Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Liver International ISSN 1478-3223

METABOLIC AND STEATOHEPATITIS

Effect of lifetime alcohol consumption on the histological severity of non-alcoholic fatty liver disease

Hellan K. Kwon[1], Joel K. Greenson[2] and Hari S. Conjeevaram[1]

1 Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA
2 Department of Pathology, University of Michigan, Ann Arbor, MI, USA

Keywords
lifetime alcohol – non-alcoholic fatty liver disease – non-alcoholic steatohepatitis

Correspondence
Hellan K. Kwon, MD, Division of Gastroenterology, Department of Internal Medicine, 3912 Taubman Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5362, USA
Tel: 734 936 6400
Fax: 734 936 7392
e-mail: hellank@med.umich.edu

Received 15 February 2013
Accepted 19 May 2013

DOI:10.1111/liv.12230
Liver Int. 2014: 34: 129–135

Abstract

Background & Aims: Non-alcoholic fatty liver disease (NAFLD) is defined based on recent alcohol consumption; however, remote or lifetime alcohol consumption is not taken into account. It is not known whether lifetime alcohol consumption contributes to the severity of disease in patients with NAFLD. To determine the effect of lifetime alcohol consumption on the histological severity in patients with NAFLD. *Patients & Methods:* Adults >18 years of age with presumed NAFLD and alcohol consumption <40 g/week were enrolled. Lifetime alcohol consumption was determined using a questionnaire. Patients with a history of long-term alcohol abuse or dependence were excluded. A liver biopsy was reviewed by a single pathologist in a blinded fashion. Demographic, clinical and histological findings were compared in those who had regular alcohol consumption and those who did not. *Results:* A total of 77 patients had fatty liver on biopsy. Fifty-two patients had a history of regular alcohol consumption. The median lifetime cumulative alcohol intake was 24 gram-years. On multivariable analysis, increasing age (OR 1.07, 95% CI 1.01–1.14) was associated with severe liver disease, whereas alcohol consumption of ≥24 gram-years was associated with less severe disease (OR 0.26, 95% CI 0.07–0.97, $P = 0.04$). Patients who continued to consume alcohol or had been abstinent for ≤1 year had less severe disease. *Conclusion:* Some degree of regular alcohol consumption over the course of a lifetime compared to minimal intake appears to have a protective effect on the histological severity of liver disease among patients with strictly defined NAFLD.

Non-alcoholic fatty liver disease (NAFLD) is now recognized as one of the most common forms of chronic liver disease in developed countries with an estimated prevalence of 10–24% in the general population (1–3). Obesity, type 2 diabetes mellitus (DM) and dyslipidaemia are common risk factors for NAFLD. A diagnosis for NAFLD is considered in patients with elevated liver enzymes and/or fatty liver on imaging, who have no significant alcohol consumption and no other causes of chronic liver disease. There is variability in the cut-off value used to determine the significance of current alcohol consumption. Lifetime alcohol consumption is not taken into consideration when NAFLD is clinically suspected. The range of current alcohol intake that has been proposed for this cut-off is 10 g per day or less to 20–40 g per day in men and 20 g per day in women. It has been suggested that a reasonable cut-off would be 20 g per day, acknowledging that there will be uncertainty in the grey areas of this limit (4).

It is well known that in patients with chronic hepatitis C, lifetime alcohol consumption is an independent risk factor for histological disease progression including the development of cirrhosis (5, 6). Studies on the role of ongoing alcohol consumption in patients with NAFLD have reported variable results with some studies showing a protective effect while others showing a role for disease progression similar to that seen in chronic hepatitis C (7–11). However, the effect of lifetime alcohol consumption on the overall disease severity in patients with clinically and histologically well-defined NAFLD has not been reported. The aim of this study was to determine if the cumulative lifetime alcohol consumption influences the overall histological severity in patients with NAFLD.

Material and methods

Patients

Adult patients seen in the general Hepatology clinic at the University of Michigan who were clinically suspected of having NAFLD were enrolled in a prospective

study between March 2003 and November 2004. The study was approved by the Institutional Review Board at our medical centre and all patients signed an informed consent to participate in the study.

