Alcoholic Liver Disease

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Abstract: Chronic intake of large quantities of alcohol causes damage to many organs, the liver being the most often affected one. In advanced countries, mortality due to liver diseases is directly proportional to alcohol consumption. 30 g of pure alcohol per day is regarded as a "safe" dose. Alcoholic liver disease may take the form of chronic illness (steatosis, steato-hepatitis, fibrosis and cirrhosis) or acute involvement (alcoholic hepatitis). Whereas steatosis is a relatively benign illness, the presence of cirrhosis of the liver means major life expectancy shortening. The actual stage of cirrhosis depends on the presence of complications – portal hypertension with bleeding oesophageal varices, ascites or hepatic encephalopathy. The median survival time of patients with advanced cirrhosis is 1–2 years. Serious alcoholic hepatitis has a mortality record of up to 50%. Absolute abstinence is a sine qua non condition for any treatment of alcoholic liver disease, the other therapeutic procedure are of a supportive nature and questionable significance. Corticoids can be used in the management of serious alcoholic hepatitis. Treatment in the stage of liver cirrhosis is similar to that in cirrhosis of any other aetiology. Cirrhotic patients who demonstrably abstain can be considered for transplantation leading to a markedly prolonged life expectancy.

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Epidemiology of alcoholic liver disease

Alcohol is a most frequent cause of liver disease in the advanced countries [1]. Mortality due to cirrhosis of the liver in those countries is in direct proportion to absolute alcohol consumption per capita – the highest in France and Spain (over 30 deaths per a population of 100,000), the lowest in the northern countries (up to 5 deaths per 100,000 inhabitants). In the Czech lands the figure is 15 deaths due to cirrhosis per 100,000. The highest mortality is in men aged 35–64 years of age, lower in women (Figure 1) [2]. The past two to three decades have seen stabilization if not a drop in the intake of alcohol in the western countries while a very adverse trend is reported from Eastern Europe and the developing countries [3]. As for the liver damage, the type of alcoholic drink makes little difference; what matters in particular is the quantity of "absolute alcohol" contained in it. 40–60 g of absolute alcohol (i.e., 2–3 beers) per day used to be taken as a safe limit for men, less so (20 g a day) for women. Recent research figures show, however, that consumption of more than 30 g of absolute alcohol daily, regardless of sex, already means an increased risk of liver damage [4]. Chronic (longer than 10 years) and regular consumption of more than 80 g alcohol/day is almost certain to cause liver damage.

For practical purposes, alcohol intake is rated by the count of "drinks" consumed, what means a quantity of drink containing 12 g of absolute alcohol (about one third of a litre of beer, 100 ml of wine, 40 ml of hard drink). Hence, a "safe" daily intake of alcohol should not be more than two "drinks".

Liver disease development also depends on the mode of alcohol intake – drinking alcohol at mealtimes will cause less damage than consumption off the main mealtimes, fitful, intermittent drinking is more sparing for the liver than continuous supply of alcohol [5].

Individual susceptibility is another factor to take into account; moreover, any other liver involvement such as virus hepatitis [6] or metabolic disease adds to the risks of alcoholism as also does obesity [7]. Of the late, there has been an influx of

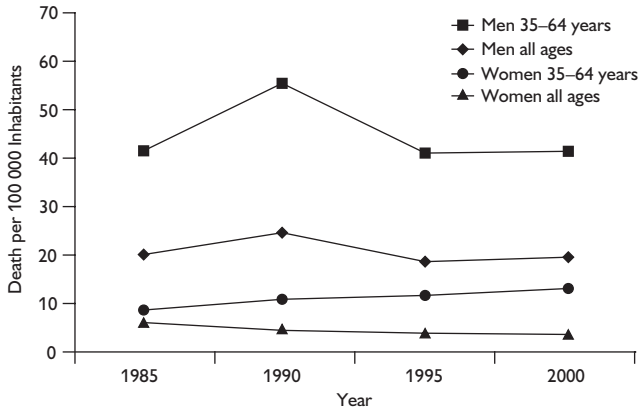

Figure 1 – Mortality from cirrhosis in Czech Republic. From: Bosetti C., Levi F., Lucchini F., Zatonski W. A., Negri E., La Vecchia C.: Worldwide mortality from cirrhosis: An update to 2002. J. Hepatol. 46: 827–839, 2007.

