

Tobacco Use Following Liver Transplantation for Alcoholic Liver Disease: An Underestimated Problem

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Alcohol and tobacco use commonly co-occur, with at least 90% of those with an alcohol problem also using tobacco. Thus, 3 years ago when we discovered higher rate of late deaths due to lung and oropharyngeal cancer in patients who had received a transplant for alcoholic liver disease (ALD), we hypothesized that these patients were continuing to expose themselves to tobacco after liver transplantation (post-LTX) and that this behavior was increasing their risk for cancer. We subsequently began a prospective investigation of post-LTX tobacco use in patients having undergone LTX for ALD (n = 172). For 33 recipients we had data starting from our first assessment at 3 months post-LTX and for this subgroup we report on the details of the timing of tobacco use resumption and the redevelopment of nicotine addiction. We found that on average more than 40% are smoking across all time periods. ALD recipients resume smoking early post-LTX, increase their consumption over time, and quickly become tobacco dependent. These data highlight an underrecognized serious health risk for these patients and demonstrate our need for more stringent clinical monitoring and intervention for tobacco use in the pre- and post-LTX periods. (*Liver Transpl* 2005;11:679-683.)

Four years ago we published data on an increased rate of late deaths (5 years and beyond) in patients who had undergone liver transplantation (LTX) for alcoholic liver disease (ALD) compared to others—deaths that were primarily caused by lung and oropharyngeal cancers.¹ We also found that their rates of lung cancer and oropharyngeal cancers were 4 and 25 times higher, respectively, than the general non-LTX population.¹ Although we did not have data on tobacco consumption in these recipients, our presumption that smoking contributed to these deaths was not ungrounded. Nearly 90% of alcoholics smoke,² compared with only 30% of the general U.S. population.³ However, from that study we recognized the lack of any data on post-LTX tobacco use by ALD LTX recipients or even any data on post-LTX tobacco use. To address this deficit, we began collecting tobacco use data on a cohort of ALD LTX recipients prospectively followed after LTX, and we present our findings herein.

Indeed, there is a general lack of such data, surprisingly even in more pertinent transplant populations such as heart and lung transplant, in which smoking

may have directly contributed to the original organ failure. One study of heart transplant recipients found that 50% of smokers resumed smoking after transplantation.⁴ In our study of heart transplant recipients, through repeated surveys on smoking habits we found 11% to 23% smoking across time points from 2 to 12 months after transplantation.⁷ Nagele et al.¹⁶ found 26% (22 of 84 heart transplant recipients) smoked after transplantation, with a mean cigarette consumption of 11 cigarettes per day. A recent cross-sectional telephone survey of all LTX recipients at the University of Florida (42% of potential subjects) found 15% smoking after LTX, with the majority smoking less than 1 pack per day.⁹

Our goal was to examine the prevalence of tobacco use, the quantity and frequency of tobacco use, and redevelopment of nicotine addiction in our ALD LTX cohort.

Patients and Methods

Subjects

All patients who underwent transplantation for ALD at the Starzl Transplant Institute from May 1998 to July 2003 were eligible for the study. At the time of enrollment, patients needed to be at least 3 months post-LTX and discharged from the medical facility. After agreeing to participate and signing informed consent forms, they were voluntarily enrolled in our study. During the period of study recruitment, 223 liver transplant recipients had either a primary or secondary diagnosis of ALD. Of these 172 participated (33 died before enrollment, 14 refused to participate, and 4 were too ill to be enrolled, e.g., still hospitalized or in a nursing home).

The pre-LTX diagnosis of ALD was determined by a consensus diagnosis from interviews and examinations by our

Abbreviations: LTX, liver transplantation; ALD, alcoholic liver disease; FTND, Fagerström test for nicotine dependence.