The main inclusion criteria were as follows: (i) Patients with clinically suspected NAFLD based on persistent elevation in aminotransferase levels (>1.5 upper limit of normal on two or more occasions at least 3 months apart) and/or radiological evidence of fatty liver; (ii) A liver biopsy performed within 1 year of enrolment into the study; and (iii) Patients should be able and willing to provide written informed consent for the study.

Patients were excluded from the study for the following reasons: (i) Other causes of chronic liver diseases; (ii) Alcohol use of more than 40 g/week (≥5 drinks/week) within the past 12 months or a history of long-term alcohol abuse or dependence in the past; (iii) Use of medications reported to cause steatosis (including amiodarone, steroids, tamoxifen, valproic acid, methotrexate, iv tetracycline) within the past 3 months or greater than 6 months in the past 2 years; (iv) Weight reduction surgery within 1 year or a history of jejunoileal bypass; (v) Weight loss medication or participation in weight loss programme in the past 3 months; and (vi) Evidence of hepatic decompensation, HIV antibody positive, pregnant or breast feeding.

Study design

Adult patients suspected of NAFLD were enrolled into the study after written consent was obtained. Medical documents were reviewed focusing on the inclusion and exclusion criteria. Anthropometric evaluation was performed and lifetime alcohol consumption history was obtained by interview using the Skinner Lifetime Drinking History. The per cent body fat was estimated by bioimpedance analysis (BIA) using the RJL Systems Body Composition Analysis system, which is a simple technique of measuring body fat. The presence of metabolic syndrome was defined by the National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) (12). The homeostasis model assessment (HOMA) to calculate insulin resistance (IR) [HOMA = (insulin (μU/ml) * glucose (mmol/L))/22.5] was utilized. A HOMA value of 2.0 or greater was defined as IR (13).

Liver biopsies were performed within 1 year of enrolment and reviewed by a single pathologist blinded to the clinical history. The histological features of NAFLD were scored according to NASH Clinical Network Scoring System by Kleiner and Brunt (14). In brief, the presence and severity of steatosis (0–3), lobular inflammation (0–3), hepatocyte ballooning (0–2) and fibrosis (0–4) were scored. The NASH activity score (0–8) is the sum of steatosis, lobular inflammation and ballooning and the Global NASH score (0–12) is the sum of the NASH activity score and fibrosis. The presence of bridging fibrosis or cirrhosis was defined as having 'severe histological disease' in this study.

Lifetime alcohol consumption

The Skinner Lifetime Drinking History is a structured interview that estimates alcohol consumption throughout an individual's lifetime (15). The interview begins with determining if the patient consumes more than one drink (beer, liquor, wine, wine cooler) per month for 1 year or more than three drinks a day for three consecutive days over the course of their life. 'Abstinence' from alcohol was defined as those who consume less than this predetermined amount. For each time period that the drinking pattern changed, the duration, frequency, average and maximum quantity each time alcohol was consumed, the style of drinking (binge, weekend, frequent, occasional), variability in consumption, type of beverage and life events that may have affected drinking patterns were obtained.

The total amount of alcohol consumption was expressed as gram-years for each drinking pattern. Gram-years of consumption were calculated by multiplying the amount of alcohol consumed (grams) per day by the duration of a particular drinking pattern (years). The total amount of alcohol consumed over a lifetime was determined by adding the gram-years for each drinking period. The duration of abstinence from alcohol was determined by subtracting the age that the patient last drank less than one alcoholic beverage per month in a year or less than three drinks for three consecutive days from the patients' age at enrolment.

