Moderate Alcohol Intake in Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is defined by hepatic steatosis in the presence of alcohol intake within safe limits, defined by guidelines of scientific associations (usually 20 g or 2 units/day in women, 30 g or 3 units in men). The diagnosis is usually followed by medical counseling of total abstinence, in order to prevent disease progression. Old evidence regarding a possible safe and eventually beneficial effect of alcohol intake in NAFLD have however been extensively challenged by data suggesting a detrimental effects of alcohol on other organs and tissues, namely the cardiovascular system and cancer risk. Current guidelines support alcohol abstinence for individuals with NAFLD.

drinking pattern | safe alcohol intake | cardiovascular system | liver disease

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic condition characterized by the accumulation of fat within hepatocytes (steatosis), potentially progressive to nonalcoholic steatohepatitis (NASH), where hepatic necroinflammation and fibrosis add to steatosis, favoring progression to cirrhosis and terminal liver failure. The term “nonalcoholic” was coined to differentiate the disease from similar histologic findings present in subjects who abuse of alcohol (alcoholic fatty liver disease (AFLD)). The difference is based on the amount of alcohol intake. By definition, individuals with NAFLD are expected to consume alcohol in amounts considered not at risk of hepatic involvement [1]. This definition raises the important question of the “safe” amount of alcohol consumption, considering that a moderate alcohol intake is very common in the population, specifically during familial or social events (social drinkers), expectedly at rates not associated with any untoward effects and possibly with positive effects on cardiovascular disease [2]. Large epidemiological data report a J-shaped curve between mortality and alcohol intake [3], with a reverse point (the point where mortality in abstainers equals mortality in alcohol users) for an average alcohol consumption of approximately 25–30 g in women and 40 g in men [4].

All NAFLD studies explicitly report the exclusion of subjects with alcohol intake at risk, defined according to pre-specified criteria, and most clinicians suggest total abstinence from alcohol as therapeutic measure for prevention NAFLD and/or disease progression. More than a decade ago a few epidemiological studies reported an inverse association between moderate alcohol consumption (within presumably safe limits) and the prevalence of NAFLD in the population [5][6], pointing to a favorable effect of moderate alcohol use extending from the cardiovascular system to the setting of metabolic liver disease. This raised a lot of debate on the correct dietary and lifestyle

treatment of NAFLD, which has not settled yet. Do we need to counsel our NAFLD patients for total alcohol abstinence to prevent disease progression?

2. Assessment of Alcohol Intake

2.1. Use or Abuse?

Current guidelines on NAFLD strictly indicate the limits of alcohol intake to dissect NAFLD and AFLD; an accurate screening for alcohol intake is mandatory for a correct diagnosis, but very few studies identify the tool(s) used for alcohol assessment. In most cases this piece of information is derived from patients themselves, and confirmed by relatives in a few cases, or simply derived from brief enquiry on family use.

A correct assessment of alcohol intake should involve a wider use of questionnaires; they were specifically developed for detecting alcohol abuse, not to grade modest/moderate alcohol intake. The 4-item CAGE (acronym for the initial letters of the four questions) questionnaire is a very short screening test for the diagnosis of lifetime alcohol abuse/dependence [7], but very rarely the four questions are all used to screen patients correctly. The questionnaire is probably totally insensitive to recent alcohol drinking [8], and scarcely applies to modest (social) drinkers. The Alcohol Use Disorder Identification Test (AUDIT, 10 items) is better than CAGE to identify subjects with recent alcohol use or dependence [9], but, as far as we know, rarely used to interview patients in busy liver units considering the length of enquiry. A shorter version of AUDIT (AUDIT-C), consisting of only three questions, has been developed and more largely used, with good specificity for heavy drinking and dependence [10], but its effectiveness to diagnose moderate alcohol drinking has never been extensively investigated. The 3 questions of AUDIT-C (*1. How often do you have a drink containing alcohol? 2. How many drinks containing alcohol do you have on a typical day when you are drinking? 3. How often do you have six or more drinks on one occasion?*) have been further simplified suggesting that question #1 might suffice, provided that a correct identification of the frequency of alcoholic drinks is carried out. Another single-question screening tool has been validated for identifying individuals consuming alcohol at risky levels in primary care: "*How many times in the past year have you had 5 (for men; 4 for women) or more drinks in a day?*" [11]. If the answer is one or more, further assessment is mandatory.

