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Dietary Fructose Intake and Severity of Liver Disease in HCV-infected Patients

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Abstract

Background & Goals—Dietary fructose intake in the United States has been increasing, and fructose intake has been associated with the metabolic syndrome and hepatic steatosis. This study aimed to determine if dietary fructose intake is associated with advanced hepatic fibrosis and inflammation in a HCV-infected male population.

Study—We conducted a cross-sectional study of HCV-infected male veterans. The main exposure variable was daily dietary fructose calculated from the National Cancer Institute Diet History Questionnaire and the main outcome variables were FibroSURE-ActiTest determined hepatic fibrosis (F0-F3=mild vs. F3/F4-F4=advanced) and inflammation (A0-A2=mild vs. A2/3-A3=advanced). We examined this association in logistic regression adjusting for demographic, clinical and other dietary variables.

Results—Among 313 HCV+ males, 103 (33%) had advanced fibrosis and 89 (28%) had advanced inflammation. Median daily fructose intake was 46.8 grams (interquartile range 30.4–81.0). Dietary fructose intake across quartiles among males with advanced vs. mild fibrosis was 21.4 vs. 25.2%, 32.0 vs. 24.8%, 24.3 vs. 25.2%, 22.3 vs. 24.8%, respectively, and among males with advanced vs. mild inflammation was 20.2 vs. 25.5%, 41.6 vs. 21.4%, 22.5 vs. 25.9%, 15.7 vs. 27.2%, respectively. In multivariate analysis, there were no significant associations between daily fructose intake and advanced fibrosis. There was a significant association only between the second quartile of daily fructose intake (30–48 grams) and advanced inflammation.

Conclusions—There were no significant associations between dietary fructose intake and hepatic fibrosis risk, as assessed by FibroSURE, in HCV-infected males. Additional research is needed to clarify the potential role of fructose intake and HCV-related hepatic inflammation.

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Keywords

Nutrition; Epidemiology; Hepatology; Infectious Diseases; Sugar

INTRODUCTION

Dietary fructose intake in the United States has increased by more than 1000% during the last 40 years (1, 2). There are a number of animal studies, primarily in mice, that confirm the adverse metabolic effects of fructose, including increased lipogenesis, insulin resistance, systemic inflammation, and obesity (2–5). Based on these metabolic properties in animals, one could extrapolate that fructose has deleterious effects in the human liver resulting in hepatic steatosis and necroinflammation (2, 4–6). Clinical studies in humans have shown dietary fructose as a possible risk factor for the development and progression of liver disease (4, 7).

It is possible that increased dietary fructose leading to the metabolic syndrome would result in increased steatosis, inflammation, or fibrosis in hepatitis C (HCV)-infected patients. Multiple studies have shown that obesity, insulin resistance and increased hepatic steatosis in HCV-infected patients is associated with increased advanced hepatic fibrosis and a reduced response to antiviral treatment (8–13). There are approximately 2.7 million people with chronic HCV in the United States (14), and HCV-related liver disease is the leading cause of liver transplantation and hepatocellular carcinoma (HCC)(15, 16). Finding a modifiable risk factor for the progression of HCV-related liver disease could have significant public health implications by reducing morbidity and mortality. However, there have been no studies examining customary dietary fructose intake as a risk factor for advanced liver disease in HCV-infected patients. Therefore, the aim of this study was to determine if dietary fructose intake is associated with increased hepatic fibrosis and inflammation in a well-characterized HCV-infected male population. We hypothesized that increased dietary fructose intake would be associated with increased hepatic fibrosis and inflammation.

METHODS

Study Population and Design

As part of an ongoing study we prospectively recruited consecutive HCV-infected veterans eligible for study participation at the time of their appointment to a HCV clinic. Details of the study were previously described(17). In this analysis, we have considered patients recruited between May 1, 2009 and January 31, 2011. This research was approved by the Institutional Review Boards for the Michael E. DeBakey VA Medical Center and Baylor College of Medicine.

