapse rates following OLT, and comorbid use of alcohol and tobacco. We further sought to identify factors that are associated with tobacco use and relapse.

Patients and Methods

Patients and Procedures

All procedures were approved by the University of Florida Institutional Review Board. All surviving adult patients who received OLT at the University of Florida between 1993 and 2002, for whom valid contact information was available, were invited to participate in a telephone survey of quality of life and health behaviors. Patients were first sent a letter to notify them of the upcoming recruitment call. Two hundred two patients (42%) provided oral informed consent and completed the entire data collection process. Data were collected via structured telephone interviews conducted by trained research staff. Interviews lasted 15 to 40 minutes, with a mean length of 22.1±6.4 minutes. Patients were not offered compensation for participation and were assured that the information they provided would be anonymized at the end of the interview. Only the interviewer was simultaneously aware of the patients' identity and data, and only for the duration of the interview.

In addition to clinical and demographic information, patients provided information on the frequency and quantity of their tobacco and alcohol use, both pre- and post-OLT. Prevalence estimates of tobacco use, alcohol use, and combined tobacco and alcohol use were calculated. Both parametric (i.e., *t*-test) and nonparametric, 2-sided tests (i.e., Chi square) were used to examine univariate relationships between tobacco use variables and sociodemographic characteristics. Significance was defined as P less than .05. For all analyses, SPSS for Windows 11.0 was used.

Results

Two hundred two OLT recipients completed the structured interview. Fourteen patients (7%) had received more than 1 transplant. Mean length of time from OLT to interview was 49.1±30.4 months. Mean age was 56.0±9.6 years. Sixty-three percent were male. Most patients (67%) were married (12% divorced, 9% single, 5% widowed, 4% separated, and 3% life partner), Caucasian (89%; 5% African American, 3% Hispanic, 2% Asian-East Indian, 1% White/Native American), and educated beyond high school (24% high school graduate or equivalent, 41% some college, 19% graduated college, 10% professional degree, 6% did not complete high school). Thirty-two percent were actively employed at time of interview.

Table 1. Summary of Tobacco Use

Characteristics	Value*
Lifetime history of smoking pre-OLT	120 (60)
Lifetime history of smokeless tobacco use pre-OLT	16 (8)
Packs per day, pre-OLT	
Less than 1 PPD	46 (38)
1 PPD	43 (36)
2 PPD	26 (22)
3 PPD	4 (3)
More than 3 PPD	1 (1)
Years smoked pre-OLT	18.3 ± 11.4
Pack-years pre-OLT†	24.3 ± 19.8
Quit time (months) pre-OLT	152.6 ± 143.7
Smoking at time of OLT	12 (10)
Used prescribed medication to help quit pre-OLT	8 (7)
History of smoking post-OLT	31 (15)
History of smokeless tobacco post-OLT	4 (2)
Packs per day, post-OLT	
Less than 1 PPD	21 (68)
1 PPD	8 (26)
2 PPD	2 (6)
3 PPD	0 (0)
More than 3 PPD	0 (0)
Quit pre-OLT, relapsed post-OLT	22 (7)
Used prescribed medication to help quit post-OLT	7 (23)

*Values expressed as mean ± SD or number (percent).
†Pack-years = number of packs per day × total number of years smoked.
Abbreviations: OLT, orthotopic liver transplantation; PPD, packs per day.

Using Chi square analyses, we compared the demographic characteristics of our sample to national data obtained from the United Network for Organ Sharing. Although the gender composition was comparable, our sample had a significantly larger proportion of older and Caucasian patients. Compared to the United Network for Organ Sharing population, our sample had proportionally fewer African Americans and Hispanics ($P < .05$).

Tobacco use characteristics of study patients are reported in Table 1. One hundred twenty patients (60%) reported a lifetime history of smoking cigarettes (defined as "smoking more than once or twice"). The majority (69 patients, 58%) smoked 1 to 2 packs per day, and the median pack-years for tobacco users was 20 (range: 1–104). Only 8 patients (7%) reported using prescribed medication to assist with smoking cessation. Of those with a smoking history, 38 (32%) reported smoking within 2 years before OLT and 12 patients

(10%) reported smoking at time of OLT. Patients quit a median of 120 months (range: 1–522) before transplant surgery. It is also noteworthy that 16 patients (8%) reported a history of using smokeless tobacco pre-OLT. In a univariate analysis, male gender (odds ratio [OR]: 2.06; 95% confidence interval [CI]: 1.15–3.17; $P = .015$), overweight (defined as pre-OLT body mass index > 25; OR: 1.79; 95% CI: 1.01–3.18; $P = .047$), pre-OLT alcohol use (OR: 5.82; 95% CI: 2.21–15.34; $P = .0001$), and pre-OLT drug use (OR: 2.56; 95% CI: 1.24–5.29; $P = .009$) were significantly associated with pre-OLT tobacco use.