2.2. How much Alcohol Is in a Single Drink?

The amount is likely to make the difference. In order to facilitate comparison between different studies, there has been a progressive agreement to focus on multiple of 10 g per single alcohol unit (1 glass of wine, 1 can of beer, a shot of hard alcohol drink). The harmonization of the amounts defined in AUDIT questions becomes mandatory in order to have the safe amount of alcohol correctly defined.

Following a rather long period where amounts and/or units were differently calculated in the various Countries, there is now agreement that the safe limits of alcohol use may be limited to 20 g/day in females and 30 g/day in males, with one unit corresponding to 10 g intake. These thresholds have been accepted by American and

European guidelines [12][13], with minimal but significant differences: 2 and 3 units/day in Europe, 14 and 21 units/week in the United States for women and men, respectively. This amount does not consider the detrimental effect of binge alcohol drinking, particularly in the young, and the debated cumulative effect of alcohol intake along the years in the elderly [14]. Lifetime alcohol intake is based on recall over long periods; it might be relatively easy to calculate in heavy drinkers, consuming alcohol regularly at meals, but may become a very difficult task in social drinkers, consuming alcohol only during special events.

In summary, the definition of alcohol intake as assessed by questionnaires still reflects a compelling need to identify alcohol abuse and the risk of alcoholic cirrhosis. The identification of modest alcohol intake, although in excess of safe limits, and the computation of lifetime alcohol intake remain at best imprecise.

3. Moderate Alcohol Consumption on NAFLD: The Evidence for Protection

The evidence for a positive effect of moderate alcohol intake on fatty liver are reported in **Table 1** [5][6][15][16][17][18][19][20][21][22][23][24][25][26][27]. Rumors date back to 2001, when Dixon et al. reported an analysis of alcohol consumption in 105 patients whose liver disease was diagnosed by laparoscopic biopsies taken at surgery for severe obesity (BMI > 35 kg/m^2) [15]. NASH was present in 26 cases (11 with advanced fibrosis). In the whole cohort, moderate alcohol consumption was associated with a decreased risk of NASH (OR, 0.35; 95% CI, 0.12–1.00). The authors suggested a possible beneficial role of alcohol mediated by reduced insulin resistance, since the effects of alcohol on NASH were no longer significant after controlling for insulin resistance.

In summary, a few studies are in keeping with a beneficial effect of modest alcohol intake on NAFLD occurrence and progression. However, only four out of 15 studies are prospective (**Table 1**). Cross-sectional analysis defines the odds of events on the basis of the present alcohol intake, but the occurrence of NAFLD and NAFLD progression is a process requiring long-term damage. The event is definitely driven by previous alcohol history, difficult to define over long periods, particularly in subjects who do not consume alcohol regularly at meals and limiting alcohol intake during special events (social drinkers).

4. Possible Mechanism(s) of Modest Alcohol Protection and Potential Confounders

Several mechanisms have been suggested as the basis for the negative association between modest alcohol consumption and liver fat, assumed as putative causal-effect protective effect. Moderate alcohol use has been associated with lower insulin resistance, a feature of metabolic syndrome-associated NAFLD and NAFLD progression, as observed in several epidemiological studies [28][29], including the ones reported in this review [15][30], also affecting triglyceride levels. Modest alcohol use was associated with improved lipid profile and anti-inflammatory properties, also producing a positive effect on cardiovascular system [31][32][33].