Statistical analysis

Using a *t*-test for continuous variables and chi square analysis for categorical variables we compared patients with a history of drinking and those who abstained. Correlation between histology and variables was analysed by Pearson's correlation coefficient. Statistical analysis was performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

The study population consisted of 77 patients with histologically confirmed NAFLD who also had had completed the lifetime alcohol consumption survey at the time of initial enrolment into the study. The characteristics of the 77 patients are in Table 1. Forty-three patients (56%) were women and 52 (68%) were obese (Body mass index ≥30 kg/m^2). The presence of metabolic syndrome as defined by ATP III (Adult Treatment Panel III, Third report of the expert panel on detection, evaluation and treatment of high blood cholesterol in adults) criteria was seen in 39% of patients (n = 30). Sixty-seven patients (87%) had evidence of insulin

Table 1. Clinical, Demographic, biochemical and histological characteristics of patients with ≥ or < than 24 gram-years Lifetime alcohol consumption

	≥24 gm-yrs (n = 40)	<24 gm-yrs (n = 37)	P-value
Age (years)	46 ± 11	48 ± 12	0.35
Gender (female %)	40	73	0.01
BMI (kg/m^2)	32 ± 7	34 ± 6	0.33
Waist-Hip ratio	0.9 ± 0.07	0.9 ± 0.07	0.66
BIA% fat	33 ± 12	43 ± 12	0.001
Metabolic syndrome (%)	37	54	0.22
HOMA index	5.2 ± 3.6	6.1 ± 3.9	0.31
Cholesterol (mg/dl)	194 ± 42	215 ± 58	0.05
TG (mg/dl)*	186 ± 97	220 ± 259	0.45
Insulin (μU/dl)*	20 ± 11	22 ± 11	0.44
Glucose (mg/dl)*	99 ± 17	104 ± 22	0.22
ALT (IU/dl)	78 ± 37	73 ± 59	0.68
AST (IU/dl)	50 ± 24	56 ± 43	0.44
Alk Phos (IU/dl)	88 ± 23	106 ± 51	0.05
Histology (NASH-CRN scoring system)			
Steatosis (0–3)	1.8 ± 0.8	2.0 ± 0.8	0.27
Lobular inflammation (0–3)	1.5 ± 0.8	1.5 ± 0.8	0.71
Ballooning (0–2)	0.5 ± 0.5	0.6 ± 0.5	0.56
NASH activity (0–8)	3.8 ± 1.5	4.1 ± 1.3	0.30
Fibrosis (0–4)	1.2 ± 1.0	1.8 ± 1.2	0.03
F3/F4 (n)	4	13	0.0001
Global NASH (0–12)	5.0 ± 1.9	5.8 ± 1.9	0.06

*TG, insulin, glucose are fasting measurements.

Data expressed as Mean ± SD values, n (%).

BMI, Body mass index; BIA, bioimpedence analysis (per cent total body fat); HOMA, homeostasis model assessment; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NASH-CRN, NASH Clinical Research Network scoring system.

resistance defined as HOMA (homeostasis model assessment) index ≥2.0. Overall, histological disease was mild in these patients with a mean NASH activity score of 3.9 (range 1–7) and mean global NASH score of 5.4 (range 1–9). Severe liver disease (bridging fibrosis or cirrhosis on liver biopsy) was seen in 17 patients (22%).

Lifetime alcohol consumption

The overall median alcohol consumption among the 77 patients with NAFLD was 24 gram-years (range 0–2251). Although the patients were recruited into the study based on the definition of <40 g per week, the patient with the alcohol consumption 2251 gram-year was the outlier – once recruited the patient gave this history on the lifetime alcohol questionnaire. Removing the patient from the analysis did not change the findings median values reported. Those who consumed equal to or more than 24 gram-years were more likely to be men (73% vs. 40%, P = 0.01), had significantly lower per cent total body fat (BIA% fat 33 ± 12 vs. 43 ± 12, P = 0.001) and lower serum total cholesterol levels (194 ± 42 vs. 215 ± 58 mg/dl, P = 0.05), when compared to patients who consumed <24 gram-years (Table 1). In addition, patients who consumed ≥24 gram-years had significantly lower fibrosis scores on liver histology (1.2 ± 1.0 vs. 1.8 ± 1.2, P = 0.03). Although there was a trend towards lower insulin resistance in the higher consumption group (HOMA index values 5.2 ± 3.6 vs. 6.1 ± 3.9), this difference was not statistically significant (P = 0.31).