Thirty-one patients (15% of total sample) reported smoking cigarettes post-OLT. All but 1 of these patients had a smoking history before transplantation. The majority (21 patients, 68%) smoked less than 1 pack per day post-OLT. Of tobacco users, 7 patients (23%) reported using prescribed medication to assist with smoking cessation. Four patients continued to use smokeless tobacco post-OLT. Of those patients who smoked cigarettes post-OLT, 22 (71%) returned to smoking after having quit pre-OLT (i.e., relapsed). When compared with those who remained abstinent, patients who relapsed post-OLT were more likely to consume alcohol post-OLT (OR: 1.79; 95% CI: 0.75–4.27; $P = .026$), have a shorter mean period of tobacco abstinence pre-OLT (defined as < 2 yrs; OR: 3.11; 95% CI: 1.14–8.51; $P = .021$), and have a longer smoking history (defined as ≥ 10 yrs; OR: 26.15; CI: 6.03–113.35; $P = .001$).

Alcohol use characteristics of study patients are reported in Table 2. One hundred seventy-seven patients (88%) reported a history of drinking alcohol pre-OLT. Of these patients, the majority (75%) had not consumed any alcohol within the year preceding OLT and 44 (25%) reported attending Alcoholics Anonymous or participating in an alcohol treatment program pre-OLT. In a univariate analysis, higher education (defined as some college or beyond; OR: 2.59; 95% CI: 1.07–6.28; $P = .03$) and not being medically disabled (OR: 3.52; 95% CI: 1.71–7.24; $P = .002$) were significantly associated with alcohol use in the year before OLT.

Forty-two patients (21%) reported alcohol use post-OLT. The majority (69%) had not consumed any alcohol within the past year, and no patients reported attending Alcoholics Anonymous or participating in an alcohol treatment program post-OLT. Eighteen (43%) of the patients who reported alcohol use post-OLT had a history of alcohol use during the year preceding OLT. When compared with those who remained abstinent, patients who relapsed post-OLT were more likely to have higher education (OR: 3.91; 95% CI: 1.46–10.53; $P = .013$), not be medically disabled (OR: 3.70; 95% CI: 1.76–7.80; $P = .007$), be employed (OR: 3.06; 95% CI: 1.52–6.18; $P = .004$), have consumed alcohol in the year before OLT (OR: 2.39; 95% CI: 1.16–4.93; $P = .001$), and have smoked cigarettes post-OLT (OR: 1.79; 95% CI: 0.75–4.27; $P = .026$). There was not a significant relationship between alcohol relapse post-OLT and pre-OLT smoking.

Table 2. Summary of Alcohol Use

Characteristics	Value*
Lifetime history of drinking pre-OLT	177 (88)
Drinking frequency, on average, pre-OLT	
Never had 12 or more drinks in any year of my life	25 (14)
12+ drinks in any one year, but not in year before OLT	107 (60)
12+ drinks in year before OLT, but <3 drinks per week	16 (9)
3 to 13 drinks per week in year before OLT	15 (8)
2+ drinks per day year before OLT	14 (8)
Drank alcohol in year before OLT	45 (25)
Alcoholics Anonymous or relapse prevention pre-OLT	44 (25)
History of drinking post-OLT	42 (21)
Drinking frequency, on average, post-OLT	
Never had 12 or more drinks in any year after transplant	27 (64)
12+ drinks in any one year after transplant, but not in past year	2 (5)
12+ drinks in the past year, but fewer than 3 drinks per week	10 (24)
3 to 13 drinks per week in past year	3 (7)
2+ drinks per day in past year	0 (0)
Alcoholics Anonymous or relapse prevention post-OLT	0 (0)

*Values expressed as mean ± SD or number (percent).

Discussion

In recent years, research has shown that tobacco use may have important implications for surgical and clinical outcomes.[2–5] There is further evidence that cigarette smoking may contribute to poor graft function, cardiovascular disease, and the development of secondary malignancies after transplantation.[7,10–18] Consequently, many OLT programs now require patients to stop smoking before either being wait-listed or undergoing transplant surgery.[6] However, data are scant

regarding the prevalence of tobacco use in transplant patients, both pre- and post-OLT.

In this study, we found that patients being evaluated for OLT have a higher lifetime history of tobacco use (both cigarettes and smokeless tobacco) than the general population in the United States.[24] However, our data on lifetime smoking are comparable to the 57% prevalence rate for OLT patients reported by Pungpapong et al.[7] Also, 19% of our population (36% of patients with a positive smoking history) reported smoking within the 2 years before OLT, identified[7] as a risk factor for vascular complications. The vast majority of patients in our sample had quit smoking many months or years before transplant surgery, so the lifetime prevalence data may overestimate the true scope of the problem confronting the transplant team at time of evaluation. In this study, for instance, only 10% of patients with a history of tobacco use were still smoking at the time of transplant surgery.

