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Moderate Alcohol Use and Insulin Action in Chronic Hepatitis C Infection

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Abstract

Background & Aims—Chronic hepatitis C (HCV) is associated with metabolic abnormalities including insulin resistance (IR) and diabetes. While moderate alcohol consumption is known to have beneficial metabolic effects in the general population, such potential effects in HCV are unknown. We aimed to assess the association between graded alcohol intake and insulin resistance, secretion, and metabolic syndrome in HCV.

Methods—Ninety-five non-diabetic HCV-infected patients underwent detailed metabolic testing. IR was directly measured via steady-state plasma glucose (SSPG) during a 240-minute insulin suppression test. Total insulin secretion and insulinogenic index was determined by 75g oral glucose tolerance test. Genotyping of CYP2E1 was performed to detect genetic polymorphisms influencing alcohol metabolism.

Results—In this cohort, 61% were abstinent from alcohol for the past 12 months, while 22% were moderate, and 17% heavy drinkers. Obesity and non-white ethnicity were the strongest predictors of IR. Moderate alcohol intake (vs none) was significantly associated with lower SSPG only among those with normal BMI (coef -72.9 , 95%CI -128.1 to -17.6 , $p=0.01$). Alcohol use was not associated insulin secretion parameters when controlling for IR and other factors. Heavy alcohol intake (OR 3.2, 95%CI 0.86–12.3) and non-white ethnicity (OR 7.1, 95%CI 1.5–33.3) were associated with metabolic syndrome. Among non-whites, the odds of metabolic syndrome were 5-fold higher for heavy drinkers.

Conclusions—Moderate alcohol intake is associated with improved insulin sensitivity in HCV, although this benefit was limited to normal-weight individuals. The potential benefit of moderate alcohol on IR and its metabolic consequences in HCV warrants further longitudinal investigation.

Keywords

Hepatitis C; Insulin Resistance; Insulin Secretion; Metabolic Syndrome; clamp testing

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INTRODUCTION

Chronic hepatitis C (HCV) infection is a major cause of cirrhosis, end-stage liver disease, and hepatocellular carcinoma, and the leading indication for liver transplantation in the United States [1]. Although HCV-induced liver disease progresses over several decades, certain factors are associated with a more rapid progression of liver fibrosis and adverse clinical consequences. One such factor is alcohol use, which is common among HCV-infected individuals [2]. Heavy alcohol use in excess of 50 grams per day is clearly associated with acceleration of liver disease in the setting of HCV [3, 4]. While many patients are counseled to cease or reduce alcohol consumption upon HCV diagnosis, at least 20% of patients with HCV in the US consume two or more drinks daily [5]. Whether moderate alcohol use, variably defined as between 10–30 grams per day, adversely impacts the course of HCV disease is, however, controversial [4, 6].

Heavy alcohol use also results in higher rates of insulin resistance (IR) and diabetes in the general population [7], while moderate alcohol consumption is associated with improved insulin sensitivity and a reduced risk of cardiovascular and metabolic disease [7, 8]. Metabolic abnormalities including the metabolic syndrome, IR, and diabetes are important to HCV disease and can also accelerate HCV liver disease progression [9, 10], and in turn, chronic HCV is associated with higher rates of metabolic abnormalities [9]. Understanding the relationship between alcohol use and metabolic abnormalities within the context of HCV infection is therefore important to both HCV management and prevention of its associated conditions.

It is unknown whether the metabolic benefits of moderate alcohol consumption exist in the setting of chronic HCV. Further, most prior studies evaluating the relationship between IR and metabolic complications in HCV have excluded heavy drinkers and not fully accounted for the role of moderate alcohol intake as compared to none. Therefore, we aimed to assess the influence of graded alcohol consumption (heavy, moderate, and none) on IR and insulin secretion, and the risk of metabolic syndrome in a multi-ethnic cohort of non-diabetic HCV-infected individuals with comprehensive metabolic characterization including direct and accurate measurement of insulin sensitivity.

