REVIEW

Gut and Liver, Vol. 13, No. 3, May 2019, pp. 308-314

Effects of Moderate Alcohol Drinking in Patients with Nonalcoholic Fatty Liver Disease

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Whether moderate alcohol intake is beneficial remains an unsolved issue. Recent studies have suggested that moderate alcohol consumption is associated with beneficial effects related to the prevention of cardiovascular diseases. Moderate alcohol consumption leads to a higher risk of hepatocellular carcinoma in patients with chronic viral liver diseases. However, the effects of moderate alcohol intake in patients with nonalcoholic fatty liver disease are unclear. In this review, we analyzed, from various perspectives, the effect of moderate alcohol consumption in patients with nonalcoholic fatty liver disease. We reviewed four cohort studies and seven cross-sectional studies. The results showed that moderate alcohol consumption was negatively related to the incidence of nonalcoholic steatohepatitis and liver fibrosis. However, moderate alcohol consumption was positively associated with the incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease. The results of the analysis of the relationship between moderate alcohol consumption and the levels of triglycerides, total cholesterol, high-density lipoprotein, and hypertension were diverse. More clinical data are needed to draw a conclusion about the effects of moderate alcohol consumption in patients with nonalcoholic fatty liver disease. **(Gut Liver 2019;13:308-314)**

Key Words: Non-alcoholic fatty liver disease; Alcohol; Moderate drinking

INTRODUCTION

Alcohol is an important cause of chronic liver disease. Chronic alcohol intake aggravates most liver diseases, and moderate alcohol intake may exacerbate certain liver diseases. For example, moderate alcohol consumption (60 g/day for men and 40 g/day for women) in patients with hepatitis B virus infection increased the incidence of hepatocellular carcinoma (HCC) by about 1.5-fold,[1-4] although the cutoff values of alcohol intake were unclear.[4]

However, effects of moderate alcohol consumption in specific liver diseases are still in debate. For example, many studies examined the effects of moderate alcohol consumption in the prevalence of nonalcoholic fatty liver disease (NAFLD). In a study by Sogabe *et al*.,[5] moderate alcohol drinking of ≤140 g/wk was associated with lower prevalence of NAFLD in Japanese females. In contrast, a study by Liu *et al*.[6] suggested moderate alcohol drinking was associated with higher prevalence of NAFLD in Chinese men. Roerecke *et al*.[7] reviewed that moderate alcohol drinking was associated with lower prevalence of NAFLD in Japanese, but not in other countries.

Interestingly, there were some researches suggesting that nonalcoholic steatohepatitis (NASH) and liver fibrosis were negatively associated with moderate alcohol consumption in patients with NAFLD, although NAFLD is similar to alcoholic fatty liver disease and has a similar pathological physiology.[8] Previously, effects of moderate alcohol drinking in NAFLD patients were reviewed by Ajmera *et al*.[9] and Boyle *et al*.[10] However, the effects were not summarized by specific clinical symptoms. In this review, we compared and analyzed studies investigating the effects of moderate alcohol drinking on NASH and fibrosis in patients with NAFLD.

OVERVIEW OF THE EFFECT OF ALCOHOL ON NAFLD

To date, 11 studies were available on the effects of alcohol on liver disease progression in patients with NAFLD (Table 1).[8,11-20] Four were cohort studies, and seven were cross-sectional stud-

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Received on April 12, 2018. Revised on June 18, 2018. Accepted on June 22, 2018. Published online October 30, 2018
pISSN 1976-2283 eISSN 2005-1212 https://doi.org/10.5009/gnl18175
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Table 1. Alcohol Consumption and Severity of Liver Disease in NAFLD

