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Phosphatidylethanol (PEth) detects moderate to heavy alcohol use in liver transplant recipients

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Abstract

Background—Alcohol dependent liver transplantation (LT) patients who resume alcohol are at risk for a number of alcohol related problems including liver injury and liver failure. Post LT patients are strongly advised to remain abstinent. However, we don't know how well this population complies due to a lack of valid methods (self-report and/or biomarkers) to identify alcohol use. Studies suggest as many as 50% resume alcohol use within 5 years. Phosphatidylethanol (PEth) is a new cell-membrane phospholipid biomarker to identify alcohol use in the past 28 days. This prospective study followed 213 LT recipients at two US liver transplant centers.

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Authors' contributions: MF obtained funding for this study through the Department of Human Services and Public Health. The transplant teams at University of Wisconsin and Northwestern Feinberg School of Medicine recruited, consented and performed all data collection (Blood samples and interview subjects) for the study. The remaining Northwestern University staff: Michael Fleming, Matthew Smith, and Erika Oslakovic organized and edited data, performed the statistical analysis, and drafted manuscript.

Methods—Sample included 213 LT subjects. 70.9% (n=151/213) had a history of alcohol dependence prior to transplantation and 29.1% (n=62/213) served as non-alcohol dependent controls. Subjects participated in face-to-face interviews to assess alcohol use using a 30-day calendar. The protocol called for collecting blood samples at baseline, 6- and 12-month follow-up.

Results—70% (149/213) who reported no alcohol use had consistently negative PEth levels (<8ng/ml). A total of 26.4% (57/213), 44 alcohol-dependent patients and 13 controls, had a positive PEth test of ≥8 ng/ml either at baseline and/or during the follow-up period. 23.8% (n=36/151) alcohol-dependent subjects and 16.1% (n=10/62) controls reported no alcohol use but had at least one positive PEth test. Of the 11.2% (24/213) post LT subjects who reported recent alcohol use over half (11/24) had a positive PEth. The 13 self-reported alcohol users with a negative PEth level reported insufficient drinking to trigger PEth formation.

Conclusions—Adoption of PEth as part of routine post-transplant care of LT recipients will enable early identification of patients at risk of alcohol use and facilitate abstinence in patients with a history of alcohol dependence and alcohol related liver damage.

Keywords

Liver transplant; Alcohol use; PEth biomarker

Introduction

Over the last 10 years, 15% of all liver transplants in the United States have been provided to patients with a history of alcohol use disorder (AUD), with most of these patients having a primary diagnosis of alcohol-associated liver disease (ALD). Patients who are alcohol-dependent who receive a liver transplant agree to stop alcohol use for the remainder of their life (Lucey, 2014). Typically, as part of the pre-transplant evaluation, transplant programs undertake careful screening of risk factors for post-transplant drinking, with the goal of selecting patients with an acceptable prognosis for long-term abstinence from alcohol. Despite the efforts of transplant programs to discriminate in favor of patients with a low risk of alcohol relapse, prospective studies suggest that up to 50% of these highly-selected patients with AUD will use alcohol in the first five years after transplant, and 20% will resume harmful drinking (DiMartini et al., 2006, 2010).

The relationship of alcohol use to clinical outcomes in post-transplant patients is complex. There are multiple factors associated with the documented increase in 5–10 year mortality rates for ALD patients who return to heavy drinking patterns. Pageaux (2003) followed a sample of 128 LT subjects for a mean follow-up of 53.8 months with 21 percent resuming heavy drinking. Of the seven deaths that occurred in the heavy drinking group three died as a direct of their resumption of alcohol use. Faure (2012) reported that out of 441 liver transplant patients (206 subjects had ALD as primary indication for transplantation) persistent alcohol use occurred in 43.7% patients with primary indication ALD, and 24.3% in non-ALD patients. Survival was 49% at 10 years for patients with excessive alcohol relapse, compared to 75% who did not resume drinking. The majority of deaths were related to liver failure, cancer and cardiovascular events.