Briefly, we restricted our analysis to: 1) males aged 18–70 years 2) no medical record or self-reported history of liver transplant, decompensated liver disease, HCC, dementia or psychosis 3) serologically-confirmed to have HCV viremia and to be negative for HIV or HBV infection, 4) complete study data including FibroSURE-ActiTest as of 1/31/2011. To help ensure the internal validity of our dietary analysis, we excluded patients with more than 10 missing food frequencies or 10 missing portion sizes on the diet history questionnaire or with daily caloric intake outside of a reasonable range (500–5,000 kilocalories).

Study Measures

We collected information on the past medical, social and family history, medication use, detailed lifetime alcohol use and risk factor history on each patient using a research assistant

administered survey questionnaire. Duration of HCV infection was determined by the number of years since first self-reported exposure to a risk factor associated with HCV, chronic alcohol abuse was examined as a dichotomous variable defined as average daily consumption of ≥ 3 drinks/day for ≥ 10 consecutive years and tobacco smoking was defined as current, former or never. The National Cancer Institute (NCI) Diet History Questionnaire (DHQ) was self-administered to collect dietary information. The DHQ is a validated Food Frequency Questionnaire developed to reflect food intake over the past 12-month period (18, 19). Responses to the DHQ were coded and then analyzed using the NCI Diet*Calc software. The results are reported as average daily intake of the various nutrients. The total fructose intake was calculated as the average daily fructose (grams) plus half of the average daily sucrose (grams), since sucrose is both fructose and glucose. Other carbohydrate intake (e.g., intake of mono- and polysaccharides like starch) were calculated as total daily carbohydrate intake minus fructose intake.

Hepatic disease severity was determined using the FibroSURE-ActiTest (BioPredictive, France), which uses a proprietary algorithm incorporating serum levels of $\alpha 2$ -macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, and γ -glutamyl-transpeptidase to determine fibrosis level and adds ALT to determine necroinflammatory activity level. These scores are categorized into METAVIR biopsy-based equivalent degrees of hepatic fibrosis (F0, no fibrosis present – F4, cirrhosis) and inflammatory activity (A0, no inflammatory activity – A3, severe inflammatory activity). FibroSURE has demonstrated a high concordance with biopsy-assessed level of METAVIR pathology in HCV-infected populations (20–25). Clinical severity of liver disease was also assessed using the Model for Endstage Liver Disease score. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) score was calculated as the fasting serum glucose (mg/dl) $\times$ the fasting serum insulin (μ IU/ml)/405. Non-diabetic participants with a HOMA-IR score ≥ 3 were classified as insulin resistant (IR). Weight in pounds was measured using the InBody520 Direct Segmental 8-point Multi-frequency Bioelectrical Impedance Analysis scale, with height in inches obtained using a study designated stadiometer. Body mass index (BMI) was calculated using the Quetelet index formula of weight in pounds $\times 703/\text{squared height in inches}$.

Data Analysis

The primary exposure variable was daily dietary fructose intake (grams). It was categorized into quartiles based upon HCV+ males with lowest fibrosis scores of F0 or F0-1 as most representative of the underlying non-diseased population corresponding to <30 , 30–48, 48–82, >82 grams/day. The primary outcome variables were FibroSURE-determined hepatic fibrosis and inflammation. Fibrosis was categorized into mild $\leq F3$ (F0, F0-F1, F1-F2, F2, F2-F3, F3) fibrosis controls and advanced $>F3$ (F3-F4, F4) fibrosis cases, while inflammation was similarly categorized into mild $\leq A2$ (A0, A0-A1, A1-A2, A2) inflammation controls and advanced $>A2$ (A2-A3, A3) inflammation cases.

We examined the association between dietary fructose intake and several possible confounders of the association between fructose and hepatic fibrosis or inflammation; these variables included demographic, dietary and clinical factors. Dietary variables were analyzed as continuous as well as categorical (quartile) variables. Non-parametric Wilcoxon rank sum testing was used for comparing continuous variables and Chi-square testing was used for comparing categorical variables.

We employed unconditional logistic regression analysis to evaluate the association between level of dietary fructose intake and risk of advanced hepatic fibrosis (F3/F4-F4) and also of advanced hepatic inflammation (A2/A3-A3) after adjustment for potential confounding by the following required predictors: age, race/ethnicity, BMI, degree of insulin resistance

(non-diabetic without IR, non-diabetic with IR, diabetic), total daily caloric intake, daily intake of other major dietary macronutrients including fat and other non-fructose based carbohydrates, and chronic alcohol abuse.