Perhaps the more salient finding for OLT programs is that 26% of patients in our sample relapsed to smoking after OLT. At first glance, this figure appears laudable in light of the 50% relapse rate reported for the general population. However, it is this group of patients (i.e., active smokers post-OLT) that may be at highest risk for deleterious health consequences secondary to immunosuppression. Assessing risk of relapse and providing services to facilitate abstinence post-OLT are clinical objectives for programs. Factors that were found in this study to be significantly associated with relapse include a shorter abstinence period, longer smoking history, and comorbid alcohol consumption. Relapse risk assessments of patients who have stopped smoking during the pre-OLT period should include a careful evaluation of these factors, as well as those variables commonly known to be triggers for relapse (e.g., high addiction level, stress, social celebrations, negative mood states, habitual smoking cues, low self-efficacy).

At our transplant center, we have implemented a policy that requires patients to cease tobacco use before transplant surgery. There are 3 primary reasons for this policy. First, the role of tobacco in the etiology of disease is well known and there is the possibility that OLT recipients with a smoking history are at increased risk for secondary malignancies and poorer outcomes after OLT. Second, recent evidence suggests that quitting smoking at least 2 years before OLT may significantly reduce the risk of post-OLT vascular complications.[7] Third, OLT provides a window of opportunity for patients to stop smoking at a time when they are expected to make other significant lifestyle and health behavior changes. Patients with a recent (i.e., < 6 mos.) or current tobacco use history are advised by their transplant physician to quit and subsequently referred to the transplant psychologist for evaluation, determination of intervention needs, and assessment of relapse risk.

Table 3. Surgeon General 2000: Tobacco Dependence Treatment[25]

Modality
Psychological/behavioral
Problem-solving skills training
Provision of social support within treatment
Assistance in securing external social support
Pharmacological
Nicotine replacement therapy (with detailed instructions on proper use)
Bupropion (sustained release)
Clonidine and nortriptyline (second line treatments)

In most cases at our center, patients do one or more of the following: attend our OLT program's 2-hour smoking cessation and relapse prevention workshop, complete a web-based smoking cessation program (e.g., American Lung Association's Freedom From Smoking Online), participate in individual counseling, or pharmacological intervention. In addition, patients undergo monthly random biochemical monitoring for nicotine and cotinine during the pre-OLT period. Positive findings trigger a reevaluation by the transplant psychologist and further treatment as needed.

We believe that this program is consistent with the Surgeon General's updated general guidelines for treatment of tobacco dependence.[25] Briefly, these recommendations include a systematic, repetitious approach to assessing tobacco use and providing treatment and follow-up appropriate to the patient's readiness to quit tobacco. The specific components of empirically supported treatments within these guidelines are listed in Table 3. Additionally, recent evidence suggests that physicians who receive training in providing brief smoking cessation advice experience greater success in helping their patients to quit smoking.[26] We are presently evaluating the effectiveness of our policy and intervention programs on tobacco use cessation and relapse rates in the OLT population.

Smokers with a history of alcohol dependency face unique challenges in quitting and preventing relapse to both tobacco and alcohol use. While many of our patients with a history of heavy alcohol use are required to participate in relapse prevention services pre-OLT, it is striking that none of the patients in our sample continued with such treatments after transplantation. Our

finding that some of these patients relapsed post-OLT highlights the need to continue to monitor and assess relapse risk factors during follow-up clinic appointments. In light of the cooccurrence rate of tobacco and alcohol use, return to smoking may be an important risk factor for relapse to drinking.

In addition to issues of transplant program policy and clinical management of patients who use tobacco, there is an important need for tobacco research in liver transplantation. Currently, much of our knowledge about tobacco use and its potential effects on transplant morbidity and mortality is generalized from nontransplant and other solid organ transplant populations. Most tobacco use data in transplant populations are retrospectively abstracted from medical records, recorded as a dichotomous variable, and not biochemically validated. Future studies of self-reported cessation should be assessed prospectively and validated through biochemical assay (e.g., urine cotinine levels), especially when data are not anonymized. The validity of self-report can be further improved by random lab draws. Lastly, future studies should utilize the vast amount of general literature available on tobacco assessment methodology and correlates of relapse to enhance our understanding of the impact of tobacco use on OLT outcomes and to identify the most effective strategies for maintaining a smoke-free lifestyle in OLT recipients.

Given the retrospective design of this study, the data analyses and interpretation reported herein have limitations that should be acknowledged. One of the limitations is that our data were collected from a single transplant center and the degree to which these data can be extrapolated to the larger OLT population is limited. Patients in our sample were essentially self-selected and not drawn at random and, therefore, may not be truly representative of the larger OLT population. For instance, patients who chose to participate in this study may be more actively involved in their health care and have better transplant outcomes. Compared to the United Network for Organ Sharing data, patients in this study were generally older and less ethnically diverse. Social desirability represents another limitation of this study. While we emphasized anonymity to reduce socially desirable responding, it is possible that some patients were motivated to present themselves in the most favorable light possible. Data in this study were derived entirely through patient self-report and they were not validated by review of medical records or any other sources (e.g., spouse or caregiver). The passage of time between smoking, transplant, and survey administration may contribute to under-reporting of true tobacco use. Lastly, patients who use tobacco are less likely to survive and thus are likely underrepresented in this study sample. Given these limitations, reported tobacco and alcohol use in this study should be considered as conservative estimates of true use.

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