MATERIALS and METHODS

Study Participants

HCV-infected adults (detectable HCV viral load) were recruited from University of California San Francisco (UCSF) affiliated clinics from 2002 to 2011. Patients with known diabetes or those with fasting plasma glucose ≥ 126 mg/dL [11] were excluded. Patients with either histologic (by liver biopsy) or clinical diagnosis of cirrhosis (as suggested by imaging or platelet count $< 120,000/L$) were excluded. Patients also had to have evidence of compensated liver disease with the following biochemical parameters: prothrombin time < 2 seconds prolonged, total bilirubin < 3 mg/dL, and albumin > 3.5 g/dL, and no clinical evidence or history of decompensation (such as presence of ascites, gastroesophageal varices, or encephalopathy). Additional exclusion criteria were presence of HBV or HIV

infection, prior HCV treatment, liver disease other than HCV (ie: steatohepatitis), steroid or anabolic therapy, or medical conditions compromising study participation. This study was approved by the UCSF Committee on Human Research and all participants provided written informed consent.

Study Procedures

At an initial screening visit, patients underwent clinical and laboratory evaluation. In a subgroup of patients, liver biopsy had been performed as part of standard of care prior to screening. Histologic evaluation was performed by a pathologist blinded to the patient's metabolic profile using the Ludwig-Batts scoring system. A thorough drinking history was obtained for each patient via face-to-face interview. Recent drinking behavior over the prior 12 months was assessed, inclusive of drinking levels (number of drinks per day and number of drinking days per week), patterns, and variability of intake. Moderate alcohol intake was defined as no more than 4 drinks on any day or 14 per week for men and no more than 3 drinks on any day or 7 drinks per week for women, consistent with the definition provided by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) [12]. Heavy alcohol intake was defined as any amount above a 'moderate' level.

Metabolic Testing

At baseline, subjects underwent a 2-day inpatient hospital admission at the UCSF Clinical and Translational Science Institute – Clinical Research Center (CRC) for study procedures including an 75-g oral glucose tolerance test (OGTT) (day 1) and a modified 240 min insulin suppression test (IST) (day 2) [13]. Based on OGTT results, subjects with 2-hour plasma glucose levels ≥ 200 mg/dL (diabetic) were excluded from further analysis. During IST, similar plasma levels of exogenous insulin are reached in all subjects and the steady-state plasma glucose (SSPG) concentration as the result of an identical glucose infusion rate measures insulin-mediated glucose uptake in muscle. Higher SSPG levels represent higher degrees of peripheral IR. IST and hyperinsulinemic-euglycemic clamp test are highly correlated ($r>0.9$) and similar to the clamp test, IST is considered a direct physiologic measurement of IR [14].

The early insulin secretory response to oral glucose load was measured using the insulinogenic index as determined by the ratio of the increment of plasma insulin to that of plasma glucose at 30 minutes during OGTT (I_{0-30}/G_{0-30}) [15]. The total insulin secretion during OGTT was reported as the area under the curve of insulin (I-AUC) divided by the area under the curve of glucose (G-AUC) using the trapezoidal method.

Metabolic syndrome was defined as reaching or exceeding the threshold levels for three of five conditions: abdominal obesity, high triglyceride levels, low HDL-cholesterol, increased fasting plasma glucose, and elevated blood pressure [16].

CYP2E1 Genotyping

All patients underwent genetic analysis to detect polymorphisms in the CYP2E1 RsaI c2 allele, an alcohol metabolizing enzyme that has a relatively high frequency in Latino populations, and lower frequency in Caucasian and African Americans [17–19]. Asian

Americans were excluded from the analysis because of the high frequency of polymorphisms in other genes encoding the main ethanol metabolizing enzymes (ADH and ALDH) that were not evaluated in this study. For detailed description of methods used, please refer to Supplementary Material.

Statistical Analysis

Descriptive analyses of patient characteristics within each alcohol category (none, moderate, heavy) were summarized using mean $\pm$ SD and frequency. Viral and host factors were compared across alcohol intake categories using Kruskal-Wallis test for continuous variables and chi-squared or Fisher's exact test for categorical variables. For insulin resistance and secretion, multivariable stepwise forward selection linear regression modeling was used. In addition, we estimated the interaction of the effect of alcohol and BMI categories. For metabolic syndrome, two-predictor logistic regression models were used. Statistical significance was defined as a p-value of <0.05 (2-sided) for all models. All analyses were performed using Stata version 12 statistical software, Stata Corp LP, College Station, TX.

RESULTS

Cohort Characteristics

Of the ninety-five included participants, the majority (73%) were male, mean age was 48 years and 42% were Caucasian, and the most common mode of HCV acquisition was injection drug use (76%). Overall, 61% were abstinent from alcohol for the past 12 months, 22% were moderate, and 17% heavy drinkers. The mean estimated duration of alcohol consumption was 28.5 years. Seventy seven patients underwent liver biopsy (81%) and of those with histologic data, 61% had at least grade 2 inflammation, 44% at least stage 2 fibrosis, and 34% evidence of steatosis (without steatohepatitis).

