

# Blood Glucose Level, Alcohol Heavy Drinking, and Alcohol Craving During Treatment for Alcohol Dependence: Results From the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) Study

Lorenzo Leggio, Lara A. Ray, George A. Kenna, and Robert M. Swift

**Background:** Heavy drinking may increase blood glucose levels. Moreover, in alcohol-dependent subjects, glucose may play a putative role in alcohol preference.

**Methods:** This study investigated the relationship between blood glucose levels and both alcohol heavy drinking and craving in alcohol-dependent subjects participating in the COMBINE Study. The primary objective was to evaluate the relationship between baseline (pretreatment) glucose levels and percentage of heavy drinking day (PHDD) during treatment. The secondary objective was to evaluate the relationship between glucose levels, baseline PHDD, and craving measured by the Obsessive Compulsive Drinking Scale (OCDS).

**Results:** This analysis consisted of 1,324 participants. Baseline glucose levels were significantly and positively associated with PHDD during treatment [ $F(1, 1225) = 5.21, p = 0.023$ ], after controlling for baseline PHDD [ $F(1, 1225) = 36.25, p < 0.0001$ ], gender [ $F(1, 1225) = 3.33, p = 0.07$ ], and body mass index (BMI) [ $F(1, 1225) = 0.31, p = 0.58$ ]. Higher glucose levels at baseline were associated with a higher percentage of PHDD at pretreatment [ $F(1, 1304) = 5.96, p = 0.015$ ], after controlling for gender [ $F(1, 1304) = 0.29, p = 0.59$ ] and BMI [ $F(1, 1304) = 0.90, p = 0.34$ ]. Glucose was not significantly associated with the OCDS total score [ $F(1, 1304) = 0.12, p = 0.73$ ], the OCDS Obsessive subscale [ $F(1, 1304) = 0.35, p = 0.56$ ], or the OCDS Compulsive subscale [ $F(1, 1304) = 1.19, p = 0.28$ ] scores, after controlling for gender and BMI.

**Discussion:** A link between pretreatment glucose levels and heavy drinking during treatment was found, suggesting a role of glucose in predicting heavy alcohol consumption. Although caution is needed in the interpretation of these results, elevated glucose and heavy drinking may be affected by a common mechanism and manipulations affecting glucose regulation may influence alcohol consumption.

**Key Words:** Alcohol Craving, Alcohol Preference, Glucose, Heavy Drinking.

**B**LOOD GLUCOSE REPRESENTS the simplest parameter able to indicate a risk for both diabetes and metabolic syndrome with the higher levels predicting higher risk (Rao et al., 2004). Low doses of alcohol consumption may have a protective effect against the risk of both diabetes and metabolic syndrome (Liu et al., 2008).

*From the Center for Alcohol and Addiction Studies, Brown University (LL, GAK, RMS), Veterans Administration Medical Center (RMS), Providence, Rhode Island; Department of Psychology, University of California Los Angeles (UCLA) (LAR), Los Angeles, California; and Institute of Internal Medicine, Catholic University of Rome (LL), Rome, Italy.*

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*Reprint requests: Lorenzo Leggio, MD, MSc, Center for Alcohol and Addiction Studies, Brown University, Box G S 121-4, Providence, RI 02912; Fax: 401-456-6762; E-mail: lorenzo\_leggio@brown.edu*

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On the other hand, heavy drinking has been associated with higher glucose levels, therefore increasing the risk of both diabetes and metabolic syndrome (Athysos et al., 2007).

A link between glucose homeostasis and alcohol-seeking behavior has been proposed. For example, Connelly and colleagues (1983) demonstrated that C57BL mice which are hyperglycemic show a preference for ethanol. Similarly, Wistar rats with glucose intolerance have shown a preference for ethanol, consuming approximately 3 times more ethanol than control animals (Zito et al., 1984). In humans, Blum and colleagues (2007) developed a model named “reward deficiency syndrome” (RDS), suggesting that subjects with an addiction disorder (i.e., alcohol dependence, binge eating) have genetic alterations of the dopamine brain system and that the dopamine-glucose link plays a key role in the RDS. The RDS model is consistent with the evidence that glucose modulates dopamine neuronal activity (Levin, 2001) and that blood glucose concentration significantly correlates with

cerebrospinal fluid concentrations of the dopamine metabolite, homovanillic acid (Umhau et al., 2003).

