Published in final edited form as:

Alcohol Clin Exp Res. 2018 March ; 42(3): 492–499. doi:10.1111/acer.13576.

Impact of moderate alcohol discontinuation on insulin action and secretion in Latinos with and without hepatitis C

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Abstract

Background/Aims—Insulin resistance (IR) is associated with hepatitis C infection (HCV), and Latinos are both at risk for IR and are disproportionately affected by HCV. Moderate alcohol consumption improves insulin sensitivity and may modify HCV-associated IR. We investigated the impact of moderate alcohol discontinuation on insulin sensitivity and secretion in Latinos using direct measurements.

Methods—Twenty-five non-diabetic, non-cirrhotic Latino adults without (n=17) or with (n=8) HCV underwent 3-day metabolic assessment before and after prescription of 6 weeks of moderate alcohol discontinuation. Peripheral IR was measured via steady-state plasma glucose (SSPG) and hepatic IR using endogenous glucose production during a two-step 240-minute insulin suppression test. Insulin secretion was measured using graded glucose infusion test.

Results—Baseline mean age was 46±11 years, 63% male, 29% had HCV, and mean BMI was 27±4 kg/m². Compared to non-HCV, HCV patients had a higher median SSPG (132 vs 98.8 mg/dL, p=1.0), hepatic IR (13.5 vs 11.3, p=0.24), and insulin secretion (ISR-AUC, 1290 vs 1250 pmol/min, p=0.98). After confirmed alcohol discontinuation, hepatic IR was the only parameter that changed significantly (increased, mean change 2.6±4.8, p=0.02). Higher baseline ALT was also associated with a greater change in hepatic IR (average 4.0 points/ALT doubling, p=0.004), and HCV was associated with a lesser change (average −7.3 points, p=0.002), independent of ALT.

Conclusions—Short-term moderate alcohol discontinuation adversely impacted hepatic IR in Latinos which was influenced by level of ALT at baseline independent of etiology. Though reduction in ALT through weight loss and HCV eradication remains a priority in improving IR, the

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Conflicts of interest: The authors have no conflicts of interest to report.

observed non-harmful effect of moderate alcohol use represents a potentially confounding variable that warrants further study.

Keywords

hepatic insulin resistance; ALT; HCV; insulin resistance; Hispanic

Introduction

It is estimated that hepatitis C virus (HCV) affects 130 million people globally, or 2.2% of the world population (Alter, 2007). In the United States alone, over 3 million individuals are chronically infected (Klevens et al., 2012). Latinos have disproportionately higher rates of HCV infection than non-Hispanic whites and African Americans, and are at higher risk of developing cirrhosis than any other ethnic group or race, in part due to higher rates of diabetes and insulin resistance (Rodriguez-Torres, 2008). HCV infection itself is also associated with diabetes and insulin resistance. Patients with HCV are at an approximately 1.7-fold increase risk of diabetes (White et al., 2008) and diabetes is considered an extrahepatic manifestation of HCV infection (Serfaty, 2017). Studies have also shown an increased prevalence of insulin resistance in HCV and an independent relationship between presence of HCV infection and increased insulin resistance (Imazeki et al., 2008, Moucari et al., 2008). HCV may impact glucose metabolism and insulin action through multiple potential pathogenic mechanisms including direct viral inhibition of insulin signaling pathways in liver, increase in proinflammatory cytokines, induction of oxidative stress, and impact on pancreatic β -cells (Serfaty, 2017). Others have implicated HCV as a mediator of insulin resistance in peripheral tissues (Milner et al., 2010), with HCV treatment resulting in reduction of insulin resistance (Brandman et al., 2012). While there is a wide distribution of insulin resistance in HCV, certain host factors including obesity and Latino ethnicity also appear to impact higher degrees of insulin resistance in this setting (Mukhtar et al., 2013, Moucari et al., 2008).

Importantly, these metabolic abnormalities contribute to progression of liver disease and higher rates of hepatic fibrosis in HCV (Hui et al., 2003). Metabolic abnormalities are also considered risk factors for development of non-alcoholic fatty liver disease, a prevalent condition that contributes to liver disease (Leite et al., 2009, Haukeland et al., 2005). Therefore, evaluation of modifiable factors (such as alcohol use) that can influence metabolic parameters and are common within the context of HCV infection is critical to improve and prevent progression of liver disease among at-risk Latinos.