Table 1 describes the patient characteristics according to alcohol use category. Patients with moderate alcohol intake were less likely to be obese and had lower mean waist circumference, in addition to lower mean triglyceride and higher HDL cholesterol levels. On the other hand, those with heavy intake had higher mean BMI and rates of metabolic syndrome (37% as compared to 14.3% of moderate and 13.8% of current non-drinkers). Heavy drinkers were also more likely to be male. The duration of past alcohol use was shorter in those who were not currently drinking.

CYP2E1 Genotyping

All 95 participants were genotyped for polymorphisms in the alcohol metabolizing gene cytochrome P4502E1 (CYP2E1) and the homozygous mutant allele (c2/c2) has been associated with higher rates transcriptional activity, protein levels, enzyme activity, and alcoholic liver disease [19]. In this cohort, there were 4 subjects that were heterozygous (c1/c2) for the allele and none were homozygous for the mutant allele (c2/c2). Therefore it was not necessary to account for underlying genetic differences in alcohol metabolism that may influence the study results.

Insulin Resistance

Figure 1 depicts the distribution of SSPG levels (range 38.7 – 306.5 mg/dL) by alcohol category. The SSPG levels were lower in those with moderate (121.2 ± 73.8 mg/dL) or heavy (125.1 ± 74.5 mg/dL) alcohol intake compared to those with no recent alcohol (140.6 ± 72.9 mg/dL). On single-predictor analysis, alcohol intake was not statistically significantly associated with SSPG (coef -19.4 , 95% CI -56.5 to 17.7 , $p=0.30$ for moderate vs none, and coef -15.5 , 95% CI -56.6 to 25.7 , $p=0.45$ for heavy vs none). Obesity was the variable most strongly associated with IR (coef 54.1 for obese vs normal BMI, 95%CI 12.9 – 95.1 , $p=0.010$).

In a multivariable model (Table 2) including age, sex, non-white race/ethnicity, BMI category, and alcohol duration, both moderate alcohol intake (coef -22.2 , 95%CI -59.2 to 14.8 , $p=0.16$) and heavy alcohol intake (coef -19.0 , 95%CI -59.1 to 21.1 , $p=0.35$) were negatively associated with SSPG, although the effects did not reach statistical significance. In addition to obesity, non-white race/ethnicity (coef 38.0 , 95%CI 8.5 to 67.6 , $p=0.012$) was significantly associated with IR. When the analysis was limited to those with histological data (81% of total sample), higher grade of liver inflammation (coef 29.9 , 95%CI 1.04 to 60.8 (0.030) and non-white race/ethnicity (coef 40.0 , 95%CI 9.7 to 70.3 , $p=0.010$) were associated with higher SSPG. Again, moderate alcohol intake was negatively associated with SSPG (coef -27.1 , 95%CI -65.3 to 11.1 , $p=0.10$) and this effect approached statistical significance.

Given that obesity has a strong effect on IR, we hypothesized that the impact of alcohol consumption on SSPG may be more evident and clinically meaningful in normal weight individuals ($BMI < 25$ kg/m²). Hence, we evaluated the primary effects of both alcohol and BMI category, and the interaction between them, in a multivariate model that controlled for associated predictors and those selected *a priori* (age, gender, race, duration of alcohol intake). For BMI category (normal < 25 kg/m², overweight 25 – 29.9 kg/m², obese 30 kg/m²) and alcohol category (none, moderate, heavy), the overall interaction between these two variables was statistically significant ($p=0.020$). Moderate alcohol was statistically significantly associated with lower levels of SSPG (coef -72.9 , 95%CI -128.1 to -17.6 , $p=0.010$) when BMI was normal (Table 3). Heavy alcohol was also associated with lower SSPG in the normal BMI range (coef -59.7 , 95%CI -127.7 to 8.2 , $p=0.084$) and this effect approached statistical significance. In addition, non-white ethnicity was associated with higher SSPG levels (coef 31.5 , 95%CI 1.6 to 61.3 , $p=0.039$). Adjusting for histologic liver inflammation, fibrosis, steatosis, and HCV genotype did not substantially alter the coefficients for alcohol category ($<3.0\%$ change).

