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HCV, HBV and Alcohol – the Dionysos Study

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Abstract
Population-based studies on the natural history of chronic viral liver disease that consider co-morbidity factors, such as alcohol or metabolic diseases, are lacking. We report here the contribution of ethanol intake and non-organ-specific autoantibodies (NOSA) to the course of chronic viral disease in the Dionysos cohort. As reported elsewhere, the Dionysos study was performed in two towns of Northern Italy, started in 1992 with 10 years of follow-up in 2002, and allowed us to quantify the burden of chronic liver disease in Northern Italy. We followed 139 subjects with chronic hepatitis C virus (HCV) infection and 61 with chronic hepatitis B virus (HBV) infection for a median (IQR) time of 8.4 (1.0) and 8.3 (0.9) years, respectively. The incidence and remission rates of steatosis were 9.0 and 29.7 per 1,000 person-years in the HCV cohort and 4.0 and 30.4 per 1,000 person-years in the HBV cohort. Progression to cirrhosis and hepatocarcinoma was more common in the HCV than in the HBV cohort. In the HCV cohort, ethanol intake was an independent predictor of liver cirrhosis and of death rate in both cohorts. We found no association between baseline NOSA and 8.4-year mortality. We conclude that morbidity and mortality rate of HBV and HCV infection in the general population is lower than that reported in secondary care populations, blood donors, or clinical series, and that ethanol intake >30 g/day is the most important and evitable risk factor for cirrhosis and death in patients with chronic HCV or HBV infection.

Alcohol is an established risk factor for liver cirrhosis and approximately 15% of alcohol-related global deaths in 2004 were due to liver cirrhosis [1]. However, some crucial points remain obscure such as to whether the relationship between alcohol and liver cirrhosis has a dose-response or threshold pattern [2, 3]. Also, the role of sex, ethanol intake, fatty liver (FL) and non-organ-specific autoantibodies (NOSA) in the progression of hepatitis B virus (HBV)/hepatitis C virus (HCV) infection and of other chronic liver diseases (CLD) is incompletely understood. The available knowledge on the natural course of CLD is based mainly on studies performed on blood donors, military recruits, and secondary or tertiary care series. Population-based studies on the natural history of CLD that consider co-morbidity factors, such as alcohol or metabolic diseases, are lacking. To address these questions, we summarize here recent studies and the results of the Dionysos study [4, 5].

As reported in detail elsewhere [2, 4–6], the Dionysos study was performed in two towns of Northern Italy, started in 1992 with a follow-up in 2002, and allowed us

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Table 1. Non-standardized liver-related and not liver-related mortality rate (n/100,000/year) in the Dionysos cohort according to different etiology

Dionysos 1 & 2	NAFLD	AFLD + alc. cirrhosis	HCV	HBV	Total
Liver-related	1.4	11.5	13.0	1.4	27.3
Not liver-related	13.0	34.7	18.8	4.3	72.2
Total	14.4	46.2	31.8	5.7	99.5

Table 2. Non-standardized annual mortality rate according to the presence of a different number of risk factors

Risk factors, n (HBV, HCV, alcohol >30 g/day, obesity, cigarette smoking)	Annual mortality rate, n (%)
0	52/2,320 (0.22)
1	82/1,618 (0.5)
2	70/615 (1.1)
3	18/116 (1.5)
4	1/3 (3.3)

to quantify the burden of chronic viral liver disease and the contribution of alcohol intake and NOSA to morbidity and mortality in a representative sample of subjects from these towns. We followed up 139 subjects with chronic HCV infection and 61 with chronic HBV infection for a median (IQR) time of 8.4 (1.0) and 8.3 (0.9) years, respectively. Ethanol intake was evaluated using a validated semiquantitative food-frequency questionnaire, FL was diagnosed by ultrasonography performed by the same operator, and liver cirrhosis and hepatocarcinoma (HCC) were diagnosed by liver biopsy.