Although current practice guidelines recommend cessation of all alcohol use in patients with HCV infection (AASLD/IDSA, 2015), one-half to two-thirds of HCV-positive individuals do not adhere to this advice (Peters and Terrault, 2002). Consequently, variable amounts of alcohol use are common in HCV. Moderate alcohol consumption is associated with a decreased risk of type 2 diabetes, decreased fasting insulin, improved insulin sensitivity, and lower HbA1c levels in non-diabetic patients (Davies et al., 2002, Koppes et al., 2005, Schrieks et al., 2015). Additionally, the presence of HCV may differentially influence the impact of moderate alcohol use on these metabolic parameters. As large studies have shown

that moderate alcohol use does not appear to adversely impact liver disease in HCV (Cheung et al., 2011, Monto et al., 2004) and current direct-acting anti-HCV medications can effectively eradicate HCV, the impact of cessation of moderate alcohol consumption on metabolic parameters is novel and has not been previously studied.

We hypothesized that discontinuation of moderate alcohol use in Latinos may influence insulin action and that certain factors including HCV infection may modify this relationship. Therefore, in this study we aimed to evaluate the impact of short-term discontinuation of moderate alcohol use in non-diabetic Latinos with and without HCV infection on comprehensive metabolic parameters including directly measured insulin resistance and secretion.

Subjects and Methods

Study subjects

Latinos 18 years of age with and without chronic HCV who drank alcohol moderately were recruited at San Francisco General Hospital between June 2013 and May 2015. Moderate alcohol consumption for women was defined as alcohol use of no more than 3 drinks on any single day and no more than 7 drinks per week and for men as no more than 4 drinks on any single day and no more than 14 drinks per week (NIAAA). Chronic HCV was confirmed by detectable HCV viral load. Latino ethnicity was defined by self-report of both parents and all four grandparents being of Latino ethnicity. Exclusion criteria included a history of diabetes (fasting plasma glucose ≥ 126 mg/dL, 120-minute glucose ≥ 200 mg/dL on oral glucose tolerance test (OGTT), a known history of diabetes, or use of anti-diabetic agents), cirrhosis (clinical or histological), HIV, chronic hepatitis B virus, or medical conditions compromising study participation. In addition 6 of the 8 patients (75%) with HCV had an available liver biopsy (66% had inflammation grade ≤ 2 , all had fibrosis stage ≤ 2) that confirmed absence of cirrhosis or other liver disease. 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 laboratory and clinical evaluation. 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. In addition, Timeline Follow back (TLFB), a validated instrument, was used to assess recent drinking behavior (Sobell and Sobell, 1992). Anthropometrics were obtained including height, weight, body mass index (BMI), and waist circumference. All subjects were then instructed to and agreed to discontinue alcohol intake for the next 6 weeks.

Metabolic testing

Metabolic testing was performed during a 3-day inpatient visit to the UCSF Clinical and Translational Science Institute-Clinical Research Center (CRC) at baseline and 6 weeks after prescribed discontinuation of all alcohol use by an OGTT (day 1), insulin suppression test (SSPG, day 2), and insulin secretion and clearance rate (graded-glucose infusion test

(GGIT), day 3). Complete alcohol abstinence during follow-up was assessed by self-report, and compliance was confirmed by weekly phone calls and reminders, as well as random urine ethyl glucuronide testing (performed twice and at least two weeks apart), a reliable indicator of recent drinking even when ethanol is no longer detectable (Dahl et al., 2011). Subjects who did not have confirmed compliance with alcohol cessation or did not return for follow-up testing were excluded from the data analysis (N=6, 3 subjects in HCV and 3 subjects in non-HCV groups, respectively).

On the first hospital day, after an overnight 12-hour fast, a 75g OGTT was performed to assess for presence of undiagnosed diabetes (120-minute glucose level ≥ 200 mg/dL (ADA, 2015)). One patient had undiagnosed diabetes at baseline based on OGTT and was therefore excluded from data analysis. On the second day, the two-step insulin suppression test (low-dose and high dose) was performed as previously described (Mukhtar et al., 2013). Plasma glucose and insulin levels obtained from 210 to 240 minutes during high-dose period were averaged to represent the steady-state plasma glucose (SSPG) and steady-state plasma insulin (SSPI) concentrations. The SSPG measures the peripheral (muscle) resistance of tissues to insulin-mediated glucose uptake.