information on correlations between genetic polymorphisms of alcohol-metabolizing enzymes and alcoholic liver disease [8]. The Asian population's hypersensitivity to alcohol can thus be put down to the polymorphisms of genes for the enzymes ADH and CYP2E1. Discovered in a similar way have been the polymorphisms for TNF-α co-responsible for an increased risk of liver disease [9]. Also alcohol dependence as such has been found associated with certain genetic polymorphisms of genes for the GABA receptor or some neuropeptides [10]. For the time being, though, we do not know how to make use of this new knowledge in routine practice.

Aetiology, pathogenesis, natural course and prognosis of alcoholic liver disease

The liver is the principal organ of alcohol metabolism. Alcohol is metabolized in the liver in three ways: with the enzyme alcohol dehydrogenase (ADH), with cytochrome P-4502E1 (CYP2E1) and with mitochondrial catalase. Only the first two are of the practical significance – ADH finds use in the degradation of relatively small quantities of alcohol, alcohol-induced CYP2E1 – in excessive alcohol intake. Apart from the liver, ADH is also present in the gastric mucosa, and the assumption is that individuals with low gastric ADH activity are more susceptible to alcoholic liver disease. This may also help to explain why women who have decreased gastric ADH activity [11] are more prone to developing alcoholic liver disease.

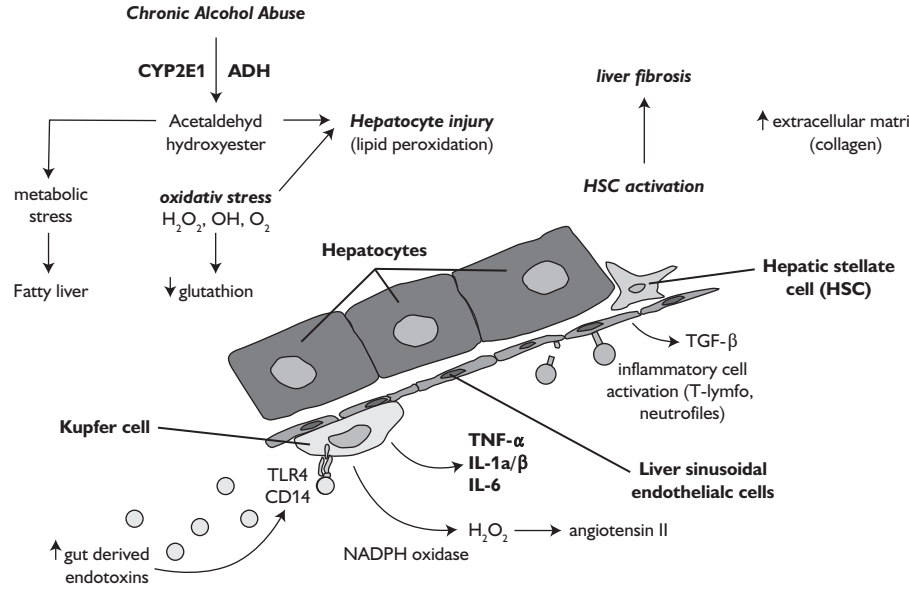

Figure 2 – Pathogenesis of inflammatory changes in ALD. From: Tilg H., Day C. P.: Management strategies in alcoholic liver disease. Nat. Clin. Pract. Gastroenterol. Hepatol. 4: 24–34, 2007.

Both enzymes convert alcohol to acetaldehyde which is in part responsible for the hepatotoxic damage. However, the liver damage process is much more complex (Figure 2) – it results from biochemical, genetic, cellular, immunologic and humoral disorders in connection with the intake and metabolism of excessive quantities of alcohol [12]. A major role has the oxidative stress which results mainly from alcohol-induced CYP2E1, by simultaneous shortage of antioxidants in the hepatocytes, but also by damage caused by acetaldehyde alone and altered balance of many cytokines – mainly TNF-α [13]. Changes in the lipid metabolism and in adipose tissue also contribute to the process [14]. Pathogenetic process starts with the damage of cell membranes and cell organelles (especially mitochondria). The mechanism of hepatocytic damage due to excessive intake of alcohol shows some similarity to changes seen in non-alcoholic steatohepatitis except that the primary insult is different [15].