Consequently in alcohol-dependent subjects, a bi-directional relationship between glucose and alcohol intake is likely to occur. In fact, on one hand heavy drinking may increase blood glucose levels, therefore increasing the risk of diabetes and metabolic syndrome, and the overall cardiovascular risk. On the other hand, among subjects with a diagnosis of alcohol dependence, glucose homeostasis may play a putative role in alcohol preference and alcohol-seeking behavior both directly and via glucose regulatory peptides.

In particular, preclinical work has shown a role of insulin on the brain dopamine system, especially in those areas related to the reward system (Figlewicz, 2003). In close agreement with this preclinical evidence, a recent clinical study showed a significant correlation between insulin level and alcohol craving in alcohol-dependent patients (Leggio et al., 2008a). This study also showed a significant relationship between alcohol craving and the C-peptide, which is cleaved off during the synthesis of insulin (Leggio et al., 2008a). Interestingly, other peptides involved in the modulation of glucose levels also correlate with alcohol craving and dependence, peptides such as ghrelin (Addolorato et al., 2006; Hillemecher et al., 2007), leptin (Hillemecher et al., 2007; Kiefer et al., 2001), thyroid hormones (Leggio et al., 2008b), and adiponectin (Hillemecher et al., 2009). Therefore, investigations aimed at examining the relationship between baseline blood glucose levels and alcohol use and craving during the course of the treatment would help to elucidate the clinical implications of glucose levels in alcoholism.

The COMBINE Study was a multisite study designed to address whether naltrexone, acamprosate, or specialized counseling, called Combined Behavioral Intervention (CBI), when given in the context of a medical management (MM) approach, were individually better than placebo or whether combining them would be superior than any one treatment alone (COMBINE Study Research Group, 2003a). The results of this trial (Anton et al., 2006) indicated that naltrexone was superior to placebo on a number of drinking outcome variables, but results were largely observable only when naltrexone was used concomitantly with MM. Acamprosate was not effective and did not significantly contribute to the response of naltrexone alone. Overall, the COMBINE Study represents a rich clinical dataset from which to examine the effects of baseline glucose levels on treatment outcomes for alcoholism. As such, the goal of this *secondary analysis* of the COMBINE Study was to examine the link between blood glucose levels and both alcohol heavy drinking (expressed by the percentage of heavy drinking days; PHDD) and alcohol craving (measured by the Obsessive Compulsive Drinking Scale; OCDS) over the course of the treatment. Specifically, the primary objective was to evaluate the relationship between baseline (pretreatment) blood glucose level and PHDD during treatment. The secondary objective was to evaluate the relationship between glucose levels, alcohol craving, and heavy drinking at baseline.

## METHODS

### *Brief Summary of the COMBINE Study*

The rationale and methods of the COMBINE study have been described in detail elsewhere (Anton and Randall, 2005; COMBINE Study Research Group, 2003b; Swift and Pettinati, 2005). Briefly, COMBINE was designed with the goal of determining whether alcohol dependence treatment outcomes can be improved upon by combining specific pharmacotherapies and behavioral therapies. Overall, the study included 1,383 participants at 11 sites in the U.S. participants were alcohol-dependent adult outpatients who had been drinking heavily during the preceding 90 days but were abstinent for at least 4 days at randomization and not experiencing significant alcohol withdrawal. Patients were excluded if they had serious mental illness, were currently dependent on any drug other than alcohol, nicotine, or marijuana, had any significant recent opioid use, had any medical condition that interfered with study participation, or required medication that would increase the potential risks of the study.

Participants were randomly assigned to 1 of 9 treatment conditions, and received 16 weeks of active treatment. Eight conditions consisted of all possible combinations of naltrexone versus placebo, acamprosate versus placebo, and CBI versus no CBI. All participants in these cells also received up to 9 sessions of MM along with the study medication. The ninth cell received CBI only, without study medication or placebo or MM.

The extensive assessment battery for the COMBINE study included measures to capture medical history and physical exam, laboratory assessments (including blood glucose levels), adverse events, treatment-related expectancies, alcohol consumption, alcohol and drug involvement, motivation, craving, psychological and psychiatric assessments, social support, quality of life, and measures of treatment compliance and process. Primary assessments were administered at baseline and at weeks 8, 16, 26, 52, and 68 postrandomization, with abbreviated assessments at 1, 2, 4, 6, 8, and 12 weeks. The primary outcomes for the main trial were percent days abstinent per month during treatment and time to first relapse to heavy drinking.

