Lifestyle and Genetic Modifiers of Liver Disease Progression

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Lifestyle Modifiers of Liver Disease Progression

Lifestyle is broadly defined as the way an individual lives, and includes habits, attitudes, and tastes. The main components of lifestyle include nutrition, physical activity/exercise, and behaviors modulating the response to stressors and mental health.

Unhealthy Lifestyle

A large body of evidence shows that some "unhealthy" lifestyle factors (alcohol intake, obesity, malnutrition, lack of physical activity, and cigarette smoke) influence the likelihood of suffering from liver disease, favor the progression of liver disease to cirrhosis and hepatic decompensation, further decompensation, and death, and reduce the likelihood of liver disease regression after removal of a main cause of liver injury (e.g., HCV infection). The burden of "unhealthy" lifestyle is difficult to estimate, but there has been an attempt to quantify its impact on the risk of liver-related mortality. In subjects included in a nationwide, prospective cohort study, subjects were considered at low risk if having all the following characteristics: never smoked or past moderate smoking, no or moderate alcohol use, BMI between 18.5 and 24.9, weekly physical activity, and diet meeting at least 40 points on a scale for healthy diet criteria. Multivariate-adjusted hazard ratios (HRs) for five

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vs. zero modifiable risk factors were 3.59 [95% confidence interval (95%CI): 1.50–7.42]) for incident hepatocellular carcinoma (HCC) and 4.27 (95%CI: 56–98) for cirrhosis-related mortality [1].

Alcohol

In addition to being a leading cause of chronic liver disease (CLD) worldwide [2, 3], alcohol intake is a well-recognized risk factor for the progression of liver fibrosis in patients with CLD of other etiologies [4]. In patients with cirrhosis, alcohol intake briskly increases portal pressure and porto-collateral blood flow [5, 6]. Importantly, alcohol and obesity synergistically interact [7], leading to a much higher risk of cirrhosis and hepatocellular carcinoma than each of these two individual risk factors [8, 9]. Ongoing alcohol intake is associated with higher mortality after a first decompensation episode [10] and after an episode of alcoholic hepatitis [11, 12]. On the other hand, remaining abstinent from alcohol improves survival by over 20% at 5 years in patients with alcoholic cirrhosis, and reduces the risk of decompensation by improving portal hypertension (PH) [13]. Alcohol abstinence also allows recovery of gut integrity, as proven by an improved diversity of the gut microbiota and by a reduced permeability [14]. Complete abstinence from alcohol should be recommended in patients with cACLD, irrespective of the underlying etiology.

Obesity

Obesity has been reported in 20%–40% of patients with compensated cirrhosis in the recently reported series [15, 16]. In addition, the incidence of cirrhosis due to NASH, which is almost invariably associated with obesity, is increasing worldwide. Obesity is also no longer uncommon in patients with decompensated cirrhosis, and has been reported in 12%–25% of patients included in the recent series [17–19].

Obesity is a cofactor of the progression of liver fibrosis, and increases the risk of liver-related events, so hepatologists should become familiar with management of it. In the HALT-C trial, histological progression to cirrhosis or clinical progression to decompensation increased by 14% per each BMI quartile [15]. In addition, body weight gain >5% at 1 year of inclusion added a further 35% of risk of progression of liver disease.

In patients with compensated cirrhosis and PH [defined by hepatic venous pressure gradient (HVPG) >5 mmHg] and no varices on endoscopy included in a randomized controlled trial on timolol vs. placebo to prevent the onset of esophageal varices, BMI as a continuous variable was associated with an increase in the risk of decompensation, independent of HVPG and albumin [16]. Risk of decompensation in patients with obesity was approximately tripled vs. patients with a normal BMI [16]. Interestingly, not only obesity per se, but also body composition markers of dysfunctional adipose tissue, such as higher subcutaneous fat density, predicted first decompensation in patients with compensated cirrhosis [20].