Using data from the Dionysos study, we were able to define the natural history, morbidity, mortality and the incidence rate of CLD in a representative sample of the general population. The incidence and remission rates of steatosis were 9.0 and 29.7 per 1,000 person-years (PY) in the HCV cohort and 4.0 and 30.4 per 1,000 PY in the HBV cohort. 8% of HCV and 3% of HBV subjects developed FL during 8.4 (0.9) and 8.3 (1.0) years of follow-up, respectively. However, 24% of the former and 25% of the latter had remission of FL during the same period suggesting that, in subjects with HBV or HCV CLD, the remission of FL is more common than its incidence. A similar finding was observed in the Dionysos cohort with CLD without HBV and HCV infection [7]. The lifestyle changes induced by participation to the study may have contributed to the remission of FL.

Progression to cirrhosis and HCC was more common in the HCV than in the HBV cohort (4.5 vs. 2.0 and 2.7 vs. 2.0 per 1,000 PY, respectively). Ethanol intake was an independent predictor of liver cirrhosis in the HCV cohort: for every increase of 30 g/day of ethanol intake at baseline, the prevalence of cirrhosis increased by 3 times. Similarly, alcohol intake was a predictor of death in both cohorts, independently of age and sex, and for every increment of 30 g/day of ethanol intake at baseline, mortality increased 3 times. On the contrary, no association was found between baseline NOSA and 8.4-year mortality.

A summary of non-standardized annual liver and not liver-related mortality in the Dionysos cohort, according to different etiology, is reported in table 1. It is evident that alcohol abuse represented almost half of the overall mortality (46.5/100,000/year). HCV infection and alcohol are the major causes of liver-related mortality (13 and 11.5/100,000/year, respectively). If we consider five different risk factors that are known to influence the natural history of CLD (HBV, HCV, alcohol intake, cigarette smoking, and obesity), as reported in table 2, it is evident that the percentage of annual mortality rate increases proportionally to the number of risk factors.

The Dionysos study showed that that alcohol intake is an independent predictor of cirrhosis in subjects with chronic HCV infection and an independent predictor of death in subjects with either HCV or HBV infection. Of notice is the observation that alcohol consumption had a significantly larger impact than viruses on the mortality of liver cirrhosis, as also confirmed by a meta-analysis of 17 studies [3]. Furthermore, alcoholic liver disease (ALD), mainly cirrhosis and hepatocellular carcinoma (HCC), is one of the most common indications for liver transplantation [8].

HCC represents approximately 4% of all new cancer cases diagnosed worldwide, and together HBV and HCV account for 80–90% of all HCC worldwide [9]. However, while HBV and HCV infections will most likely decrease during the coming decades, due to the widespread use of the HBV vaccine in the newborns, and to the more hygienic conditions in the hospitals worldwide, obesity and diabetes are rapidly increasing throughout the world, and they have to be considered a 'new entry' in the risk factors of HCC [10–14] as they would account for more HCC cases in the future. Insulin resistance, and its subsequent in-

Table 3. Alcohol drinks as cofactor of risk in HBsAg and HCV chronic liver infections (modified from Stroffolini et al. [18])

Cofactor of risk	Risk (odds ratio)
HBsAg + alcohol: 1–3 drinks	0.2
HBsAg + alcohol: >3 drinks	4.8
HCV + alcohol: 1–3 drinks	0.4
HCV + alcohol: >3 drinks	3.2
BMI >30 + alcohol: 1–3 drinks	0.5
BMI >30 + alcohol: >3 drinks	2.0

flammatory cascade that is associated with the development of non-alcoholic steatohepatitis (NASH), may play a significant role in the carcinogenesis of HCC [12]. Insulin resistance, metabolic syndrome, obesity and type 2 diabetes are frequently associated with NASH, and are well-recognized causes of cirrhosis and have been increasingly associated with the development of HCC [10, 15–17]. Multiple recent case reports and case reviews support the associations of diabetes and obesity with the risk of HCC as well as with advanced fibrosis. In limited series of patients, NASH-related HCC showed survival and recurrence rates similar to HCC due to HCV [13], even if alcohol consumption appears to be still the most significant factor associated with risk of HCC development in different studies population [10, 14]. Similarly, by increasing the amount of alcohol above the 3 drinks daily, as shown in table 3 [18], the risk of developing liver cirrhosis increases proportionally.

The future of the natural history studies of each CLD should inevitably explore the interrelationship between old and new emerging different risk factors, and the presence of more than one will exponentially increase the morbidity and mortality rate of patients with CLD (also see table 2), but alcohol abuse (>2–3 drinks/day) will still remain probably the most important and avoidable risk factor.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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