We conducted three sensitivity analyses. 1) To assess if diabetes status resulted in alterations in fructose intake that may have biased our observed associations between fructose intake and risk of advanced hepatic fibrosis or inflammation, we repeated our multivariate analyses in the subset of the cohort without diabetes. 2) To assess if insulin resistance status impacted the effect of fructose intake on hepatic fibrosis or inflammation, we repeated our multivariate analyses in the subset of the cohort with insulin resistance or diabetes. 3) We also repeated our multivariate analyses in the entire study cohort using an alternate categorization of daily fructose intake (<30 vs. ≥30 grams) to determine if this categorization would alter our observed associations between fructose intake and hepatic fibrosis or inflammation.

All effect estimates from logistic regression analysis are reported as odds ratios (OR) and 95% confidence intervals (95% CI). All statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

The study eligible cohort included 313 HCV-infected patients. The median age was 57 years (interquartile range (IQR) 54–61 years). The majority of the cohort was African-American (53.7%) and Caucasian (43.1%). None were on antiviral treatment at enrollment and only 18.5% had a history of antiviral treatment. The median daily caloric intake was 2,062 kilocalories with median daily dietary fructose intake 46.8 grams (IQR 30.4–81.0). There were 210 (67%) HCV+ male veterans with fibrosis stage ≥F3 and 103 (33%) with fibrosis stage <F3, and 224 (72%) with inflammation grade ≥A2 and 89 (28%) with inflammation grade <A2 based on FibroSURE testing.

The median age of HCV+ males was lower with increasing fructose intake ($p=0.05$) (Table 1). Fewer diabetics had daily fructose intake ≥48 grams/day (31.6% vs. 53.7% vs. 54.3% for diabetics, non-diabetics with IR and non-diabetics without IR, respectively, $p=0.01$). Median daily caloric intake as well as median daily intake of protein, fat and non-fructose carbohydrates were significantly higher in patients with higher fructose intake (all p -values <0.0001). There was no significant difference in MELD score among HCV+ males across quartiles of fructose intake ($p=0.64$). As shown in Table 2, there was no linear dose-response trend across quartiles of daily fructose intake among patients with mild (<F3, <A2) vs. advanced (≥F3, ≥A2) hepatic fibrosis or inflammation. Patients with advanced fibrosis or inflammation had the largest proportions of second quartile fructose intake (30–48 grams/day), but the lowest proportion of the highest quartile of fructose intake (≥82 grams/day) and mostly similar proportions of first and third quartiles compared to patients with mild fibrosis or inflammation.

In the multivariate logistic regression analysis, fructose intake was not significantly associated with advanced fibrosis risk (Table 3). Although the second quartile of daily fructose intake (30–48 grams) was associated with an increased odds of advanced fibrosis ($OR_{adj}=1.19$; 95% CI 0.54–2.64) and the fourth quartile of daily fructose intake (≥82 grams) was associated with a decreased odds of advanced fibrosis ($OR_{adj}=0.86$; 95% CI 0.28–2.63) compared to the lowest quartile of daily fructose intake (<30 grams), these findings were not statistically significant. In the multivariate logistic regression model for hepatic inflammation (Table 4), the second quartile of daily fructose intake (30–48 grams) was significantly associated with an increased odds of advanced inflammation ($OR_{adj} 2.51$;

95% CI 1.06–5.95) compared to the lowest quartile of daily fructose intake. Although the fourth quartile of daily fructose intake (>82 grams) was associated with a decreased odds of advanced inflammation (ORadj 0.49; 95% CI 0.14–1.77) the association was not statistically significant compared to the lowest quartile of daily fructose intake. Diabetes was significantly associated with advanced inflammation (ORadj= 2.19; 95% CI 1.02–4.71).