The largest long-term outcome study to date was conducted on behalf of the European Liver Transplant Center with a sample of 9,988 patients who received a liver transplant from 1988–2005 (Burra et al., 2010). While patients with a primary diagnosis of Alcohol Liver Disease had improved five-year survival compared to patients with hepatitis induced liver disease, the differences reversed at 10 years in patients who relapsed. Causes of death include higher rates of cancer and cardiovascular disease, which the authors of the European study suggesting tobacco use as the causal factor in many of these deaths. The effects of non-compliance with immunosuppressive medication, poor follow-up, genetics and other comorbid disorders also complicates our understanding of the assumed mechanistic role of alcohol use on adverse outcome in the post transplant period.

Assuming the identification and treatment of any alcohol use in liver transplant patients is the norm, there are a number of alcohol biomarkers in current use to supplement and confirm patient and family member self-report alcohol use. These include BAC, GGT and CDT. All of these markers, however, have significant clinical limitations and none are considered standard of care in transplant centers. For example the half-life of Blood Alcohol Levels is too short. Gamma glutamyl transpeptidase (GGT) is an indirector marker of alcohol use and is primary marker for liver inflammation by dozens of drugs, diseases and infections. Another marker in current use and FDA approved is carbohydrate-deficient transferrin (CDT). While it can be falsely elevated in female recipients and patients with liver disease (Fleming et al., 2000) it can be of some help in healthy subjects. While no alcohol marker is considered standard of care in transplant centers (Lucey, 2016) Phosphatidylethanol (PEth) offers many advantages over other biomarkers and is the subject of this report.

A study reported by Wurst and colleagues (2010) at three settings in Europe, in a sample of 57 alcohol dependent patients during detoxification, reported the following sensitivities – PEth 100%, MCV 40%, GGT 73%, CDT 69. A recent systematic review of 58 studies and meta-analysis of 12 by Veil and colleagues (2012) found that PEth was a sensitive and specific alcohol biomarker. Stewart reported high sensitivity and specificity in a sample of 212 drinking patients with liver disease who had PEth levels >8ng/ml (Stewart et al., 2014).

The goal of the study was to determine the frequency of a positive PEth level in a sample of liver transplant patients with a history of alcohol dependence and a non-alcohol-dependent control sample. Second, we compared self-reported drinking, and physician assessment of return to drinking with PEth levels. *To the best of our knowledge there have been no previous reported PEth studies in a large sample of post-liver transplant patient's. Previous work in the post transplant population has been limited to other biomarkers such as GGT, CDT and EtG* (Staufer et al., 2011).

Methods

We conducted a prospective study of LT recipients at two US transplant centers located in Chicago, Illinois and Madison, Wisconsin. The primary aim of the study was to assess the clinical utility of PEth as an indicator of recent drinking by LT recipients. The study enrolled a convenience sample of 151 LT recipients with a history of alcohol dependence prior to

their transplant and a control sample of 62 recipients with no history of an alcohol use disorder. The study was conducted from 2012–2015 and was approved by the Institutional Review Boards at the University of Wisconsin, Madison and Northwestern University Feinberg School of Medicine.

The primary inclusion criterion was a history of liver transplantation, one year or more before study entry. Alcohol use in the past 30 days was assessed using the traditional calendar time line follow back method developed by Sobell (1992). Research staff asked each subject about use of alcohol during each study visit, by using reminder cues such as weekend activities, special events, holidays, and family activities to minimize recall bias. Patients were told the information was confidential and their responses would not be shared with any clinical members of the research team, nor with the transplant program personnel. Additional variables of interest transcribed from the pre-transplant evaluation included underlying diagnosis of liver disease, gender, age, race, history of using tobacco or illicit drugs. *In addition to the baseline interview and PEth tests subjects were expected to participate in a 6 and 12-month follow-up interview and PEth. There was variable success in obtaining follow-up samples due to driving distance from the clinic, co morbid medical problems and transportation challenges.*