Insulin Secretion

Mean total insulin secretory response was 0.52 ± 0.28 and early insulin secretory response (insulinogenic index) was 1.47 ± 1.63 . When adjusting for degree of IR (data not shown), alcohol intake was not substantially associated with total insulin secretory response (coef -0.05 , 95%CI -0.17 to 0.07 , $p=0.38$ for moderate versus none; coef -0.04 , 95%CI -0.18 to 0.10 , $p=0.55$ for heavy versus none) or early insulin secretory response (coef -0.44 , 95%CI -1.26 to 0.39 , $p=0.30$ for moderate versus none; coef 0.23 , 95%CI -0.69 to 1.14 , $p=0.62$ for

heavy versus none). On multivariate analysis when assessing the impact of alcohol use on total insulin secretory response and adjusting for SSPG levels, age, sex, ethnicity, and duration of alcohol use, there was no significant association with moderate (coef -0.038 , 95%CI -0.16 to 0.09 , $p=0.54$) or heavy (coef -0.026 , 95%CI -0.17 to 0.12 , $p=0.72$) alcohol use. The only statistically significant predictor of higher insulin secretory response was obesity (coef 0.21 , 95%CI 0.07 to 0.35 , $p=0.004$). Duration of alcohol use was also associated with lower levels of total insulin secretory response but this did not quite reach statistical significance (coef -0.05 per decade, $p=0.06$).

Metabolic Syndrome

When evaluating the effect of alcohol consumption on metabolic syndrome, heavy alcohol use was associated with significantly higher odds of metabolic syndrome (OR 3.75 , 95% CI 1.1 to 13.2 , $p=0.039$). When adjusting for age, sex, duration of alcohol use, and nonwhite ethnicity, heavy alcohol use remained similarly associated with higher odds of metabolic syndrome (OR 3.2 , 95% CI 0.86 to 12.3 , $p=0.08$). In this cohort, nonwhite ethnicity was associated with the largest effect and increased the odds of metabolic syndrome by approximately 7-fold (OR 7.1 , 95%CI 1.5 to 33.3 , $p = 0.01$). In fact, metabolic syndrome was present in only two white subjects and this racial/ethnic group was strongly predictive of *not* having metabolic syndrome. We therefore limited the multi-predictor analysis to nonwhite patients for modeling purposes. Further, given the low number of remaining metabolic syndrome outcomes ($n=15$), we analyzed the effect of alcohol on metabolic syndrome using two-predictor models as depicted in Table 4. Among non-white subjects, heavy alcohol intake was independently associated with nearly 5-fold higher odds of metabolic syndrome.

DISCUSSION

Clinical and epidemiologic studies in the general population confirm that moderate alcohol consumption confers a reduced risk of adverse metabolic outcomes [8, 20] in addition to cardiovascular and all-cause mortality [21]. The greatest health benefits are seen among those consuming between one and three drinks per day (10–30 grams), the NIAAA definition of moderate alcohol intake [12]. For healthy adults, the relationship between alcohol use and diabetes is therefore J- or U-shaped, with moderate alcohol consumption resulting in lowest levels of insulin secretion and resistance [8, 22, 23]. In a study by Davies et al, after 8 weeks of moderate alcohol consumption, insulin sensitivity improved by 7.2% among post-menopausal women [8], and Sierksma et al found a 21% improvement in insulin sensitivity in the subgroup of patients with existing IR who consumed moderate alcohol [24]. Alcohol is a potential modifier of metabolic disease, and alcohol use is common among HCV-infected individuals who are at disproportionate risk for metabolic abnormalities [25]. This is the first study to assess the impact of graded alcohol consumption on directly measured insulin resistance as well as metabolic syndrome in a multi-ethnic cohort of individuals with chronic HCV infection.

According to the most recent American Association for the Study of Liver Diseases (AASLD)/Infectious Disease Society of America (IDSA) guidelines, HCV-infected

individuals should be counseled to abstain from *any* alcohol use [26]. Our study suggests that moderate alcohol consumption may portend metabolic benefits, namely reduction of IR, in some HCV-infected individuals. In this cohort and as previously shown, obesity was associated with IR and decreased insulin secretory response [27]. We also observed a statistically significant interaction between alcohol use and obesity. Indeed, as compared to non-drinkers moderate alcohol consumption resulted in a 72.9 g/dL lower levels of SSPG when BMI was within the normal range. Moderate alcohol consumption however did not seem to have a substantial effect on insulin secretion when controlling for degrees of insulin resistance, suggesting that the effect of alcohol on insulin metabolism is predominantly through alteration in insulin sensitivity.