Several other factors might be involved, limiting the significance of the association. Moderate users might belong to higher socio-economic classes, with higher levels of education, more prone to physical activity, always used to consume alcohol within safe limits. On the contrary, cohorts of totally abstinent individuals might be enriched with formerly heavy drinkers, the so-called sick-sitter cohort [3], not identified in cross-sectional analyses, with significant liver disease [34], as well as with subjects with higher prevalence of obesity and other comorbid conditions. These factors are likely to produce a selection bias and reverse causality. Alternatively, the effect might be due to genetic factors specifically associated with ethnic groups, although the variety of cohorts tested in the different studies should reduce this bias.

Finally, the specific effect indicated for wine, not for beer or liquor drinking, might point to specific metabolic activity of individual constituents of alcoholic beverages. Both alcohol and non-alcohol components of wine might be involved. Resveratrol is a potential candidate, considering that it reduced or attenuated steatosis in experimental animals [35][36], although a direct effect in humans has never been definitely proven. In a randomized study vs. total abstention, moderate wine intake (3.0 and 1.5 U/day in men and women, respectively) for 3 months produced only a minimal increase in hepatic triglyceride content, insufficient to define hepatic steatosis [37]. This is the only trial on this topic, and will probably remain an isolated experiment, due to ethical concern. Wine is a component of the Mediterranean diet; totally abstinent individuals are considered non-adherent to the Mediterranean diet style as much as heavy drinkers, and the Mediterranean diet has been associated with better NAFLD outcome [38][39][40]. This made the Mediterranean diet the meal composition of choice for people with NAFLD [41], as also recommended by International guidelines [12]. The Mediterranean diet has long been associated with reduced cardiovascular risk; a recent randomized study conducted for 18 months in 278 individuals with NAFLD confirmed the superiority of a Mediterranean-style diet vs. a low fat diet on hepatic fat content, measured by magnetic resonance imaging, also in the presence of similar weight loss [42]. However, in the presence of conflicting results [43], the role of alcohol vs. other dietary components should be better defined.

5. Moderate Alcohol Consumption and the Liver within and outside NAFLD: The Evidence for Detrimental Effects

The evidence for protection given by moderate alcohol intake on NAFLD has however been challenged (**Table 1**) [44][45][46][47][48][49][50][51][52][53][54][55][56][57][58]. In the Italian Dionysos study, a study exploring the prevalence of liver disease in the general population of two Italian towns [44], alcohol use was associated with both fatty liver incidence and remission when graded for any 20 g/day in both men and women. In 71 patients with biopsy-proven NAFLD who had a second biopsy after a mean follow-up of 13.8 years, the proportion of patients reporting at risk episodic alcohol drinking (at least once a month) was higher among those with significant fibrosis progression, defined as increase by one or more fibrosis stage or occurrence of end-stage liver disease [45]. The authors concluded that patients should be advised to refrain from heavy episodic drinking. In the Finnish Health 2000 Study, a nationally representative cohort where alcohol consumption and metabolic factors were extensively investigated, alcohol was selected as risk factor for liver disease both in heavy alcohol users and in those who consumed alcohol within expected safe limits (<2–3 U/day in women and men, respectively) [46]. In a larger reappraisal of two database

(FINNRISK 1992–2012 or Health 2000) comprising a selected cohort of 8345 individuals with hepatic steatosis defined by the Fatty Liver Index [59], alcohol was selected as risk factor for liver related events throughout the five strata of alcohol intake from none to 50 g/day [47]. All these subjects were at higher risk of composite fatal and non-fatal liver-related events (liver-related mortality, hospital admission, liver cancer) (hazard ratios between 2.18 and 8.79 for the different strata of alcohol intake), with a possible beneficial effect on cardiovascular outcomes.

Table 1. Summary of studies suggesting a detrimental effect of alcohol intake, although moderate, on the liver within and outside NAFLD.