The laboratory procedure for phosphatidylethanol (PEth) analysis used dried blood spot samples from finger picks. Specimens were analyzed at United States Drug Testing Lab (USDTL) in Chicago Illinois using a previously published method (Gnann et all,2009; Nalesso et al,2011; Faller et al 2011;Zheng et al 2011). *PEth has been found to be stable as dried sample for more than 28 days* (Bakhiereva et al 2016; Kummer et al 2016). Three standard blood spot punches (3.1mm) are prepared for each dried human blood spot specimen, calibrator, and control. The punches are extracted with methanol (1 mL), evaporated under a stream of nitrogen, and the residues are reconstituted in 0.5 mL of mobile phase A (20% 2 mM ammonium acetate: 58% acetonitrile: 22% isopropanol). Separation is achieved with an Agilent Zorbax Eclipse Plus (50 mm × 2.1 mm, 1.8 mm particle size) C-8 column held at 30 °C using an Agilent 6460 liquid chromatography-tandem mass spectrometry (LC-MS/MS) as the detector.

The chemical name for PETh is 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanol. The method monitors a single isomer of PEth (palmitoyl/oleoyl), which is the most prevalent PEth species. The laboratory reports levels of the PEth 16:0/18:1 isoenzyme (Jones et.al, 2011). The limit of detection is 2 ng/mL, the limit of quantitation is 8 ng/mL, and the assay is linear up to 800 ng/mL. For the purpose of this study a positive PEth test is defined as 8 ng/ml or above. *Stewart's work showed that a PEth level of 8 ng/ml had a sensitivity (79%) for any reported alcohol use and 98% for 4 or more drinks per day*. (Stewart et al. 2014)

The data were entered at each transplant research team site into a REDCap database while maintaining a back-up hard copy of the research interview. Data collection and management was completed using Research Electronic Data Capture (REDCap) tools hosted at each site (Harris et al., 2009). REDCap is a secure, Web-based application designed to support electronic data capture for research studies. The data was cleaned and data discrepancies were resolved using the back-up hard copies. The analysis was limited to descriptive

statistics. We elected to only report the baseline level of alcohol use (see table 2) as the 6 and 12-month levels were similar in subjects who participate in the follow-up tests. We reported all patients who had a positive PEth level at baseline, 6 or 12 months. While most patients with a positive test did so at baseline there were some who only had a positive test at 6 and/or 12 months. In table 3, we included all patients with a positive test even if the test was only positive at one time point. We didn't conduct a sensitivity and specificity analyses of PETh in this sample due to extreme minimization of alcohol use in this population and a literature base of studies that have established a PETh specificity of 100% and sensitivity of 90% or better in heavy drinking populations (Veil et al.,2012; Stewart et al.,2014).

Results

As noted in Table 1, the sample consisted of 213 patients who were more than one-year post-LT. The majority of the sample lived in Wisconsin or Illinois. There were more males with an average age of 59 and more African Americans in the alcohol dependent group. Of the 151 alcohol-dependent subjects, 13 had other primary causes for liver failure such as hepatitis C viral (HCV) infection. There were also eight patients in the control group, who did not meet criteria for alcohol dependence at the time of transplant, who had evidence of alcohol-related disease and cirrhosis after LT. They were placed in the control group for this study based on pre-LT evaluation by an addiction medicine specialist.

Table 2 lists self-reported drinking in the two groups. As noted, only 14.5 % of the controls and 8.6 % of alcohol dependent subjects reported use of alcohol at baseline. Among the subjects who reported use of alcohol at baseline, modest amounts of consumption were typical. Only six subjects reported drinking more than six drinks in the past 30 days. At the extreme end of the spectrum of alcohol use, two alcohol dependent subjects reported they had six or more days of drinking in the past 30 days.