Liver steatosis is the most frequent primary change in chronic alcohol abuse. The above changes may subsequently trigger an inflammatory reaction which again can result in alcoholic hepatitis or chronic liver disease (Figure 3).

Serious alcoholic hepatitis, though relatively rare, has a death rate of up to 50%. Damage is more likely to take the form of chronic changes (steato-hepatitis and fibrosis) and these again, after many years, lead to cirrhosis. This spectrum of histological findings can be described as a dynamic process (Figure 4). Simple steatosis is reversible after a number of weeks of abstinence; steatohepatitis, a condition seen in only a small part of alcoholics, is a fibrogenic process which can induce changes leading to cirrhosis. Steato-hepatitis is also reversible although a certain degree of fibrosis may persist.

Heavy alcoholics develop liver disease at a rate of nearly 100%. In a detailed study of alcoholics admitted for hospitalization for other than liver complaints, the liver biopsy steatosis was found in 45%, steatohepatitis in 34%, steatohepatitis with cirrhosis in 10% and cirrhosis alone also in 10% [16]. Steatohepatitis in particular often coincides with liver cirrhosis in active alcoholics and is a frequent cause of decompensation of cirrhosis.

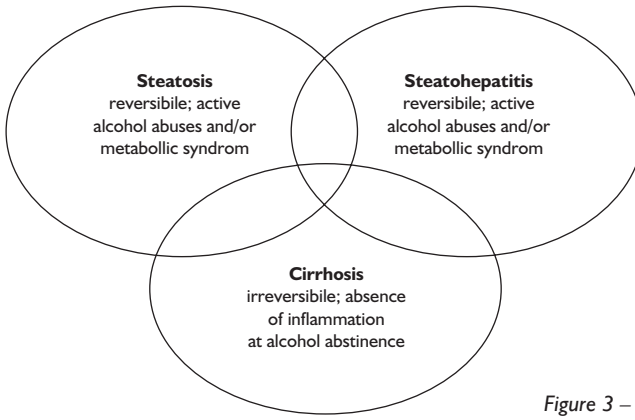

Figure 3 – Spectrum of alcoholic liver disease.

Simple steatosis is regarded as a benign condition; nevertheless, given continued abuse, it, too, can induce fibrogenesis [17]; in any case, up to 20% of patients with simple steatosis are likely to develop fibrosis or cirrhosis within a period of ten years [18]. The prognosis of a patient with ethylic cirrhosis depends mainly on the presence of portal hypertension complications and any continued abuse of alcohol. Abstainers with decompensated cirrhosis have five-year survival at a rate of 60% against 30% in those who continue the abuse [19].

The severity of alcoholic hepatitis is assessed with the Maddrey score (bilirubin mg/dL + 4.6 × prothrombin time) [20] or, alternatively, with the more recent Glasgow alcoholic hepatitis score [21]. A Glasgow score in excess of 9 is associated with poor prognosis (Table 1).

Clinical manifestation and laboratory findings

Patients in the stage of steatosis are usually symptom-free; they may have slightly increased liver tests and enlarged liver (both are often discovered accidentally during examination for other reasons).

In the stage of alcoholic hepatitis there may be nausea, loss of appetite, gradual loss of weight, icterus and other symptoms of hepatic dysfunction (prolonged prothrombin time, hypoalbuminaemia). Increased values of liver test including gamma-glutamyl transferase (GGT), hypergammaglobulinemia, and enlarged liver are usually also present.

Sonography is the basic imaging technique for liver examination. Liver biopsy – while not always necessary – can help to differentiate simple steatosis from steatohepatitis, fibrosis or incipient cirrhosis. Non-invasive examination with FibroScan can be an alternative to liver biopsy. This method takes advantage of the fibrotic liver tissue property to change the velocity of ultrasound propagation. The results of this approach correlate well with the bioptically ascertained degree of fibrosis [22].

