The effect of moderate alcohol consumption on nonalcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is accepted as a counterpart to alcohol-related liver disease (ARLD) since it is defined as a hepatic steatosis without excessive use of alcohol. However, the amount of moderate alcohol consumption is controversial, and previous studies have shown heterogeneous evidence of whether moderate alcohol consumption is beneficial or detrimental. In this review, we compare and summarize the findings of studies with high-quality evidence for the impact of moderate alcohol consumption in NAFLD patients to date.
Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease characterized by serial progression from isolated steatosis to steatohepatitis, fibrosis, and cirrhosis. NAFLD is associated with the metabolic conditions of insulin resistance, type 2 diabetes, and obesity. Mirroring the obesity epidemic, the global prevalence of NAFLD among adults is estimated to be 23–25%, and it has become a major global concern as a dominant cause of chronic liver disease with increases in obesity and type 2 diabetes. In particular, as the proportion of young patients is increasing, the burden of disease is expected to increase, and long-term management strategies are needed.

NAFLD is defined as hepatic steatosis occurring in over 5% of hepatocytes without excessive use of alcohol, viral hepatitis, or autoimmune liver disease. It is accepted as the counterpart of alcohol-related liver disease (ARLD). NAFLD and ARLD share a common pathophysiological basis involving gut dysbiosis and subsequent changes. Also, single nucleotide polymorphisms in patatin-like phospholipase domain-containing 3, transmembrane 6 superfamily member 2, membrane bound O-acyltransferase domain containing 7, 17-β hydroxysteroid dehydrogenase 13 gene are significant genetic risk factors for NAFLD and ARLD. These two entities are difficult to distinguish as both histologically include a certain degree of steatosis, lobular inflammation, and ballooning. However, these two conditions are distinguished by excessive alcohol consumption based on history taking and questionnaire, and the amount of safe alcohol consumption accepted as “non-alcoholic” is disputed. Previous studies showed heterogeneous evidence on whether moderate alcohol consumption is protective or detrimental for development of NAFLD.

In this review, we compare and summarize the clinical results to date on the effects of moderate alcohol consumption in NAFLD patients.

Definitions for moderate alcohol consumption

The effects of alcohol on patients appear over a long period of time, and since randomized control trials are difficult to perform, they can only be estimated by observational studies. Several definitions for significant alcohol consumption to date are as follows (Table 1). The definition of moderate alcohol consumption adopted by most guidelines and previous studies is <21 units of alcohol per week in males and <14 units of alcohol per week in females. Some researchers adopt other definitions according to their needs, but many experts recommend the above definition for comparison and objectivity of studies. One unit of alcohol is usually 10 milliliters of pure alcohol, but standard-drink definitions vary worldwide from 8 grams to 20 grams of alcohol. Therefore, it is necessary to confirm the definition used when reviewing previous
Although alcohol is a carcinogen with a well-known dose-risk relationship, meta-analyses based on many previous studies have published results that moderate alcohol consumption showed a protective effect against NAFLD (Table 2).

Interestingly, Sookoian et al. suggest that moderate alcohol consumption is associated with a significant protective effect against NAFLD (Table 2). Body mass index (BMI) was not a statistically significant confounding factor in meta-regression analysis (slope=0.01, p<0.44) but moderate alcohol consumption was more protective in women than men (53% in women, 30% in men). This result was consistent with the odds of having steatohepatitis (odds ratio (OR), 0.501, 95% CI, 0.340 to 0.740, p<0.0005, I²=0%) without heterogeneity. Cao et al. showed similar results. In pooled OR for the prevalence of NAFLD, low- and moderate-risk alcohol consumption consistently showed a protective effect regardless of sex or BMI (≥25 vs. <25). A similar conclusion was presented in a recent meta-analysis. Recent meta-analyses have evaluated the risk of alcohol consumption on advanced fibrosis in patients with NAFLD. In Wijarnpreecha et al. and Wongtrakul et al., moderate alcohol consumption was associated with a lower risk of advanced fibrosis and steatohepatitis with lower to intermediate heterogeneity, even though their definitions of alcohol consumption were different (Table 2). Furthermore, NAFLD patients with moderate alcohol consumption had a lower mortality risk than lifelong abstainers (hazard ratio (HR), 0.85; 95% CI 0.75-0.95; I²=64%).

