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CLINICAL STUDIES

Interaction of alcohol intake and cofactors on the risk of cirrhosis

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Abstract

Objective: Evaluation of the interaction between alcohol intake and cofactors [hepatitis B virus (HBV), hepatitis C virus (HCV), body mass index] and coffee consumption on the risk of cirrhosis. *Design:* Seven hundred and forty-nine consecutive patients with chronic liver disease referring to units for liver or alcohol diseases in Italy during a 6-months period. Teetotalers were excluded. The odds ratios (OR) for cirrhosis were evaluated using chronic hepatitis cases as the control group. *Results:* An alcohol intake of more than 3 units/day resulted associated with the likelihood of cirrhosis both in males (OR 4.3; 95% CI = 2.5–7.3) and in females (OR 5.7; 95% CI = 2.3–14.5). A multiplicative interaction on the risk of cirrhosis between risky alcohol intake and HBsAg or HCV-Ab/HCV-RNA positivity was observed. A reduction of cirrhosis risk was observed in subjects consuming more than 3 alcohol units/day with increasing coffee intake. The OR for the association with cirrhosis decreased from 2.3 (95% CI = 1.2–4.4) in subjects drinking 0–2 cups of coffee/day to 1.4 (95% CI = 0.6–3.6) in those drinking more than 2 cups/day. *Conclusions:* In subjects with an alcohol intake >3 units/day the coexistence of HBV or HCV multiplies the risk of cirrhosis. Coffee represents a modulator of alcoholic cirrhosis risk.

It is well known that ethanol is a major risk factor for chronic liver disease. It has been shown repeatedly that in the general Italian population, the amount of alcohol intake that causes liver damage is >3 units/day (1–3). Moreover, ethanol may be an important cofactor for the progression of chronic liver damage when it is present together with other causative agents. It has been shown that hepatitis C virus (HCV) chronic infection interacts multiplicatively with alcohol intake in determining cirrhosis (4), while the role of hepatitis B virus (HBV) chronic infection is still being debated (5). In the past years, the role of obesity as an important cofactor of cirrhosis in alcoholics has also been stressed (6) Finally, it has also been shown that an inverse relation exists between coffee intake and the risk of cirrhosis, and that coffee has a favourable effect on alcohol-related cirrhosis risk (7–9). However, all the reported studies have evaluated the interaction of alcohol with a single cofactor [i.e. HCV or body mass index (BMI) or coffee], whereas studies assessing the role of various cofactors in the same cohort of alcoholic patients are lacking. Moreover, the interaction, if any, between HBsAg and alcohol is still unclear.

The aim of this paper was to evaluate in the same setting of patients the interaction between alcohol intake and various cofactors such as chronic HCV infection, chronic HVB infection and BMI on the risk of cirrhosis. The effect of coffee consumption on the risk of alcoholic cirrhosis has also been assessed.

Patients and methods

During a 6-month period (January–June 2007), all consecutive patients with chronic liver disease referring to a 9 units of internal medicine and/or gastroenterology for the management of their pathology were recruited. These units were distributed homogeneously across Italy. Teetotalers were excluded. For each patient, demographical, clinical and aetiological data were recorded using a precoded questionnaire. The amount of alcohol intake was determined using a standard questionnaire containing information on the daily alcohol intake of various

alcoholic beverages, according to previously codified methods by us and other groups (10, 11). One alcoholic unit corresponds to a glass of wine, a can of beer or a measure of spirits, and contains 12–13 g of ethanol. For alcohol intake, we also considered the type of beverage used more frequently, the duration of use and the modalities of ingestion (at fasting, during meals, etc.). We also collected the amount of lifetime coffee consumption (at least during the last 10 years), using as the unit of measure the number of cups of 'espresso' coffee per day. The use of other types of coffee was absent in our cases. Demographical data also included the evaluation of comorbidities such as diabetes, hypertension, dyslipidaemia or others. Patients who consumed drugs for the nervous system (or other well-known hepatotoxic drugs) were excluded from the study owing to their possible interference with liver damage.

Hepatitis B surface antigen and antibodies to HCV (anti-HCV) were determined using enzyme-linked immunosorbent assays. HCV-RNA was assessed by polymerase chain reaction. Chronic hepatitis was diagnosed on the basis of liver histology or in the presence of persistently (>6 months) abnormal ALT without clinical, biochemical and ultrasound markers of cirrhosis. Cirrhosis was diagnosed by liver biopsy or in the presence of clinical, biochemical and ultrasound signs (12).

Statistical analysis

The odds ratio (OR) of cirrhosis and their 95% confidence intervals were evaluated using chronic hepatitis cases as the control group . Interaction may be additive or multiplicative. Additive interaction means that the observed joint effect of two factors on the disease incidence (in this case cirrhosis) exceeds the sum of the effect of exposure to each single factor minus 1. Multiplicative interaction means that the observed joint effect of two factors on the disease incidence exceeds the product of the effect of exposure to each single factor.