Hepatic glucose production was assessed using an infusion of deuterated glucose ([6,6-d₂]-glucose) during the insulin suppression test, as an index of hepatic insulin resistance. Exogenous insulin levels were achieved to simulate basal (fasting) conditions (SSPI at ~ 10 – 15 μ U/mL) that partially inhibit endogenous insulin production during the low dose period (Abbasi et al., 2000). At these insulin concentrations, endogenous glucose production is not significantly suppressed from fasting rates. We therefore assessed the ability of basal insulin to maintain glucose homeostasis by measuring the rate of endogenous (hepatic) glucose production (EGP) using the low-dose period of the two-step insulin suppression test. Mass spectrometric analysis was used to quantify hepatic glucose production by the isotope dilution technique, wherein the steady-state plasma [6,6-d₂]-glucose enrichment is measured in the plasma during a constant intravenous infusion of [6,6-d₂]-glucose (Christiansen et al., 2000, Schwarz et al., 1995). $EGP \text{ (mg/kg-min)} = ([6,6-d_2]\text{glucose infusion rate} / [6,6-d_2]\text{glucose enrichment}) - [6,6-d_2]\text{glucose infusion rate}$. Hepatic insulin resistance was then calculated as $EGP \text{ (mg/min/Kg)} \times \text{insulin } (\mu\text{U/mL})$.

On the third day, a graded glucose infusion test (GGIT) was performed to measure insulin secretory function as previously described (Kim et al., 2014). Patients received graded intravenous infusions of glucose at increasing rates (1, 2, 3, 4, 6, 8 mg/kg/min). Each rate was administered for a total of 40 minutes. Glucose, insulin, and C-peptide concentrations were measured fasting, and then 30 and 40 minutes into each infusion period. The last two values were averaged at the end of each infusion period to calculate the mean for that infusion. The area under the curve (AUC) for glucose, insulin, and C-peptide were calculated. Insulin secretion rates (ISRs) were derived by deconvolution of peripheral plasma C-peptide concentrations, using a two-compartment model of C-peptide kinetics and standard parameters for C-peptide clearance estimated for each participant based on body surface area and age. For each participant, the mean ISR before and during the six glucose infusion periods was plotted against the corresponding mean glucose to construct a dose-response relationship. The best-fit line was then drawn through the data to allow comparison

of ISRs at the same glucose level. The ISR at molar increments of plasma glucose from 5 to 9 mmol/l was therefore obtained by interpolation. To evaluate the effect of alcohol cessation on measurements obtained during the graded glucose infusion, the total integrated area under the curve (ISR-AUC) was calculated using the trapezoidal rule.

Estimation of individual ancestry for Latinos

Latinos are an admixed population and are assumed to be comprised of three ancestral populations: African, European, and Native American. To identify and control for the heterogeneity among Latinos from different origins, in all subjects we estimated the proportion of global ancestry for each individual using the genotype data of 37 Africans, 42 Europeans, and 30 Native Americans. One hundred and four autosomal ancestry informative markers (AIMs) across the genome were used for the inference of individual ancestry proportions for Latinos (%African, %Native American, and %European heritage) (Tsai et al., 2005). These AIMs were selected because their allele frequencies vary between those of African, European, and Native American descent. Samples were genotyped using Sequenom iPLEX platform. The population structure for Latino individuals was inferred by a model-based clustering method (Pritchard et al., 2000). This method assumes the loci are at Hardy-Weinberg equilibrium and linkage equilibrium within each ancestral population group. It introduces population structure to the individuals so the assumed equilibrium is achieved. The method was implemented in the software package STRUCTURE (version 2.2) (<http://pritchardlab.stanford.edu/structure.html>) which was used to analyze the population structure of Latino individuals.

CYP2E1 genotyping

All patients underwent genetic analysis [as previously described (Burman et al., 2016)] 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 (Beulens et al., 2007, Neafsey et al., 2009, Wan et al., 1998). 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 (Wan et al., 1998).

Statistical analysis

Baseline characteristics of study patients were reported using mean $\pm$ standard deviation, median, or interquartile range. P-values comparing HCV-infected to HCV-uninfected participants on continuous variables were obtained by Mann-Whitney tests, and for categorical variables they were obtained by Chi-squared tests. For comparison of parameters before and after alcohol cessation, paired t-test were used. We used linear regression to examine the associations of participant characteristics with changes in metabolic parameters. We selected multivariable models by forward stepwise selection with forced inclusion of HCV and an entry criterion of $P < 0.05$ for other variables. These selected at most one other predictor variable. For a model of particular interest, we also evaluated how the estimated effects changed due to addition of any one several possible explanatory variables (specifically within-person changes from pre- to post-alcohol discontinuation in BMI, waist circumference, ALT, and AST and also between HCV and non-HCV group differences in

duration of alcohol discontinuation). All analyses were performed using the Statistical Analysis System version 9.4 (SAS Institute, Cary, NC).

