Research Article

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Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD)

Winston Dunn[1,2,†], Arun J. Sanyal[3,†], Elizabeth M. Brunt[4,†], Aynur Unalp-Arida[5,†], Michael Donohue[6,†], Arthur J. McCullough[7,†], Jeffrey B. Schwimmer[8,9,*,†]

[1]*Departments of Pediatrics and Medicine, University of California, San Diego, La Jolla, CA, United States;* [2]*Gastroenterology and Hepatology, Department of Medicine, University of Kansas Medical Center, Kansas City, KS, United States;* [3]*Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, Virginia Commonwealth University Medical Center, Richmond, VA, United States;* [4]*John Cochran VA Medical Center, Saint Louis and Division of Gastroenterology, Saint Louis University School of Medicine, Saint Louis, MO, United States;* [5]*Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States;* [6]*Division of Biostatics and Bioinformatics, Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, CA, United States;* [7]*Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH, United States;* [8]*Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics University of California, San Diego, CA, United States;* [9]*Department of Gastroenterology, Rady Children's Hospital, San Diego, CA, United States*

Background & Aims: Non-alcoholic fatty liver disease (NAFLD) is a cardiovascular risk factor. Although modest alcohol consumption may reduce the risk for cardiovascular mortality, whether patients with NAFLD should be allowed modest alcohol consumption remains an important unaddressed issue. We aimed to evaluate the association between modest alcohol drinking and non-alcoholic steatohepatitis (NASH), among subjects with NAFLD.

Methods: In a cross-sectional analysis of adult participants in the NIH NASH Clinical Research Network, only modest or non-drinkers were included: participants identified as (1) drinking >20 g/day, (2) binge drinkers, or (3) non-drinkers with previous alcohol consumption were excluded. The odds of having a histological diagnosis of NASH and other histological features of NAFLD were analyzed using multiple ordinal logistic regression.

Results: The analysis included 251 lifetime non-drinkers and 331 modest drinkers. Modest drinkers compared to non-drinkers had lower odds of having a diagnosis of NASH (summary odds ratio 0.56, 95% CI 0.39–0.84, $p = 0.002$). The odds of NASH decreased as the frequency of alcohol consumption increased within the range of modest consumption. Modest drinkers also had significantly lower odds for fibrosis (OR 0.56 95% CI 0.41–0.77) and ballooning hepatocellular injury (OR 0.66 95% CI 0.48–0.92) than lifetime non-drinkers.

Conclusions: In a large, well-characterized population with biopsy-proven NAFLD, modest alcohol consumption was associated with lesser degree of severity as determined by lower odds of the key features that comprise a diagnosis of steatohepatitis, as well as fibrosis. These findings demonstrate the need for prospective studies and a coordinated consensus on alcohol consumption recommendations in NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the United States (US) affecting as many as one third of adults [1]. Only a small subset of patients with NAFLD, namely those with a more severe subtype known as steatohepatitis (NASH), which is characterized by inflammatory infiltrates, ballooning hepatocellular injury, and fibrosis in addition to steatosis, are thought to be at risk for cirrhosis-related mortality.

The metabolic risk factors for NAFLD are also closely associated with coronary heart disease (CHD) [2]. Patients with NAFLD [3], and especially those with NASH [4], are at risk for coronary heart disease. Patients with NAFLD are approximately two times more likely to die from coronary heart disease than liver disease [5]. Therefore, management of CHD risk in patients with NAFLD is imperative. CHD risk can be modified through lifestyle changes, including diet, exercise, and smoking cessation. In addition, modest alcohol consumption has been shown to reduce the risk of coronary heart disease mortality and improve metabolic risk factors related to both coronary heart disease and NAFLD [6,7]. As

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* Corresponding author. Address: Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Diego, 200 West Arbor Drive, San Diego, CA 92103-8450, United States. Tel.: +1 858 966 8907; fax: +1 619 543 7537.

E-mail address: jschwimmer@ucsd.edu (J.B. Schwimmer).

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Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; CHD, coronary heart disease; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NASH CRN, Non-alcoholic Steatohepatitis Clinical Research Network; OR, odds ratio.

many as 50% of the adults in the United States regularly consume a modest amount of alcohol [8]. Excessive alcohol, however, can cause alcoholic liver disease [9]. In the general population, the daily threshold [10–12] of alcohol for liver injury is thought to be between 1–3 drinks per day in women and 2–3 in men. In patients with metabolic risk factors for NAFLD, the threshold may be lower [13]. Despite this, cross-sectional studies have suggested that modest alcohol consumption may protect the liver from NASH and NAFLD [14,15]. The relationship between modest alcohol consumption and NAFLD severity has not been analyzed in detail. Whether patients with NAFLD should abstain from alcohol or be allowed modest alcohol consumption remains an important question. In practice, physicians often recommend abstinence from alcohol for patients with NAFLD, although the data to support this approach are lacking.

To provide counseling on alcohol consumption for patients with NAFLD, it is important to know whether modest alcohol consumption is associated with NAFLD disease severity. We hypothesize that modest alcohol consumption is associated with lower prevalence of NASH in patients with NAFLD. The primary aim of this study was to investigate a potential association between modest alcohol drinking and steatohepatitis in patients with NAFLD. Secondary aim was to test the association between modest alcohol drinking and the individual histological features of NAFLD including fibrosis.