Interestingly, we also observed lower degrees of IR in those with heavy alcohol consumption (mean SSPG 59.7 mg/dL less than abstainers), again only in those individuals with normal BMI. This is in contrast to prior studies in the general population using surrogate measure of IR (HOMA-IR) that have shown that those consuming heaviest amounts of alcohol (variably defined) are more insulin resistant [28, 29]. However, these studies did not evaluate the potential interaction of alcohol and obesity. It is also possible that the relationship between alcohol and IR is unique in the setting of HCV infection. Whether the reduction in IR with moderate alcohol use translates into a cardio-protective effect or reduction in mortality is not clearly known. In fact, in a population-based study, limited by inclusion of relatively few HCV-infected individuals, the presence of chronic HCV increased the risk of both liver-related and overall mortality, and this risk was further increased in those who consumed alcohol excessively, but also moderately [30]. Longitudinal studies are therefore warranted to clarify the impact of improved insulin sensitivity on morbidity and mortality among HCV-infected individuals who consume alcohol moderately.

The impact of alcohol consumption on metabolic syndrome is more controversial. In a cross-sectional analysis of NHANES-III data, mild to moderate alcohol use was associated with lower prevalence of metabolic syndrome, specifically with favorable effects on lipids, waist circumference, and fasting insulin [31]. In contrast, in a prospective study, Baik et al found no association between light and moderate alcohol intake and metabolic syndrome, but did note a 63% increase in the odds of metabolic syndrome among heavy drinkers (>30 g/day) [32]. Further, in a recent meta-analysis of six prospective studies, heavy alcohol consumption appeared to increase the overall risk of metabolic syndrome [33]. Similarly, in our study, metabolic syndrome was more prevalent among HCV-infected heavy drinkers (37%) when compared to moderate (14.3%) and non-drinkers (13.8%). Moreover, non-white ethnicity (predominantly Latinos) was by far the strongest predictor of metabolic syndrome, as previously observed [34]. Though we did not observe an independent effect of moderate alcohol use on metabolic syndrome, heavy alcohol use increased the odds significantly (by about 5 fold) especially among those with non-white ethnicity. Given that heavy alcohol use accelerates HCV liver fibrosis [4], HCV-infected patients should be counseled that alcohol consumption above a moderate level portends a significant and potentially synergistic risk for both HCV liver disease progression and metabolic syndrome.

Given our cross-sectional design, a cause and effect relationship between alcohol consumption and metabolic outcomes could not be assessed. Patients that choose to enroll in

clinical studies may not be representative of the general HCV population, as is the case with any clinical trial. Further, given the logistics of performing extensive 2-day metabolic testing including direct physiologic measurement of IR that would be impractical with a larger cohort, the sample size was limited. Nevertheless, this is the first and largest study to investigate the impact of graded alcohol on directly measured IR in the setting of HCV. Important strengths include use of insulin suppression testing, detailed alcohol intake history, as well as CYP2E1 genotyping of all participants that would have impacted categorization of alcohol consumption.

This study provides evidence that in the setting of HCV infection, moderate alcohol improved insulin sensitivity, although this benefit was only observed in normal-weight individuals. On the other hand, heavy alcohol use was associated with overall risk of metabolic syndrome, and most convincingly among ethnic minorities. Given that known metabolic risk factors, notably obesity, are likely to exert a more dominant effect on metabolic outcomes in HCV as in the general population, interventions directed at weight reduction and abstinence from heavy alcohol use are primary goals for prevention of HCV-related liver disease progression. The potential for moderate alcohol consumption to exert a positive effect on IR and its metabolic consequences in the setting of HCV infection warrants further longitudinal investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

HCV	Hepatitis C virus
IR	Insulin resistance
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
NIAAA	National Institute on Alcohol Abuse and Alcoholism
OGTT	Oral glucose tolerance test
IST	Insulin suppression test
SSPG	Steady state plasma glucose
I-AUC	Area under the curve of insulin
G-AUC	Area under the curve of glucose

BMI	Body mass index
ALT	Alanine aminotransferase
HDL	High density lipoprotein
ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
HOMA	Homeostatic model assessment

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Figure 1. Distribution of insulin resistance (SSPG, mg/dL) by alcohol intake category defined as none, moderate, and heavy intake.