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Table 1. The Fagerström Test For Nicotine Dependence*

Question	Answers	Score
How soon after you wake up do you smoke your first cigarette, (cigar, pipe)?	Within 5 minutes	3
	6-30 minutes	2
	31-60 minutes	1
	>60 minutes	0
Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in a cinema)?	Yes	1
	No	0
Which cigarette, (cigar, pipe) would you hate most to give up?	First one in the morning	1
	Others	0
How many cigarettes, (cigars, bowls) per day do you smoke?	<10	0
	11-20	1
	21-30	2
	>31	3
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

* Scores are totaled to a single value with scores >3 indicating nicotine dependence.

transplant surgeons, hepatologists, and psychiatry team (psychiatric nurse clinical specialist [M.G.F.] and psychiatrist [A.D.]). Psychiatric diagnoses of alcohol dependence or alcohol abuse were also made by the psychiatry team during this evaluation. Patients with ALD had a history of excessive alcohol use defined as >20 grams of ethanol a day for women or >60 grams of ethanol a day for men,¹⁰ and the majority had consumed this amount for 10 years or longer.

Procedures

Data on post-LTX tobacco use were gathered through 2 instruments: the Fagerström test for nicotine dependence (FTND) and the Smokeless Tobacco Use (chewed tobacco or snuff) version of the Fagerström. The FTND was added to the post-LTX questionnaires in April 2002. Participants complete questionnaires about their health habits in a repeated fashion, every 3 months for the first post-LTX year and every 6 months thereafter to quantify their ongoing tobacco use and to determine whether they achieved a diagnosis of nicotine dependence. Participants enrolled in the study before April 2002 began completing the FTND at their next scheduled interview. These instruments are widely used in studies of tobacco use and tobacco cessation to both identify nicotine dependence and quantify the severity of the addiction. Six items capture features of dependence, including highly controlled or compulsive use and difficulty refraining from smoking/chewing, as well as quantity and frequency of use (numbers of cigarettes smoked per day or tins per week). The item scores of the FTND are summed for a maximum total score of 10. Scores >3 indicate nicotine dependence (see Table 1 for items and scoring of FTND). The FTND has high test-retest correlations with positive correlations between items. Cronbach's alpha coefficient of internal consistency is 0.64.¹⁷

All candidates are strongly advised to discontinue tobacco use in preparation for LTX if they had not already done so, although continued tobacco use has not been a reason to preclude a candidate. Although we do not know if or for how long recipients may have discontinued tobacco use before LTX, no recipient was allowed to smoke during the LTX hospitalization and thus all had at least a 7-day period of nonconsumption.

Statistical Analysis

Continuous variables are presented as the mean \pm standard deviation, and categorical variables as proportions. For specific time points after LTX, tobacco use is presented as point prevalence. For those participants on whom we have data starting from 3 months after LTX ($n = 33$) we performed life tables analysis to present data of the onset of tobacco use after LTX and the timing of development of nicotine dependence. The cross-tabulation procedure was used to test associations between categorical variables (χ^2 reported). All analyses were performed using the Statistical Package for Social Sciences for Windows software (version 11.0; SPSS, Chicago, IL).

Results

Demographics

The cohort was predominately male (86%), which is typical for ALD. Ages ranged from 32 to 72 years old (51 ± 8 years). The majority (95%) were Caucasian, with 5% African American. A total of 53% were married, 21% divorced, 11% single, 5% widowed, and 10% other (engaged, separated, etc.). A total of 83%

Table 2. Point Prevalence of Smoking at Time Points After LTX	
Month after LTX (n)	Percent smoking
3 (33)	48%
6 (40)	55%
9 (43)	49%
12 (47)	47%
18 (26)	58%
24 (25)	40%
30 (26)	39%
36 (31)	39%

had at least graduated from high school and 35% had some college education (13% had a bachelor's degree or higher). A total of 75% worked in nonprofessional jobs prior to LTX. In addition to having ALD, 54% of our cohort were infected with hepatitis C virus and/or hepatitis B virus. A total of 75% met psychiatric diagnostic criteria for alcohol dependence (the more severe form of an alcohol use disorder). Our cohort is demographically similar both to many prior studies of patients transplanted for ALD^{5,12,15} and to a prior study of ALD recipients at our center.²⁰