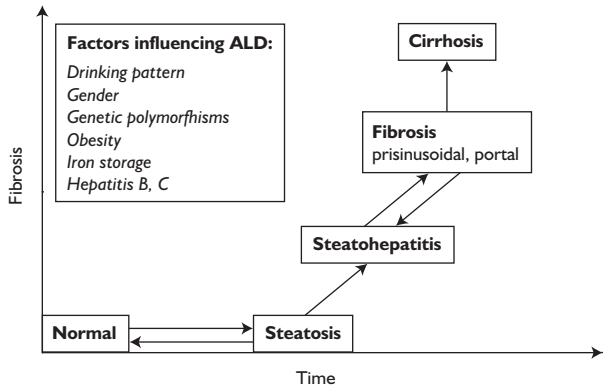

Figure 4 – Dynamic process of ALD.

As for the clinical picture, the state of alcoholic liver cirrhosis shows no difference from cirrhoses of other aetiology [23].

Assessment of active abuse of alcohol

Assessment of continued alcohol abuse in patients with alcoholic liver disease is essential for their treatment as well as for their prognosis. Those with alcoholic cirrhosis of the liver also make up a significant part of patients indicated for liver transplant operation (30–50%), bearing in mind that abstinence is an essential condition for considering liver transplantation.

Continued alcohol abuse is evaluated on the basis of clinical history, psychological examination and laboratory testing. As for laboratory tests, continued abuse can be read from higher GGT values, increased AST/ALT ratio or a greater volume of read blood cells (MCV). In advanced cases of liver cirrhosis, however, the values of hepatic enzymes fall short of sufficient sensitivity or specificity levels. More information about the actual abuse of alcohol can be derived from carboxy-deficient transferrin estimation (%CDT). With the CDT value greater than 2.8%, the sensitivity and specificity of this method for active alcohol abuse rating is 79% and 92% resp. [24].

Treatment

Absolute abstinence is essential to any treatment for alcoholic liver disease. Even major changes including cirrhotic restructuring may show partial regression if total abstinence is observed. Portal hypertension abatement and even regression of oesophageal varices have been reported in abstainers. This, however, appears to have resulted from the abatement of inflammatory changes and steatosis rather than from regressing fibrosis or cirrhosis. Sustained abstinence markedly improves the patient's prognosis in any phase of the liver disease [25], prevents the progression of the disease and fibrosis and, probably, also the development of hepatocellular carcinoma [26].

Medicines have but a supportive and rather dubious relevance there. Treatment with silymarin, essential phospholipids or vitamin preparations used to be very popular in the past. However, there are no conclusive data to prove the efficacy

Table 1 – Glasgow alcoholic hepatitis score

Parameter/score	1	2	3
Age	<50	≥50	–
Leucocytes (109/l)	<15	≥15	–
Urea (mmol/l)	<5	≥5	–
INR	<1.5	1.5–2	>2
Bilirubin (μmol/l)	<125	125–250	>250

INR – International normalized ratio.

The score is to be added to each parameter, the sum total being between 5 and 12 points. The value of 9 and higher implies poor prognosis.

of those medicaments for longer survival time or improved clinical conditions so that these are mostly cases of rather costly placebo [27]. Nor have all sorts of antioxidants been found efficacious. In contrast, dietary readjustment in the sense of sufficient energy intake and good supply of proteins is of value because malnutrition is a very poor prognostic factor. What is known as "liver diet" with its increased supply of saccharides at the expense of proteins and fats has no substantiation.

Severe alcoholic hepatitis could be treated with corticoids in patients with hepatic encephalopathy, Maddrey score >32 or Glasgow score >9 [28, 29]. The Glasgow score is very simple to evaluate and also its prognostic value is greater than that of any other classification (Figure 5). The corticoid dose in that case is 40 mg prednisolone per day. Many studies with diverse conclusions have been published on the subject of enteral nutrition and its effect on alcoholic hepatitis; indeed, comparisons with corticoid therapy showed a lower annual mortality in a group of patients treated with enteral nutrition [30]. Nevertheless, the prognosis of patients with severe alcoholic hepatitis is still poor.