Table 1

Patient characteristics according to current alcohol intake

Patient Characteristics	No alcohol N=58	Moderate N=21	Heavy N=16	p-value
Age (years), mean $\pm$ SD	47.3 $\pm$ 7.1	48.9 $\pm$ 5.7	48.9 $\pm$ 4.4	0.53
Range	30–60	35–60	37–57	
Male sex, N (%)	45 (78)	11 (52)	13 (81)	0.06
US born, N (%)	48 (83)	16 (76)	11 (69)	0.45
Race/Ethnicity, N (%)				
Caucasian	28 (48.3)	7 (33.3)	5 (31.3)	0.50
Latino	12 (20.7)	4 (19.0)	3 (18.8)	
African American	16 (27.6)	7 (33.3)	7 (43.8)	
Other	2 (3.4)	3 (14.3)	1 (6.3)	
* Past alcohol duration (years), mean $\pm$ SD	26.4 $\pm$ 10.2	30.7 $\pm$ 11.0	33.1 $\pm$ 5.8	0.014
BMI (kg/m ²), mean $\pm$ SD	26.6 $\pm$ 4.5	26.0 $\pm$ 4.3	27.5 $\pm$ 4.5	0.73
BMI category, N (%)				
Normal (<25 kg/m ²)	21 (36.2)	9 (43.0)	5 (31.3)	0.31
Overweight (25 – 29.9 kg/m ²)	26 (44.8)	9 (43.0)	7 (43.8)	
Obese (> 30 kg/m ²)	11 (19.0)	3 (14.0)	4 (25.0)	
Waist circumference (cm) $\pm$ SD	94.7 $\pm$ 12.0	88.7 $\pm$ 9.1	97.7 $\pm$ 12.1	0.06
** HCV duration (years), mean (range)	26.4 (7–48)	23.5 (1–37)	29.1 (19–39)	0.28
HCV Genotype				
1	42 (56.7)	13 (62.0)	10 (62.4)	0.71
2	7 (12.0)	5 (23.8)	3 (18.8)	
3	7 (12.0)	3 (14.2)	3 (18.8)	
Indeterminate	2 (3.4)	0	0	
HCV viral load (logIU/mL), mean $\pm$ SD	5.78 $\pm$ 0.7	5.87 $\pm$ 0.66	5.68 $\pm$ 0.78	0.70
*** Liver Biopsy				
Inflammation, grade > 2, N/total (%)	35/51 (68.6)	9/17 (52.9)	3/9 (33.3)	0.10
Fibrosis, stage > 2, N/total (%)	22/51 (43.1)	8/17 (47.1)	4/9 (44.4)	0.96
Presence of steatosis, N/total (%)	16/51 (31.4)	5/17 (29.4)	5/9 (55.5)	0.33
ALT (U/L), mean $\pm$ SD	101.7 $\pm$ 89.3	83.2 $\pm$ 92.7	69.7 $\pm$ 43.5	0.19
Range	19–273	26–466	31–189	
AST (U/L), mean $\pm$ SD	74.2 $\pm$ 58.3	66.4 $\pm$ 48.5	54.3 $\pm$ 21.8	0.61
Range	2–331	22–240	27–97	

Patient Characteristics	No alcohol N=58	Moderate N=21	Heavy N=16	p-value
Ferritin (ng/mL), mean $\pm$ SD	163.7 $\pm$ 136.5	137.9 $\pm$ 126.8	218.7 $\pm$ 207.4	0.56
Fasting glucose, (mg/dL), mean $\pm$ SD	94.5 $\pm$ 9.8	93.3 $\pm$ 9.5	97.4 $\pm$ 9.4	0.31
Total cholesterol (mg/dL), mean $\pm$ SD	175.6 $\pm$ 43	170.3 $\pm$ 36.6	168.9 $\pm$ 32.7	0.95
LDL (mg/dL), mean $\pm$ SD	104.7 $\pm$ 35.5	96.0 $\pm$ 34.9	95.7 $\pm$ 26.1	0.80
HDL (mg/dL), mean $\pm$ SD	49.3 $\pm$ 12.5	56.0 $\pm$ 17.0	50.7 $\pm$ 10.0	0.28
Triglycerides (mg/dL), mean $\pm$ SD	104.8 $\pm$ 56.5	90.5 $\pm$ 43.7	112.3 $\pm$ 56.8	0.34
Diabetes family history, N (%)	25 (43.1)	13 (61.9)	7 (43.8)	0.32
Current tobacco smoking, N (%)	35 (60.3)	12 (57.1)	11 (68.8)	0.76

* 98% of those with no current alcohol use (over the past 12 months) had drank alcohol previously and past duration refers to prior use for these subjects

** HCV duration was estimated by the date of the exposure to first known risk factor for acquisition of HCV to enrollment date

*** Histologic evaluation (HCV-induced inflammation grade and fibrosis stage) was performed using the Ludwig-Batts scoring system and there were no evidence of concomitant steatohepatitis or non-HCV liver disease on any of the liver biopsy specimens.