We also compared patients with lifetime alcohol consumption at cut-off values of 10 gram-years and 40 gram-years. In both settings, the per cent total body fat (BIA%) and the fibrosis score remained significantly lower in the group that consumed more alcohol (data not shown).

Table 2 compares patients who consumed alcohol vs. those who had had abstained from alcohol in their lifetime (non-drinkers). Twenty-five patients (32%) were abstinent from alcohol and were more likely to be women (83% vs. 44%, P = 0.0001) and had a higher body fat percentage measured by bioimpedance assay (44.9% vs. 34.5%, P = 0.0003). There was, however, no statistically significant difference in the overall NAFLD histology assessment (steatosis, lobular inflammation and hepatocyte ballooning grades or fibrosis stage) between the two groups.

Factors associated with severe liver disease (Fibrosis stage 3-4)

Severe liver disease (fibrosis stage 3-4: F3/F4) was associated with increasing age, per cent total body fat (BIA %), serum aspartate aminotransferase and alkaline phosphatase levels and NASH histological feature of ballooning (P < 0.05 – < 0.001). As seen in Tables 1 and 2, the number of patients who were non-drinkers or had lifetime alcohol consumption below less than 24 gram-years was significantly higher in the F3/F4 group compared to the group with less severe (F0-2) liver disease with regards to fibrosis severity. The presence of severe liver disease was inversely related to the quantity of lifetime alcohol consumption (≥24 vs. < 24 gram-years, relative risk −0.32, P = 0.005). In multivariate analysis, as shown in Table 3, after controlling for other characteristics including age, gender, BMI, BIA% fat, HOMA-IR index, liver enzymes and selected histological features, the independent risk factors for severe liver disease were an increase in age (years) and smaller quantities (<24 gram-years) of lifetime alcohol consumption. Patients who consumed equal to or above the median level of alcohol during their lifetime had a significantly lower risk of bridging fibrosis or cirrhosis (OR: 0.26, 95% CI: 0.07–0.97, P = 0.046). In addition, the protective effect of alcohol consumption was even seen in patients consuming above the lower cut-off level of 10 gram-years (odds ratio 0.24, 95% CI: 0.07–0.89, P = 0.03) when controlling for other factors, however, it was no longer significant above the higher cut-off value of ≥40 gram-years of lifetime alcohol consumption (data not shown).

Table 2. Clinical, demographic, biochemical and histological characteristics of all patients diagnosed with NAFLD and those with and without previous alcohol consumption

	All (N = 77)	Alcohol use (N = 52)	Abstinent (N = 25)	P-value
Age (years)	46.9	45.8	49.1	0.26
Sex (Female%)	56	42	84	0.0001
BMI (kg/m^2)	33.0	32.7	33.8	0.44
Waist-Hip ratio	0.94	0.94	0.93	0.74
Metabolic syndrome (%)	39	39	40	0.90
BIA (% fat)	37.9	34.5	44.9	0.0003
Systolic BP (mmHg)	128	129	126	0.35
Diastolic BP (mmHg)	76	77	74	0.16
Cholesterol (mg/dl)	204	201	211	0.40
HDL (mg/dl)	54	55	51	0.65
LDL (mg/dl)	115	116	116	0.97
TG (mg/dl)*	202	191	225	0.59
Insulin (UU/dl)*	21.3	20.4	23.4	0.28
Glucose (mg/dl)*	101	101	103	0.72
HOMA index	5.6	5.3	6.2	0.36
ALT (IU/dl)	76	74	69	0.38
AST (IU/dl)	54	54	55	0.91
Alk Phos (IU/dl)	97	94	101	0.43
Histology (NASH-CRN scoring system)				
Steatosis score (0–3)	1.9	1.8	2.0	0.45
Lobular inflammation (0–3)	1.5	1.5	1.6	0.45
Ballooning (0–2)	0.5	0.5	0.6	0.19
NASH activity (0–8)	3.9	3.8	4.2	0.18
Fibrosis score (0–4)	1.5	1.4	1.8	0.17
F3/F4 (n)		8	9	0.04
Global NASH (0–12)	5.4	5.1	5.9	0.13

*TG, insulin, glucose are fasting measurements.