Results

Twenty-five non-diabetic, non-cirrhotic Latino participants with (n=8) or without HCV (n=17) who drank alcohol moderately were enrolled in the study. Patients underwent metabolic evaluation at baseline and after a median of 6.9 weeks (interquartile range 6 – 7.6 weeks) following prescribed discontinuation of all alcohol use. Baseline patient characteristics are outlined in Table 1 and were notable for a mean age of 45.9 ± 11.3 years, 60% male, and a mean BMI of 26.8 ± 4.2 kg/m². Among the HCV patients, 88% had HCV genotype 1 (12% genotype 3), with a mean log₁₀HCV viral load of 6.1 ± 0.6 IU/mL. A higher proportion of HCV patients were born in United States (62.5% vs. 11.8% for non-HCV patients) and HCV patients had higher baseline ALT (mean ALT 55.5 versus 28.6 U/L) and AST levels (mean AST 53.0 versus 25.9 U/L) compared to HCV-negative patients. HCV positive patients also had lower LDL and total cholesterol levels compared to HCV negative patients (64 versus 110 mg/dL and 134 versus 183 mg/dL, respectively). With respect to metabolic parameters, patients with HCV showed a trend toward higher degrees of peripheral insulin resistance (SSPG, 132 versus 98.8 mg/dL), hepatic insulin resistance (13.5 versus 11.3), and insulin secretion (ISR AUC, 1290 vs 1250 pmol/min) at baseline than those without HCV, though these did not reach statistical significance. With respect to CYP2E1 genotyping, four patients were heterozygous (c1/c2) (two with HCV and two without) and two were homozygous for the mutant allele (c2/c2) both without HCV. There were no significant genetic differences (p=1.0) in alcohol metabolism between the two groups.

Tables 2 and 3 compares metabolic and laboratory parameters before and after alcohol discontinuation in all patients, and in those without and with HCV infection, respectively. After discontinuation of alcohol use, in all subjects (Table 2) AST levels decreased (mean change -2.8 ± 7.6 U/L, p=0.091) and hepatic insulin resistance increased (mean change 2.6 ± 4.8 , p=0.014). Although there were no statistically significant differences in mean changes of laboratory and metabolic parameters after alcohol discontinuation when comparing those without or with HCV infection (Table 3), there was a trend towards a greater increase in hepatic insulin resistance in those without HCV compared to those with HCV infection (mean change 3.7 vs 0.1, p=0.058).

Factors associated with change in metabolic parameters following moderate alcohol discontinuation

Table 4 summarizes univariable analysis evaluating the impact of baseline clinical and laboratory parameters on change in SSPG, hepatic insulin resistance and insulin secretion (ISR-AUC) following moderate alcohol discontinuation in all patients. On univariable analysis, there were no variables that predicted change in SSPG or insulin secretion (ISR-AUC) following discontinuation of alcohol that reached statistical significance (p<0.05); the estimated effect of HCV on SSPG was 10.2 mg/dL lower (95% CI -47.4 to 27.0 mg/dL, p=0.58) and on ISR-AUC was 63.7 pmol/min higher (95% CI -178.8 to 306.2, p=0.59) in

those with HCV (vs non-HCV). However, the increase in hepatic insulin resistance following discontinuation of alcohol was on average 0.9 points higher for each 10% increase in Native American ancestry proportion (95% CI 0.1 to 1.7, $p=0.03$), and 0.3 points higher for every 10 ng/mL increase in ferritin (95% CI 0.1 to 0.5, $p=0.01$) at baseline.