Sensitivity Analysis

Patients with diabetes had significantly less fructose intake than patients without diabetes ($p=0.01$, Table 1). We repeated the multivariate logistic regression analysis using the sub-cohort of 224 patients without diabetes (155 with mild and 69 with advanced fibrosis) (Table 5). There was still no significant association observed between daily fructose intake and advanced fibrosis. In a similar multivariate analysis in the same sub-cohort of 224 patients without diabetes (169 with mild and 55 with advanced inflammation), there was also no significant association between any quartile of daily fructose intake and advanced inflammation (Table 5). The association of the second quartile of daily fructose with advanced inflammation was still present, but no longer statistically significant.

We repeated the multivariate logistic regression analysis using the sub-cohort of 171 patients with insulin resistance or diabetes (104 with mild and 67 with advanced fibrosis) (Table 5). There was still no significant association observed between daily fructose intake and advanced fibrosis. In a similar multivariate analysis in the same sub-cohort of 171 patients with insulin resistance or diabetes (110 with mild and 61 with advanced inflammation), there was again a significantly increased odds of hepatic inflammation among patients with a daily fructose intake of 30–48 grams (ORadj 3.90; 95% CI 1.29–11.78). There was no significant association with any other quartile of daily fructose.

We performed another sensitivity analysis in the entire study population with daily fructose intake categorized as a dichotomous variable (≥ 30 compared to <30 grams), and found the adjusted OR for advanced fibrosis was 1.12 with a 95% CI of 0.52–2.41, and the adjusted OR for advanced inflammation was 1.99 with a 95% CI of 0.86–4.60.

DISCUSSION

This is the first study to evaluate dietary intake of fructose and risk of advanced hepatic fibrosis and inflammation in chronically HCV-infected males. The overall findings from this study indicate no consistent relationship between daily dietary fructose intake and risk of advanced hepatic fibrosis or inflammation. However, there was suggestion of a non-linear relationship as the second quartile of fructose intake (30–48 grams/day) was associated with an increased risk of both advanced hepatic fibrosis and inflammation compared with lowest quartile of fructose intake (<30 grams/day), which was stronger and reached statistical significance for inflammation.

Only one previous study looked at the effect of dietary fructose on advanced liver histology in humans. Abdelmalek et al. performed a cross-sectional study in 427 patients with biopsy-confirmed non-alcoholic fatty liver disease (NAFLD) in whom the amount of fructose-containing beverages was measured as a surrogate for fructose intake. The highest fructose consumers (≥ 7 servings/week based on the Block food questionnaire) had significantly increased fibrosis, but significantly less steatosis. There was no significant association between fructose intake and hepatic inflammation, except in patients ≥ 48 years of age (7). There are several differences in the study designs that may account for the observed discrepancies in our results. Abdelmalek et al. used fructose-containing beverages as opposed to our use of dietary fructose intake which makes it difficult to determine whether the nutrient fructose itself or other components in the beverage were associated with

advanced fibrosis risk in their study. We also adjusted for other dietary factors including total caloric intake and intake of non-fructose carbohydrates to more fully evaluate the independent effects of fructose on risk of advanced FibroSURE-determined liver disease. In our cohort, the majority of patients were African-American and the average BMI was categorized as overweight as opposed to obese. These two factors may be associated with less steatosis in our HCV population and result in a different influence of dietary fructose on patients with HCV versus those with NAFLD. Additional research in larger and comparably evaluated samples of patients is necessary to determine if the impact of fructose intake on liver disease progression differs in patients with NAFLD compared to those with HCV-related liver disease.

Our study has some limitations. The cross-sectional design prevents temporal assessments necessary to establish causal associations. Additionally, there are reasons it may have been difficult for our study to reliably identify a significant association between fructose intake and hepatic fibrosis or inflammation. Dietary fructose was analyzed as a categorical variable due to the skewedness of the variable, and there may have been inadequate power in the study sample to detect a difference among fructose quartiles. Fructose intake was estimated for the last one year only and it is possible that a dietary avoidance pattern may have masked or altered any possible association. For example, patients who already developed diabetes or who had more severe liver disease may avoid fructose as a way of coping or treating their condition. Indeed, in this study we found that patients with diabetes consumed less fructose. However, our observed risk estimates for the associations between fructose intake and risk of advanced hepatic fibrosis and inflammation were similar in a sensitivity analysis limited to patients without diabetes, and were not altered with adjustment for MELD score. Our estimate of fructose intake did not specifically examine that derived from high fructose corn syrup which is used as a sweetener in several beverage and food products.