Data expressed as Mean values, n (%).

BMI, Body mass index; BIA, bioimpedance analysis (per cent total body fat); BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; HOMA, homeostasis model assessment; AST, aspartate aminotransferase;ALT,alanine aminotransferase; NASH-CRN, NASH Clinical Research Network scoring system.

Table 3. Associations with severe liver disease (Fibrosis stage 3–4) found in Multivariable Logistic Regression

Characteristics	Odds ratio	95% CI	P-value
Age	1.07	1.01–1.14	0.027
Gram-years (≥24 vs. <24)	0.26	0.07–0.97	0.046

Duration of abstinence from alcohol

Forty-three patients had a history being of abstinent from alcohol for ≤1 year of enrolment into the study, whereas 34 patients had a history of being abstinent from alcohol for over a year prior to enrolment. Those who had been abstinent for more than a year had a significantly higher per cent total body fat (BIA% 41.2 ± 12.4 vs. 33.6 ± 12.4, P = 0.01) and also a higher fibrosis score on liver biopsy (1.7 ± 1.2 vs. 1.2 ± 1.0, P = 0.04) compared to those who were still drinking or were abstinent for ≤1 year. There was a tendency among the patients with a longer duration of abstinence from alcohol consumption to have a higher BMI, HOMA and serum triglyceride levels although the differences between the two groups were not statistically different (P > 0.05). We also compared patients with a longer duration of abstinence from alcohol consumption (≤5 years vs. >5 years). The per cent total body fat was significantly higher (BIA% 41.7 ± 12.4 vs. 34.4 ± 12.5, P = 0.01) and there was a trend towards a higher fibrosis score (1.8 ± 1.2 vs. 1.3 ± 1.0) although this was not statistically significant (P = 0.07) in those patients who were abstinent for ≤5 years compared to those who were abstinent for >5 years.

Discussion

The acceptable criteria to define nonalcoholic fatty liver disease (NAFLD), which was also used in this study, were alcohol consumption of less than 40 g a week, no history of alcohol abuse or dependence and exclusion of other causes of chronic liver disease. With these criteria, we were able to show that over a lifetime, some amount of regular alcohol consumption has a protective effect on the histological severity in individuals with NAFLD. In this study, patients who had equal to or higher than median levels (24 gram-years) of lifetime alcohol consumption and those consuming any amount of alcohol regularly (ongoing or within the past 1 year) had a significantly lower risk of fibrosis compared to those who consumed less alcohol or had abstained from alcohol for longer durations. Furthermore, the protective effect of alcohol consumption was seen at levels as low as 10 gram-years of lifetime alcohol consumption. However, this protective effect was no longer seen when the alcohol consumption was >40 gram-years in our patient population suggesting that there may be a threshold protective effect of alcohol (both below and above a certain amount consumed) on the overall histological disease severity/progression in NAFLD. For example, for a 50-year old patient, 0.3 alcoholic beverages per day or 2.4 alcoholic beverages per week (10 gram-years at the age of 50) may have a protective effect and 1.4 drinks per day or 10 drinks per week (40 gram-years) would not have a protective effect.

Recently there have been several reports showing that alcohol consumption especially wine in modest amounts may lead to a decrease in prevalence of NAFLD and or risk of NASH, suggesting the beneficial role of alcohol in some individuals at risk (7–9). Other studies have shown that mild to moderate alcohol consumption is associated with a lower prevalence of the metabolic syndrome (16–19). None of the studies have assessed the role of lifetime alcohol consumption as was done in this study. In the study by Dunn *et al.*, when comparing 7211 non-drinkers with 945 modest wine drinkers, the