Tobacco Use Outcomes

Nearly 40% or more of ALD LTX recipients were smoking across all time points (see Table 2 for the point prevalences at each specific time point). A total of 5% used smokeless tobacco. The majority of smokers (88%) smoked cigarettes, 12% smoked pipes or cigars. Most smokers smoked daily (90%) and smokeless tobacco users also mostly used daily (81%). Of those who chewed tobacco, 94% used less than 10 chews a day with 69% keeping the chew in their mouth for 30 minutes or less. Most tobacco chewers chewed 2 or less tins (pouches) per week. Nearly 50% of those who smoked at all after LTX were dependent on nicotine (score >3 on the FTND), and 53% of those who were first nondependent became nicotine dependent over time.

Those patients for whom we had continuous data from the first 3-month assessment (n = 33) were plotted as a "survival curve" to identify the onset of tobacco use (Fig. 1). It is clear that smokers resume smoking quickly after LTX, most having restarted smoking by 3 months after LTX. In this group the rate of smoking by 1 year after LTX was 61%, representing a true rate compared to point prevalences. Additionally, we could examine the changes in tobacco use and development of nicotine dependence in this subgroup. Figure 2 shows

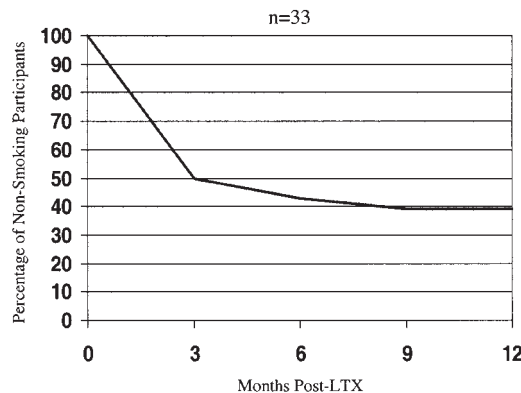


Figure 1. Rate of smoking after LTX.

that of those who resumed smoking, 60% became nicotine dependent by 9 months after LTX. In addition, consumption patterns of nicotine increase over the first year, from smokers using mostly less than one-half a pack of cigarettes at 3 months after LTX to mostly using more than one-half to a pack of cigarettes per day (Fig. 3).

We investigated associations between post-LTX smoking and demographic and medical characteristics (Table 3). While none of the demographic variables were associated with smoking, recipients with hepatitis B virus/hepatitis C virus were more likely to smoke after LTX as were those with a history of other (nonalcohol) substance use prior to LTX. Recipients with a pre-LTX diagnosis of alcohol dependence were also more likely to smoke after LTX. We also looked at the association between those with depressive symptoms at their first assessment (determined by a score on the Beck Depression Inventory of 19 or higher) and post-LTX tobacco use. Although depression and smoking often co-oc-

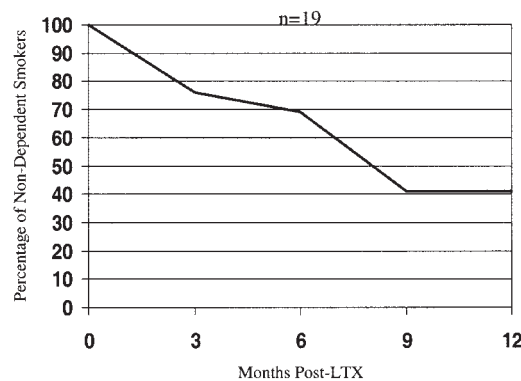


Figure 2. Development of nicotine dependence in smokers after LTX.

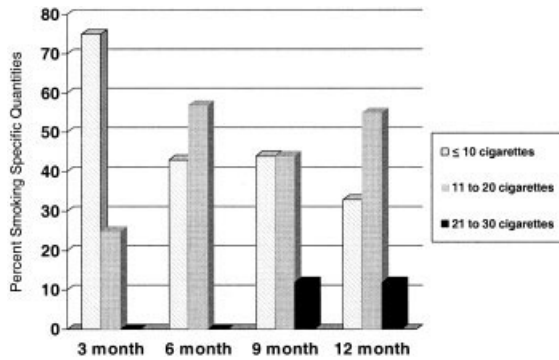


Figure 3. Change in number of cigarettes smoked per day.

cur,¹³ we found no association between depressive symptoms and smoking (Table 3).