To evaluate the interaction between alcohol intake and cofactors, subjects unexposed to either factor were taken as the reference category for all calculations.

We dichotomized alcohol intake as 1–3 units/day (low or moderate drinkers) and >3 units/day (heavy drinkers), according to the threshold of 3 units of alcohol considered necessary for the development of alcohol-mediated injury (13).

Results

A total of 749 cases were enrolled during the study period. A preponderance (66.3%) of males was observed. The majority of subjects (63.4%) reported low or moderate alcohol intake (1–3 units/day); nearly a quarter admitted a very heavy alcohol intake (>5 units/day). The proportion of subjects who were HBsAg positive was 8.1%, while 53.0% of the subjects were anti-HCV and HCV-RNA positive. Chronic hepatitis was diagnosed in 81.8% of cases (Table 1). An alcohol intake of >3 units/day resulted associated with the likelihood of cirrhosis in both males (OR = 4.3; 95% CI = 2.5–7.3) and females (OR = 5.7; 95% CI = 2.3–14.5).

The amount of 3 units/day resulted unassociated in both sexes (Table 2).

A multiplicative interaction between alcohol intake and HBV- or HCV-related disease is observed. In fact, excluding subjects who were HCV/HCV-RNA positive, the OR of cirrhosis for joint exposure to >3 alcohol units/day and HBsAg positivity was 4.8 (95% CI = 1.9–12.4), while the OR for exposure to only >3 alcohol units/day was 2.4 (95% CI = 1.3–4.2) and the OR for exposure to only HBsAg positivity was 0.2 (95%

Table 1. Characteristics of 749 enrolled patients

Characteristics	%
Sex	
Males	66.3
Females	33.7
Age distribution (years)	
<45	37.0
46–65	39.5
>65	23.5
BMI	
<25	42.4
>25	57.6
Number of drinks/day	
1–3	63.4
4	7.6
5	3.6
6–10	13.4
>10	12.0
$HBsAg^+$	8.1
$HCVAb^+/HCV\text{-}RNA^+$	53.0
Chronic hepatitis	81.8
Cirrhosis	18.2

BMI, body mass index; HCV, hepatitis C virus.

Table 2. Progression from chronic hepatitis to cirrhosis according to amount of alcohol intake stratified by sex

	Males ($n = 510$)			Females ($n = 259$)		
Number of drinks/day	Chronic hepatitis	Cirrhosis	OR (95% CI)	Chronic hepatitis	Cirrhosis	OR (95% CI)
1–2	$n = 192$	$n = 23$	1	$n = 190$	$n = 14$	1
3	$n = 49$	$n = 7$	1.2 (0.5–2.9)	$n = 17$	$n = 1$	0.8 (0.1–6.5)
>3	$n = 158$	$n = 81$	4.3 (2.5–7.3)	$n = 26$	$n = 11$	5.7 (2.3–14.5)

Crude odds ratios (O.R.) derived by univariate analysis.

CI = 0.1–1.1). Similarly, excluding HBsAg-positive subjects, the OR of cirrhosis for joint exposure to >3 alcohol units/day and HCV/HCV-RNA positivity was 3.2 (95% CI = 1.8–5.7), while the OR for exposure to only >3 alcohol units/day was 2.4 (95% CI = 1.3–4.2) and the OR for exposure to only HCV/HCV-RNA positivity was 0.2 (95% CI = 0.2–0.8). No interaction was found in subjects exposed to the joint effect of obesity and risky alcohol intake (OR = 2.0; 95% CI = 0.7–5.6) (Table 3). Other aspects such as the type of alcoholic beverage used, the duration of use and the presence of comorbidities did not significantly influence the results. A reduction in cirrhosis risk was observed in subjects consuming >3 alcohol units/day with increasing coffee intake. The OR for the association with cirrhosis decreased from 2.3 (95% CI = 1.2–4.4) in subjects drinking 0–2 cups of coffee/day to 1.4 (95% CI = 0.6–3.6) in those drinking >2 cups/day. (Table 4).

Discussion

Firstly, the present findings confirm previous studies (1–3) showing that the amount of alcohol intake that causes liver damage is >3 units/day. In order to evaluate the interaction between alcohol intake and cofactors on the risk of cirrhosis, we have used an internal control, which is the best control group. Cases (i.e. cirrhotic patients) and controls (i.e. chronic hepatitis cases) were subjects extracted from the same population (i.e. subjects with chronic liver disease) and thus exposed to the same potential selective factors. In a case–control study comparability between cases and controls is the crucial factor, which means avoidance of potential selective factors regarding the enrollment of cases and controls.