Finally, we used FibroSURE-ActiTest to determine the degree of hepatic fibrosis and inflammation. FibroSURE-ActiTest is not routinely used in our clinical practice otherwise, but was performed in all study patients. Although liver biopsy may be considered the gold standard for grading and staging liver disease, it is also known to be vulnerable to sampling variability with reported 25% misclassification even for a 25mm sample (26). In designing this study, we were aware of the low likelihood of performing liver biopsies on all comers with HCV. In our hospital, the low number of liver biopsies (around 20%) is related to the large number of patients with contraindications to HCV treatment for whom a liver biopsy may not have been useful. Increasing the liver biopsy rate to an acceptably high level for study purposes would have been costly, impractical and probably not ethical. Even if a large enough cohort of patients with liver biopsies could be assembled, this would introduce considerable selection bias related to indications for and acceptability of liver biopsy. We believe that the threat to study validity from such bias exceeds the possibility of small misclassification with the use of FibroSURE-ActiTest. The FibroSURE-ActiTest has been well-validated with good performance characteristics in multiple HCV populations (20–25). Any concern regarding discordance between liver biopsy and FibroSURE-ActiTest should be minimal since utilizing only FibroSURE-ActiTest to comparably determine hepatic pathology across all our study patients limits selection bias and the impact of misclassification on study results. FibroSURE-ActiTest does not provide information on hepatic steatosis; therefore, the association of daily fructose consumption and hepatic steatosis in a HCV population could not be analyzed.

Our study has multiple strengths including prospective recruitment of male veterans with serologically-confirmed HCV and extensive phenotype data including alcohol/risk factor history. We also used the validated NCI Diet History Questionnaire to provide information on daily fructose intake instead of using surrogates for fructose. The observed trend of

increasing fructose intake with increasing protein, fat and non-fructose carbohydrate intake and also finding that a well-established risk factor like diabetes was also associated with increased risk of inflammation is supportive of internal validity and also of external generalizability of our findings on fructose intake and advanced liver disease risk in comparable populations of HCV-infected males.

In summary, our findings suggest increased daily dietary fructose intake is not associated with an increased risk of advanced hepatic fibrosis, as assessed by FibroSURE, in males with chronic HCV. Our findings for hepatic inflammation were equivocal, but suggest a potentially non-linear association between fructose intake and inflammation risk. The reason for this possible non-linear association is unclear. Limitations in study power may have influenced the detection of a clear association between fructose and advanced liver histology. However, this is an important question to explore in future studies given the societal increases in dietary fructose intake.

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Abbreviations

HCV	hepatitis C virus
NCI	National Cancer Institute
DHQ	Diet History Questionnaire
HOMA-IR	The Homeostasis Model Assessment of Insulin Resistance
BMI	body mass index
IQR	interquartile range

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Table 1

Characteristics of 313 HCV-infected patients based on self-reported daily dietary fructose intake presented in quartiles. Continuous variables are presented in median and interquartile ranges.