Table 3 reports the frequency of a positive PEth testing in the sample. In the control group, we observed 13 subjects with a positive PEth test, of which only three reported recent alcohol use. In the alcohol-dependent group, we observed a total of 44 positive PEth tests. Only eight of these 44 subjects admitted they used alcohol in the past 30 days. The mean PEth level varied by group with the 10 positive controls, who did not report recent alcohol use, with the lowest mean PEth level of 17.6 (SD=9.2) ng/ml and the alcohol dependent group who reported drinking with the highest mean level of 169 (226.3 SD) ng/ml.

We also asked each subject's post-LT physician whether they thought that the individual subject had drunk alcohol recently. This data was collected by medical record reviews. Recent alcohol use was reported on 12 of the subjects with an even distribution of subjects in the control and alcohol dependent groups. There was no significant correlation between physician medical record data on either self-reported subject alcohol use or PEth levels.

Discussion

First discovered by Alling in 1984, PEth is a unique phospholipid formed from phosphatidylcholine present in the membranes of red blood cells. Phospholipase D normally converts phosphatidylcholine to phosphatidic acid. Human red blood cells do not have the

enzymatic machinery to efficiently degrade PEth, causing the accumulation of PEth in the cellular membranes following exposure to ethanol (Gustavsson and Alling, 1987). The natural decomposition of PEth results in a slow elimination, with a half-life of approximately 4 days in adults and PEth detectable in blood for up to 28 days following the last drinking episodes (Wurst et al., 2010). PEth has been shown to be a sensitive and specific marker of repeated intake of high amounts of alcohol (Veil et al., 2012), with some evidence for the correlation between alcohol intake and concentration of PEth in blood PEth is produced as soon as alcohol is consumed and is detectable for 24 hours after a single drinking episode of >4 standard drinks.

Research suggests that PEth is 100% specific and detects more than 90% of moderate to heavy drinkers (Viel et al., 2012). Moreover, PEth can remain elevated for up to 28 days after the last drink with repeated episodes of drinking. In one recent study, PEth was detectable in 93% of subjects consuming an average of 2 or more drinks per day. PEth can be measured on a blood spot collected on dried blood spot filter paper cards. Using this method, the blood sample is stable at room temperature for more than 28 days (Bakhiereva et al., 2015). Thus, PEth, when measured using a sensitive liquid chromatography-tandem mass spectrometry assay (Jones et al, 2011), is a sensitive indicator of moderate alcohol consumption (Kechagias et al., 2015; Stewart et al.,2009,2014)

In his 2014 article Stewart found that “in subjects with quantifiable PEth, the relationship between PEth concentration and alcohol use did not depend on gender, age, or liver disease severity” and that his “results suggest that the validity of PEth remains high regardless of age, gender and liver disease severity.” In this study at the limit of quantitation (PEth 20 ng/ml), PEth was 73% sensitive and 96% specific for any drinking in the past month. The subjects who reported 30-day abstinence but with quantifiable PEth either reported heavy drinking within the past six weeks or medical record data that suggested underreported drinking.

In the absence of a gold standard there remains some question on potential false positive PEth levels as has been found with indirect markers such as CDT. The issue of PEth formation in the absence of recent ethanol intake or formation by other factors has been studied extensively in animal, invitro RBC exposure and clinical studies. None of these studies have found any PEth formation in the absence of ethanol. Phospholipase D is unable to convert phosphatidylcholine into PEth without the presence of ethanol (Frohman 1999, Gustavsson et al.,1987, 1990, 1991; Kobayashi et al., 1987; Ludqvist et al.,, 1994; Metz et al.,1991, Stewart et al.,2014). There remain additional questions, however, regarding PEth levels and duration of detection that may be affected by individual metabolism of ethanol, genetic differences and unknown mechanisms.

