WINE CONSUMPTION IS NOT ASSOCIATED WITH A DECREASED RISK OF ALCOHOLIC CIRRHOSIS IN HEAVY DRINKERS

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Abstract — Aims: While it was thought that all alcoholic beverages share a similar liver toxicity when drunk at a high level, recent epidemiological surveys have suggested that wine drinking might decrease the risk of alcoholic cirrhosis in heavy drinkers. Therefore, we performed a study aiming to analyse the type and the intake levels of alcoholic beverages in heavy drinkers according to the severity of the liver disease. Methods: This is a case–control study enrolling 42 cirrhotic and 60 non-cirrhotic patients. Liver status was assessed using clinical, biological, histological and ultrasonographic procedures. Alcohol consumption was recorded using the Lifetime Drinking History method. Results: We did not find any significant differences in total alcohol consumption between cases and controls and, moreover, in our series, the relative percentage of pure alcohol drunk in wine was significantly higher in cirrhotic, than in non-cirrhotic, patients. Conclusions: Our results confirm that the absence of a link between the type of alcoholic beverage and the occurrence of cirrhosis is still valid.

INTRODUCTION

Heavy drinking is associated with the development of liver cirrhosis, a severe disease often leading to death. Indeed, in France, in 1998, up to 9000 deaths directly due to alcoholic cirrhosis were recorded (Service d’information sur les causes médicales des décès, INSERM SC8, Paris). However, only about 20% of heavy drinkers develop a liver cirrhosis (Leibach, 1976), suggesting that factors other than alcohol are required to promote this liver disease. Several studies, conducted in either animals or in humans, investigated the risk factors for alcoholic liver cirrhosis. Among them, female sex (Mezey et al., 1988; Corrao et al., 1997; Limuro et al., 1997), nutritional status (Lieber, 1991) and the severity of liver steatosis (Giraud et al., 1998) appear to be particularly involved.

Finally, the type of alcoholic beverage was thought not to be associated with the risk of cirrhosis (Tuyns et al., 1984) until recently. Indeed, a prospective epidemiological study performed in Denmark concluded that, for a given daily dose of pure alcohol, the risk of cirrhosis was significantly decreased when wine accounted for 30–50% of the total dose (Becker, 1998); a similar, although not significant, trend was found in a study from the USA (Chou et al., 1998). Although, these results are unexpected, they fit well with both experimental and clinical data. First, wine contains several polyphonic compounds exhibiting anti-oxidative properties and experimental data suggest that they can alleviate ethanol-induced liver toxicity (Sun et al., 1999). Second, in the south of France, a wine producing and consuming area, the mortality rate for alcoholic cirrhosis is significantly lower than in the north (Michel et al., 1997) and it could not be excluded that this figure is related to a lower occurrence of cirrhosis. In order to shed light on the relationship between wine consumption and alcoholic cirrhosis, we designed a case–control study aiming to compare the type and the intake level of alcoholic beverages in cirrhotic and non-cirrhotic patients.

PATIENTS AND METHODS

Patients

Four alcohol treatment units located in the Languedoc-Roussillon (LR) area participated in the study. Patients were consecutively recruited if they fulfilled the following criteria: (1) male sex, in order to avoid any bias related to the known gender difference in alcohol liver toxicity; (2) born and having always lived in the LR area; (3) free of viral infections with human immunodeficiency virus, hepatitis B or C virus; (4) able to complete an interview on their alcohol consumption during their life.

Liver disease classification

Patients were classified in the cirrhotic or non-cirrhotic group on the basis of standard criteria (Sherlock, 1981).

Cirrhotic group: liver histological analysis or presence of at least two of the following signs: firm liver with tense edge; splenomegaly; ultrasonographic (USN) and/or endoscopic signs of portal hypertension; clinical and/or biological signs of liver failure; hypergammaglobulinaemia; ascites; platelet count less than 100 000/mm²; liver dysmorphia at USN examination.