Conclusions

These results show a disturbing trend in our ALD population; that a significant percentage (39%-58% across time points) use tobacco after LTX. ALD LTX recipients resume tobacco consumption early on, typically smoke daily in increasing amounts over time, and quickly become nicotine dependent. This statistic compares unfavorably to statistics at multiple U.S. transplant programs showing only 10% to 15% of ALD LTX recipients drink in either a heavy or dependent fashion after LTX.^{8,10,11} That Ehlers et al. found 15% of LTX recipients smoking is most likely due to their use of all LTX recipients, not just ALD LTX recipients.⁹

Furthermore, a 1993 survey of practices at trans-

plant programs around the United States showed only 2.6% of heart transplant programs felt current cigarette use was an absolute contraindication to transplantation, while at the same time 81% of LTX programs felt heavy alcohol use was an absolute contraindication.¹⁴ Interestingly, at that time no LTX program felt current tobacco use was an absolute contraindication to LTX.¹⁴ Thus, while the field of transplantation has significantly impacted the post-transplantation use of alcohol through selection practices, pre-transplantation requirements, and policies, we are lacking in a concerted approach to tobacco use.

Most prior studies of tobacco use in transplant patients have shown the significant persisting health risks of *pre*-transplantation tobacco use on *post*-transplantation health outcomes.^{6,18,19} For example, Pungpapong et al. found a higher rate of vascular complications in liver transplant recipients with a history of smoking (17.8% vs. 8%; $P = 0.02$).¹⁸ Those who quit smoking 2 years prior to transplantation reduced the incidence of vascular complications by 58%.¹⁸ In one study of heart transplant recipients, those who smoked after transplantation had a higher rate of vasculopathy, a higher rate of malignancies ($P = 0.0001$), and significantly worse survival compared with nonsmokers.¹⁶ After 11.5 years after transplantation no smokers were alive compared with 80% of nonsmokers.¹⁶

Our data are unique in that we have prospective repeated measures of post-LTX tobacco consumption, including quantity, frequency, and duration of use. In addition, we have identified associations between post-LTX smoking and those with a prior substance use history and those with hepatitis C virus/hepatitis B virus (these risk factors most likely representing similar

Table 3. Associations Between Post-LTX Smoking and Other Variables

	Smoking	Nonsmoking	χ^2
Demographic			
Age (% <50 years old)	45	45	.01
Gender (% male)	80	87	1.65
Education (% < high school)	45	57	2.40
Work (% nonprofessional)	76	75	.01
Medical			
Alcohol diagnosis (% dependent)	82	70	4.14*
Other substance (% with pre-LTX use)	49	34	3.75†
HCV/HBV (% with either virus)	64	47	4.96‡
Post-LTX depression (% nondepressed)	85	89	.53
* $P = 0.04$.			
† $P = 0.05$.			
‡ $P = 0.026$.			

groups). These results are consistent with a recent large epidemiologic study showing increased odds of having nicotine dependence and an alcohol dependence disorder (odds ratio 6.4) or other drug dependence (odds ratio 15.9).¹³ Although the odds of having a major depression are 3 times more likely for those with nicotine dependence than those without,¹³ we did not find an association between symptoms of depression and post-LTX smoking in our cohort. As our prospective study continues, we plan to investigate the associations between tobacco consumption to morbidity and mortality after LTX (including cardiovascular events as well as cancer).

Considering all associations between tobacco use and poor health outcomes, tobacco use may well outweigh alcohol use for impact on post-LTX morbidity and mortality. Tobacco use has become the next compelling issue for LTX candidates and one of the most important indications for treatment after LTX.