The present findings confirm previous report that in subjects with risky alcohol intake, the coexistence of HCV infection multiplies the risk of cirrhosis (4). Several lines of evidence provide the biological plausibility for this epidemiological finding.

Firstly, both HCV and alcohol may stimulate hepatic-oxidative stress, which leads to the activation of liver fibrogenic cells, and the consequent acceleration of fibrogenesis (14–16).

Secondly, immune response is affected by alcohol; finally, alcohol may promote apoptosis in hepatocytes infected by HCV (17–19).

The observed joint effect in terms of multiplicative interaction between alcohol intake and HBV infection on the risk of cirrhosis is a new finding. However, a clear biological plausibility for that has not yet been provided. It may be presumed that the mechanisms enhancing liver damage are similar to those involved in HCV infection (i.e. enhanced oxidative stress, interaction with immune response and activation of pro-inflammatory cytokine pathways).

An interesting finding, even though not new is that of the protective effect of coffee on alcohol-related cirrhosis risk. There is a continuum of clinical and epidemiological evidence to support a favourable effect of coffee on liver function (8) and liver disease, including cirrhosis (20) and hepatocellular carcinoma (21). There is some concern that the inverse relation observed between coffee intake and liver disease may be spurious, as a consequence of the fact that subjects with liver disease may reduce their coffee consumption. Hypothetically, some persons with liver disease might have reduced coffee intake or quit drinking coffee, thus spuriously increasing the risk of the referral group. However, as the coffee consumption concerned the last 10 years and the control group was represented by subjects with chronic liver disease (and thus exposed to similar selective factors than cases), this bias has resulted likely avoided. Various components of coffee have been related to act a protective effect including caffeine (via adenosine receptor antagonists or antioxidant action), cafertol (via induction of the

Table 3. Interaction between alcohol intake and cofactors in the progression from chronic hepatitis to cirrhosis

Cofactor	Chronic hepatitis	Cirrhosis	Likelihood of cirrhosis OR (95% CI)
HBsAg and alcohol (excluding HCV^+ cases)			
$HBsAg^-$/1–3 drinks	*n* = 143	*n* = 25	1
$HBsAg^+$/1–3 drinks	*n* = 37	*n* = 1	0.2 (0.1–1.1)
$HBsAg^-$/ > 3 drinks	*n* = 87	*n* = 36	2.4 (1.3–4.2)
$HBsAg^+$ > 3 drinks	*n* = 13	*n* = 11	4.8 (1.8–12.4)
HCV and alcohol (excluding $HBsAg^+$)			
HCV^-/1–3 drinks	*n* = 143	*n* = 25	1
HCV^+/1–3 drinks	*n* = 260	*n* = 20	0.4 (0.2–0.8)
HCV^-/ > 3 drinks	*n* = 87	*n* = 36	2.4 (1.3–4.2)
HCV^+/ > 3 drinks	*n* = 75	*n* = 42	3.2 (1.8–5.7)
BMI and alcohol (excluding $HBsAg^+$ and HCV^+)			
BMI < 30/1–3 drinks	*n* = 110	*n* = 22	1
BMI ≥ 30/1–3 drinks	*n* = 32	*n* = 3	0.5 (0.1–1.7)
BMI < 30/ > 3 drinks	*n* = 69	*n* = 27	1.3 (1.0–3.7)
BMI ≥ 30/ > 3 drinks	*n* = 17	*n* = 7	2.0 (0.7–5.6)

Table 4. The effect of coffee intake on the progression from chronic hepatitis to liver cirrhosis according to the amount of alcohol intake ($HBsAg^+$ and HCV^+ subjects were excluded from the analysis)

	0–2			>2		
Cups of coffee/day	Chronic hepatitis	Cirrhosis	OR (95% CI)	Chronic hepatitis	Cirrhosis	OR (95% CI)
Number of alcohol drinks/day						
1–3	*n* = 101	*n* = 21	1	*n* = 40	*n* = 3	0.4 (0.1–1.3)
>3	*n* = 59	*n* = 28	2.3 (1.2–4.4)	*n* = 27	*n* = 8	1.4 (0.6–3.6)

synthesis of glutathione, a cellular protective factor) and anti-oxidant substances from coffee beans, such as flavonoids and anthocyanes (22–24). However, no definite evidence is available for any of these components.

In conclusion, even though some findings are not new, this is one of the few papers assessing in the setting of patients the role of various cofactors on the progression of liver disease in alcoholics, and the use of an internal control group may have avoided spurious associations. Results indicate that alcohol intake interacts with hepatitis viruses in the progression of liver disease and, firstly, the role of HBsAg positivity has been defined. Coffee represents a modulator of alcoholic cirrhosis risk. In any case, even if coffee may be considered to be protective, the primary approach to the reduction of alcoholic cirrhosis includes the avoidance or cessation of heavy alcohol drinking.

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