Non-cirrhotic group: absence of all the signs listed above; normal clinical and USN liver examination; normal routine biological liver tests except for an increase in aspartate aminotransferase (ASAT) activity less than two times the normal values (65 IU/l). An increase in serum gamma-glutamyl transpeptidase did not preclude a classification in this group, since such an increase is usual in heavy drinkers even in the absence of liver disease.

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**Alcohol consumption recording**

We used a method derived from that proposed by Skinner and Sheu (1982). Briefly, the life is divided into sequential periods, the first starting at the age when the subject began to drink once a month at least, and finishing at the age when alcohol consumption has significantly changed. For each period, we recorded the mean number of glasses of wine, beer and spirits (i.e. whisky, gin, aniseed drinks, rum, etc.) drunk during meals and out of meal times each day of a typical week; aperitifs were included in the mealtime period. Therefore, we calculated the weekly consumption of each alcoholic beverage, assuming that whatever its type, a single glass contains 11 g of pure alcohol, and multiplied it by the number of weeks of the corresponding period. The endpoint for recording alcohol consumption was the year of diagnosis of cirrhosis or the year of inclusion in the present study for non-cirrhotic patients.

**Statistical analysis**

Qualitative parameters were compared using the Pearson \( \chi^2 \) test and the Fisher exact test when necessary; quantitative parameters were compared using Student’s \( t \)-test or non-parametric tests (Mann–Whitney, Wilcoxon) when the data were skewed. A \( P \) level less than 0.05 was considered as significant. All the analyses were done using the 10.0 SPSS software (SPSS Inc., Chicago, IL, USA).

**RESULTS**

One hundred and two male alcoholic patients were studied, including 42 cirrhotic (cases) and 60 non-cirrhotic (controls) patients; their main characteristics are presented in Table 1. Diagnosis of cirrhosis was assessed on liver biopsy in 21 patients. By the time of recruitment 11 cases had stopped drinking for 3.5 ± 2.2 years. None had complications of cirrhosis (jaundice, ascites, gastro-intestinal bleeding) at the time of diagnosis. The mean age (± SD) of cirrhotic patients at the time of diagnosis was significantly higher than that of the controls (51 ± 8.4 vs 44.3 ± 7.8 years, \( P < 0.006 \)), as were, though not significantly, the mean age at which a regular alcohol consumption started (cases 25.7 ± 11.6 years; controls 21.8 ± 9.2 years) and the length of consumption (cases 24.8 ± 10.7 years; controls 21.6 ± 8.1 years).

Data concerning alcohol consumption are presented in Table 2. The mean total lifetime alcohol consumption was 2306 ± 1942 kg in cirrhotic patients and 1748 ± 1114 kg in controls; their main characteristics are presented in Table 1. Diagnosis of cirrhosis was assessed on liver biopsy in 21 patients. By the time of recruitment 11 cases had stopped drinking for 3.5 ± 2.2 years. None had complications of cirrhosis (jaundice, ascites, gastro-intestinal bleeding) at the time of diagnosis. The mean age (± SD) of cirrhotic patients at the time of diagnosis of cirrhosis was significantly higher than that of the controls (51 ± 8.4 vs 44.3 ± 7.8 years, \( P < 0.006 \)), as were, though not significantly, the mean age at which a regular alcohol consumption started (cases 25.7 ± 11.6 years; controls 21.8 ± 9.2 years) and the length of consumption (cases 24.8 ± 10.7 years; controls 21.6 ± 8.1 years).

**Table 1. Main characteristics of the cirrhotic and non-cirrhotic patients studied**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cirrhotic patients</th>
<th>Non-cirrhotic controls</th>
<th>Significance (( P ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at diagnosis</td>
<td>51.0 ± 8.4</td>
<td>44.3 ± 7.8</td>
<td>0.006</td>
</tr>
<tr>
<td>ASAT (IU/l)</td>
<td>90 ± 75</td>
<td>54 ± 30</td>
<td>0.009</td>
</tr>
<tr>
<td>GGT (IU/l)</td>
<td>422 ± 440</td>
<td>194 ± 170</td>
<td>0.004</td>
</tr>
<tr>
<td>Age at beginning of regular drinking (years)</td>
<td>25.7 ± 11.6</td>
<td>21.8 ± 9.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Duration of alcohol consumption (years)</td>
<td>24.8 ± 10.7</td>
<td>21.6 ± 8.1</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Age is that at cirrhosis diagnosis or age at the time of the present study. ASAT, aspartate aminotransferase; GGT, \( \gamma \)-glutamyl transferase.