The clinical implications of light and social drinking in post-transplant patients is unclear particularly in patients where ALD was not the primary reason for the liver transplant. As noted in our study a significant number of controls who received a liver transplant for viral hepatitis, hepatic cancer, drug toxicity etc. had positive PEth levels. Since not a single study had demonstrated a clinical benefit to alcohol use following liver transplantation it seems obvious that it isn’t worth the risk to the individual or society. However one can make the

argument from the other side of the argument that until we demonstrate measurable effects to 1–2 drinks a few times a month why should physician encourage total abstinence. With the advent of biosensors on the back of watches (continuous use, NIAAA 2016), PEth (28 days) and EtG (past 90 days, Staufer et al., 2011) in nails a long term study of post-transplant to address this question is now possible and potentially establish the relative risk of varying levels of alcohol use in this population (1.0 or no risk? 1.5? 2.0?). We also need more data on tobacco use associated with alcohol use and its relationship to laryngeal and esophageal malignancies that are a major cause of death in ALT transplant patients.

The use of biomarkers to confirm abstinent self-report both before and after liver transplant is more than a clinical issue. While the direct effects of social drinking on the long-term survival of transplant patients remains unclear, except in the case of the patient who resumes dependent patterns of alcohol use (Dumortier et al., Rice et al., 2013) physicians have a social contract to do everything possible to minimize loss of any transplant even one. Someday if livers are available to all people who need one the recommendation for complete abstinence could be revisited in patients who receive a transplant for ALD.

The most striking observation in the present study was that PEth revealed an unexpected frequency of clandestine drinking. Borrowing from a previous study of treatment of AUD in the setting of LT, we adopted a study model to encourage a candid admission of alcohol use by the study subject, by creating a firewall between the study responses and the transplant program (Weinrieb et al., 2011). Despite this protection of the confidences that our subjects might have shared, many patients denied drinking while having positive PEth. Indeed, the extent of covert alcohol use was surprising, with 29% of alcohol dependent patients having a positive PEth, the great majority of whom (91.4%) reported being abstinent from alcohol. At the same time, the managing physician usually was unaware of the patients drinking, emphasizing the limitations of physician enquiry as a means of identifying the at-risk post-LT population.

The drinking behavior described in this prospective study occurred after the LT recipient was advised by their treating physician to stop drinking alcohol. This begs two questions: 1) why are these patients not abstinent? and 2) Why are they hiding their drinking? Regarding the first question, one possibility is that the patients had not received a clear message to stop drinking, or had poor recollection of that advice, as has been reported (Tang et al., 1998). This possibility reinforces the need for patients to receive explicit directions regarding the expectation for long-term abstinence. Moreover, our results suggest that important changes in health care policy could focus on including an ‘abstinence contract’ in the pre-LT evaluation process. However, we think there is a greater likelihood that alcohol-dependent patients in our study were aware that they need to remain abstinent.

Regarding the second question about patients hiding their drinking, we know that LT recipients with a history of alcohol dependency who return to alcohol use are often reticent about their drinking, either out of shame or for fear of disapproval by the transplant team, or fearful of the loss of privileges such as access to retransplantation were it to become indicated. This issue has been called the ‘risk of candor’ (Weinrieb et al., 2000). We are less

clear as to why non-dependent LT recipients should deny alcohol use, other than to speculate that this behavior reflects a fear of a punitive action by the transplant team.

Our study was not designed to describe the consequences of clandestine alcohol use in LT recipients. The value of an effective biomarker is that it provides an opportunity to open a dialogue with the patient, to explore their reasons for drinking, and to encourage entry into treatment for alcohol use disorders. We are not able to say whether the subgroups of dependent and non-dependent covert drinkers progressed to overt and/or harmful drinking. Similarly, we cannot determine whether we would have been successful in guiding our covert drinkers into treatment for addiction, nor whether such an intervention would be accompanied by successful cessation of alcohol use.

In summary, our study suggests that PEth is a useful biomarker to identify mild-to-moderate alcohol use by LT recipients, and that drinking behavior is often hidden from the patient's transplant team. PEth is quickly becoming the standard alcohol use detection test of drunk driver programs, professional impairment programs, alcohol treatment studies and medication interactions in clinical care. While some medical insurance companies don't reimburse for alcohol biomarkers, the test is <$100. PEth levels are a fraction of the cost for many transplant related laboratory tests. Future studies will be directed at linking identification of covert drinking with strategies to establish abstinence.