Author, Year	Type of Study/Patients	Alcohol Assessment	Outcome Measures	Results
Suzuki, 2007 [5]	Cross sectional and prospective community-based study. 1177 male subjects with annual check-up. 326 subjects without elevated ALT with had a 5-year F-UP	Questionnaire. Alcohol graded as none, light, moderate, excessive	Raised ALT	Light (70–140 g/week: OR 0.6; 95% CI 0.4–1.0) and moderate (140–208 g/week: OR 0.5; 95% CI 0.3–0.9) alcohol consumption was negatively associated with raised ALT in the older and younger groups, respectively, vs. subjects with none or minimal intake. At F-UP, moderate intake was associated with decreased incidence of raised ALT (adjusted HR 0.4; 95% CI 0.1–0.9)
Gunji, 2009 [6]	Cross-sectional, community-based study. 5599 Japanese men with regular medical survey	Questionnaire. Alcohol graded in g/week	US-detected fatty liver	Both light (40–140 g/week) and moderate (140–280 g/week) alcohol intake independently reduced the risk of fatty liver (OR 0.82; 95% CI 0.68–0.99 and OR 0.75; 0.61–0.93)
Dixon, 2001 [15]	Cross sectional cohort study. 105 patients with liver	Medical consultation, questionnaire	Presence of biopsy-proven NASH	Moderate alcohol consumption was associated with a decreased risk of NASH (OR, 0.35; 95% CI, 0.12–1.00).

Author, Year	Type of Study/Patients	Alcohol Assessment	Outcome Measures	Results
	disease submitted to bariatric surgery			
Dunn, 2008 [16]	Cross sectional, community-based study of 7211 NHANES III participants not consuming alcohol and 945 wine drinkers	Questionnaire. Modest consumption: defined <100 g/week	Raised ALT (both laboratory range and updated definition) [60]	Irrespective of the reference cut-point, modest wine consumption was associated with 50% reduced risk of elevated ALT (OR 0.51; 95% CI 0.33–0.79 with updated normal ranges); no effect was demonstrated for beer or liquor drinking, whereas mixed drinking was protective.
Gunji, 2009 [6]	Cross-sectional, community-based study. 5599 Japanese men with regular medical survey	Questionnaire. Alcohol graded in g/week	US-detected fatty liver	Both light (40–140 g/week) and moderate (140–280 g/week) alcohol intake independently reduced the risk of fatty liver (OR 0.82; 95% CI 0.68–0.99 and OR 0.75; 0.61–0.93)
Yamada, 2010 [17]	Cross-sectional + longitudinal study (5444 men, 4980 women on regular check-ups. F-UP, 6 years	Frequency and amount of drinking in g/week	US-detected fatty liver	Occasional, daily moderate (1 U/day) or heavy (≥ 2 U/day) drinking was negatively associated with liver fat. On follow-up, moderate drinking maintained a negative association with fatty liver in men (OR 0.72, 95% CI 0.58–0.89), not in women
Hiramine, 2011 [18]	Cross-sectional cohort (9886 males	Questionnaire. Classified as none, light (≤ 20	US-detected fatty liver	Fatty liver was positively associated with obesity and negatively alcohol intake (light,

Author, Year	Type of Study/Patients	Alcohol Assessment	Outcome Measures	Results
	on regular health check-ups)	g/day), moderate (20–59), heavy		OR 0.71, 95% CI 0.59–0.86; moderate, OR 0.55, CI 0.45–0.67; heavy, OR 0.44, CI 0.32–0.62). The frequency of alcohol consumption was more relevant than total amount.
Moriya, 2011 [19]	Cross sectional, community-based study. 4957 men and 2155 women, median age 49, free of known liver disease	Lifestyle data derived from questionnaire (g/day)	US-detected NAFLD. Raised ALT by updated reference [60]	The prevalence of fatty liver was significantly lower in drinkers than in nondrinkers (28% vs. 40% in men and 10% vs. 16% in women ($p < 0.001$ for both). NAFLD prevalence was inversely associated with both amount and frequency of alcohol intake.
Gunji, 2012 [20]	Cross-sectional, community-based study. 1138 Japanese men with regular check-up, age ≥ 40	Questionnaires	CT-detected NAFLD	Alcohol consumption was associated with a reduced risk of liver fat, independently of features of metabolic syndrome, physical activity ad raised liver enzymes.
Hamaguchi, 2012 [21]	Cross-sectional community-based study. 8571 Japanese men and women, aged 18–88; mean BMI, 22.6 kg/m^2	Questionnaires. Alcohol intake categorized into 4 grades	Fatty liver by ultrasounds	For both men and women, light and moderate alcohol intake was inversely associated with fatty liver (Men: OR 0.69, 95% CI 0.60–0.79 and OR 0.72, 95% CI 0.63–0.83; Women: OR 0.54, 95% CI 0.34–0.88 and OR 0.43,95% CI 0.21–0.88).

