Review

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Review

Trends in the management and burden of alcoholic liver disease

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Summary

Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease in Europe and is the leading cause of death among adults with excessive alcohol consumption. There is a dose-response relationship between the amount of alcohol consumed and the risk of ALD. The relative risk of cirrhosis increases in subjects who consume more than 25 g/day. The burden of alcohol-attributable liver cirrhosis and liver cancer is high and is entirely preventable. Health agencies should develop population-based policies to reduce the prevalence of harmful and/or hazardous alcohol consumption and foster research in this field to provide new diagnostic and therapeutic tools. Disease progression of patients with ALD is heavily influenced by both genetic and environmental factors. Non-invasive methods for the diagnosis of fibrosis have opened new perspectives in the early detection of advanced ALD in asymptomatic patients. Alcoholic hepatitis, the most severe form of ALD, carries a high short-term mortality (around 30–50% at 3 months). Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis but duration of therapy should be adapted to early response. Liver transplantation is the best option for patients with severe liver dysfunction. However, alcohol relapse after transplantation remains a critical issue and drinking habits of transplanted patients need to be routinely screened.

Burden of alcohol liver disease

Abusive alcohol consumption is a major cause of preventable morbidity and mortality worldwide. Besides organ damage, alcohol consumption is a major cause of accidents and violence [1]. The health consequences of alcohol consumption vary according to the extent and method of usage (excessive or not, acute or chronic), and depend on numerous environmental and individual factors. Demographic characteristics, the amount of alcohol intake, frequency, duration and profile of consumption vary among alcohol drinkers [2]. In men, daily drinking is associated with an increased risk of alcoholic cirrhosis. Interestingly, recent alcohol consumption rather than earlier in life consumption is associated with higher risk of alcoholic cirrhosis [3]. Alcohol drinkers consuming up to 2 drinks/day (men) or 1 drink/day (women) are defined as moderate drinkers and do not disclose increased risk of organ damage compared to abstainers. Daily consumption above those limits can lead to health, personal and social problems. This definition does not capture the pattern of binge drinking that is quite different from that of chronic drinkers. There is wide heterogeneity in the definition of binge drinking, according to the threshold of alcohol intake per episode. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) proposed a consensual definition of binge drinking episodes as the consumption of 5 or more drinks (male) or 4 or more drinks (female) in about 2 h [4]. This definition fails to recognize the amount of alcohol intake per binge episode. Moreover, the possibility of having several binges during the same day is not included. Finally, a binge alcohol drinker can have periods of continuous alcohol use. The phenomenon of binge drinking continues to grow in Western countries, and is particularly striking in beer- and spirit-drinking cultures in the UK and northern Europe [5]. Between 1993 and 2001 in the USA, binge drinking episodes per person per year increased by 17%, with the highest rates occurring among youth aged 18 to 25 years [6]. In the UK, the Health Survey for England (HSE) reported that 57% of young males were binge drinkers [7]. Most European countries exhibit the same trend towards an increase in binge drinking, even in southern countries. As an example, one French 17-year-old population reported having had binge drinking episodes over the previous month, of one, three or ten times in 45.8%, 17.9%, and 2.2% of cases, respectively [8]. Since 1998, American college students aged 18–24 have had a significantly higher increase in alcohol-related deaths than population totals for the same age group [9]. Thus, public health policies should be targeted towards young people, though they may be less receptive to the prevention messages against this pattern of drinking [10]. Up until now, policies have failed to reduce binge drinking in adolescents and adults, which remains an

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Abbreviations: AH, alcoholic hepatitis; ALD, Alcoholic liver disease; ASH, alcoholic steatohepatitis; DF, discriminant function; HCC, hepatocellular carcinoma; LPS, lipopolysaccharide; NIAAA, National Institute on Alcohol Abuse and Alcoholism.

important health objective in Western countries. The question arises as to whether specialists in liver disease should be concerned by the increase in binge drinkers. However, data concerning the impact of binge drinking on the liver are limited because it has been insufficiently investigated [8,11].

There is a significant disparity in the sex distribution of deaths attributable to excessive alcohol consumption. As an example, 11% of deaths in men and 1.8% in women in Europe are attributable to alcohol [2]. Chronic alcohol consumption may lead to cirrhosis and is associated with an increased risk for hepatocellular carcinoma (HCC) [4]. Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease in Europe and cirrhosis is the leading cause of death due to alcohol among adults [2]. There is a dose-response relationship between the volume of alcohol consumed with the risk of ALD. Previous epidemiological studies strongly suggested a considerable association between alcohol consumption and cirrhosis and emphasized the correlation between severity and duration of alcohol abuse and the presence of cirrhosis. Above a threshold of daily alcohol consumption, the risk of developing cirrhosis increases exponentially. However, the threshold value of daily alcohol consumption associated with increased risk of cirrhosis has long been controversial. The amount of alcohol intake can be expressed in g/day, number of drinks (each drink contains 14 g of alcohol) or alcohol units (each unit has 8 g of alcohol in the UK or 14 g in USA). A meta-analysis observed that consumption of more than 25 g/day increases the relative risk of cirrhosis [12]. This threshold has been validated in the Dionysos project assessing the prevalence of alcoholic cirrhosis in a cohort derived from a general population of two cities in northern Italy [13]. Six thousand nine hundred and seventeen adult subjects were asked about their alcohol consumption. Twenty-one percent of the population had a daily alcohol consumption of more than 30 g/day. The rate of cirrhosis was significantly higher in patients who consumed $\geqslant$30 g/day (2.2%) than among abstainers or those with consumption <30 g/day: 2.2% *vs.* 0.08%. The risk of cirrhosis increased with the amount of alcohol consumed. Subjects who consumed more than 120 g/day had the highest risk of cirrhosis, with a prevalence of 13.5%.