	Daily Fructose Intake (grams)			P-value
Age	< 30 n= 75	30–48 n= 85	> 48–82 n= 78	> 82 n= 75
	58 (55–62)	58 (55–61)	57 (53–61)	56 (53–59)
Race/Ethnicity (%)				
Caucasian	33 (44.0)	37 (43.5)	32 (41.0)	33 (44.0)
African-American	38 (50.7)	46 (54.1)	45 (57.7)	39 (52.0)
Hispanic	2 (2.7)	1 (1.2)	1 (1.3)	2 (2.7)
Other	2 (2.7)	1 (1.2)	0 (0.0)	1 (1.3)
BMI	28.5 (26.0–32.4)	28.3 (25.4–32.6)	27.2 (23.3–29.7)	27.5 (24.8–30.9)
Insulin Resistance *				0.09
No insulin resistance	27 (36.5)	36 (42.4)	43 (56.6)	32 (43.2)
Insulin resistance	20 (27.0)	24 (28.2)	27 (35.5)	24 (32.4)
Diabetes	27 (36.5)	25 (29.4)	6 (7.9)	18 (24.3)
MELD	7.34 (6.65–8.62)	7.50 (6.90–8.87)	7.67 (6.79–8.88)	7.60 (6.65–8.77)
Daily Calorie Intake (kcal)	1096 (762–1688)	1603 (1224–2459)	2433 (1796–3268)	3334 (2530–4253)
Daily Protein Intake (grams)	42.9 (30.3–75.3)	60.8 (43.3–95.1)	93.3 (59.5–113.8)	105.7 (59.7–140.1)
Daily Fat Intake (grams)	42.1 (27.3–74.4)	63.1 (46.1–94.4)	89.0 (59.0–124.0)	103.0 (61.1–147.5)
Daily Non-fructose Carbohydrate Intake (grams)	108.3 (76.9–151.8)	159.62 (124.7–209.7)	227.9 (171.3–287.5)	338.9 (283.1–406.4)
Chronic alcohol abuse ^				
3 drinks/day > 10 years	42 (56.0)	51 (60.0)	43 (55.8)	50 (66.7)
Tobacco Smoking ^				0.16
Current	38 (50.7)	45 (52.9)	55 (70.5)	42 (56.0)
Former	24 (32)	24 (28.2)	12 (15.4)	23 (30.7)
Never	13 (17.3)	16 (18.8)	11 (14.1)	10 (13.3)
Duration HCV Infection (years)	32 (24–39)	35 (28–39)	34 (24–39)	33 (26–37)

* Insulin resistance= HOMA-IR 3

^ Self-reported

BMI=body mass index; MELD= Model for Endstage Liver Disease

Table 2

Characteristics of 313 HCV-infected patients based on FibroSURE-determined hepatic fibrosis and inflammation. Continuous variables are presented as medians and interquartile ranges.

	Fibrosis Stage			Inflammatory Activity		
	Mild (F0-3) n=210 (%)	Advanced (F3/4-4) n=103 (%)	P-value	Mild (A0-2) n=224 (%)	Advanced (A2/3-3) n=89 (%)	P-value
Daily Fructose Intake (grams)						
<30	53 (25.2)	22 (21.4)	0.58	57 (25.5)	18 (20.2)	<0.01
30-48	52 (24.8)	33 (32.0)		48 (21.4)	37 (41.6)	
>48-82	53 (25.2)	25 (24.3)		58 (25.9)	20 (22.5)	
>82	52 (24.8)	23 (22.3)		61 (27.2)	14 (15.7)	
Daily Calorie Intake (kcal)						
	2098 (1279-3146)	1984 (1339-3015)	0.98	2049 (1287-3059)	2178 (1275-3058)	0.51
Daily Protein Intake (grams)						
	66.7 (43.3-107.4)	75.3 (45.7-107.6)	0.63	66.1 (42.3-106.3)	76.3 (52.1-110.1)	0.11
Daily Fat Intake (grams)						
	72.4 (43.8-116.3)	71.5 (45.2-113.5)	0.88	71.1 (43.0-114.4)	71.9 (50.2-120.9)	0.41
Daily Non-fructose Carbohydrate Intake (grams)						
	197.0 (124.7-293.8)	194.0 (139.8-298.0)	0.86	194.3 (127.4-295.6)	196.8 (125.7-276.0)	0.91
Age						
	57 (53-61)	58 (55-61)	0.04	57 (54-61)	57 (53-60)	0.24
Race/Ethnicity						
White	91 (43.3)	44 (42.7)	0.71	92 (41.1)	43 (48.3)	0.05
African-American	114 (54.3)	54 (52.4)		128 (57.1)	40 (44.9)	
Hispanic	3 (1.4)	3 (2.9)		2 (0.9)	4 (4.5)	
Other	2 (1.0)	2 (1.9)		2 (0.9)	2 (2.3)	
BMI						
	27.9 (24.5-31.1)	28.2 (25.7-31.9)	0.42	27.8 (24.7-30.3)	28.8 (25.7-32.6)	0.04
Insulin Resistance						
No insulin resistance	102 (49.5)	36 (35.0)		110 (50.0)	28 (31.5)	
Insulin resistance	57 (27.7)	38 (36.9)	0.05	62 (28.1)	33 (37.1)	0.01
Diabetes	47 (22.8)	29 (28.2)		48 (21.8)	28 (31.5)	
Chronic alcohol abuse[^]						
3 drinks/day > 10 years	127 (60.8)	59 (57.3)	0.56	135 (60.5)	51 (57.3)	0.60
Duration HCV infection (years)						
	33.0 (26-39)	36 (28-39)	0.11	33 (25-39)	34 (27-39)	0.56
Tobacco Smoking[^]						