Biological treatment with anti-TNF-α fell short of expectations so that it can be no longer recommended for the management of alcoholic hepatitis [31, 32]. In contrast, another drug with anti-TNF-α activity – pentoxyphyllin – was found to have a favourable effect in the treatment of patients with severe alcoholic hepatitis and with the hepatorenal syndrome [33]. But this observation should be confirmed at a larger patient population.

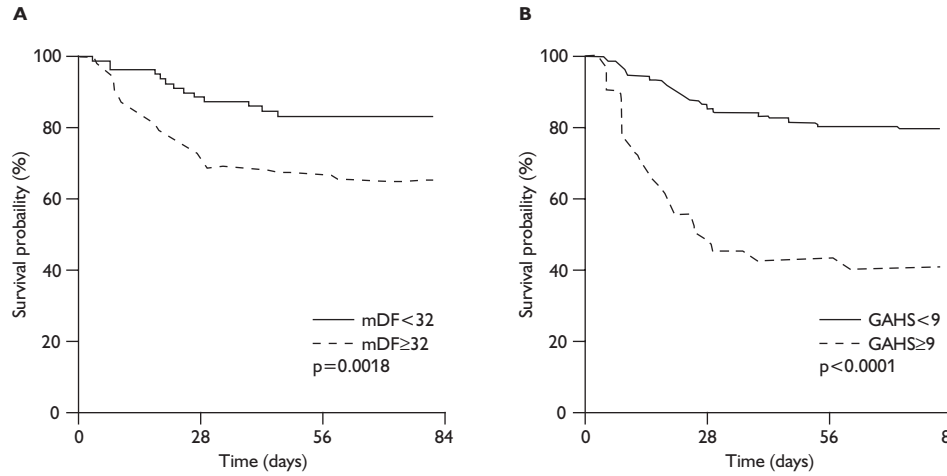

Figure 5 – Kaplan-Meier survival analysis relative to the modified Maddrey discriminant function (mDF) (A) and the Glasgow alcoholic hepatitis score (GAHS) (B). The Glasgow score was developed on 241 patients and validated on 195 separate patients. From: Forrest E. H., Evans C. D., Stewart S., Phillips M., Oo Y. H., McAvoy N. C., Fisher N. C., Singhal S., Brind A., Haydon G., O'Grady J., Day C. P., Hayes P. C., Murray L. S., Morris A. J.: Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. Gut 54: 1174–1179, 2005.

Cirrhosis as such is treated in the same way as cirrhosis of other aetiology; in particular, with adequate nutrition, bone disease prevention, and prevention or treatment of the complications of liver cirrhosis (e.g., bleeding from oesophageal varices, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy). Quite a few medicinal products were tested for the treatment of alcoholic cirrhosis: antiphlogistics (propylthiuracil [34], colchicine [35]), antioxidants (silymarin [36, 37]) and also phosphatidylcholine [38]. However, none of these was found to have a favourable effect on survival time, and none are recommended in this particular indication any longer.

Patients with advanced cirrhosis can be considered for liver transplantation provided they are total abstainers. In such cases, a five-year post-transplantation survival can reach anything up to 85% [39].

Conclusion

- Long-term intake of more than 30 g of absolute alcohol per day will increase the risk of alcoholic liver disease; liver damage is nearly certain in long-term consumption in excess of 80 g absolute alcohol/day.
- Liver damage may take the form of steatosis, steatohepatitis, fibrosis or cirrhosis of the liver. Steatosis is fully reversible, which does not apply to the other conditions, and cirrhosis is associated with a markedly shortened life expectancy.
- Typical laboratory test results in alcoholic liver disease include: increased GGT, AST/ALT ratio greater than 2, increased MCV. Sonography will reveal enlarged liver and signs of steatosis.
- Absolute abstinence is an essential therapeutic precaution; no hepatoprotective will improve the course of the disease. Likewise, there is no medicine that would demonstrably "protect" against the effects of alcohol.
- The clinical course of severe alcoholic hepatitis can be controlled with corticoids and enteral nutrition, but the prognosis is still poor.
- Patients with advanced cirrhosis should be considered for liver transplantation provided they are verifiable abstainers.

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