On multivariable forward regression analysis that controlled for HCV status, we did not identify any baseline factor that was associated with change in SSPG levels after discontinuation of alcohol use. On the other hand, baseline ALT levels and HCV status were independently associated with change in hepatic insulin resistance after alcohol discontinuation when modeled together in the 2-predictor model (Table 5). The average change in hepatic insulin resistance was 4.0 points higher for every doubling of ALT levels at baseline (95% CI 1.4 to 6.7, $p=0.004$) when controlling for HCV status. In addition, the change in hepatic insulin resistance was on average 7.3 points lower in those with HCV infection compared to without HCV when controlling for baseline ALT levels (95% CI -11.5 to -3.2 , $p=0.002$). Although statistically significant in univariable analysis, the percent native American ancestry did not meet the inclusion criterion when added to the model with HCV status and ALT (0.7 higher change in hepatic insulin resistance per 10% higher native American ancestry, 95% CI -0.1 to 1.4, $p=0.065$). Similarly, the effect of ferritin was 0.19 per 10-point increase (95% CI -0.01 to 0.39, $p=0.062$). When controlled for duration of alcohol discontinuation, both effects in the primary model were slightly larger in magnitude (data not shown), indicating that the difference in duration of alcohol discontinuation at baseline between HCV and non-HCV subjects (shown in Table 1) did not bias the estimation of the HCV effect. In addition, the impact of HCV status and ALT levels at baseline on change in hepatic insulin resistance remained similar when controlled for change in ALT levels, AST levels, BMI, or waist circumference from baseline to follow-up after discontinuation of alcohol use ($<10\%$ change in coefficients in all cases). With respect to insulin secretion, the only baseline factor that predicted change in ISR-AUC was triglycerides, independent of HCV status. The average change in insulin secretion following discontinuation of alcohol was 20.1 points higher (95% CI 1.1 to 39.2, $p=0.040$) for every 10-point increase in triglyceride levels at baseline. (Table 5) We further assessed whether the association between the effect of alcohol cessation on insulin secretion and triglyceride levels was confounded by insulin sensitivity, given that higher triglyceride levels are associated with insulin resistance. When accounting for degrees of insulin resistance, the observed association between insulin secretion and triglyceride levels decreased modestly, but it was no longer statistically significant (coefficient 15.3 per 10 mg/dL, 95% CI -3.3 to 34.0, $p=0.10$).

Discussion

Moderate alcohol use has been demonstrated to have beneficial health effects across a spectrum of conditions, including decreased risk of atherosclerotic heart disease, ischemic stroke, systemic inflammation, dementia, insulin sensitivity, and metabolic syndrome (Poli et al., 2013, Churilla et al., 2014). Specifically with regards to metabolic parameters, moderate alcohol use in healthy subjects has been associated with lower plasma glucose and insulin concentrations following oral glucose administration, and improved insulin-mediated glucose uptake (Facchini et al., 1994). Moreover, alcohol use is common in the setting of

HCV infection and despite counselling to stop at risk alcohol use, many individuals continue to drink alcohol at moderate levels. Though the recent introduction of highly effective antiviral HCV therapy has provided unprecedented opportunity for HCV eradication, the impact of viral eradication on reversing adverse metabolic outcomes is not fully known. In addition, some patients including underserved populations that include a high proportion of ethnic minorities and those especially at risk for health disparity may have limited access to HCV therapy due to high costs. Thus, assessment of the impact of moderate alcohol use on metabolic parameters, and potential differential effects in the presence of HCV infection, are timely and important to both HCV disease and prevention of metabolic complications.

This is the first study to comprehensively evaluate the impact of discontinuation of moderate alcohol use on metabolic parameters including direct measurements of peripheral and hepatic insulin resistance as well as insulin secretion among the at-risk Latino population with and without HCV infection. Overall, hepatic insulin resistance was the only metabolic parameter of insulin action that significantly increased after short-term discontinuation of alcohol use. After cessation of moderate alcohol consumption, those subjects with higher baseline ALT levels displayed worsening of hepatic insulin resistance, regardless of HCV status. We also show that although short term moderate alcohol discontinuation did not seem to significantly impact peripheral insulin resistance (SSPG) overall, when controlling for HCV status, there was a trend towards a lesser change in SSPG in older patients. This suggests that the metabolic benefits of moderate alcohol consumption on peripheral insulin resistance may be more pronounced in younger patients independent of HCV status. While baseline triglyceride levels were associated with change in insulin secretion after alcohol discontinuation, the effect was about 25% smaller when also controlled for insulin resistance at baseline, so some of its effect could be due to confounding with insulin resistance. Indeed, elevated triglyceride levels have been associated with decreased insulin sensitivity and increased insulin secretion in non-diabetic healthy subjects (Owei et al., 2016).

The relationship between alcohol use and insulin resistance is U-shaped with moderate alcohol consumption improving insulin resistance while higher degrees of alcohol use worsen insulin sensitivity. Cellular mechanisms implicate the liver in playing an important role in improved insulin sensitivity with moderate alcohol use, leading to higher hepatic glycogen content, increased liver insulin receptor substrate-1 (IRS-1) and protein kinase B phosphorylation (Tomie Furuya et al., 2005). The adenosine monophosphate-activated protein kinase-alpha (AMPK) is an enzyme that acts to control glucose and lipid homeostasis, and this protein's expression and phosphorylation status (as well as downstream targets) were studied in an animal model following moderate alcohol ingestion (Nammi and Roufogalis, 2013). This study showed increased AMPK-alpha activation via phosphorylation, and decreased SREBP-1 expression in the liver, indicating protection against the risk of fatty liver disease and other metabolic disorders. Our observations lend support to these findings and that hepatic inflammation and elevated liver enzymes also contributes to hepatic insulin resistance as previously shown (Bonnet et al., 2011). The novel finding that the adverse effect of discontinuation of moderate alcohol use on hepatic insulin sensitivity is more pronounced in those with higher ALT levels suggests that moderate alcohol consumption seems to have metabolic benefits in a subset of individuals with elevated ALT levels. The fact that there was little increase in hepatic insulin resistance in