	Fibrosis Stage		Inflammatory Activity		P-value
	Mild (F0-3) n=210 (%)	Advanced (F3/4-4) n=103 (%)	Mild (A0-2) n=224 (%)	Advanced (A2/3-3) n=89 (%)	
Current	128 (61.0)	52 (50.5)	130 (58.0)	50 (56.2)	0.40
Former	51 (24.3)	32 (31.1)	62 (27.7)	21 (23.6)	
Never	31 (14.7)	19 (18.5)	32 (14.3)	18 (20.2)	

[^] Self-reported
BMI-body mass index

Table 3

Risk factors for advanced fibrosis in 303 HCV-infected patients (98 patients had advanced fibrosis; Hispanics and other race/ethnicity not analyzed, n=10).

	Fibrosis Stage			
	Univariate Models		Multivariate Models	
	Odds Ratio (95% CI) F3 vs. > F3	P-value	Odds Ratio (95% CI) F3 vs. > F3	P-value
Daily Fructose Intake (grams)^{^^}				
<30	Reference		Reference	
30–48	1.46 (0.73–2.90)	0.28	1.19 (0.54–2.64)	0.67
>48–82	1.14 (0.52–2.48)	0.75	0.98 (0.38–2.54)	0.96
>82	1.14 (0.48–2.73)	0.77	0.86 (0.28–2.63)	0.79
Daily Fat Intake (grams)^{^^}				
<44	Reference		Reference	
44–73	0.99 (0.41–2.41)	0.98	0.85 (0.30–2.44)	0.77
>73–116	0.81 (0.28–2.40)	0.71	0.78 (0.21–2.83)	0.70
>116	0.94 (0.27–3.22)	0.92	0.76 (0.18–3.30)	0.72
Daily Non-fructose Carbohydrate Intake (grams)^{^^}				
<127	Reference		Reference	
127–195	1.68 (0.64–4.45)	0.29	1.97 (0.68–5.67)	0.21
>195–294	1.54 (0.43–5.48)	0.51	1.47 (0.34–6.24)	0.61
>294	2.92 (0.62–13.82)	0.18	2.89 (0.47–17.87)	0.25
Age				
<50	Reference		Reference	
50–59	2.35 (0.77–7.21)	0.13	1.94 (0.58–6.48)	0.28
>59	2.84 (0.90–8.91)	0.07	2.06 (0.59–7.18)	0.26
Race/Ethnicity				
Caucasian	Reference		Reference	
African-American	1.01 (0.62–1.65)	0.96	0.94 (0.55–1.63)	0.83
BMI				
<25	Reference		Reference	
25–29	1.42 (0.76–2.67)	0.27	1.24 (0.60–2.55)	0.56
>29	1.42 (0.73–2.78)	0.30	1.20 (0.55–2.64)	0.64
Insulin Resistance				
No insulin resistance	Reference		Reference	
Insulin resistance	1.89 (1.08–3.30)	0.03	1.74 (0.90–3.37)	0.10
Diabetes	1.75 (0.96–3.18)	0.07	1.80 (0.90–3.61)	0.10
Chronic alcohol abuse[^]				
3 drinks/day > 10 years	0.87 (0.54–1.40)	0.56	0.84 (0.49–1.46)	0.54
Duration HCV infection (years)	1.02 (1.00–1.05)	0.05	1.01 (0.99–1.04)	0.34

^{^^} Adjusted for daily caloric intake in univariate and multivariate analyses

[^]Self-reported

BMI-body mass index

Table 4

Risk factors for advanced inflammation in 303 HCV-infected patients (83 had advanced inflammation, Hispanics and other race/ethnicity not analyzed, n=10)