prevalence of suspected NAFLD based on NHANES laboratory criteria for elevated aminotransferase values was 3.2% among non-drinkers compared to only 0.4% among modest wine drinkers (8). Using the recent healthy subject cut-off values, the prevalence of suspected NAFLD was 14.3% and 8.6%, respectively, in the two groups with an adjusted odds ratio of 0.51 (95% CI 0.33–0.79) among modest wine drinkers (8). In this study, we did not assess the type of alcohol consumption among our patients. In another study of 1177 male subjects 20–59 years of age, light to moderate alcohol consumption was associated with lower prevalence of abnormal transaminases suggestive for NAFLD (7). In the same study, there was also an age-related effect where moderate alcohol consumption was associated with decreased odds of abnormal transaminases among the younger age (<41 years) group. Light consumption was associated with decreased odds and excess consumption was associated with increased odds of abnormal transaminases in the older age (≥41 years) group. In addition, during a follow-up period of up to 5 years, moderate alcohol consumption was associated with a decreased incidence of hypertransaminasemia compared to those with none or minimal consumption (adjusted hazard ratio 0.4, 95% CI: 0.1–0.9, $P = 0.02$) (7).

Other studies have shown a relationship between alcohol consumption and presence of fatty liver among individuals clinically suspected of NAFLD or those being investigated for abnormal liver enzymes among whom, alcohol intake was measured along with performance of ultrasound to detect presence of fatty liver (20–24). Majority of these studies are cross-sectional population-based studies from Japan where fatty liver was diagnosed based on ultrasound and histological information is not available. Nearly all these studies have shown a protective effect on the prevalence of NAFLD as diagnosed by ultrasound in individuals consuming variable amounts of alcohol.

Very few studies with histological information have been published assessing the role of alcohol consumption and histological severity in NAFLD. A recent study by Cotrim and colleagues in contrast to this study was performed among morbidly obese individuals undergoing bariatric surgery (Cotrim HP *et al.* 2009) (25). In this cross-sectional study from USA, there was no effect of alcohol consumption on steatosis and/or inflammation and fibrosis among morbidly obese individuals with fatty liver disease. The only significant finding was that insulin resistance appeared to be lower only among individuals with only light alcohol consumption (alcohol intake less than 20 g/day).

A few studies have shown that alcohol consumption is associated with progression of fibrosis in patients with NAFLD (10, 11) while some have shown no significant effect (25). Dixon *et al.* showed that in obese patients undergoing gastric bypass surgery and who had alcohol consumption of less than 200 g per week, the odds ratio for having NASH was 0.35 in alcohol consumers vs. non-consumers (9). However, when alcohol consumption was controlled for insulin resistance and diabetes, alcohol consumption did not appear to be an independent predictor of NASH. In the study of Ekstedt and colleagues, 71 patients with biopsy proven NAFLD were re-evaluated after a mean duration of 13.8 years with a repeat liver biopsy (10). In this study, the investigators assessed weekly alcohol consumption and also frequency of episodic drinking. Significant fibrosis progression, defined as increase in ≥1 fibrosis stage or development of end-stage liver disease, was seen in 17 patients (24%). Patient with fibrosis progression were more likely to have a history of heavy episodic drinking (defined as > 60 g of alcohol in men and 48 g in women consumed on one occasion) and also a trend towards having higher weekly consumption of alcohol. Heavy episodic drinking was an independent risk factor for significant fibrosis progression along with the presence of insulin resistance in these patients (10). On the basis of the definition, we used for clinically suspected NAFLD in this study, patients consumed much less alcohol and therefore the effects of episodic heavy alcohol consumption on disease severity could not be assessed in our patients. The role of alcohol intake on the initial histological presentation as investigated in our study, however, was not available in this study.

