The Human Gut-Liver-Axis in Health and Disease

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Springer

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ISBN 978-3-319-98889-4 ISBN 978-3-319-98890-0 (eBook)
https://doi.org/10.1007/978-3-319-98890-0

Library of Congress Control Number: 2018959617

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Acknowledgments

The authors behind this publication have received funding from GALAXY and MicrobLiver research projects.

GALAXY has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 668031.

MicrobLiver is supported by a Challenge Grant from the Novo Nordisk Foundation – grant number NNF15OC0016692.

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About the Editors

Aleksander Krag is a clinical specialist in gastrointestinal and liver diseases. He is professor and head of hepatology at the University of Southern Denmark and Odense University Hospital. He is also director for the Centre for Liver Research. Professor Krag is educated from the University of Copenhagen, where he also obtained his PhD degree. In addition, he has studied leadership and innovation at Harvard Business School. Professor Krag is involved in several international research consortia in the field, including being coordinator in Galaxy, a Horizon 2020-funded project on gut-liver interactions in liver diseases. He has been invited speaker for scientific meetings in more than 20 different countries and published more than 130 papers on clinical aspects of chronic liver disease. He has for long served in the Scientific Committee of the Baveno Group and the Executive Committee of the International Club of Ascites to promote research in the field and develop international guidelines.

Torben Hansen is a professor of metabolic genetics at the Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen. He is also an adjunct professor of molecular diabetology at the University of Southern Denmark, and since 2005, he has been responsible for molecular genetic diagnostics at Steno Diabetes Center in Copenhagen. Professor Hansen's major research interests are the pathophysiology and pathogenesis of type 2 diabetes and obesity, identification of genetic determinants for both mono- and polygenic components of type 2 diabetes and obesity, and the impact of the gut microbiome on disease and health. Professor Hansen has been an invited speaker at numerous international scientific meetings, and he has published more than 490 original peer-reviewed papers. H-index 75. Citations >35,000.

Part I

Clinical Aspects of Fatty Liver Disease

Clinical Aspects of Alcoholic Liver Disease

1

Mads Israelsen, Aleksander Krag, and Maja Thiele

1.1 The Burden of Alcoholic Liver Disease

Alcohol overuse is globally a leading risk factor for morbidity and premature death [1]. It is estimated that alcohol accounts for 3.3 million annual deaths or 5.9% of deaths globally [2]. In 2012, 5.1% of the global burden of disease and injury were attributable to alcohol consumption [2]. The burden of excessive drinking varies among the individual countries and despite current knowledge, countries like UK are suffering from a dramatic 3.5 fold increase in burden of liver disease since 1979 [3] and in contrast to various other diseases, the mortality rates from liver diseases are raising [4]. Alcohol is associated to more than 60 different diseases [5]. Alcohol consumptions is directly related to burden of liver disease and cirrhosis and alcohol is the leading cause of liver cirrhosis in the world, accounting for >50% of all cases of cirrhosis with known aetiology [1]. Alcoholic liver diseases was accountable for 493.300 deaths and 12.7 million disability adjusted life years (DALYs) in 2010 [2]. Alcoholic liver disease accounts for 60–80% of liver mortality and 1.8% of all deaths in Europe. WHO estimated that the total tangible cost of alcohol in the European Union in 2003 was €125 billion. Yet it is striking that no approved treatments of alcoholic liver fibrosis exist. Key barriers to advance the field include: the disease is asymptomatic until late stages, there are no approved surrogate markers of treatment effect, slow disease progression, lack of pathophysiological understanding, individual susceptibility and drivers for disease progression.

With the introduction of effective treatments for hepatitis C and B and emerging treatments for non-alcoholic fatty liver diseases the next frontier in hepatology is

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A. Krag, T. Hansen (eds.), *The Human Gut-Liver-Axis in Health and Disease*,
https://doi.org/10.1007/978-3-319-98890-0_1

alcoholic liver disease, which will continue to grow as the dominating cause of end stage liver disease and mortality [6].