Table 2

Multivariate analysis of the effect of alcohol intake on insulin resistance (SSPG) in all patients (N=95) and in those with histologic data based on liver biopsy (N=77)

	All Patients (N=95)		Patients with Histologic Data (N=77)	
Predictor	Coefficient	95% CI (p-value)	Coefficient	95% CI (p-value)
Age, per decade	-13.2	-37.3 – 10.9 (0.28)	-8.2	-32.8 – 16.4 (0.51)
Male sex	19.3	-14.6 – 53.3 (0.26)	27.9	-6.7 – 62.4 (0.11)
Non-white race/ethnicity	38.0	8.5 – 67.6 (0.012)	40.0	9.7 – 70.3 (0.010)
BMI (vs normal)				
Overweight	21.0	-11.7 – 53.7 (0.20)	18.7	-15.7 – 53.1 (0.28)
Obese	55.4	14.5 – 96.4 (0.009)	56.5	14.0 – 99.0 (0.010)
Duration of alcohol use, per decade	-7.7	-26.8 to 11.4 (0.45)	-14.3	-33.7 to 5.1 (0.14)
Alcohol use (vs. none)				
Moderate	-22.2	-59.2 to 14.8 (0.23)	-27.1	-65.3 – 11.1 (0.10)
Heavy	-19.0	-59.1 to 21.1 (0.35)	-23.4	-73.8 – 23.9 (0.31)
Inflammation grade >2			29.9	1.04 – 60.8 (0.030)

Table 3

Multivariate model of the interaction of alcohol intake and body mass for predicting insulin resistance (SSPG)

Predictor	Coefficient	95% CI	p-value
Age, per decade	−13.0	−36.8 to 10.8	0.28
Male sex	24.8	−8.9 to 56.5	0.15
Non-white race/ethnicity	31.5	1.6 to 61.3	0.039
Duration of alcohol, per decade	−4.0	−20.1 to 12.1	0.62
Alcohol (vs none) when BMI<25			
Moderate	−72.9	−128.1 to −17.6	0.010
Heavy	−59.7	−127.7 to 8.2	0.084
Alcohol (vs none) when BMI 25 to <30			
Moderate	21.7	−30.6 to 74.0	0.41
Heavy	4.9	−52.3 to 62.2	0.87
Alcohol (vs none) when BMI ≥30			
Moderate	−25.5	−112.7 to 61.7	0.56
Heavy	−38.8	−80.9 to 73.3	0.92
BMI category (vs normal) when alcohol intake=0			
Overweight	−10.6	−50.3 to 29.2	0.60
Obese	34.9	−16.7 to 86.5	0.18

Table 4

Multivariable analysis of factors associated with metabolic syndrome among nonwhite subjects (N=55)

	Model 1			Model 2			Model 3			Model 4		
	OR (95% CI)	p-value		OR (95% CI)	p-value		OR (95% CI)	p-value		OR (95% CI)	p-value	
Alcohol intake												
Moderate	1.09 (0.23–5.19)	0.91		1.06 (0.22–5.08)	0.94		1.09 (0.23–5.22)	0.91		1.04 (0.21–5.07)	0.93	
Heavy	4.80 (1.09–21.22)	0.04		5.20 (1.14–23.72)	0.03		4.84 (1.10–21.93)	0.04		5.02 (0.92–22.24)	0.050	
Male sex				1.67 (0.43–6.58)	0.46							
Age, per decade							0.97 (0.36–2.60)	0.95				
Alcohol duration, per decade										1.01 (0.53–1.92)	0.21	

Model 1–4: Analysis of the effect of moderate and heavy alcohol use (compared to none) on metabolic syndrome in a one predictor-model (model 1), and when adjusting for sex (model 2), age (model 3), and duration of alcohol use (model 4).