Author, Year	Type of Study/Patients	Alcohol Assessment	Outcome Measures	Results
Dunn, 2012 [22]	Cross-sectional cohort study. 251 lifetime modest drinkers; 331 non-drinkers (NIH NASH CRN)	AUDIT test. Alcohol intake <140 g/week: extensive analysis of drinking pattern	Liver biopsy	Modest drinking within safe limits reduced the odds of NASH (OR 0.56, 95% CI 0.39–0.84), fibrosis (OR 0.56; 95% CI 0.41–0.77) and ballooning (OR 0.66, 95% CI 0.48–0.92) vs. lifetime non-drinking habits
Kwon, 2013 [23]	Cross-sectional cohort study. 77 patients with biopsy-assessed NAFLD, alcohol intake < 40 g/day	Lifetime retrospective alcohol intake by questionnaire	Liver biopsy	Increasing age (OR 1.07, 95% CI 1.01–1.14) was associated with more severe liver disease, whereas lifetime alcohol intake ≥ 24 g-years was associated with less severe disease (OR 0.26, 95% CI 0.07–0.97).
Moriya, 2015 [24]	Prospective analysis of several community-based cohorts (3773 men and 1524 women); F-UP, NS	Questionnaire	US-assessed NAFLD incidence	In both men and women, modest alcohol intake was associated with negative odds of NAFLD. In men, NAFLD was also reduced by alcohol intake in the range ≥280 g/week, after adjustment for confounders (OR 0.68; 95% CI 0.58–0.79)
Hagstrom, 2017 [25]	Cross-sectional, cohort study. 120 subjects with biopsy-proven NAFLD	Questionnaires for lifetime alcohol intake. PEth for recent alcohol	Liver biopsy	Alcohol intake up to 13 U/week was associated with reduced risk of fibrosis (OR 0.86 per U/week, 95% CI 0.76–0.97). High PTth was associated with a higher risk of fibrosis (OR 2.77, 95% CI 1.01–7.59)

Author, Year	Type of Study/Patients	Alcohol Assessment	Outcome Measures	Results
Mitchell, 2018 [26]	Cross-sectional, cohort study. 187 NAFLD patients (24% with advanced fibrosis)	Questionnaires for previous and actual alcohol intake and binge drinking	Liver biopsy	Modest consumption was associated with a decreased risk of advanced fibrosis (OR 0.33, 95% CI 0.14–0.78). The association was not confirmed in binge drinking. Exclusive wine, not beer drinking, was negatively associated with advanced fibrosis (OR 0.20, 95% CI 0.06–0.69), compared to lifetime abstinence.
Hajifathalian, 2018 [27]	Prospective, community-based study of 4568 NHANES participants. F-UP, 70 months	Questionnaire for amount and type of alcohol drinking	Hepatic Steatosis Index [61]	Modest alcohol consumption was associated with decreased overall mortality (HR 0.64, 95% CI 0.42–0.97 for a drinking pattern of 0.5–1.5 U/day). However, in NAFLD alcohol consumption ≥ 1.5 U/day had a harmful effect on mortality (HR 1.45, 95% CI 1.01–2.10), after adjustment for confounders.