Materials and methods

Study sample

This was a cross-sectional study of the association between modest alcohol consumption and histological presence and/or severity of recognized lesions in NAFLD. We included baseline data from participants 21 years or older enrolled in two recently published NASH Clinical Research Network (CRN) studies: (1) a cohort study, the NAFLD Database [16]; and (2) a clinical trial, Pioglitazone versus Vitamin E versus Placebo for the Treatment of Non-diabetic Patients with Non-alcoholic Steatohepatitis (PIVENS; Clinical Trial number NCT00063622) [17]. For the NAFLD Database, inclusion required histological diagnosis of NAFLD, imaging suggestive of NAFLD, histological diagnosis of cryptogenic cirrhosis, or clinical evidence of cryptogenic cirrhosis. Patients were excluded if they had other forms of liver diseases, or average alcohol consumption >20 g daily during the 2 years before entry. PIVENS inclusion additionally required patients to have histological evidence of NASH without cirrhosis and the absence of diabetes. Details of the study design can be found elsewhere [16,17]. The dataset for the current analysis was made up of participants who had central review of pathology completed as of May 2010. The inclusion and exclusion flowchart is illustrated in Fig. 1. A minimum age of 21 was chosen for inclusion in this analysis because it is the legal drinking age in the US. Participants who had liver biopsy more than 24 months before completing the Alcohol Use Disorders Identification Test (AUDIT) were excluded. Participants consuming on average more than 140 g of alcohol per week were already excluded as a part of the enrollment criteria in the NASH CRN. In addition, those reporting consumption of more than two drinks of alcohol in a typical drinking day and those reporting binge drinking at least once a month were excluded. In order to reduce potential selection bias that subjects may also stop drinking alcohol because of illness related to alcohol, non-drinkers who previously drank alcohol were also excluded. Finally, participants whose biopsy did not have at least 5% steatosis on central reading by the NASH CRN Pathology Committee were not considered to have NAFLD and were excluded from these analyses. Study protocols were approved by all participating center Institutional Review Boards. Each participant provided written informed consent.

Histological features

The primary outcome for this analysis was the diagnosis of steatohepatitis, reported as none, borderline or definite, by the central review by the Pathology Committee. The assignment of a diagnostic category was based on consensus recognition of the global histological features including those characteristic of steatohepatitis including steatosis and ballooning hepatocellular injury with a zone 3 predominance as well as lobular inflammation [18]. Secondary outcomes included the following histological variables: fibrosis (stage 0, 1, 2, 3, 4), steatosis (5–33%, 34–66%, >66%), lobular inflammation (<2, 2–4, and >4 under 20× magnification), portal inflammation (none, mild, more than mild), ballooning hepatocellular injury (none, few, many), microvesicular steatosis (absent, present), Mallory-Denk bodies (absent or rare, many), megamitochondria (absent or rare, many), acidophil bodies (absent or rare, many), large lipogranulomas (absent, present).

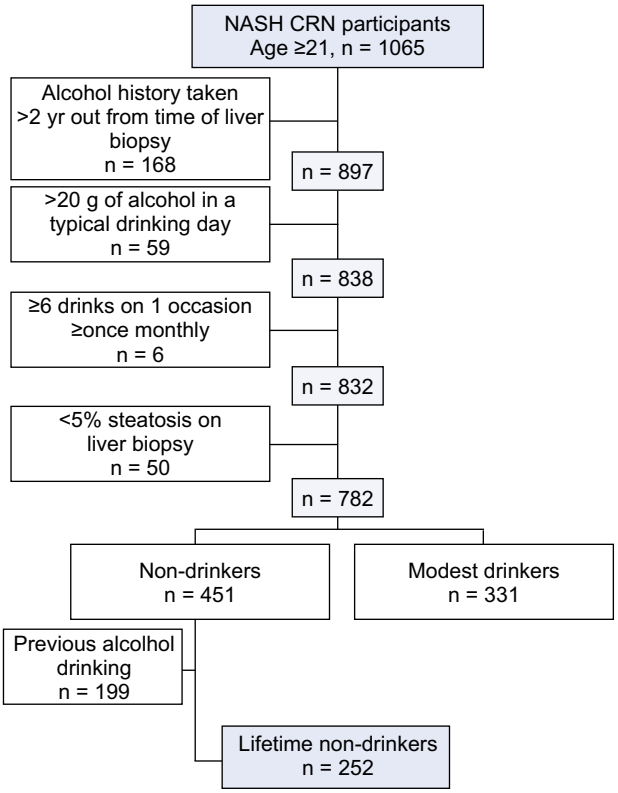

Fig. 1. Inclusion and exclusion flow chart.

Alcohol consumption

The primary exposure was modest alcohol consumption compared to lifetime abstinence from alcohol. Current alcohol consumption was assessed using the AUDIT [19]. Participants were asked "how often do you have a drink containing alcohol?" Those who responded "never" were considered non-drinkers. Participants were subsequently asked "how many drinks containing alcohol do you have on a typical day when you are drinking?" Those who reported drinking more than two drinks on a drinking day were excluded. Participants were asked "how often do you have six or more drinks on one occasion". Those who reported binge drinking once monthly or more were excluded because previous publications have indicated that episodic heavy drinking as little as once a month is associated with fibrosis progression in patients with NAFLD[20].

Prior alcohol consumption was measured using the lifetime drinking history questionnaire [21]. Participants were asked "Over the course of your lifetime have you ever had at least one drink of alcohol, beer, liquor, wine, or wine coolers, per month during a 12-month time period, or at least three drinks per day for at least three consecutive days?" Non-drinkers who responded "yes" to this lifetime drinking history question were also excluded as being previous drinkers.

Social, demographic, and lifestyle confounders

Social, demographic, and lifestyle confounders including age, gender, race, income, education, and physical activity level were collected using standardized questionnaires. Race and ethnicity were categorized into Asian, Hispanic,