1.2 Natural History of Alcoholic Liver Disease

Excess drinking causes alcoholic fatty liver (Fig. 1.1). Simple steatosis occurs in around 90% of patients. It is therefore the most common manifestation of alcoholic liver disease (ALD) and can be induced by just a week of binge drinking. In contrast, less than half of patients with alcoholic steatosis will develop liver inflammation and progress to steatohepatitis if the alcohol overuse continues for months. Depending on the severity and duration of excess drinking, only 10–40% of ALD patients accumulate collagen in the liver and advance to a fibrogenic liver disease. Even fewer have severe collagen accumulation and develop cirrhosis [7]. Fibrogenic liver disease develops over decades of continued alcohol overuse, but with substantial inter-individual differences. For example, the liver toxic effects of alcohol are dose-dependent both on an individual and on a population level [8], but the relationship is not clearly linear and there are large inter-individual differences. Consequently, the majority of heavy drinkers never develop cirrhosis or end-stage liver failure, while some with a moderate overuse do. There do however seem to be a minimum threshold for development of significant alcoholic liver fibrosis, at 24–36 g of alcohol per day for at least 5 years [9]. The differences in inter-individual susceptibility are a challenge to primary and secondary healthcare, when assessing at-risk populations for diagnosis, prognosis and risk assessment. While a liver biopsy is the gold standard for fibrosis staging, it is hampered by sampling error, was not developed for fibrosis staging and is invasive with an estimated major bleeding rate of 1 in 500 [10]. Non-invasive markers of fibrosis have therefore been extensively investigated. The current non-invasive markers can be categorised into imaging techniques and serum markers.

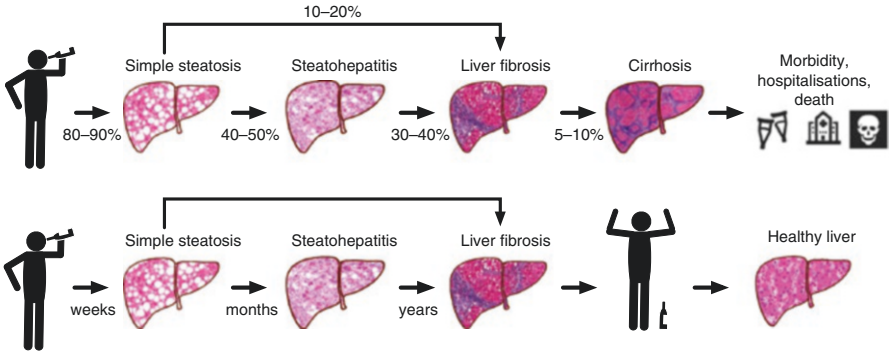

Fig. 1.1 Natural history of alcoholic liver disease. The top section shows the risk of progression in a population of people who drink in excess. The bottom section shows the typical time to progression

1.2.1 Simple Steatosis

Alcohol is metabolised in the liver and the acute effect of alcohol consumption includes disturbance of the liver fat metabolism, resulting in excess storage of triglycerides and accumulation of intrahepatic fat. Simple steatosis is generally considered a benign condition, since the disturbed lipid metabolism normalises with abstinence, resulting in removal of the excess fat within few months [7, 11]. The high prevalence of steatosis in most liver diseases has also cast doubt on the role of hepatic fat on fibrogenesis. Many consider steatosis as a secondary effect rather than a causative factor [12]. Yet, 7% of patients with simple alcoholic steatosis have been shown to progress to cirrhosis within 5 years [13]. Simple steatosis is often diagnosed by imaging methods, routinely ultrasonography. Few serum markers of steatosis exist for non-alcoholic fatty liver disease, but none that have been validated for alcohol-induced steatosis [14].

1.2.2 Steatohepatitis

Steatohepatitis is the more severe, inflammatory active state of ALD. It is not clear what exactly causes the transition from simple steatosis to steatohepatitis in susceptible individuals. While presence of sub-clinical steatohepatitis is not in itself a risk factor for liver-related disease in ALD, it is probably a driver of more rapid progression to severe fibrosis and cirrhosis [15]. Steatohepatitis is a histological diagnosis, characterised by ballooning, lobular inflammation and steatosis. Ballooning degeneration of hepatocytes represents apoptotic cell death with cytoplasmic clearing and swelling. Lobular inflammation is characterised by infiltration of lymphocytes, neutrophils, eosinophils and macrophages (Kupffer cells) in the acinar zone 3 of the liver, in close proximity to a central vein. Other histological characteristics may be present in the inflammatory active ALD liver, such as Mallory-Denk bodies, portal inflammation, megamitochondria and hepatocellular accumulation of iron [16]. There are no available non-invasive markers with sufficient sensitivity and specificity to accurately diagnose steatohepatitis, but often physicians use elevated transaminases or an aspartate transaminase (AST) – alanine transaminase (ALT) – ratio above 2 [17].

Like simple alcoholic steatosis, steatohepatitis is reversible with abstinence within months, if the patient has no other risk factors (obesity, type 2 diabetes, metabolic syndrome).