It is clear based on most studies published to date that whereas mild to modest alcohol consumption may have a protective effect compared to minimal or no alcohol consumption, higher amounts of alcohol may have no effect or even a detrimental effect on fibrosis progression. This suggests that there may be a threshold effect of alcohol consumption on the fibrosis severity in patients with NAFLD. To our knowledge, ours is the only study that assessed the role of life-time alcohol consumption in a population of histologically confirmed NAFLD. In our own study, the number of patients who were non-drinkers was significantly higher in the F3/F4 group compared to the group with less severe (F0-2) liver disease with regard to fibrosis severity ($P = 0.039$). Patients with lifetime alcohol consumption of at least 10 gram-years had a significantly lower prevalence of severe disease even after controlling for other factors such as insulin resistance whereas, above 40 gram-years, this protective effect was no longer seen. Another interesting finding in this study was that patients who had a longer duration of abstinence also had more severe fibrosis suggesting that some amount of regular alcohol may be important for the protective effect seen with alcohol consumption. This finding is similar to that of another recently reported study which found that NAFLD patients who had abstained from alcohol had a significantly higher risk of having advanced fibrosis (26). In this study, patients with longer duration of abstinence had significantly higher amounts of total body fat and a trend to having more features of metabolic

syndrome. Whether these features played a significant role in disease severity could not be adequately assessed in this study.

The role of some alcohol consumption in protecting against fibrosis progression is not well understood. NAFLD has been shown to be associated with insulin resistance and more common in patients with metabolic syndrome. Mild to moderate alcohol consumption has been shown to decrease insulin resistance and improve components of metabolic syndrome (27). This potentially may explain the effects of small amounts of alcohol use in mediating these protective effects and thereby associated with less histological injury in patients with NAFLD. It is interesting to speculate that ongoing alcohol consumption in small amounts might influence disease severity over time. In the study by Cotrim *et al.*, light alcohol consumption was associated with decreased prevalence of insulin resistance (10). Gunji and colleagues recently published a study of 1902 individuals with fatty liver diagnosed by ultrasound of whom 249 participants were insulin resistant (defined as HOMA-IR $\geq$2.5) (28). Compared to non-drinkers, light, moderate and heavy alcohol consumption was inversely associated with HOMA-IR scores and this effect of alcohol on HOMA-IR was independent of metabolic syndrome and presence of fatty liver on ultrasound. In this study, although there was a trend towards lower insulin resistance in the higher consumption group, this difference did not reach statistical significance. However, the effect on insulin sensitivity appears to be more a function of body mass index and central adiposity (29) rather than just alcohol alone. Moreover, whether there is a threshold of alcohol consumption that is associated with improved insulin sensitivity independent of features of metabolic syndrome is not known.

The limitations of this study were the sample size and importantly patients with overall mild disease. With a larger study and a broader spectrum of NAFLD histological scoring we may see a more clear association between alcohol consumption and its effect on insulin sensitivity and features of metabolic syndrome and the relationship to disease severity on liver histology. The lifetime alcohol consumption history although obtained at the time of enrolment of this prospective study, is based on retrospective review of alcohol consumption over a long time with the patients and although an attempt was made to increase accuracy by including life events, it relies on recall and there may also be over or underreporting.

In conclusion, among patients with clinical and histologically defined NAFLD using stringent criteria, some alcohol consumption appears to have an independent protective effect on fibrosis severity. Larger studies with a wider spectrum of histologically well-defined NAFLD and well-determined alcohol consumption are needed to better delineate the true effect of alcohol independent of other risk factors for disease progression.

Acknowledgements

Financial support: This research was conducted at the University of Michigan General Clinical Research Center (GCRC) with funding from the GCRC (GCRC Grant #M01-RR0004).