Liver diseases are an important cause of global burden of mortality and morbidity [14,15]. The burden of liver diseases in North America and Europe is mainly attributable to alcohol whereas in Africa and Asia viral hepatitis is the dominant force. In 2010, cirrhosis accounted for more than 493,300 deaths (156,900 female and 336,400 male deaths) and for more than 14.5 million DALYs (disability-adjusted life year) (around 4.1 million DALYs for women and 10.4 million DALYs for men) [14–16]. In addition, around 82,000 deaths (around 14,000 female and 66,000 male deaths) and 2.1 million DALYs were due to alcohol-induced liver cancer [14–16]. The weight of alcohol on liver-related mortality is strongly supported by data showing a relationship between standard liver death rate and overall alcohol consumption in several European countries (Fig. 1) [17].

Variations in alcohol consumption largely contribute to cirrhosis mortality trends and its variability across countries [18,19]. Also, reduction in alcohol consumption in most countries is followed by a decrease in cirrhosis mortality. In North America, Australia and Southern Europe alcohol consumption decreased in recent years, leading to comparable decline in cirrhosis mortality [18,20–22]. Conversely, the high rates of cirrhosis mortality in Hungary and other countries of central and Eastern Europe are

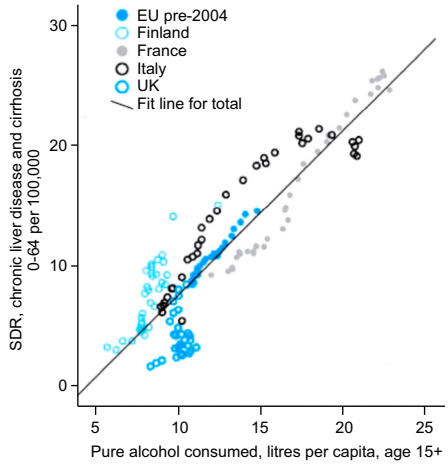

Fig. 1. Relationship between standard liver death rate and overall alcohol consumption in several European countries. The relationship between standard liver death rate (SDR) (per 100,000) and overall alcohol consumption (pure alcohol litres per capita, age 15+) in the four countries in the EU (pre-2004) with the largest rises or falls in liver deaths between 1970 and 2008. Data from the World Health Organization, European Health for All database (HFA-DB): http://data.euro.who.int/hfadb/. Reproduced with permission from [17].

mainly due to their high per capita alcohol consumption [18]. The marked rises in cirrhosis mortality in Ireland and the UK (particularly Scotland) are related to the fact that total recorded alcohol consumption in Britain doubled between 1960 and 2002 [10]. Indeed, one study compared age-standardized mortality rates for cirrhosis in the UK with the rates from 12 Western European countries for the period between 1955 and 2001 [10]. UK standardized mortality rates for cirrhosis increased in men from 3.4 between 1957 and 1961, to 14.1 per 100,000 per year between 1997 and 2001, with the same trend in women, whereas it decreased in other European countries. Cirrhosis mortality rates in Scotland are among the highest in Western Europe, with mortality rates in men and women of 42.2 and 20 per 100,000 per year, respectively [10]. Another study obtained records of all patients in a longitudinal database of 13 million subjects followed in general practice [23]. This study confirmed a 45% increase in the incidence of cirrhosis in the UK during the last decade.

These studies indicate that the burden of alcohol-attributable liver cirrhosis and liver cancer is high and entirely preventable. Health agencies should develop population-based policies to reduce levels of harmful and/or hazardous consumption and provide financial support for research aimed at developing improved therapies for patients with ALD [2,16]. Public health policies should include taxation escalations for alcoholic beverages that should be partially used to cover patient costs and to develop new therapies for alcohol use disorders and ALD. Several approaches have been used, including policies to decrease availability of alcohol by limiting the hours and places of sale and establish minimum age purchase laws [2]. Moreover, several studies have shown that the rising price of alcohol decreases morbidity and mortality [24,25]. The advent of cheap alcohol has had a particularly deleterious effect in the UK and Ireland, which have, in turn, lead to efforts to curb excess consumption by raising the minimum price of alcohol or banning the sale of alcohol below cost (in England and Wales). Recent modeling