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Abbreviations

LT	Liver transplantation
PEth	Phosphatidylethanol
AUD	alcohol use disorder
ALD	alcohol-associated liver disease
USDTL	United States Drug Testing Lab
GGT	gamma glutamyl transpeptidase
BAL	blood alcohol level
CDT	carboxy- deficient transferrin

References

Bakhiereva L, Shrestha S, Gutierrez HL, Berry M, Schmtt C, Sarangarm D. Stability of PEth in dry blood spot cards. Alcohol and Alcoholism. 2015; 51(3):275–280. [PubMed: 26519350]

Burra P, Sensolo M, Adam R, Delvert V, Karan V, Germani G, for ELITA and of behalf of ELTR Liver Transplant Centers Liver. Transplantation for Alcoholic Liver Disease in Europe: A Study from the ELTR (European Liver Transplant Registry). American Journal of Transplantation. 2010; 10:138–148. [PubMed: 19951276]

DiMartini A, Day N, Dew MA, Mary Grace Fitzgerald MG, Ashok Jain A, Fung JJ, Fontes P. Alcohol Consumption Patterns and Predictors of Use Following Liver Transplantation for Alcoholic Liver Disease. Liver Transplantation. 2006; 12:813–820. [PubMed: 16528710]

DiMartini A, Dew MA, Day N, Fitzgerald MG, Jones BL, DeVera M, et al. Trajectories of alcohol consumption following liver transplantation. American Journal of Transplantation. 2010; 10(10): 2305–12. [PubMed: 20726963]

Dumortier J, Dharancy S, Cannesson A, Lassailly G, Rolland B, Pruvot F-R, et al. Recurrent alcoholic cirrhosis in severe alcoholic relapse after liver transplantation: a frequent and serious complication. The American journal of gastroenterology. 2015; 110(8):1160–6. [PubMed: 26169514]

Faller A, Richter B, Kluge M, Koenig P, Seitz HK, Thierauf A, et al. LC-MS/MS analysis of phosphatidylethanol in dried blood spots versus conventional blood specimens. Anal Bioanal Chem. 2011; 401(4):1163–6. [PubMed: 21743983]

Faure S, Herrero A, Jung B, Duny Y, et al. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. Journal of Hepatology. 2012; 57:306–312. [PubMed: 22521352]

Fleming MF, Anton RF, Spies CD. A review of genetic, biological, pharmacological and clinical factors that affect carbohydrate-deficient transferrin levels. Alcohol Clin Exp Res. 2004; 28(9): 1347–1355. [PubMed: 15365305]

Frohman MA, Sung TC, Morris AJ. Mammalian phospho- lipase D structure and regulation. Biochim Biophys Acta. 1999; 1439:175–186. [PubMed: 10425394]

Gnann H, Weinmann W, Engelmann C, Wurst FM, Skopp G, Winkler M, et al. Selective detection of phosphatidylethanol homologues in blood as biomarkers for alcohol consumption by LC-ESI-MS/MS. J Mass Spectrom. 2009; 44(9):1293–9. [PubMed: 19526466]

Gustavsson L, Alling C. Formation of phosphatidylethanol in rat brain by phospholipase D. Biochemical and biophysical research communications. 1987; 142(3):958–63. [PubMed: 3827907]

Gustavsson L, Hansson E. Stimulation of phospholipase D activity by phorbol esters in cultured astrocytes. J Neurochem. 1990; 54:737–742. [PubMed: 2303809]

Gustavsson L, Moehren G, Hoek JB. Phosphatidylethanol formation in rat hepatocytes. Ann NY Acad Sci. 1991; 625:438–440. [PubMed: 2058899]

Harris PA, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (Redcap) A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42:377–81. [PubMed: 18929686]

Jones JJ, Plate C, Lewis D. The detection of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanol in human dried blood spots. Analytical Methods. 2011; 3(5):1101–6.