HCV after cessation of moderate alcohol intake support the notion that HCV infection affects metabolic parameters. Moreover, moderate alcohol cessation did not appear to be harmful to metabolic parameters, in those with HCV infection in this study.

Latinos are an admixed population (Choudhry et al., 2006) and Native Americans are at high risk of insulin resistance, diabetes, and adverse metabolic outcomes (Lorenzo et al., 2001). Our study was strengthened by incorporating patient ancestry background in analysis of the impact of alcohol use on insulin parameters. Interestingly, we observed that a higher proportion of Native American ancestry among Latinos was associated with greater change in hepatic insulin resistance independent of presence of HCV infection. Therefore, future studies should assess for the possible confounding effect of ancestry background when studying alcohol effect and metabolic parameters among Latinos.

Strengths of our study include the direct and comprehensive measurements of insulin metabolism rather than indirect surrogates commonly utilized in metabolic evaluations, along with assessment of ancestry background among the Latinos enrolled. Our sample size is similar to other studies assessing these accurate and comprehensive metabolic studies due to impracticality of performing extensive 3 days inpatient testing in a larger sample (Beulens et al., 2006, Kim et al., 2009). Despite use of validated instrument to assess recent alcohol intake and drinking behavior in this study, it is possible that alcohol intake by self-report may underestimate drinking. Although impact of longer term duration of alcohol cessation was not evaluated, the 6-week period was chosen to ensure complete alcohol abstinence and minimize influence of other confounding factors that may occur longer interval periods, and is also consistent with durations used in other studies evaluating the influence of alcohol use interventions on metabolic parameters (Beulens et al., 2006, Kim et al., 2009). There was some imbalance in the duration of alcohol discontinuation between the HCV-infected and uninfected subjects, but this was in the opposite direction from what would explain the observed HCV effect. On the other hand, it is possible that short duration of alcohol discontinuation may be one of the reasons for the lack of a stronger impact on hepatic insulin resistance in the presence of HCV that may become more evident with longer duration of alcohol discontinuation.

In summary, in this Latino cohort, short term moderate alcohol discontinuation appeared to have an adverse effect on hepatic insulin sensitivity, and this effect was influenced by elevation of ALT levels at baseline independent of etiology. Though reduction in ALT levels through lifestyle modification and weight loss in those with fatty liver disease and viral eradication in those with HCV infection remain priorities in improving insulin sensitivity, the observed potential positive effect of moderate alcohol use in these settings warrants further study.

Acknowledgments

Financial support: Financial Support: This work was in part supported by K24AA022523 (M.K.) and UL1 TR000004 (NIH/NCATS UCSF-CTSI).

List of Abbreviations

HCV	Hepatitis C virus
OGTT	oral glucose tolerance test
TLFB	Timeline Followback
BMI	body mass index
SSPG	steady state plasma glucose
GGIT	graded-glucose infusion test
EGP	endogenous glucose production
AUC	area under the curve
ISR	insulin secretion rate
AIM	ancestry informative marker
ALT	alanine aminotransferase
AST	aspartate aminotransferase
IRS	insulin receptor substrate
AMPK	adenosine monophosphate-activated protein kinase
SREBP-1c	sterol regulatory element protein-1c
IR	insulin resistance