In addition, obesity may promote other conditions that contribute to clinical deterioration in patients with cirrhosis. In one study in patients awaiting liver transplantation, obesity was an independent predictor of onset of portal vein thrombosis (hazard ratio 13.1) [21]. Moreover, the risk of developing hepatocellular carcinoma

increases in patients with obesity; however, a large part of the effect of the association might be explained by the coexistence of diabetes mellitus [22].

Finally, obesity reduces the likelihood of histological regression of cirrhosis in patients in whom the main cause of liver injury has been removed (e.g., chronic hepatitis B on long-term viral suppression) [23].

From the above-described data, obesity emerges as an important but potentially modifiable risk factor in patients with compensated advanced chronic liver disease (cACLD). Three studies demonstrated that intentional weight loss of at least 5% is able to improve liver fibrosis on histology in the long term and to impact favorably on the HVPG [15, 24, 25]. A weight loss of at least 5% was achieved in over 50% of cases, except in diabetic patients who achieved lower success rates. In the SportDiet study, a proof-of-concept study looking at changes in HVPG after 16 weeks of intensive lifestyle changes (moderate caloric restriction and supervised exercise) in compensated cirrhosis with PH, a weight loss >10% was associated with a statistically significant and clinically meaningful reduction of HVPG [25].

In decompensated cirrhosis, data are less abundant. Overall, obesity increases the risk of serious bacterial infection requiring ICU admission [26], and severe obesity is associated with increased risk of acute-on-chronic liver failure [27] and represents a challenge if liver transplantation is indicated due to higher risk of complications [28, 29]. In one paper, obesity was associated with a lower risk of death during the ICU stay [30], but in another one, obesity was a risk factor for death after admission for septic shock [31]. Therefore, whether an "obesity paradox" in critically ill patients with cirrhosis exists, remains to be confirmed.

Malnutrition, Sarcopenia, and Frailty

Protein-energy malnutrition (PEM) is a common complication of cirrhosis present in almost all patients with decompensated cirrhosis, which contributes to skeletal muscle mass and function loss (sarcopenia) and to frailty, which can be defined as decreased physiologic reserve and increased susceptibility to health stressors. While defining malnutrition in cirrhosis can be challenging, sarcopenia can be assessed by several different methods, ranging from simple tools (hand-grip strength test; mid-arm circumference measurement) to imaging methods [32]. Skeletal muscle index assessed on a single-slice CT scan at L3-L4 is considered accurate and reproducible in cirrhosis. Irrespective of the method used for assessment, sarcopenia and frailty have been consistently associated with increased mortality in patients with decompensated cirrhosis, independent of liver function [33, 34]. In compensated cirrhosis, there are less data, which are however fully in line with what observed in decompensated cirrhosis. Old studies suggested that malnourished patients (low hand-grip strength or low mid-arm circumference) [35, 36] have higher risks of decompensation and bacterial infections. In a recent large monocentric study, liver frailty index held predictive value for decompensation in compensated patients and for mortality in decompensated patients [37]. Nutritional assessment and supplementation should be part of the clinical routine in cirrhosis, together with measures aimed at improving physical activity [34, 38].

Cigarette Smoke

Cigarette smoke is pro-fibrogenic in the liver [39, 40], and increases the risk of liver cirrhosis independent of alcohol intake [41]. Importantly, cigarette smoke is a major risk factor for the development of HCC in patients with alcoholic and viral cirrhosis [42–44], and the risk increases in a dose-dependent manner in the general population [45]. In patients with alcoholic cirrhosis, cigarette smoke also synergistically increases the risk of oral cavity, throat, and esophagus cancer [46]. Vice versa, smoking cessation was associated with a reduction in HCC risk [45], and this lifestyle change should be recommended in patients with cirrhosis.