Author (year)	Study population	Study design	Sample size	Definition of moderate alcohol use	Method for determining NAFLD	Outcome measure	Conclusion
Kwon *et al*. (2014)[11]	USA, NAFLD	Cross-sectional	77 (43 female)	≤40 g/wk	Liver biopsy	Fibrosis stage, fibrosis score, ALT, AST, fibrosis score	Lower fibrosis score in the above-median alcohol consumption group
Dunn *et al*. (2012)[8]	USA, NAFLD	Cross-sectional	582 (384 female)	≤140 g/wk	Liver biopsy	Fibrosis stage, steatohepatitis state	Lower risk for fibrosis and steatohepatitis in moderate alcohol consumption group
Ekstedt *et al*. (2009)[12]	Scandinavia, NAFLD	Prospective cohort	71 (20 female)	≤140 g/wk	Liver biopsy	Fibrosis stage, ALT, AST	Heavy episodic drinking positively relates with higher fibrosis stage
Hagström *et al*. (2017)[13]	Sweden, NAFLD	Prospective cohort	120 (37 female)	≤168 g/wk	Liver biopsy	Fibrosis stage, ALT, AST	Moderate alcohol consumption and fibrosis stage relates negatively
Cotrim *et al*. (2009)[14]	Brazil, obese (BMI >40 kg/m^2)	Cross-sectional	132 (91 female)	≤280 g/wk	Liver biopsy	Fibrosis stage, ALT, AST, IR	Alcohol and NAFLD severity had no correlation
Sinn *et al*. (2014)[15]	Korea, NAFLD	Cross-sectional	2280 (male only)	≤140 g/wk	Ultrasound	Fibrosis score, ALT, AST, carotid plaque	Moderate alcohol consumption and carotid plaques formation relates negatively
Dixon *et al*. (2001)[16]	Australia, obese	Cross-sectional	105 (23 female)	≤200 g/wk	Liver biopsy	ALT, AST	Less NASH probability in the moderate alcohol drinking group
Ascha *et al*. (2010)[17]	USA	Retrospective cohort	510 (183 female), NASH 195 (109 female)	≤308 g/wk	Liver biopsy	HCC development	Alcohol consumption positively relates with risk of HCC
Ajmera *et al*. (2018)[18]	NASH-CRN participants	Longitudinal cohort	285 (199 female)	≤140 g/wk	Liver biopsy	Resolution of definit NASH, Fibrosis score, ALT, AST	Less improvement of NAFLD in the consistent moderate alcohol drinking group
Yamada *et al*. (2018)[19]	Japanese, NAFLD	Cross-sectional	178 (85 female)	≤140 g/wk	Liver biopsy	Fibrosis score, steatosis score	Less fibrosis score in the moderate alcohol drinking group
Patel *et al*. (2017)[20]	Australian, diabetes and NAFLD	Cross-sectional	151 (55 female)	≤140 g/wk	Controlled attenuation parameter	Liver stiffness, ALT, AST	Alcohol consumption is not associated with lifer fibrosis in diabetic and NAFLD patients

NAFLD, nonalcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IR, insulin resistance; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma; NASH-CRN, Nonalcoholic Steatohepatitis Clinical Research Network.

ies. One cohort study suggested a negative correlation between moderate alcohol drinking and fibrosis,[13] while another cohort study suggested no correlation.[12] The longitudinal cohort study suggested less improvement of NAFLD in the consistent moderate alcohol drinking group.[18] The other cohort study suggested even moderate alcohol drinking may exacerbate HCC development.[17]

Three cross-sectional studies suggested that moderate alcohol drinking was negatively associated with the prevalence of NASH and advanced hepatic fibrosis.[8,11,19] However, four cross-sectional studies suggested that moderate alcohol drinking was not associated with NASH progression and fibrosis deterioration.[14-16]

METHOD OF ASSESSING ALCOHOL CONSUMPTION

Each study used various methods to analyze the alcohol intake of patients (Table 2). Eight studies obtained alcohol intake data through the self-reports of patients,[8,11-13,16,18-20] and four studies interviewed patients through experts.[11,12,14,16] Two studies used both the self-report method and the interview method.[12,16] One study was unclear how alcohol consumption was analyzed.[17]

In most studies, alcohol intake was measured at a specific time point. Two studies used the alcohol use disorder identification test (AUDIT) or AUDIT – consumption (AUDIT-C) questionnaires.[8,12,18,20] However, AUDIT is intended to identify persons with hazardous and harmful patterns of alcohol consumption.[21] This questionnaire consists of 10 questions, of which questions 1 to 3 are direct questions about the amount of alcohol consumption. AUDIT-C is a questionnaire that includes only these three questions. Therefore, AUDIT and AUDIT-C have limitations in accurately analyzing the amount or pattern of alcohol consumption. Only four studies included the lifetime drinking history of patients.[8,11,13,18] A lifetime drinking history questionnaire was designed to record all alcohol consumptions up to the time the patient was asked. The items listed included drinking duration, a frequency of drinking, intake per serving, and type of alcohol.[22] Including the lifetime drinking history is important because past drinking behavior can alter the patients' current health status.

WHAT IS "MODERATE" ALCOHOL CONSUMPTION?