1.2.3 Liver Fibrosis

Liver fibrosis is characterised by the accumulation of collagen in the liver. Traditionally liver fibrosis is said to be significant, when fibrotic bridges start to occur, intersecting the portal-portal, central-central or portal-central space between liver veins and portal tracts. Fibrosis severity in ALD is semiquantitatively divided in five stages: F0 is no fibrosis, F1 is portal or periportal fibrosis only, F2 is

perisinusoidal fibrosis in combination with portal or periportal fibrosis, F3 is bridging fibrosis and F4 is cirrhosis [18]. Progression of liver fibrosis from pericellular 'chicken-wire' fibrosis to bridging fibrosis and cirrhosis marks a event of prognostic value, which puts the ALD patient at high risk of dying from liver-related outcomes [19]. Bridging fibrosis and cirrhosis – advanced fibrosis (≥F3) – is the sole histological predictor of liver-related mortality in ALD patients. The non-invasive method elastography can accurately diagnose advanced fibrosis [20]. Elastography is based on ultrasound or magnetic resonance to measure liver visco-elasticity (liver stiffness) as a marker of liver fibrosis [21].

A key feature of survival in ALD patients is abstinence versus continued drinking. If a patient ceases harmful drinking while at a compensated, asymptomatic state of liver disease, survival matches the background population, most likely due to slow regression of fibrosis [19, 22]. Similarly, abstinence improves survival in patients with advanced, decompensated alcoholic liver cirrhosis [23].

1.2.4 Cirrhosis

Cirrhosis is defined as presence of regeneration nodules on liver biopsy, characteristic lesions on ultrasonography (lobuled liver surface, heterogeneous liver parenchyma), liver biochemistry indicating portal hypertension and liver failure, esophageal varices on gastroscopy or other clinical findings characteristic of decompensated liver disease such as ascites and hepatic encephalopathy. Cirrhosis is usually divided into compensated and decompensated cirrhosis. Compensated cirrhosis describes an asymptomatic patient without clinical evidence of liver disease, normal liver function blood tests and a 5-year survival of up to 98% [24]. In contrast, decompensated cirrhosis describes the occurrence of one or more events that is related to advanced disease with liver failure and increased blood pressure in the portal vein system (portal hypertension). The typical events associated with decompensation are ascites, esophageal variceal bleeding, hepatic encephalopathy, jaundice, sepsis and a compromised immune response leading to severe bacterial infections [25, 26]. A multitude of other liver-related complications characterises the decompensated patient, leading to frequent hospitalisation, excess morbidity and mortality (Fig. 1.2). Life expectancy drops significantly, when decompensation occurs. The 5-year survival is down to 12% in the most severely decompensated stage of cirrhosis, and the median survival overall in alcoholic cirrhosis is 3 years [24, 27]. When compared with other aetiologies of liver cirrhosis, such as chronic viral hepatitis, alcohol-related cirrhosis have a poorer prognosis and patients die in excess from liver-related complications [28]. Disease severity and short term mortality in cirrhosis can be monitored and predicted by simple scores combining clinical and serological variables: The Child-Pugh score (hepatic encephalopathy, ascites, bilirubin, INR, albumin) and the MELD and MELD-Na scores (model of end-stage liver disease; creatinin, bilirubin, INR with or without sodium).

Portal hypertension is the key pathophysiological factor predictive of decompensation [29]. Portal hypertension is the result of two events: (I) increased