	Inflammatory Activity				
	Univariate Models		P-value	Multivariate Models	
	Odds Ratio (95% CI)	A2 vs. > A2		Odds Ratio (95% CI)	A2 vs. > A2
Daily Fructose Intake (gm) ^{^^}					
<30	Reference			Reference	
30–48	2.24 (1.10–4.58)		0.03	2.51 (1.06–5.95)	0.04
>48–82	0.86 (0.37–2.01)		0.73	1.20 (0.42–3.43)	0.73
>82	0.46 (0.17–1.22)		0.12	0.49 (0.14–1.77)	0.28
Daily Fat Intake (grams) ^{^^}					
<44	Reference			Reference	
44–73	2.30 (0.87–6.12)		0.10	1.81 (0.56–5.87)	0.32
>73–116	1.91 (0.57–6.38)		0.29	1.34 (0.31–5.78)	0.70
>116	2.51 (0.66–9.54)		0.18	1.51 (0.30–7.53)	0.61
Daily Non-fructose Carbohydrate Intake (grams) ^{^^}					
<127	Reference			Reference	
127–195	0.98 (0.35–2.75)		0.97	1.08 (0.33–3.53)	0.89
>195–294	0.93 (0.24–3.55)		0.91	1.21 (0.24–6.11)	0.82
>294	0.55 (0.11–2.79)		0.47	1.44 (0.19–10.96)	0.73
Age					
<50	Reference			Reference	
50–59	0.77 (0.31–1.93)		0.58	0.53 (0.18–1.57)	0.25
>59	0.69 (0.27–1.80)		0.45	0.40 (0.12–1.28)	0.12
Race/Ethnicity					
Caucasian	Reference			Reference	
African–American	0.66 (0.40–1.10)		0.11	0.65 (0.36–1.17)	0.15
BMI					
<25	Reference			Reference	
25–29	1.08 (0.55–2.12)		0.82	0.87 (0.39–1.95)	0.73
>29	2.13 (1.07–4.24)		0.03	1.84 (0.79–4.30)	0.16
Insulin Resistance					
No insulin resistance	Reference			Reference	
Insulin resistance	2.09 (1.16–3.78)		0.02	1.45 (0.70–3.01)	0.32
Diabetes	2.29 (1.23–4.28)		<0.01	2.19 (1.02–4.71)	0.05
Chronic alcohol abuse [^]					
3 drinks/day > 10 years	0.88 (0.53–1.45)		0.61	0.74 (0.41–1.35)	0.33
Duration HCV infection (years)	1.01 (0.98–1.03)		0.58	1.01 (0.99–1.04)	0.36

^{^^} Adjusted for daily caloric intake in univariate and multivariate analyses

[^]Self-reported

BMI-body mass index

Table 5

The association between daily fructose intake with advanced fibrosis and inflammation in two groups: 224 HCV-infected patients without diabetes (69 had advanced fibrosis and 55 had advanced inflammation), and 171 HCV-infected patients with insulin resistance or diabetes (67 had advanced fibrosis and 61 had advanced inflammation). Results of two separate multivariate logistic regression analyses.

	Fibrosis Stage [^]			Inflammation Activity [^]		
	Multivariate Models			Multivariate Models		
	Odds Ratio (95% CI)	F3 vs. > F3	P-value	Odds Ratio (95% CI)	A2 vs. > A2	P-value
Patients without diabetes Fructose (grams/day)						
<30	Reference			Reference		
30–48	0.85 (0.32–2.27)		0.74	2.05 (0.69–6.10)		0.20
>48–82	0.61 (0.20–1.84)		0.38	1.04 (0.31–3.52)		0.95
>82	0.88 (0.24–3.25)		0.85	0.61 (0.14–2.72)		
Patients with diabetes or IR Fructose (grams/day)						
<30	Reference			Reference		
30–48	1.75 (0.60–5.09)		0.31	3.90 (1.29–11.78)		0.02
>48–82	0.86 (0.22–3.32)		0.83	1.16 (0.28–4.75)		0.83
>82	0.28 (0.06–1.29)		0.10	0.31 (0.06–1.67)		0.17

[^] Adjusted for age, race/ethnicity, daily caloric intake, fat and daily non-fructose carbohydrate intake, BMI, chronic alcohol abuse and duration HCV infection