Healthy Lifestyle—Protective Factors

Physical Activity and Exercise

Sedentary lifestyle is very frequent in the general population, and even more in patients with cirrhosis, who according to the available data spend on average 76% of waking hours in sedentary state [47]. Physical inactivity is a risk factor for the onset of non-alcoholic fatty liver disease (NAFLD), and in later stages of CLD it contributes to sarcopenia and physical deconditioning [48]. Exercise decreases intrahepatic fat content independent of weight loss in NAFLD and improves aerobic capacity (oxygen consumption) and has multiple beneficial effects on the cardiovascular system, lung function, endothelial function, mental health, and eventually on quality of life [48]. In murine models of liver disease and in large epidemiological studies, exercise reduces the risk of HCC in a dose-dependent manner [49].

In patients with cirrhosis, 10 randomized controlled trials using 8–16 weeks of supervised or unsupervised exercise as intervention have been published so far. The studies are heterogenous in design and include mostly compensated patients (Child A and B), but in this population no safety issue has been detected. The results showed homogenous positive effects on muscle mass, functional status, HVPG, and quality of life. Rehabilitation including exercise tailored to patients' status in decompensated cirrhosis is currently being implemented in several centers.

Increasing physical activity and exercising should be considered a cornerstone of lifestyle management for CLD.

Coffee Consumption and Mediterranean Diet

In a large study based on participants of the UK Biobank study including 384,818 coffee drinkers and 109,767 non-coffee drinkers, all types of coffee were found to be protective against the development of CLD and cirrhosis [50], confirming previous smaller reports. Coffee drinkers had lower adjusted HRs of CLD (HR: 0.79, 95%: CI 0.72–0.86), CLD or steatosis (HR: 0.80, 95%CI: 0.75–0.86), death from CLD (HR: 0.51, 95%CI: 0.39–0.67), and HCC (HR: 0.80, 95%CI: 0.54–1.19). These results have been confirmed using systematic review and meta-analysis approaches [51, 52].

The benefits of Mediterranean diet (rich in olive oil, vegetables, and fruit) on cardiovascular risk and on other chronic diseases have been established by several

large studies [53–57]. In patients with cirrhosis, one study reported a lower risk of hospitalization due to liver-related events in patients adhering to Mediterranean diet vs. Western diet. In this study, patients with cirrhosis on Mediterranean diet showed a higher gut microbiome diversity, which may explain the better clinical outcomes [58].

Genetic Modifiers of Progression of cACLD

There is an extensive body of evidence indicating that genetic factors impact the susceptibility for CLD and the progression to advanced chronic liver disease (ACLD), particularly in NAFLD [59], alcohol-related liver disease (ALD) [60], and hepatitis C [61]. Moreover, some genetic factors have also been shown to promote disease progression beyond this point. However, with the exception of rare monogenetic liver diseases, individual variants explain only a small proportion of the variation in CLD (e.g., NAFLD) [62] prevalence/severity, highlighting the polygenic nature of CLD. Polygenic risk scores have been recently shown to improve (vs. simple blood tests for liver fibrosis) the prediction of liver-related events (incident cirrhosis, HCC, or liver transplantation) in the general population as well as in subjects at risk for NAFLD [63], and profoundly modify the likelihood of cirrhosis in subjects with heavy alcohol consumption [60]. However, even when combining multiple disease-modifying variants, only a minor proportion of variance is explained [62], which could be attributed to the limited knowledge on the genetics underlying CLD, or more plausibly, to the overwhelming contribution of lifestyle factors. Moreover, genetic factors are not modifiable (at present). Despite this, genetic studies offer unique possibilities: First, they circumvent the chicken or the egg causality dilemma, which commonly impedes the interpretation of studies on ACLD. Second, the genetic factors are constant over time; this is in contrast to other patient characteristics (including, but not limited to lifestyle factors) and conventional biomarkers that are applied for risk stratification and treatment individualization.