Despite the above results, alcohol consumption does not guarantee a protective effect on the progression of cirrhosis. In a large NAFLD cohort study in Korea, patients with low fibrosis-4 index (FIB-4) progressed to intermediate or high FIB-4 with light alcohol drinking [<10 g/day, adjusted HR 1.06, (0.98-1.16)] and moderate alcohol drinking [>10 - <20 g/day, adjusted HR 1.29 (1.18-1.40)], respectively. In a recent NAFLD cohort study, moderate amounts of alcohol intake in NAFLD patients increased the risk of type 2 diabetes and the risk of advanced fibrosis with the synergistic effect of insulin resistance. In a study evaluated the longitudinal association between moderate use of alcohol (≤2 drinks/day) and histology findings on follow-up liver biopsy more than 1 year apart, non-drinkers had a greater mean reduction in steatosis grade (reduction, 0.49) than moderate drinkers (reduction, 0.30; P=0.04) and moderate drinkers had significantly lower odds of steatohepatitis resolution compared with nondrinkers (adjusted OR, 0.32; 95% CI, 0.11–0.92; P=0.04).

Alcohol is also a well-known primary cause of development of hepatocellular carcinoma (HCC).
In a previous meta-analysis, the dose–risk curve suggested a linear relationship with dose of alcohol consumption, estimated excess risk of 46% for 50 g/day and 66% for 100 g/day. Moreover, a meta-analysis indicates that the risk of HCC decreases after alcohol cessation by 6% to 7% a year. A meta-analysis by Wongtrakul et al., narrowed down the analysis target to NAFLD patients with moderate alcohol consumption only, suggested significant HR (3.77, 95% CI, 1.75-8.15; I²=0%) for developing HCC.

There are pitfalls to consider before accepting the conflicting research results discussed above. Previous meta-analyses had some limitations inherent in the design of the included studies. Almost all studies had a cross-sectional design, which limits establishment of causality of the observed factors with associations with selection bias and reverse causality issues. Even if the researchers used a well-designed survey tool such as Alcohol Use Disorders Identification Test (AUDIT) and Cut, Annoyed, Guilty, and Eye (CAGE), it may be associated with recall bias. Population surveys could produce underestimation of alcohol consumption of approximately 40%-50%. Drinking patterns as well as quantity are known to have an effect as binge drinking affects lipid profile and liver function test and aggravates liver fibrosis compared to non-binge drinking. Several studies have suggested that moderate alcohol drinkers tend to have higher socio-economic status (SES) and less obesity than life-long abstainers. This may confound the association between alcohol consumption and NAFLD through interference from the interaction between NAFLD and obesity.

**[Potential confounding factors remain unmeasured]**

- **Gut microbiota**

  There may be confounding factors that are not identified through history taking or blood tests in routine clinic service. Recent studies show that not only consumption of alcohol, but also alcohol produced by the gut microbiome can affect development of NAFLD. When blood alcohol concentration increases without significant alcohol consumption, autobrewery syndrome can be suspected. Some microbiota, particularly Proteobacteria (especially Klebsiella pneumoniae and Escherichia coli) can ferment dietary sugars into ethanol. Engstler et al. reported that patients with NAFLD, even children, have increased blood ethanol level through endogenously produced ethanol. Recently, Yuan et al. found high-alcohol-producing Klebsiella pneumoniae (HiAlc Kpn) in the gut microbiome of up to 60% of NAFLD patients. When clinically isolated HiAlc Kpn was transferred into mice by fecal microbiota transplant, it caused NAFLD in the recipient mice. In another in vivo study using proteome and metabolome analyses, researchers demonstrated that HiAlc Kpn catabolizes carbohydrates via the 2,3-butanediol fermentation pathway and is a potential causative agent of NAFLD. Accordingly, the fecal microbiome in NAFLD patients should be
considered as a confounding factor.