**Table 2. Total lifelong consumption of pure alcohol in wine, beer and spirits in the cirrhotic and non-cirrhotic patients studied**

<table>
<thead>
<tr>
<th>Type of alcoholic beverage</th>
<th>Cirrhotic patients</th>
<th>Non-cirrhotic controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>%</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Wine (kg)</td>
<td>1318 ± 1063</td>
<td>57.7</td>
</tr>
<tr>
<td>Beer (kg)</td>
<td>505 ± 494</td>
<td>21.2</td>
</tr>
<tr>
<td>Spirits (kg)</td>
<td>730 ± 752</td>
<td>21.1</td>
</tr>
<tr>
<td>Total (kg)</td>
<td>2306 ± 1942</td>
<td>100</td>
</tr>
</tbody>
</table>

No differences were significant when means were compared; comparisons between percentages were significant for wine (\( P = 0.04 \)) and spirits (\( P = 0.01 \)).

higher in cases (2306 ± 1942 kg, median = 1646 kg) than in controls (1748 ± 1114 kg, median = 1564 kg) and such an increase concerned all the types of alcoholic beverages; however, these differences did not reach statistical significance.

Analysis of the respective proportions of each type of alcoholic beverage drunk all along the life showed that cirrhotic patients displayed a significantly different pattern of consumption than non-cirrhotics (Table 2): in the cirrhotic group, wine accounted for 57.7% of total alcohol intake, against 45.9% in controls (\( P = 0.04 \)), and spirits for 21.1% against 31.7% (\( P = 0.01 \)); in contrast, the proportion of alcohol drunk as beer did not differ (21.2 vs 22.4%).

The proportions of total pure alcohol drunk during meals and out of meal times were similar in both groups: cirrhotic patients had drunk 62 ± 28% of the total dose during meals and 38 ± 28% out of meal times; the corresponding figures in controls were 64 ± 22 and 36 ± 22%, respectively. Analysis after stratification on the type of alcoholic beverages showed that wine was drunk mainly at mealtime, beer out of meal times and spirits during and out of mealtimes without any significant difference between groups (Table 3).

In order to better analyse the impact of wine consumption on the risk of cirrhosis, patients were split into two groups, those having drunk more or less than 50% of the total alcohol dose as wine; the total alcohol consumption of these two groups was not different, since wine high drinkers drank less beer and spirits than the wine low drinkers (data not shown). The rate of cirrhosis was similar in both subgroups, since among
the 50 who were wine high drinkers, 21 (42%) had a cirrhosis against 21 (40.6%) out of the 52 who were wine low drinkers (Fig. 1).

**DISCUSSION**

This work aimed to assess whether, in heavy drinkers, wine drinking might have a differential impact on the development of liver cirrhosis, than other alcoholic beverages. Our results do not fit with those of epidemiological studies recently reported (Becker, 1998; Chou et al., 1998). Indeed, we did not find any significant differences in total alcohol consumption and, moreover, in our series, the relative percentage of alcohol drunk in wine was significantly higher in cirrhotic, than in non-cirrhotic, patients. Our data thus suggest that old results (Tuyns et al., 1984) demonstrating the absence of a link between the type of alcoholic beverage and the risk of cirrhosis are still valid.

As the design of our work was retrospective, one could suspect that recording alcohol consumption for a long period might not be reliable, owing to memory bias. Such a possibility could not be completely excluded; however, we used several precautions in order to avoid a potential bias. First, patients included were all in-patients who were volunteers for an alcohol detoxification, therefore, a denial possibility could not be completely excluded; however, we might not be reliable, owing to memory bias. Such a suspect that recording alcohol consumption for a long period might not fit with those of epidemiological studies in which alcohol consumption was recorded through written self-reports.