### *Assessments Considered for the Present Study*

To assess the outcomes of this study, the following measurements were considered and analyzed:

*Pretreatment blood glucose levels.* After signing an informed consent, all patients provided blood samples for glucose level quantification before randomization as part of the labs required by the protocol. All subjects provided glucose levels with a breath alcohol concentration (BrAC) = 0.00 g/dl. In other words, no patients were acutely intoxicated, a feature of importance given the ability of alcohol to acutely modify blood glucose levels (Swift and Davidson, 1998; Vonghia et al., 2008). Moreover, subjects experiencing significant alcohol withdrawal [Clinical Institute Withdrawal Assessment for Alcohol—Revised (CIWA-Ar) score  $\geq 8$ ] were excluded, eliminating a potential confounding factor as significant alcohol withdrawal can be associated with acute changes of glucose levels (Lieber, 1991; Williams and McBride, 1998).

*Pretreatment craving assessed by the OCDS* (Anton et al., 1996). The OCDS consists of 2 subscales evaluating both the obsessive (OB) and compulsive (CP) components of craving. Both the total score and obsessive and compulsive subscores were evaluated separately.

*Percentage of heavy drinking day during the treatment period.* A heavy drinking day was defined as 5 or more drinks in a day for men, 4 or more drinks in a day for women; PHDD represented one of the primary outcomes for the main trial and hence was selected as the primary drinking outcome in this study. Data on alcohol consumption were collected by the TimeLine Follow-Back (TLFB; Sobell and Sobell, 1992) by trained staff.

*Baseline PHDD*, referring to the 90 days before screening and collected by the TLFB.

*Baseline body mass index (BMI)*, calculated as the ratio between the weight expressed in kg and the height expressed as m<sup>2</sup>.

#### Data Analysis

Study hypotheses were tested using the general liner model (GLM), treating the predictor (glucose levels), as a continuous variable. First, we examined the relationship between baseline (pretreatment) blood glucose levels and (i) percent heavy drinking days (PHDD); and (ii) craving, each tested separately, at baseline. Second, we performed GLM-based analyses with repeated trials, such that blood glucose level at baseline, treated as a continuous variable, was used to predict during-treatment PHDD at weeks 4, 8, 12, and 16, while controlling for baseline PHDD. Additionally, as blood glucose levels are influenced by both BMI (Ferrannini et al., 2004) and gender (Regitz-Zagrosek et al., 2007), all analyses statistically controlled for both BMI and gender. All analyses were performed using SAS statistical software (SAS Inc., 2003) and statistical significance was set at  $p < 0.05$ .

## RESULTS

### Descriptive Statistics

A detailed description of the Combine Study sample is provided elsewhere (Anton et al., 2006). Here, we review the descriptive statistics most relevant to this investigation. The present analyses consisted of 1,324 participants, 69% of whom were male. The average age was 44.43 years ( $SD = 10.22$ ), the average BMI was 27.06 ( $SD = 5.08$ ), and the average blood glucose level was 93.57 mg/dl ( $SD = 21.65$ ). Regarding craving measures, the average OCDS total score was 26.64 ( $SD = 98.26$ ), the average Obsessive subscale score was 8.59 ( $SD = 4.51$ ), and Compulsive subscale score was 18.08 ( $SD = 4.90$ ). In terms of drinking behavior, the average PHDD across assessment points were: 68.8% at pretreatment (i.e., baseline), 13.2% at week 4, 16.5% at week 8, 16.2% at week 12, and 16.6% at week 16.

### Primary Aim: Glucose and Heavy Drinking During Treatment

Analyses suggested that overall, baseline blood glucose levels were significantly and positively associated with PHDD during treatment [ $F(1, 1225) = 5.21, p = 0.023$ ], after controlling for baseline PHDD [ $F(1, 1225) = 36.25, p < 0.0001$ ], gender [ $F(1, 1225) = 3.33, p = 0.07$ ], and BMI [ $F(1, 1225) = 0.31, p = 0.58$ ]. As expected, there was also a main effect of time in treatment, such that PHDD increased across the trial [ $F(3, 1225) = 2.90, p = 0.049$ ] suggesting decreased treatment effects at longer follow-ups, however, there was no significant glucose  $\times$  time interaction [ $F(3, 1225) = 2.15, p = 0.09$ ]. The associations between baseline blood glucose level and PHDD across treatment and follow-up, captured by Pearson Product Moment Correlations, were as follows:  $r = 0.082$  ( $p = 0.002$ ) at week 4,  $r = 0.067$  ( $p = 0.014$ ) at week 8,  $r = 0.042$  ( $p = 0.13$ ) at week 12, and  $r = 0.034$  ( $p = 0.22$ ) at week 16. Overall, these results sug-

gested that blood glucose level at baseline was positively associated with PHDD during the course of the treatment and that this relationship reached statistical significance at weeks 4 and 8.