- Types of alcoholic beverages

Is beer or wine safer than liquor or distilled spirits in regard to NAFLD? The Centers for Disease Control and Prevention (CDC) revealed the amount of alcohol consumed as the most influential factor rather than the type of alcoholic drink.56 In a cross-sectional study utilizing the data from NHANES III, conducted in the United States from 1988 to 1994, in 7,211 nondrinkers and 945 moderate wine drinkers (alcohol consumption <10 g/day), suspected NAFLD (ALT >43 IU/L) was observed in 3.2% and 0.4%, respectively, and the adjusted OR was 0.15 (95% CI, 0.05-0.49).57 In a recent study that evaluated the association between fibrosis and type and pattern of alcohol consumption in a biopsy-proven NAFLD cohort, moderate (<70 g/week) alcohol consumption, particularly wine in a non-binge pattern, was associated with lower fibrosis in NAFLD patients. In an animal study using a NAFLD mouse model fed a high-fat diet, extended-maceration wine improved glucose tolerance and reduced hepatic fat accumulation. Pomace also improved insulin sensitivity and reduced hepatic triglyceride.58

Recently, a randomized controlled trial was announced to evaluate the effects of beer on human gut microbiota. Marques et al. recruited 22 healthy men in Portugal, who were assigned to drink one can of alcoholic or non-alcoholic lager each day for four weeks. Intestinal microbial diversity improved as determined by the Shannon index.59 This study indicates that drinking beer once a day can improve intestinal microbiome diversity regardless of alcohol content. This is simultaneously consistent with and contradictory to previous studies exploring the effects of beer on the microbiome. One study in Mexico found that healthy men and women who consumed 355 mL of non-alcoholic beer a day for 30 days saw an increase in gut microbiome diversity, especially the relative abundance of Bacteroidetes. However, a separate group who drank 355 mL of beer with 4.9% alcohol did not see the same improvement.60 The above positive effects of fermented alcoholic beverages are presumed to be due to polyphenols, although additional evidence is needed.

[CONCLUSION]

Clinical data have not allowed a firm conclusion on the effects of moderate alcohol consumption, and it has not been determined the amount of safe alcohol consumption for NAFLD patients. Moderate alcohol consumption in patients with NAFLD has various effects, and conflicting results have been reported. Unregulated factors such as sex, age, ethnicity, obesity, comorbidities, genetic factors, incomplete study design, unclear endpoints, economic and social aspects, and underreporting alcohol use confound the results. Considering the basic medical principle of “First,
do not harm,” it is premature to recommend moderate drinking to NAFLD patients, especially those with comorbid diseases or advanced liver fibrosis. Additional longitudinal studies are expected to demonstrate the interactions between moderate alcohol consumption, impact of type/pattern of alcohol use, and SES according to stage of NAFLD.

**Abbreviations**

- nonalcoholic fatty liver disease (NAFLD)
- alcohol related liver disease (ARLD)
- body mass index (BMI)
- odds ratio (OR)
- hazard ratio (HR)
- fibrosis-4 index (FIB-4)
- hepatocellular carcinoma (HCC)
- socio-economic status (SES)
- Alcohol Use Disorders Identification Test (AUDIT) and Cut, Annoyed, Guilty, and Eye (CAGE)
- high-alcohol-producing Klebsiella pneumoniae (HiAlc Kpn)
- alanine transaminase (ALT)

**Authors’ contributions**

HO, WS, and YKC contributed to the design and writing of the manuscript.