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Table 1

Baseline Patient, Laboratory and Metabolic Characteristics

Characteristic	All Subjects N=25	Without HCV N=17	With HCV N=8	P-value
Mean age (years) $\pm$ SD	45.9 $\pm$ 11.3	43.6 $\pm$ 11.2	50.9 $\pm$ 10.3	0.12
Median (range)	51 (25–65)	41 (25–65)	54.5 (26–59)	
Male sex (%)	15 (60)	10 (58.8)	5 (62.5)	0.86
Family history of diabetes (%)	19 (76.0)	13 (76.5)	6 (75.0)	0.94
Ancestry proportions				
% African, mean $\pm$ SD	8.0 $\pm$ 11.6	6.0 $\pm$ 12.3	13.4 $\pm$ 8.1	0.018
% European, mean $\pm$ SD	50.2 $\pm$ 21.5	46 $\pm$ 23.0	61.3 $\pm$ 12.8	0.25
% Native American, mean $\pm$ SD	41.8 $\pm$ 25.2	47.9 $\pm$ 26.3	25.3 $\pm$ 12	0.02
USA born (%)	7 (28%)	2 (11.8%)	5 (62.5%)	0.0084
Mean duration of alcohol abstinence (weeks), $\pm$ SD	6.8 $\pm$ 1.2	6.4 $\pm$ 1.0	7.5 $\pm$ 1.1	0.028
BMI (kg/m ²), mean, $\pm$ SD	26.8 $\pm$ 4.2	27.7 $\pm$ 4.0	25 $\pm$ 4.3	0.058
Waist circumference (cm), mean $\pm$ SD	91 $\pm$ 13.9	92.8 $\pm$ 15	88.3 $\pm$ 11.5	0.31
Mean ALT (U/L) $\pm$ SD	37.2 $\pm$ 24.6	28.6 $\pm$ 17.3	55.5 $\pm$ 28.9	0.0094
Mean AST (U/L) $\pm$ SD	34.6 $\pm$ 24	25.9 $\pm$ 9.3	53.0 $\pm$ 34.7	0.0073
Mean cholesterol (mg/dL) $\pm$ SD	167 $\pm$ 39.8	183 $\pm$ 33.6	134 $\pm$ 31.9	0.0073
Mean LDL (mg/dL) $\pm$ SD	95 $\pm$ 36	110 $\pm$ 30	64 $\pm$ 28	0.0024
Mean HDL (mg/dL) $\pm$ SD	52 $\pm$ 12	51 $\pm$ 12	56 $\pm$ 12	0.32
Mean triglycerides (mg/dL) $\pm$ SD	100 $\pm$ 62	112 $\pm$ 68	73 $\pm$ 36	0.20
Median fasting glucose (mg/dL) $\pm$ SD	96.1 $\pm$ 7.9	94.5 $\pm$ 7.8	99.4 $\pm$ 7.5	0.11
Median SSPG (mg/dL), (range)	98.8 (61.5–267)	98.8 (61.5–256)	132 (62.7–267)	1.00
Median hepatic insulin resistance, (range)	12 (7.3–28.9)	11.3 (7.3–27.2)	13.5 (8.4–28.9)	0.24
Median ISR AUC, (range)	1250 (699–1970)	1250 (782–1970)	1290 (699–1860)	0.98

SSPG, Steady state plasma glucose; ISR, Insulin secretion rate; AUC, Area under the curve

Table 2

Summary of Changes in Metabolic and Laboratory Parameters at Baseline and Follow-up after Discontinuation of Alcohol in All Patients

Metabolic and Laboratory parameters	N	Baseline	Follow-up	Mean Change $\pm$ SD	P-value
BMI (kg/m ²), Mean $\pm$ SD	25	26.8 $\pm$ 4.2	27 $\pm$ 4.4	0.2 $\pm$ 0.7	0.17
Waist circumference (cm), Mean $\pm$ SD	24	91.5 $\pm$ 13.9	92.6 $\pm$ 14.8	0.4 $\pm$ 2.9	0.55
ALT (U/L), Mean $\pm$ SD	24	37.2 $\pm$ 24.6	35.5 $\pm$ 24.2	-2.0 $\pm$ 15.6	0.54
AST (U/L), Mean $\pm$ SD	24	34.6 $\pm$ 24.0	31.5 $\pm$ 21.2	-2.8 $\pm$ 7.6	0.091
Fasting glucose (mg/dL), Mean $\pm$ SD	25	96.1 $\pm$ 7.9	98 $\pm$ 7.8	1.9 $\pm$ 6.3	0.16
Fasting insulin (μ U/mL), Mean $\pm$ SD	25	13.1 $\pm$ 6.5	14.3 $\pm$ 8.1	1.2 $\pm$ 5.6	0.29
SSPG (mg/dL), Mean $\pm$ SD	25	144 $\pm$ 78.6	147 $\pm$ 76.2	2.9 $\pm$ 41.3	0.72
Hepatic insulin resistance, Mean $\pm$ SD	25	13.9 $\pm$ 5.7	16.5 $\pm$ 5.8	2.6 $\pm$ 4.8	0.014
ISR AUC (pmol/min, 4 h), Mean $\pm$ SD	23	1270 $\pm$ 351	1260 $\pm$ 381	-15.9 $\pm$ 262.1	0.77