The definitions of moderate alcohol consumption were different in each article (Fig. 1). The lowest cutoff was 40 g/wk, and the highest was 308 g/wk. The mean was 167 g/wk. Excluding the outlying lowest cutoff value of Kwon *et al*.,[11] the mean was 180 g/wk. The cutoff value for moderate alcohol consumption in most articles ranged between 140 and 200 g/wk. This is similar to the cutoffs of 210 g/wk for men and 140 g/wk for women that distinguish between alcoholic steatohepatitis and NASH.[23]

EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON LIVER FIBROSIS IN NAFLD

Eight studies showed the relationship between moderate alcohol intake and the degree of fibrosis (Table 3).[8,11-13,15,16,18,20] Scoring system used to assess the degree of intrahepatic fibrosis were various. Five studies used the NASH Clinical Research Network scoring system for assessing the progression of NASH. Among them, four studies suggested that the level of liver fibrosis was low in patients with moderate alcohol consumption ($p \leq 0.05$),[8,11,13,19] while the other study showed no correlation.[18]

Other three studies used different scoring systems. One study[12] used the Brunt system to evaluate the degree of NAFLD.[24] Another study[15] used NAFLD fibrosis scores without biopsy to evaluate the degree of liver fibrosis.[25] The other study[20] used controlled attenuation parameter method to evaluate the degree of liver fibrosis. The three studies showed that moderate alcohol intake and fibrosis severity were not associated.[12,15]

Above finding changed after subgroup analysis according to types of study design. Among the eight studies, five were cross-sectional studies.[8,11,15,19] Three of them showed the negative association between liver fibrosis and moderate alcohol consumption.[8,11,19] Only one study among the three cohort studies showed the negative association between liver fibrosis and moderate alcohol consumption.[12,13,18]

Interestingly, above finding was related to methods of assessing alcohol consumption. Most studies that evaluated lifetime drinking history suggested a negative association between liver fibrosis and moderate alcohol consumption,[8,11,13,19] except for one study.[18]

EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON THE PRESENCE OF NASH

Four studies suggested the effects of moderate alcohol intake on the incidence of intrahepatic inflammation in patients with NAFLD,[8,13,16,18] however, the results were diverse (Table 4). Alcohol consumption of <20 g/day was negatively associated with the incidence of NASH (p=0.0006) in a study by Dunn *et al*.[8] However, in a study by Hagström *et al*.,[13] moderate alcohol consumption was not associated with the incidence of NASH. Dixon *et al*.[16] reported that moderate alcohol intake was negatively associated with the incidence of NASH in patients with high obesity. Nevertheless, there was no association between alcohol consumption and the incidence of NASH after adjusting for diabetes or insulin resistance. In a study by Ajmera *et al*.,[18] moderate alcohol drinking was associated with less prevalence of NASH at the baseline. However, after 4 years, consistent moderate drinkers showed less resolution of definite NASH than consistent nondrinkers.

Table 2. Method of Assessing Alcohol Consumption

Author (year)	Self-report/ interview	Interview	Including life-time drinking patterns	Types of food frequency questionnaire
Kwon *et al*. (2014)[11]		O	O	Skinner Lifetime Drinking History interview
Dunn *et al*. (2012)[8]	O		O	Skinner Lifetime Drinking History and AUDIT questionnaires
Ekstedt *et al*. (2009)[12]	O	O		AUDIT-C questionnaire
Hagström *et al*. (2017)[13]	O		O	Skinner Lifetime Drinking History questionnaire
Cotrim *et al*. (2009)[14]		O		-
Sinn *et al*. (2014)[15]	O			-
Dixon *et al*. (2001)[16]	O	O		-
Ascha *et al*. (2010)[17]				Not clearly stated
Ajmera *et al*. (2018)[18]	O		O	Skinner Lifetime Drinking History and AUDIT-C questionnaires
Yamada *et al*. (2018)[19]	O			-
Patel *et al*. (2017)[20]	O		O	AUDIT questionnaires

AUDIT, alcohol use disorder identification test; AUDIT-C, alcohol use disorder identification test-consumption.

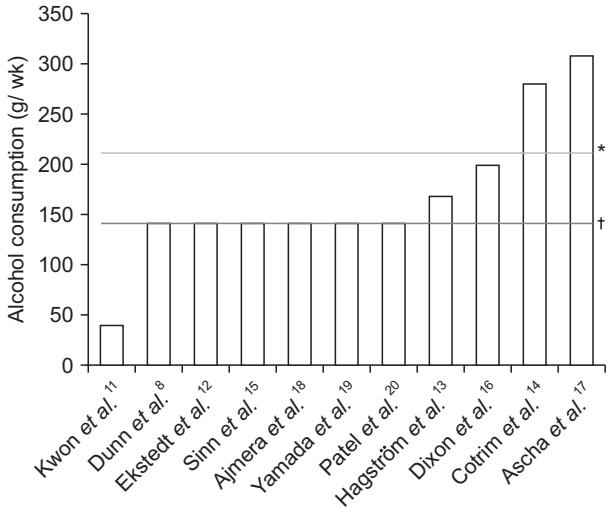

Fig. 1. Definition of moderate alcohol drinking used in each study. *Significant alcohol consumption in men (210 g/wk); †Significant alcohol consumption in women (140 g/wk).

EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON AMINOTRANSFERASE ACTIVITY IN NAFLD

Seven articles suggested the relationship between alcohol consumption and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.[11,13-15,18-20] The AST levels were not different between moderate drinkers and nondrinkers in all seven studies (Table 5). While there was no difference of ALT levels between the two groups in most studies, ALT levels were lower in patients consuming <20 g/day of alcohol than in nondrinkers in one study. This study also suggested that ALT and AST levels were higher in patients consuming 20–40 g/day of alcohol.[14]

EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON BIOCHEMICAL PARAMETERS AND CARDIOVASCULAR DISEASE IN NAFLD

The effect of moderate alcohol intake on cholesterol levels in patients with NAFLD was controversial in the three studies (Supplementary Table 1).[11,13,19] The triglyceride levels were not significantly different between alcohol drinkers and nondrinkers in the four studies ($p>0.05$).[8,11,18,19] In general, there was no significant difference of high-density lipoprotein (HDL) and homeostasis model assessment of insulin resistance (HOMA-IR) between the two groups.[11,13-15,18,19]

Two studies suggested the relationship between moderate alcohol intake and hypertension in patients with NAFLD (Supplementary Table 2). In one study, the incidence of hypertension in the moderate alcohol user group was lower than that in the nondrinking group,[13] while the other study suggested a lower incidence of hypertension in the 20–40 g/day alcohol consumption group than in the nondrinking group.[14] In the study by Sinn *et al*.,[15] the prevalence of carotid plaques and carotid stenosis were lower in patients with moderate alcohol intake.

DISCUSSION

In conclusion, moderate alcohol intake in patients with NAFLD has varied results. However, moderate alcohol intake is associated with a low incidence of intrahepatic fibrosis and NASH despite variety and uncertainty on methods of assessing

Table 3. Effects of Moderate Alcohol Drinking on Liver Fibrosis

Author (year)	Fibrosis	Remarks
Kwon *et al*. (2014)[11]	↓	Fibrosis score (1.2±1.0 vs 1.8±1.2, p=0.03) among the above-median alcohol consumption versus below-median alcohol consumption groups
Dunn *et al*. (2012)[8]	↓	Higher fibrosis stage: OR, 0.56 (95% CI, 0.41–0.78; p=0.0005) among moderate alcohol users versus lifelong nondrinkers
Ekstedt *et al*. (2009)[12]	-	Fibrosis progression: OR, 1.012 (95% CI, 1.000–1.025; p=0.055) among alcohol users versus nondrinkers
Hagström *et al*. (2017)[13]	↓	Higher fibrosis stage: OR, 0.86 (95% CI, 0.77–0.97; p=0.016) among the above-median alcohol consumption versus below-median alcohol consumption groups
Sinn *et al*. (2014)[15]	-	Fibrosis score (–1.9 vs –1.9; p=0.93) among moderate alcohol drinkers versus nondrinkers
Ajmera *et al*. (2018)[18]	-	Change in fibrosis score (0.08±0.16 vs 0.06±0.18; p=0.85) among moderate alcohol drinkers versus nondrinkers
Yamada *et al*. (2018)[19]	↓	Fibrosis score: OR, 0.707 (95% CI, 0.512–0.977; p=0.035) among moderate alcohol users versus lifelong nondrinkers
Patel *et al*. (2017)[20]	-	Liver stiffness measurement over 0.82 kPa: OR, 0.91 (95% CI, 0.27–3.10; p=0.881) among moderate alcohol users versus lifelong nondrinkers

OR, odds ratio; CI, confidence interval.