References

- Jain A, DiMartini A, Kashyap R, Youk A, Ronal S, Fung J. Long-term follow-up after liver transplantation for alcoholic liver disease under tacrolimus. *Transplantation* 2000;70:1335-1342.
- Burling TA, Ziff DC. Tobacco smoking: a comparison between alcohol and drug abuse inpatients. *Addict Behav* 1988;13:185-190.
- SAMHSA. Findings from the 2002 National Survey on Drug Use and Health, Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA), Office of Applied Studies, National Survey on Drug Use and Health, 2002. Available at: <http://www.samhsa.gov>. Accessed: January 28, 2005.
- Bell M, Van Trigt P. Addictive behavior patterns in cardiac transplant patients. *J Heart Lung Transplant* 1991;10:158.
- Belle SH, Beringer K, Detre KM. Liver transplantation for alcoholic liver disease in the U.S. 1988-1995. *Liver Transpl Surg* 1997;3:212-219.
- Cosio FG, Falkenhain ME, Pesavento TE, Yim S, Alamir A, Henry ML, et al. Patient survival after renal transplantation: II. The impact of smoking. *Clin Transplant* 1999;13:336-341.
- Dew MA, Kormos RL, Roth LH, Moralis S, DiMartini A, Griffith BP. Early post-transplant medical compliance and mental health predict physical morbidity and mortality one to three years after heart transplantation. *J Heart Lung Transplant* 1999;18:549.
- DiMartini A, Day N, Dew M, Lane T, Fitzgerald MG, Magill J, Jain A. Alcohol use following liver transplantation: a comparison of follow-up methods. *Psychosomatics* 2001;42:55-62.
- Ehlers SL, Rodrigue JR, Widows MR, Reed AI, Nelson DR. Tobacco use before and after liver transplantation: a single center survey and implications for clinical practice and research. *Liver Transpl* 2004;10:412-417.
- Everson G, Bharadhwaj G, House R, Talamantes M, Bilir B, Shrestha R, et al. Long-term follow-up of patients with alcoholic liver disease who underwent hepatic transplantation. *Liver Transpl Surg* 1997;3:263-274.
- Fireman M. Outcome of liver transplantation in patients with alcohol and polysubstance dependence. Presented at the Symposium on Liver Transplantation for the Alcohol Dependent Patient, Research Society on Alcoholism; Denver, CO. June, 2000.
- Gish RG, Lee AH, Keefe EB, Rome H, Concepcion W, Esquivel C. Liver transplantation for patients with alcoholism and end-stage liver disease. *Am J Gastroenterol* 1993;88:1337-1342.
- Grant BF, Hasin DS, Chou P, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States. *Arch Gen Psychiatry* 2004;61:1107-1115.
- Levenson JL, Olbrish ME. Psychosocial evaluation of organ transplant candidates: a comparative survey of process, criteria, and outcomes in heart, liver and kidney transplantation. *Psychosomatics* 1993;34:314-323.
- Lucey MR, Merion RM, Henley KS, Campbell DA Jr, Turcotte JG, Nostrant TT, et al. Selection for and outcome of liver transplantation in alcoholic liver disease. *Gastroenterology* 1992;102:1736-1741.
- Nagele H, Kalmar P, Rodiger W. Smoking after heart transplantation: an underestimated hazard? *Eur J Cardiothorac Surg* 1997;12:70-74.
- Pomerleau CS, Carton SM, Lutzke ML, Flessland KA, Pomerleau OF. Reliability of the Fagerström Tolerance Questionnaire and the Fagerström Test for Nicotine Dependence. *Addict Behav* 1994;19:33-39.
- Pungpapong S, Manzarbeitia C, Ortiz J, Reich DJ, Araya V, Rothstein KD, Munoz SJ. Cigarette smoking is associated with an increased incidence of vascular complications after liver transplantation. *Liver Transpl* 2002;8:582-587.
- Sung RS, Althoen M, Howell TA, Ojo AO, Merion RM. Excess risk of renal allograft loss associated with cigarette smoking. *Transplantation* 2001;71:1752-1757.
- Tringali RA, Trzepacz PT, DiMartini A, Dew MA. Assessment and follow-up of alcohol-dependent liver transplantation patients. *Gen Hosp Psychiatry* 1996;18(Suppl):S70-S77.