Table 3

Summary of Changes in Metabolic and Laboratory Parameters at Baseline and Follow-up after Discontinuation of Alcohol in Those with and Without HCV Infection

Metabolic and Laboratory Parameters	Without HCV (N= 17)	With HCV (N= 8)	P-Value
Mean change in BMI (kg/m ²), $\pm$ SD	0.2 $\pm$ 0.8	0.1 $\pm$ 0.4	0.84
Mean change in waist circumference (cm), $\pm$ SD	0.2 $\pm$ 3.4	0.7 $\pm$ 1.1	0.15
Mean change in ALT (U/L), $\pm$ SD	-3.9 $\pm$ 14.4	2.0 $\pm$ 18.1	0.98
Mean change in AST (U/L), $\pm$ SD	-2.8 $\pm$ 6.0	-2.8 $\pm$ 10.7	0.83
Mean change in fasting glucose (mg/dL), $\pm$ SD	2.7 $\pm$ 6.7	0.1 $\pm$ 5.5	0.32
Mean change in fasting insulin (μ U/mL), $\pm$ SD	0.2 $\pm$ 5.0	3.4 $\pm$ 6.6	0.5
Mean change in SSPG (mg/dL/L), $\pm$ SD	6.2 $\pm$ 42	-4.0 $\pm$ 41.8	0.79
Mean change in hepatic insulin resistance, $\pm$ SD	3.7 $\pm$ 4.4	0.1 $\pm$ 5.1	0.058
Mean change in ISR AUC (pmol/min, 4 h), $\pm$ SD	-38.1 $\pm$ 255	25.6 $\pm$ 287	0.54

Univariable Analysis of Baseline Factors Associated with Change in Metabolic Parameters after Discontinuation of Alcohol in All Patients

Table 4

Predictor Variable	Change in SSPG			Change in Hepatic Insulin Resistance			Change in Insulin Secretion (ISR-AUC)		
	Coef	95% CI*	P-value	Coef	95% CI*	P-value	Coef	95% CI*	P-value
HCV (vs non-HCV)	-10.2	-47.4 to 27.0	0.58	-3.6	-7.7 to 0.5	0.08	63.7	-178.8 to 306.2	0.59
Female gender	-5.2	-40.8 to 30.4	0.77	-0.3	-4.4 to 3.9	0.90	-195.5	-412.7 to 21.8	0.08
Age (per decade)	-14.0	-28.6 to 0.6	0.06	-0.7	-2.5 to 1.2	0.45	13.0	-93.0 to 119.0	0.80
BMI (per 5 kg/m ²)	3.7	-17.3 to 24.7	0.72	0.02	-2.4 to 2.5	0.98	40.0	-96.6 to 176.6	0.55
% Native American ancestry (per 10%)	1.6	-6.5 to 9.8	0.68	0.9	0.1 to 1.7	0.03	-0.2	-49.9 to 49.4	0.99
Log _e ALT (U/L)	5.3	-17.5 to 28.1	0.64	1.4	-1.2 to 4.1	0.26	13.5	-133.0 to 159.9	0.85
Log _e AST (U/L)	0.9	-23.6 to 25.4	0.94	1.1	-1.7 to 3.9	0.43	-29.9	-188.1 to 128.3	0.70
Triglycerides (mg/dL), (per 10 point)	-1.3	-4.1 to 1.6	0.37	0.03	-0.3 to 0.4	0.85	15.4	-2.6 to 33.4	0.09
Ferritin (ng/mL), per 10 point	0.4	-1.8 to 2.4	0.74	0.3	0.1 to 0.5	0.01	6.5	-7.1 to 20.1	0.33

* 95% CI; 95% confidence interval

Table 5

Multivariable Analysis of Baseline Factors Associated with Change in Metabolic Parameters after Discontinuation of Alcohol in All Patients Adjusted for HCV Status

Predictor Variable	Change in Hepatic Insulin Resistance			Change in Insulin Secretion (ISR-AUC)		
	Coef	95% CI*	P-value	Coef	95% CI*	P-value
HCV	-7.3	-11.5 to -3.2	0.002	160.1	-81.5 to 401.6	0.18
Log ₂ ALT (U/L)	4.0	1.4 to 6.7	0.004			
Triglycerides (mg/dL), (per 10 point)				20.1	1.1 to 39.2	0.040

* 95% CI; 95% confidence interval