**Conflicts of Interest**

The authors have no conflicts to disclose.
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Table 1. International definitions of alcohol consumption for exclusion of NAFLD diagnosis and significant alcohol consumption

<table>
<thead>
<tr>
<th>Definitions</th>
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</tr>
</thead>
</table>
| NIAAA<sup>14</sup>  
(1 standard drink = 14g) | Heavy Alcohol Use:  
Male : >14 standard drinks/week  
Female : >7 standard drinks/week |
| WHO<sup>15</sup> | Low risk: Male : < 40 g/day, Female : < 20 g/day  
Medium risk: Male : 40-60 g/day, Female : 20-40 g/day  
High risk: Male : > 60 g/day, Female : > 40 g/day |
| NICE thresholds for assessing for liver cirrhosis<sup>16</sup> | Male : > 30 units/week, Female : > 20 units/week |
| AASLD, AACE, AGA<sup>2,7,17</sup> | Male : > 21 standard drinks/week, Female : > 14 standard drinks/week  
(over a 2-year period preceding baseline liver histology) |
| EASL–EASD–EASO<sup>7,8</sup> | Male : > 30 g/day, Female : > 20 g/day |
| EASL Patient guideline<sup>18</sup>  
(1 unit equals 8 g of alcohol) | Male : > 21 units/week for men, > 14 units/week for women |
| APASL<sup>9,19</sup> | Male : two standard drinks per day (i.e., 140 g ethanol per week)  
Female : one standard drink per day (i.e., 70 g ethanol per week) |
| China<sup>20</sup>  
(during the past 12 months) | Male : > 210 g/week, Female : > 140 g/week |
| KASL<sup>9</sup> | Male : > 210 g/week, Female : > 140 g/week |

NIAAA, National Institute on Alcohol Abuse and Alcoholism; WHO, World Health Organization; NICE, National Institute for Health and Care Excellence; AASLD, American Association for the Study of Liver Diseases; AACE, American Association of Clinical Endocrinology; AGA, American Gastroenterological Association; EASL, European Association for the Study of the Liver; EASD, European Association for the Study of Diabetes; EASO, European Association for the Study of Obesity; APASL, Asian Pacific Association for the Study of the Liver; KASL, Korean Association for the Study of the Liver
Table 2. Comparison of previous meta-analyses assessing the effect of moderate alcohol consumption among NAFLD patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Search</th>
<th>Number of included studies</th>
<th>Primary Outcome</th>
<th>Participants (n)</th>
<th>Definition of moderate alcohol consumption</th>
<th>Pooled OR (95% CI)</th>
<th>Heterogeneity (I^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sookoian et al(23)</td>
<td>2014</td>
<td>Unknown</td>
<td>8 studies</td>
<td>NAFLD prevalence</td>
<td>43175</td>
<td>less than 40 g/day</td>
<td>0.684 (0.580 - 0.806)</td>
<td>NA</td>
</tr>
<tr>
<td>Cao et al(21)</td>
<td>2016</td>
<td>Without Restriction</td>
<td>13 cross-sectional studies, 2 cross-sectional following longitudinal studies, 1 cohort study</td>
<td>NAFLD prevalence</td>
<td>76608</td>
<td>WHO definition</td>
<td>Light; 0.76 (0.72-0.80) Moderate; 0.75 (0.70-0.80)</td>
<td>66% 82.7%</td>
</tr>
<tr>
<td>Wijampreecha et al(22)</td>
<td>2021</td>
<td>February 2019</td>
<td>6 cross-sectional studies</td>
<td>prevalence of advanced liver fibrosis</td>
<td>8936</td>
<td>&lt; 28 g/day in males &lt; 14 g/day in females</td>
<td>modest drinkers vs. non-drinkers; 0.51 (0.35-0.75)</td>
<td>47%</td>
</tr>
<tr>
<td>Wongtrakul Et al(29)</td>
<td>2021</td>
<td>October 2020</td>
<td>14 cross-sectional or cohort studies</td>
<td>prevalence of steatohepatitis</td>
<td>14435</td>
<td>210 g/week for male 140 g/week for female</td>
<td>steatohepatitis; 0.59, (0.45-0.78) advanced fibrosis; 0.59, (0.36-0.95)</td>
<td>12% 75%</td>
</tr>
</tbody>
</table>

OR, odds ratio; NAFLD, non-alcoholic fatty liver disease; WHO, World Health Organization