Genetic factors that have been studied in context of ACLD can be divided into two categories:

1. Those, that are primarily modifiers of liver metabolism, and thus, metabolic-associated fatty liver disease. However, the same variants may also impact the course of other etiologies of CLD. Examples are *patatin-like phospholipase domain-containing protein 3* (*PNPLA3*) *rs738409 C > G* and *17β-hydroxysteroid dehydrogenase type 13* (*HSD17B13*) *rs72613567 T > TA*. Both of them affect hepatic lipid metabolism and are common variants that are associated with only moderate changes in risk for ACLD development due to MAFLD [59, 60]. *Serpin peptidase inhibitor clade A member 1* (*SERPINA1 rs28929474 G > A*), which encodes the alpha-1 antitrypsin deficiency (A1AD) Z-allele, is less common. While homozygosity for the Z-allele results in A1AD-related liver disease (i.e., a rare, monogenetic CLD with incomplete penetrance due to a toxic

gain-of-function), heterozygosity (affecting approximately 2% of Europeans [64] with considerable regional differences) is accompanied by profoundly increased risks of ACLD [65].

2. In addition, there are several genetic factors that orchestrate etiology-independent pathophysiological mechanisms that may contribute to the progression of liver disease/PH. Besides inherited thrombophilia promoting liver fibrosis progression [66–69], variants in *nucleotide-binding oligomerization domain-containing protein 2* (*NOD2*; encoding an intracellular pathogen recognition receptor) and nuclear receptor subfamily 1 group H member 4 (*NR1H4*; encoding the Farnesoid X receptor) have been shown to modify the course of ACLD.

Individual Genetic Variants

PNPA3 and HSD17B13

PNPLA3 encodes a lipase with activity toward triglycerides localized on the surface of lipid droplets [70]. The loss-of-function *rs738409 C > G*-variant not only increases hepatic triglyceride content upon accumulation of the mutant protein on the surface of lipid droplets [70] but also potentiates the proinflammatory and -fibrogenic features of HSC [71]. It has been linked to NAFLD/NASH and disease severity [72, 73] and ALD-induced cirrhosis [74–77]. Moreover, it was associated with hepatic steatosis/liver fibrosis in HCV-monoinfected [78] and HIV/HCV-coinfected patients [79], although its impact in viral hepatitis was less consistent, as compared to MAFLD. Importantly, in the context of CLD, *PNPLA3* is the most thoroughly investigated variant and there are also studies suggesting a role as a disease-modifying variant in established ACLD. In cACLD patients with NAFLD, harboring the *G*-allele doubled the risk of hepatic decompensation [80]. Moreover, the *PNPLA3 G/G*-genotype doubled the mortality risk of patients with PH due to MAFLD, even after the development of CSPH (defined by HVPG ≥10 mmHg) [81]. This is in line with an earlier study of Friedrich et al. [82], which investigated the effect of *PNPLA3* in patients listed for liver transplantation and reported increased risks of (further) hepatic decompensation and mortality. An analysis based on data of the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial [83], which included patients with and without ACLD, revealed an association between *PNPLA3* genotype and disease severity as well as mortality; of note, the latter effect was limited to patients who were abstinent. Although this may be interpreted as evidence for *PNPLA3* genotype impacting the course of ACLD after eradication/suppression of the primary etiological factor, *PNPLA3* and other variants did not impact the dynamics of liver disease in ACLD patients who achieved HCV cure [84].

HSD17B13 rs72613567 T > TA has been shown to decrease the susceptibility for ALD/NAFLD as well as the risk of cirrhosis in these etiologies; in patients undergoing bariatric surgery, it decreased the odds of NASH and liver fibrosis [85–87]. While patients with ACLD of viral or MAFLD etiology harboring the protective variant had less pronounced liver disease at baseline, *HSD17B13* did not impact progression of ACLD in a longitudinal analysis [88]. Accordingly, the importance of this variant in the context of ACLD remains to be established.