### Secondary Aim: Glucose, Heavy Drinking, and Craving at Pretreatment

Higher blood glucose levels at baseline were associated with a higher PHDD at pretreatment [ $F(1, 1304) = 5.96, p = 0.015$ ], after controlling for gender [ $F(1, 1304) = 0.29, p = 0.59$ ] and BMI [ $F(1, 1304) = 0.90, p = 0.34$ ]. However, glucose level was not significantly associated with alcohol craving, measured by the OCDS total score [ $F(1, 1304) = 0.12, p = 0.73$ ], the OCDS Obsessive subscale [ $F(1, 1304) = 0.35, p = 0.56$ ] or the OCDS Compulsive subscale [ $F(1, 1304) = 1.19, p = 0.28$ ] scores, after controlling for gender and BMI.

## DISCUSSION

The main findings of this study are that: (i) pretreatment (i.e., baseline) blood glucose level was significantly and positively correlated with pretreatment PHDD; (ii) pretreatment blood glucose level was positively correlated with PHDD during treatment, and that association reached statistical significance for weeks 4 and 8 of treatment; and (iii) pretreatment glucose levels did not correlate significantly with alcohol craving, as measured by the OCDS.

The significant association between pretreatment glucose level and pretreatment PHDD suggests that alcohol-dependent subjects reported higher PHDD (during the 90 days before starting the trial) also have higher glucose levels. This result was consistent with our initial hypothesis and suggests important clinical implications. In fact, this result is consistent with the notion that heavy alcohol drinking represents a risk factor for cardiovascular diseases through the increase of blood glucose level, and increasing the risk of several related conditions such as diabetes, obesity, metabolic syndrome, atherosclerosis, and hypertension (O'Keefe et al., 2007).

As a consequence, our finding further supports the value of medical interventions aimed at achieving alcohol abstinence or at least a significant reduction of alcohol consumption in heavy drinkers. In keeping with this medical need, it has been demonstrated that 3 months of total alcohol abstinence leads to reductions in both blood glucose level and consequently, the risk of developing metabolic and cardiovascular disorders (Addolorato et al., 1998).

Notably, a recent secondary analysis of the COMBINE data set showed a blood pressure reduction during treatment in those subjects who were above the median blood pressure at baseline (Stewart et al., 2008). This effect was similar regardless of age, sex, BMI, reported history of hypertension, and use of antihypertensive medications (Stewart et al., 2008).

This study also showed that pretreatment blood glucose level significantly correlated with the first 8 weeks of during-treatment PHDD. This finding suggests that pretreatment blood glucose level could predict PHDD during treatment, and therefore that glucose could be able to influence the alcohol use behavior and the related alcohol consumption. These results were obtained over and above the effects of baseline PHDD, gender, and BMI, all of which represent important independent predictors of both drinking and blood glucose levels. Overall, these findings are consistent with preclinical data demonstrating the role of glucose in alcohol preference, alcohol intake, and alcohol-seeking behavior in animal models. For example, C57BL mice which are hyperglycemic show a preference for ethanol (Connelly et al., 1983). A comparison of C57 B/6j mice (alcohol preferring) and DBA/2j mice (alcohol avoiding) also showed that after the administration of an identical amount of glucose, the C57 B/6j mice have significantly higher levels of plasma glucose than the DBA/2j strain (Goas et al., 1979). Furthermore, a functional relationship between this diabetogenic disturbance and alcohol preference was shown in C57 B/6j mice which were allowed to choose between water or a 10% alcohol solution (Goas et al., 1979). Zito and colleagues (1984) showed that Wistar rats with glucose intolerance displayed an immediate preference for ethanol and consumed approximately 3 times more ethanol than the control animals (Zito et al., 1984). Finally, Forsander and Pösö (1987) demonstrated that the AA strain (with an inherited preference for alcohol) and the ANA strain (with an aversion to alcohol) maintain their blood glucose concentration by different mechanisms. In fact the ANA rats utilize both glycogenolysis and gluconeogenesis but the AA rats only gluconeogenesis (Forsander and Pösö, 1987), an observation suggesting that carbohydrate metabolism is genetically related to alcohol drinking (Forsander and Pösö, 1988). Together these experiments suggest a role for glucoregulatory processes in alcohol intake. This study is consistent with these animal studies, as pretreatment glucose level was significantly and directly related to PHDD of alcohol-dependent subjects at baseline and during the first 8 weeks of treatment.