Kechagias S, Dernroth DN, Blomgren A, Hansson T, Isaksson A, Walther L, et al. Phosphatidylethanol compared with other blood tests as a biomarker of moderate alcohol consumption in healthy volunteers: a prospective randomized study. Alcohol and Alcoholism. 2015; 50(4):399–406. [PubMed: 25882743]

Kobayashi M, Kanfer JN. Phosphatidylethanol formation via trans-phosphatidylation by rat brain synaptosomal phospholipase D. Neurochem. 1987; 48:1597–1603.

Kummer N, Ingels AS, Wille S, Hanak C, Verbanck P, Lamber WE, Samyn N, Stove CP. Quanitifiction of phosphatidylethano 16:0/18:1 in venous blood and venous and capillary dried blood spots from patients in alcohol withdrawal and control volunteers. Analytical and Bioanalytical chemistry. 2016; 408(3):825–838. [PubMed: 26597914]

Lucey MR. Liver transplantation for alcoholic cirrhosis in Japan. Liver Transplantation. 2014; 20(3): 255–6. [PubMed: 24478042]

Lucey MR. personal communication. University of Wisconsin liver transplantation program. 2016 Dec 1.

Lundqvist C, Aradottir S, Alling C, Boyano-Adanez MC, Gustavson L. Phosphatidylethanol formation and degradation in brains of acutely and repeatedly ethanol-treated rats. Neurosci Lett. 1994; 179:127–131. [PubMed: 7845607]

Metz SA, Dunlop M. Inhibition of the metabolism of phosphatidylethanol and phosphatidic acid, and stimulation of insulin release, by propranolol in intact pancreatic islets. Biochem Pharmacol. 1991; 41:R1–R4. [PubMed: 1989625]

Nalesso A, Viel G, Cecchetto G, Mioni D, Pessa G, Favretto D, et al. Quantitative profiling of phosphatidylethanol molecular species in human blood by liquid chromatography high resolution mass spectrometry. J Chromatogr A. 2011; 1218(46):8423–31. https://www.nih.gov/…/niaaa-selects-winners-its-wearable-alcohol-biosensor-challenge 2016. [PubMed: 21999914]

Pageaux GP, Bisuth M, Perney P, Costes V, Jaber S, et al. Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter? J Hepatology. 2003; 38:629–634.

Rice JP, Eickhoff J, Agni R, Ghufran A, Brahmbhatt R, Lucey MR. Abusive drinking after liver transplantation is associated with allograft loss and advanced allograft fibrosis. Liver Transplantation. 2013; 19(12):1377–86. [PubMed: 24115392]

Staufer, Kr, Andresen, H., Vettorazzi, E., Tobias, N., Nashan, B., Sterneck, M. Urinary Ethyl Glucuronide as a Novel Screening Tool in Patients Pre- and Post–Liver Transplantation Improves Detection of Alcohol Consumption. Hepatology. 2011; 54:1640–1649. [PubMed: 21809364]

Stewart SH, Koch DG, Willner IRRF, Reuben A. Validation of blood phosphatidylethanol as an alcohol consumption biomarker in patients with chronic liver disease. Alcohol Clin Exp Res. 2014; 38(6):1706–11. [PubMed: 24848614]

Stewart SH, Reuben A, Brzezinski WA, Koch DG, Basile J, Randall PK, et al. Preliminary evaluation of phosphatidylethanol and alcohol consumption in patients with liver disease and hypertension. Alcohol Alcohol. 2009; 44(5):464–7. [PubMed: 19535495]

Tang H, Boulton R, Gunson B, Hubscher S, Neuberger J. Patterns of alcohol consumption after liver transplantation. Gut. 1998; 43(1):140–5. [PubMed: 9771419]

Weinrieb RM, Van Horn DH, Lynch KG, Lucey MR. A randomized, controlled study of treatment for alcohol dependence in patients awaiting liver transplantation. Liver transplantation. 2011; 17(5): 539–47. [PubMed: 21506242]