Abbreviations: ALT—alanine aminotransferase; AUDIT—Alcohol Use Disorder Identification Test; BMI—body mass index; CI—confidence interval; CT—computed tomography; F-UP—follow-up; HR—hazard ratio; NS—not specified; NHANES—National Health and Nutrition Examination Survey; NIH NASH CRN—National Institute of Health NASH Clinical Research Network; OR—odds ratio; PEth—phosphatidyl ethanol; US—ultrasonography.

6. Effects of Alcohol Intake Beyond the Liver

The effects of alcohol extend well beyond the liver; the literature has been extensively revised in a Consensus document of a team of Italian experts, coordinated by the Nutrition Foundation of Italy and endorsed by several scientific Societies [62]. Two areas deserve particular attention for the interaction between alcohol and extra-hepatic disease: (a) cardiovascular disease; (b) cancer. For all areas, a relevant effect of gender was reported, with women at much higher risk than men.

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6.1. Cardiovascular Disease

Several meta-analyses tested the association between alcohol and coronary artery disease, showing the J-shaped curve reported for total mortality, particularly in women, whereas in men there was a linear decrease in cardiovascular events for levels of alcohol consumption much higher than safe limits [63]. The effects were in the order of magnitude of a 25–40% reduction in fatal and non-fatal coronary events for an alcohol intake in the modest amounts (1–2 U/day), irrespective of the presence of diabetes or pre-existing coronary disease [62], the type of alcoholic beverage and the consumption with/without meals [31]. The risk of arrhythmias, particularly atrial fibrillation, associated with alcohol use even in moderate amounts should however be mentioned [64], as well as the risk associated with binge drinking [65].

The J-shaped curve was confirmed for stroke [66], where the consumption of alcohol above 5 U/day started to increase the risk of events, particularly in women, confirming the gender effect also reported for coronary disease [63]. Protection by modest alcohol intake added to the protection exerted by healthy lifestyles [67] and to secondary prevention in 1320 participants in the Physician's Health Study [68]. The association with peripheral artery disease has been less clearly investigated, but the overall studies are in line with those reported above, possibly mediated by blood pressure, also showing a J-shaped curve in relation with alcohol intake. In this case the nadir was initially observed at very modest amount of alcohol (1–2 U/day) [69], with conflicting results in relation to gender [62]. Notably, the protection exerted by alcohol might also extend to subjects with established fatty liver [47]. Both the prevalence of carotid plaques and carotid artery stenosis were also reduced in subjects consuming modest amounts of alcohol (<20 g/day), and were negatively associated with alcohol use [33]. Reduced blood pressure and prevention of cerebrovascular involvement might also account for the association of modest alcohol use with reduced incidence of cognitive dysfunction and risk of dementia reported in two meta-analyses [70][71], with a nadir at 0.5 U/day and increased risk above 2 U/day [71].

6.2. Cancer

The harmful effects of alcohol consumption on cancer risk have been extensively investigated; on cancer outcomes, the effects of moderate alcohol intake in specific organs are beyond dispute, although the mechanism(s) have not been completely understood. The most widely tested association is the risk of breast cancers, where several studies and meta-analyses/review articles are available [72][73]. The risk, possibly mediated by the effect of alcohol on estrogen concentration, increases by 7–10% for any unit of alcohol/day, without a floor effect [73]. In the prospective observational study of 105,986 women enrolled in the Nurses' Health Study followed and 2.4 million person-years of follow-up, also very modest alcohol consumption was associated with increased breast cancer risk, starting at levels equivalent to only 3–6 U/week, without any relation with drinking pattern, total consumption, and age [74]. A detrimental effect of modest alcohol consumption was also found for oral and pharyngeal cancer risk, whereas the effects of low dose alcohol intake on the risk of colo-rectal cancer remain uncertain and probably null. Overall, the burden of cancer associated with alcohol is extremely high; Europe is the area of heaviest consumption and higher cancer risk, with alcohol drinking accounting for an estimate 4.2% of all disability-adjusted life-years and 5.2% of deaths [75]. Apparently, no safe limits of alcohol intake may be defined to prevent cancer risk.

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