References

1. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003; **98**: 960–7.
2. Angulo P, Lindor KD. Non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2002; **17**(Suppl.): S186–90.
3. Rhul CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* 2003; **124**: 71–9.
4. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003; **37**: 1202–19.
5. Ostapowicz G, Watson KJR, Locarnini SA, Desmond PV. Role of alcohol in the progression of liver disease caused by hepatitis C virus infection. *Hepatology* 1998; **27**: 1730–5.
6. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998; **28**: 805–9.
7. Suzuki A, Angulo P, St Sauver J, *et al.* Light to moderate alcohol consumption is associated with lower frequency of hypertransaminasemia. *Am J Gastroenterol* 2007; **102**: 1912–9.
8. Dunn W, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. *Hepatology* 2008; **47**: 1947–54.
9. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* 2001; **121**: 91–100.
10. Ekstedt M, Franzen LE, Holmqvist M, *et al.* Alcohol consumption is associated with progression of hepatic fibrosis in non-alcoholic fatty liver disease. *Scand J Gastroenterol* 2009; **44**: 366–74.
11. Ruhl CE, Everhart JE. Joint effects of body weight and alcohol on elevated serum alanine aminotransferase in the United States population. *Clin Gastroenterol Hepatol* 2005; **3**: 1260–8.
12. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–97.
13. Chitturi S, Abeygunasekera S, Farrell GC, *et al.* NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology* 2002; **35**: 373–9.
14. Kleiner DE, Brunt EM, Van Natta M, *et al.* Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313–21.
15. Skinner HA, Sheu WJ. Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. *J Stud Alcohol* 1982; **43**: 1157–70.

16. Freiberg MS, Cabral HJ, Heeren TC, Vasan RS, Curtis Ellison R. Alcohol consumption and the prevalence of the Metabolic Syndrome in the US.: a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004; **27**: 2954–9.
17. Djousse L, Arnett DK, Eckfeldt JH, *et al.* Alcohol consumption and metabolic syndrome: does the type of beverage matter? *Obes Res* 2004; **12**: 1375–85.
18. Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: a systematic review. *Ann Intern Med* 2004; **140**: 211–9.
19. Wannamethee SG, Camargo CA Jr, Manson JE, Willett WC, Rimm EB. Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. *Arch Intern Med* 2003; **163**: 1329–36.
20. Gunji T, Matsuhashi N, Sato H, *et al.* Light and moderate alcohol consumption significantly reduces the prevalence of fatty liver in the Japanese male population. *Am J Gastroenterol* 2009; **104**: 2189–95.
21. Yamada T, Fukatsu M, Suzuki S, *et al.* Alcohol drinking may not be a major risk factor for fatty liver in Japanese undergoing a health checkup. *Dig Dis Sci* 2010; **55**: 176–82.
22. Hiramine Y, Imamura Y, Uto H, *et al.* Alcohol drinking patterns and the risk of fatty liver in Japanese men. *J Gastroenterol* 2011; **46**: 519–28.
23. Moriya A, Iwasaki Y, Ohguchi S, *et al.* Alcohol consumption appears to protect against non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2011; **33**: 378–88.
24. Hamaguchi M, Kojima T, Ohbora A, *et al.* Protective effect of alcohol consumption for fatty liver but not metabolic syndrome. *World J Gastroenterol* 2012; **18**: 156–67.
25. Cotrim HP, Freitas LA, Alves E, *et al.* Effects of light-to-moderate alcohol consumption on steatosis and steatohepatitis in severely obese patients. *Eur J Gastroenterol Hepatol* 2009; **21**: 969–72.
26. Zein CO, Unalp A, Colvin R, McCullough AJ. Advanced fibrosis in NAFLD is associated with lifetime alcohol use, diabetes, and age but not with lifetime cigarette smoking. *Hepatology* 2007; **46**(Suppl. 1): 739A.
27. Alkerwi A, Boutsen M, Vaillant M, *et al.* Alcohol consumption and the prevalence of metabolic syndrome: a meta-analysis of observational studies. *Atherosclerosis* 2009; **204**: 624–35.
28. Gunji T, Matsuhashi N, Sato H, *et al.* Alcohol consumption is inversely correlated with insulin resistance, independent of metabolic syndrome factors and fatty liver diseases. *J Clin Gastroenterol* 2011; **45**: 808–13.
29. Bell RA, Mayer-Davis EJ, Martin MA, D'Agostino RB Jr, Haffner SM. Associations between alcohol consumption and insulin sensitivity and cardiovascular disease risk factors: the Insulin Resistance and Atherosclerosis Study. *Diabetes Care* 2000; **23**: 1630–6.