Weinrieb RM, Van Horn DH, McLellan AT, Lucey MR. Interpreting the significance of drinking by alcohol-dependent liver transplant patients: Fostering candor is the key to recovery. Liver Transplantation. 2000; 6(6):769–76. [PubMed: 11084066]

Wurst F, Thon N, Aradottir S, Hartmann S, Wiesbeck G, Lesch O, et al. Phosphatidylethanol: normalization during detoxification, gender aspects and correlation with other biomarkers and self-reports. Addiction biology. 2010; 15(1):88–95. [PubMed: 20002024]

Veil G, Boscolo-Berto R, Cecchetto G, Fais P, Nalesso A, Ferrara SD. Phosphatidylethanol in blood as a marker of chronic alcohol use: a systematic review and meta-analyses. Int J Mol Sci. 2012; 13:14788–14812. [PubMed: 23203094]

Zheng Y, Beck O, Helander A. Method development for routine liquid chromatography-mass spectrometry measurement of the alcohol biomarker phosphatidylethanol (PEth) in blood. Clin Chim Acta. 2011; 412(15–16):1428–35. [PubMed: 21531215]

Table 1

Participant Characteristics

	Control Group (*n* = 62)	Alcohol Dependent Group (*n* = 151)	X^2/t Statistics
Demographics			
Age, mean (SD)	59.02 (10.33)	59.26 (8.09)	0.18
Male)	38 (61.3%)	109 (72.2%)	2.44
Race[a]			
Caucasian)	60 (96.8%)	123 (82.6%)	
African American)	1 (1.6%)	8 (5.3%)	7.80 *
Other)	1 (1.6%)	18 (12.1%)	
Mental Health History[a]			
Beck Depression Inventory Rating, mean (SD)	6.77 (6.06)	8.99 (7.98)	1.96 *
>9 on Beck Depression Inventory)	19 (30.6%)	51 (35.7%)	0.49
Physical Health History			
Alcohol Liver Disease or Cirrhosis	8 (12.9%)	138 (91.4%)	
Hepatitis C	18 (29.0%)	4 (2.6%)	
Non-Alcoholic Steatohepatitis	10 (16.1%)	0 (0.0%)	130.42 ***
Primary Biliary Cirrhosis	6 (9.7%)	0 (0.0%)	
Other	20 (32.3%)	9 (6.0%)	
Lifetime Treatment for Alcohol or Drug Abuse (n, % present)	6.5	38.3	21.55 ***

Notes. Alcohol dependent participants: 2 missing data on race; 8 missing data on Beck Depression Inventory.

*** p<0.001;

* p<0.05

Table 2

Measures of Alcohol Use, n (%)

	Control Group (*n* = 62)	**Alcohol Dependent Group (*n* = 151)**	**X^2/t Statistics**
Self-reported alcohol use			
Number of drinking days (past 30 days)			
No days	53 (85.5%)	138 (91.4%)	
1–5 days	9 (14.5%)	11 (7.3%)	3.44
6+ days	0 (0.0%)	2 (1.3%)	
Number of drinks in past 30 days			
none	53 (85.5%)	138 (91.4%)	
1–5 drinks	8 (12.9%)	8 (5.3%)	4.01
6+ drinks	1 (1.6%)	5 (3.3%)	

Table 3

Cross Tabulation of PEth Results with Self-Reported Drinking, n (%)[a]

	Negative PEth	Positive PEth	Mean (SD) PEth level	Median PEth level
Control Group (n=62)				
No, self-reported drinking	41 (80.4%)	10 (19.6%)	17.4 (9.2)	14.3
Yes, self-reported drinking	8 (72.7%)	3 (27.3%)	31.0 (16.6)	40.0
Alcohol Dependent Group (n=151)				
No, self-reported drinking	102 (73.9%)	**36 (26.1%)**	74.5 (118.3)	23.7
Yes, self-reported drinking	5 (38.5%)	8 (61.5%)	169.0 (226.3)	54.0

[a] X^2=9.39, df=3, p=0.025