SERPINA1/Alpha-1 Antitrypsin Deficiency

SERPINA1 rs28929474 G > A (i.e., the Z-allele) is less prevalent, as compared to the previously mentioned variants; however, heterozygosity for this allele is an even stronger (odds ratios of 6 to 7) risk factor for cirrhosis of non-alcoholic and alcoholic etiology [65] and also CSPH [89]. Approaching the resulting MZ genotype from the other direction (i.e., assessing subjects without previously known CLD who have been diagnosed by genetic testing) indicates that lifestyle factors (obesity and diabetes mellitus) are key modulators of the risk of liver fibrosis in subjects heterozygous for this strong risk allele [90]. This supports the notion that genetic, metabolic, and environmental factors contribute to MAFLD—a concept that may also be extrapolated to CLD in general [91]. Finally, there is also some evidence suggesting that the MZ genotype may confer a worse prognosis in patients with established cirrhosis [92].

NOD2

NOD2 senses muramyl dipeptide (MDP) in the cytosol and activates NF-κB signaling. Loss-of-function variants adversely impact gut barrier function and bacterial translocation, leading to increases in bacterial DNA and interleukin 6 in the systemic circulation, as well as increased risks of spontaneous bacterial peritonitis (SBP) and bacterial infections in general [93–99]. These observations have led to the hypothesis that NOD2 variants may guide the use of norfloxacin in patients with cirrhosis and ascites, but without a history of SBP. In the "Impact of NOD2 genotype-guided antibiotic prevention on survival in patients with liver Cirrhosis and Ascites (INCA)" trial, patients harboring a NOD2 variant are randomized to receive norfloxacin or placebo. Survival and SBP/bacterial infections/hospitalization within 1 year are being evaluated as primary and secondary endpoints, respectively. Accordingly, NOD2 provides an example for the potential clinical application of genetics for risk stratification, i.e., the identification of patients who may be at a particularly high risk of a specific outcome, thereby increasing the absolute risk reduction and decreasing the number need to treat/sample size for a clinical trial.

Of note, there are also other genetic variants in innate immunity receptors, which may be of relevance in patients with acute decompensation and bacterial infection [100].

NR1H4/FXR

Farnesoid X receptor (i.e., a bile acid receptor) [101] signaling has important implications for the gut-liver-axis and is a promising target in the treatment of PH [102]. ACLD patients harboring the *NR1H4 rs35724 rs35724 G > C* allele had a decreased risk of first hepatic decompensation and mortality. These findings may be explained by the gain-of-function that is conferred by this variant, which was accompanied by increased hepatic FXR expression [103]. In the latter study, it was also found to be linked to decreased odds of steatosis, steatohepatitis, and liver fibrosis in patient who underwent liver biopsy for the suspicion of NASH. These findings add to the body of evidence supporting the detailed evaluation of FXR agonists in the context of PH. The implications of this variant on the efficacy of FXR agonists have yet to be evaluated in clinical trials. Of note, this variant may not only inform about risk in

an individual patient (see *NOD2*), but also modify the effectiveness of pharmacological intervention, i.e., the relative risk reduction.

Conclusions and Outlook

The importance of genetic variants in patients who have already progressed to ACLD is less well established, as compared to their impact on the progression to ACLD. Although the contribution of genetic factors seems to be considerably lower, as compared to lifestyle factors, genetics may provide information on the risk of specific complications of ACLD and mortality in an individual, which may guide the use of pathophysiology-oriented interventions (e.g., norfloxacin). Moreover, improvements in the understanding of genetics may lead to novel treatments for (A)CLD in the future, as *HSD17B13* (e.g., ARO-HSD; NCT04202354) and *SERPINA1* (e.g., ARO-AAT; NCT03946449) are druggable by small interfering RNA (siRNA). Finally, the impact of *NR1H4* variants on the effectiveness of FXR agonists (e.g., obeticholic acid and numerous other compounds [101]) warrants further study.

The interaction between genetic background and lifestyle on the risk of decompensation in the specific setting of ACLD has not been studied, and is a topic for future research.

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