Another major problem could arise from a misclassification of the patients in the cirrhotic or non-cirrhotic group. Such a problem applies to both our case–control and epidemiological studies, although more in the latter, than in the former. Indeed, in our case–control study, diagnosis of cirrhosis was done either on histological examination of the liver or on the presence of several well-defined and widely accepted medical criteria when liver biopsy was not performed. For the control group, we used an inverse procedure, which excluded all the medical signs potentially associated with liver cirrhosis before final classification as controls; performing a liver biopsy in this group of patients, however, was not possible for obvious ethical reasons. Altogether, the risk of an error in classification was therefore extremely low. Epidemiological surveys are more sensitive to that risk, particularly regarding the non-cirrhotic group: as medical diagnoses are recorded from hospital or from mortality databases, patients with alcoholic cirrhosis might well be classified in the non-cirrhotic group as long as they have not been admitted to hospital, or a complete medical examination has not been done; as liver cirrhosis remains compensated and silent for many years before medical complications occur, there is a large risk for an uncorrected classification.

Several reports demonstrated that drinking alcohol moderately (about 2 units/day) is associated with a decrease in mortality (Gronbaek et al., 2000; Meister et al., 2000) from all causes, but particularly from cardio-vascular diseases. Although the anti-oxidative properties of polyphenols contained in wine have been emphasized (Nigdikar et al., 1998; German and Walzem, 2000), there is still a controversy in this regard (Duthie et al., 1998; Cleophas, 1999), and it cannot at present be concluded that moderate consumption of any particular alcoholic beverage is superior in reducing mortality (Gronbaek, 2001). On the contrary, our results show that, when the alcohol intake is high, the risk for the development of alcoholic cirrhosis is equal, whatever type of alcoholic beverage, and that the anti-oxidant content of wine is not sufficient enough to reduce the alcohol-related liver toxicity.

Another question regarding the occurrence of alcoholic liver cirrhosis concerns the possible impact of drinking alcohol during meals, since it is known that eating while drinking delays gastric emptying and therefore reduces intestinal absorption of alcohol. It has been reported that drinking alcohol both during meals and out of mealtime significantly increases the risk of cirrhosis, as compared with drinking alcohol during meals only (Bellentani et al., 1997); however, in that study, subjects drinking during meals only had a rather low alcohol consumption (24 g/day), a dose probably not sufficient to lead to liver toxicity. In our study, the major bulk of alcohol consumption occurred during meals, about 65% of the total dose, and was not different between cases and controls. This suggest that, when the alcohol consumption is high, drinking with food is not protective enough against alcohol hepatotoxicity.

The absence of striking differences between our cirrhotic and non-cirrhotic patients as regards the amount of alcohol consumed demonstrates that, although alcohol consumption is a pre-requisite for the development of an alcoholic liver disease, other factors may be involved. Among these, genetic (Hrubec and Omenn, 1981) as well as nutritional factors (Lieber, 1991) might well play a role; however, the age of the drinker could also be involved. Indeed, cirrhotic patients were about 7 years older than non-cirrhotic ones at the time of

**Fig. 1.** Proportion of cirrhosis in patients having drunk more (n = 50) or less (n = 52) than 50% of the pure alcohol total dose as wine. There was no statistically significant difference between groups.
diagnosis (51 vs 44 years). Epidemiological data on hepatitis C virus-related liver diseases showed that patients affected after the age of 40 years develop a severe liver disease faster than the younger ones (Pol et al., 1998); moreover, experimental data in animals showed that alcohol clearance decreases with age (Fernandez et al., 1988). Altogether, drinking heavily after the age of 45 years might be critical for the liver, particularly, also in view of the age-related immunological disturbances. Further studies are needed in this regard to verify such a hypothesis.

In conclusion, wine, as with other alcoholic beverages, can lead to alcoholic cirrhosis when consumed heavily.

REFERENCES