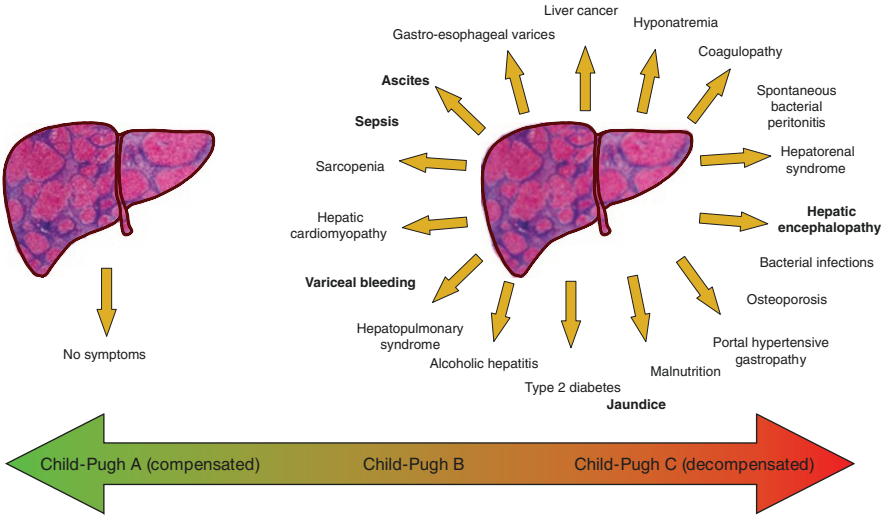

Fig. 1.2 Complications to cirrhosis. Compensated cirrhosis (Child-Pugh A) is characterised by absence of symptoms or complications. Decompensated cirrhosis (Child-Pugh B to C) is characterised by a spectrum of symptoms and complications. Five-year survival in decompensated cirrhosis patients with a history of both variceal bleeding, ascites and encephalopathy is down to 12%

hepatic resistance caused by fibrosis in the liver and contraction of the small intrahepatic vessels; (II) increased portal venous blood flow due to splanchnic vasodilation. Portal hypertension can be measured by liver vein catheterisation, whereby a pressure monitor on a catheter is wedged into a small hepatic vein. The hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic pressure and the free hepatic pressure. In normal livers, HVPG is less than 5 mmHg, while clinically significant portal hypertension and severe portal hypertension are defined by a HVPG of 10 mmHg and 12 mmHg, respectively [30]. Patients with HVPG above 12 mmHg are in risk of developing variceal bleeding and ascites [30].

1.2.5 Timely Identification and Intervention for Alcoholic Liver Disease

The key discrepancy in alcoholic liver disease is that, on one hand, abstinence easily prevents alcoholic liver cirrhosis and liver-related mortality and that it takes several years to develop decompensated alcoholic cirrhosis. On the other hand, the vast majority of patients are referred for hospital care at a far too advanced stage, when cirrhosis has developed and mortality exceeds most cancer diagnoses. Despite treatment options and a slow progressing disease, portal hypertension, decompensation and high mortality characterises 75% of newly diagnosed alcoholic liver cirrhosis patients [27, 31].

1.3 Clinical Unmet Needs

To improve the prognosis of alcoholic liver disease we need (A) better knowledge of the natural history and pathophysiology, (B) accurate non-invasive markers for diagnosis, prognosis, monitoring and assessing efficacy of intervention, (C) effective treatment options, and (D) wide implementation of all of the above. The table (Table 1.1) provides an overview of the main unmet needs, what is currently known and gaps in knowledge for future studies.

Table 1.1 Clinical unmet needs in alcoholic liver disease

	What is currently known?	Where are the gaps in knowledge?
Natural history		
Role of alcohol	Dose-dependent risk for progression to cirrhosis on individual and population level [1, 9]	Large inter-individual differences are unexplained. For example, why do only 25% of heavy drinkers progress to end-stage cirrhosis [35]
Role of comorbidity	Excessive drinking in obese patients increase risk of fibrosis and cirrhosis [52]	In patients with ALD, do metabolic risk factors such as obesity, diabetes and dyslipidaemia increase risk and speed of progression to advanced fibrosis?
Evolution of alcoholic liver disease	Men are more likely to suffer from alcohol use disorders, but women are more susceptible to alcohol-induced liver injury [13]	What is the string of events leading to alcoholic cirrhosis (health trajectory)
Pathophysiology		
Causative factors	3–4 genetic markers are known to influence a patient's risk of progressive alcoholic liver disease, but genetic variation only explains 10% of the inter-individual differences [53]	What is the role of environmental and non-genetic host factors – e.g. the gut microbiome – for the development and progression of alcoholic liver fibrosis?
Stage jumps	Some patients with simple alcoholic steatosis change stage to steatohepatitis, or develop cirrhosis in the absence of hepatic inflammation [13]	Unknown factors predict changes in histological classifier stage; e.g. from simple steatosis to steatohepatitis, or from slowly to accelerated fibrogenesis
Robust livers	Certain patients never develop advanced liver fibrosis, despite long and heavy exposure to excess alcohol	Which environmental, genetic and host-non-genetic factors may protect an exposed liver from fibrosis inducing injury?
Non-invasive markers		
Monitoring	Ultrasound elastography is a highly accurate diagnostic marker of advanced alcoholic fibrosis and compensated cirrhosis [20, 36]	Dynamic markers of extracellular matrix remodelling would be superior to static diagnostic markers to detect speed of progression and monitor for fibrosis improvement or worsening [38]
Prognostication	Liver stiffness at baseline and its evaluation during follow up predicts survival in HCV patients [54]	There is not yet evidence to support that improvement in static liver fibrosis markers predicts an improved outcome in ALD [55]