This study did not find a significant correlation between blood glucose level and alcohol craving. A previous human study found a direct correlation between insulin and alcohol craving and between C-peptide and alcohol craving, but not between alcohol craving and IGF-1 nor between alcohol craving and glucose (Leggio et al., 2008a). Using a larger sample size but a similar population (treatment-seeking alcohol-dependent subjects), the present findings confirm the lack of correlation between glucose and alcohol craving. Notably, in both studies the OCDS scale was used and analysis included both the total OCDS score as well as the 2 main subscales, namely obsessive and compulsive. These findings suggest that the putative role of glucose on heavy alcohol drinking may not be mediated by through the effects of glucose on alcohol craving and instead, other mechanisms underlying this association may be at play. Furthermore, the possible role of differ-

ences in the sample analyzed (i.e., alcohol-dependent subtypes; see Leggio et al., 2009) cannot be ruled out.

These results should be interpreted in light of the study's strengths and limitations. The results were obtained in a clinical trial and not in a typical treatment setting; therefore the findings may not readily generalize to traditional clinical settings outside of the context of a clinical trial. Fasting was not a mandatory requirement in this trial before performing blood draws. This limit was inevitable as the COMBINE study was not designed to assess blood glucose as a treatment outcome. Therefore, blood laboratory tests were not performed after an overnight fasting, although it was usually performed after >2 hours fasting. Furthermore, all of our drinking and craving measures were based on self-report. However, data were collected by experienced staff who had received supervised training in assessing alcohol consumption (Sobell and Sobell, 1992) and craving (Anton et al., 1996; Roberts et al., 1999). Finally, we also recognize the small magnitude of the relationships found in this study, therefore recommending caution in future applications of the results.

In this study, we did not consider the glucose levels performed successively during the treatment since the presence of different bias able to influence our analysis, in particular:

1. The use of different medications that could influence differently the glucose levels. In fact, naltrexone is able to influence blood glucose level (see, for example, Raingeard et al., 2004) whereas acamprosate is not. This is consistent with the ability of naltrexone to ameliorate insulin sensitivity in peripheral tissues (Guido et al., 2006). Therefore, as the goal of this study was to investigate the relationship between glucose and heavy alcohol consumption, we did not address differences between patients treated by different medications (i.e., naltrexone, acamprosate, naltrexone + acamprosate, placebo). The presence of different conditions during the treatment could also explain, at least partially, the reason why baseline blood glucose level and during-treatment PHDD correlated at week 4 and week 8, but not at week 12 and week 16, although future prospective studies are needed to better address this feature.
2. The possible presence of glucose levels acutely influenced by alcohol in intoxicated subjects. In fact, in the COMBINE trial, a BrAC  $\leq 0.05$  g/dl was acceptable during the follow-up visits. Acute alcohol intoxication can acutely influencing blood glucose levels (Vonghia et al., 2008). Therefore, glucose levels performed during the follow-up visits could be acutely influenced by BrACs > 0.00 g/dl across the subjects of the trial.

Study strengths include the large sample of subjects studied, making this analysis the largest one in which the link between glucose and heavy drinking has been studied. Moreover, we noted the results were obtained in the context of a methodologically rigorous research protocol. The exclusion of severely ill patients with alcoholism, and those with medical, psychiatric, and comorbid substance misuse problems improved the homogeneity of the sample population and eliminated several

possible confounding factors, such as medical disorders able to influence glucose levels (e.g., diabetes, liver cirrhosis, etc.) or patients prescribed drug classes (e.g., antipsychotics) known to be associated with altered glucose levels.

In summary, our analysis demonstrated: (i) a link between pretreatment blood glucose levels and pretreatment heavy drinking, pointing out the role of heavy drinking as a metabolic and cardiovascular risk factor via increased glucose levels; (ii) a link between pretreatment blood glucose levels and during treatment heavy drinking, suggesting a role of glucose in predicting heavy alcohol consumption. Although further work needs to be done to assess the possible involvement of glucose in the alcohol-seeking behavior, these results suggest that elevated glucose and heavy drinking may be affected by a common mechanism and manipulations affecting glucose regulation may influence alcohol consumption.

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