Table 4. Effects of Moderate Alcohol Drinking on NASH

Author (year)	NASH	Remarks
Dunn *et al*. (2012)[8]	↓	NASH: OR, 0.52 (95% CI, 0.36–0.76; p=0.0006) among moderate alcohol users versus lifelong nondrinkers
Hagström *et al*. (2017)[13]	-	NASH: OR, 0.98 (95% CI, 0.86–1.11; p=0.71) among the above-median alcohol consumption versus below-median alcohol consumption groups
Dixon *et al*. (2001)[16]	↓	NASH: OR, 0.35 (95% CI, 0.12–1.0; p=0.040) among moderate alcohol users versus lifelong nondrinkers before adjusting for diabetes or insulin resistance
	-	NASH after adjusting for diabetes or insulin resistance
Ajmera *et al*. (2018)[18]	↓	Definite NASH prevalence at the baseline (57% vs 74%, p=0.01) among moderate alcohol users versus lifelong nondrinkers
	↑	Resolution of definite NASH after 4 years: difference in adjusted mean change, 0.32 (95% CI, 0.11–0.92; p=0.04) among consistent moderate drinkers and consistent nondrinkers

NASH, nonalcoholic steatohepatitis; OR, odds ratio; CI, confidence interval.

alcohol consumption.

Several studies demonstrated possible mechanisms for beneficial effects of moderate alcohol consumption. In the animal study by Kanuri *et al*.,[26] moderate alcohol drinking was associated with lower inflammation in liver. The hepatoprotective property was associated with an induction of the sirtuin-1/adiponectin-signaling cascade in visceral fat tissue and activation of protein kinase B in the liver. Wang and his coworkers found that moderate alcohol intake induces thermogenic brown/beige adipocyte formation and promotes glucose and lipid oxidation via elevating retinoic acid signaling.[27] This resulted in the prevention of high-fat-diet-induced obesity and metabolic dysfunction. Yamada *et al*.[19] evaluated the effects of light alcohol consumption on gene expression in the liver. The moderate alcohol drinking was associated with lowered expression of Toll-like receptor 4, nuclear factor-kappa beta and more genes which are involved in immune response pathways.

Yet, it may be early to recommend drinking to patients with NAFLD. Firstly, there were no randomized control trials and all studies were cross-sectional studies or cohort studies. Secondly, the effect of alcohol intake on liver cancer in patients with NAFLD is controversial. Among the 11 journals we reviewed, only one journal analyzed the effect of moderate alcohol drinking on the risk of HCC.[17] The study used 308 g/wk as a cutoff value for the definition of moderate alcohol drinking. This is a much higher value compared to other journals we reviewed since the average was 167 g/wk. More clinical data is needed to further analyze the effect of moderate alcohol drinking on HCC

Table 5. Effects of Moderate Alcohol Drinking on ALT/AST

Author (year)	ALT	Conclusion, IU/L	AST	Conclusion, IU/L
Kwon *et al*. (2014)[11]	-	78±37 vs 73±59, p=0.68; among the above-median alcohol consumption versus below-median alcohol consumption groups	-	50±24 vs 56±43, p=0.44
Hagström *et al*. (2017)[13]	-	61 vs 55, p=0.22; among moderate alcohol drinkers versus below-median drinkers	-	44 vs 44, p=0.76
Cotrim *et al*. (2009)[14]	↓	48 vs 30 vs 35; among G1 (20–40 g/day) vs G2 (0–20 g/day) vs G3 (nondrinkers)	-	30 vs 23 vs 24
Sinn *et al*. (2014)[15]	-	29 vs 28, p=0.11; among moderate alcohol drinkers versus nondrinkers	-	24 vs 24, p=0.85
Ajmera *et al*. (2018)[18]	-	62 vs 57, p=0.08; among moderate alcohol drinkers versus nondrinkers	-	43 vs 42, p=0.37
Yamada *et al*. (2018)[19]	-	68.5±49.8 vs 64.1±79.8, p=0.0610; among moderate alcohol drinkers versus nondrinkers	-	40.1±22.9 vs 46.1±42.6, p=0.6993
Patel *et al*. (2017)[20]	-	36.4±26.4 vs 38.4±29.5 vs 37.4±15.8; among nondrinkers versus light drinkers versus moderate drinkers	-	29.0±17.6 vs 28.6±26.1 vs 24.7±11.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

development in the patient with NAFLD. Thirdly, the methods used for assessing alcohol consumption have many limitations. Fourthly, the longitudinal cohort study suggested that the modest alcohol use is associated with less improvement of NASH.[18] Lastly, the amount of moderate alcohol consumption defined in each article was different. Clinical data are still lacking, and the conclusion cannot be drawn on how much alcohol is appropriate for each individual patient. Additional studies should be undertaken on the analysis of adequate alcohol intake, patterns of intake, and positive and negative effects.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

Author contributions: guarantor of the article, D.W.J. D.W.J. contributed to the study design. I.K. wrote the manuscript. J.H.M. contributed to critical review and manuscript polishing.

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