Etiological Treatments: Lifestyle Management

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Introduction

Cirrhosis is a markedly heterogeneous disease with a very different risk profile during its natural history, influencing the therapeutic management. In the earliest phases of the disease, the main end point should be the prevention of decompensation, while in the advanced stages, the target is survival improvement. In general, lifestyle changes tend to be overlooked in the management of cirrhosis. However, besides etiologic interventions and specific treatment of complications, there is important information suggesting that lifestyle interventions may have a role in the treatment of cirrhosis. Moreover, lifestyle changes are easy to implement, relatively inexpensive, and with little risk of side effects. Firstly, the classical alcohol abstinence should be considered in the management of cirrhosis independently of the etiology. However, lifestyle interventions may be especially relevant when considering the emerging pathogenic role of obesity and insulin resistance in chronic liver disease that may be affected by nutritional and exercise interventions. Such an

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approach would be extremely appealing because of its appropriateness and affordable costs. Thus, the aim of this chapter is to summarize the most recent advances in this field.

Alcohol Abstinence

Excessive alcohol consumption is a major public health issue that can lead to the development of liver fibrosis and cirrhosis. It is widely accepted that alcohol abstinence improves the general prognosis of patients with alcoholic cirrhosis. Several studies have shown that alcohol abstinence is associated to a short-term decrease in portal pressure, maintenance of hemodynamic improvement during follow-up, and clinical improvement [1]. In addition, a prospective study indicated that after variceal hemorrhage, abstinent alcoholic cirrhotic patients had better hemodynamic response to drugs than cirrhotic patients of viral etiology [2]. Finally, a more recent study clearly showed that alcohol abstinence and giving the maximum tolerable dose of beta-blockers were independently associated to a decrease in the risk of rebleeding and death [3]. On the other hand, a recent study has shown that liver stiffness significantly decreased after alcohol abstinence [4]. Altogether, these data clearly indicate that alcohol abstinence has a relevant impact in the natural history of cirrhosis. Nevertheless a recent meta-analysis has suggested that the beneficial impact of alcoholic abstinence on survival requires at least 1.5 years of lack of alcohol consumption, indicating that efforts should be made to maintain long-term abstinence [5].

Obesity and Human Health

Obesity is probably one of the major health problems worldwide, especially in Western countries. This is not only because of the constant increase in its prevalence, but it is also due to the severity of the consequences.

The most commonly accepted definition of obesity is based on the body mass index (BMI). Thus, those subjects having a (BMI) greater than 30 Kg/m^2 are considered obese [6]. Overall, it is estimated that 20–30 % of inhabitants of North America and Europe are obese [7]. Although genetic factors may be responsible of part of the problem, the main reason that probably explains the rising incidence of obesity is the unbalanced proportion between a high caloric ingestion and a reduced caloric consumption due to sedentary lifestyle.

Obesity is associated with a vast constellation of health problems especially including type 2 diabetes, hyperlipidemia, cardiovascular diseases including arterial hypertension, and malignancies. Nevertheless, other chronic diseases such as psychosocial, neurological, kidney, and pulmonary disturbances are also associated to obesity. Consequently, obesity is responsible of a shortening of life expectancy. Therefore, it is not surprising that health costs associated to obesity management are growing in the Western world.

The negative effect of obesity on health is related to the onset of a chronic low-grade inflammation originating in the excessive white adipose tissue that functionally behaves as an endocrine gland, producing peptides (adipokines) and metabolites. The phenotype of adipose tissue is markedly different in obese subjects, especially the visceral and perivascular tissue. Adipocyte size increases, and adipose tissue becomes hypoxic [8] promoting the previously mentioned inflammation and cellular dysfunction. Importantly, these conditions promote a modification of adipokine secretion from a protective to a damaging profile with additional macrophage infiltration and releasing of macrophage-derived cytokines [9]. These changes are associated to a well-known increase in insulin resistance but also to a pro-inflammatory, pro-fibrogenic, pro-angiogenic, and pro-oxidant consequences in different organs [8–10].

Clinical Implications of Obesity in Cirrhosis

Regarding the spectrum of liver diseases, the influence of obesity in the natural history of chronic liver disease (CLD) has been clearly recognized. Nonalcoholic fatty liver disease (NAFLD), as the liver side of metabolic syndrome, probably will become the most important challenge for hepatologists in the following decades.

Besides its implication in NAFLD, obesity is also very prevalent in patients with chronic liver disease independently of the etiology. Several studies have shown that obesity is associated to severe fibrosis in alcoholic liver disease [11, 12] as well as in nonalcoholic steatohepatitis (NASH) [13] and in chronic viral hepatitis [14]. Furthermore, obesity is an independent factor of fibrosis progression in HCV patients [15, 16]. Finally, a recent nested cohort study [17] performed in the well-known timolol trial, has shown that in patients with compensated cirrhosis and without varices, clinical decompensation of cirrhosis developed in 14 % of patients with normal weight, in 31 % of overweight patients, and in 43 % of patients with obesity. Importantly, BMI, together with albumin and the severity of portal hypertension, was an independent predictive factor of the risk of decompensation. In quantitative terms, obese patients had a threefold risk of decompensation as compared with normal weight patients, independently of the etiology of cirrhosis. Interestingly, the data showed that obesity also negatively impacts on portal hypertension. Indeed, after 1 year of treatment with timolol or placebo, only patients with normal weight or overweight showed a reduction of HVPG, whereas obese patients had a slight increase in HVPG. Moreover, insulin resistance and obesity predict the occurrence of hepatocellular carcinoma (HCC) [18].

Conversely [15], a modest weight reduction was associated to a decrease in hepatic inflammation and steatosis in patients with hepatitis C and advanced fibrosis (HALT-C cohort).

All these findings clearly indicate the existence of an interaction between obesity, portal hypertension, and the natural history of cirrhosis. From a clinical point of view, it is possible to speculate that body weight reduction may have a beneficial effect in decreasing portal pressure with a potential for decreasing the risk of decompensation. To answer this important question regarding the impact of lifestyle

interventions in the natural history of cirrhosis, a proof-of-concept study (sport-diet study) has been recently communicated [19]. The main end point of the study was to evaluate whether a reduction in body weight induced by a16-week intensive lifestyle intervention including individually tailored dietary and exercise plan is associated to a decrease in portal pressure estimated by HVPG measurements. Fifty patients with compensated cirrhosis underwent a hemodynamic and nutritional study before and after a predefined and individualized lifestyle intervention. In brief, all the patients received a personalized caloric reduction and moderate physical exercise (60 min/week).

After the intervention, a majority of patients (52 %) had a clinically relevant decrease in body weight (previously defined as a reduction greater than 5 %), entirely due to a significant decrease in fat mass. Interestingly, the lifestyle intervention was associated to a significant decrease in HVPG (13.9 ± 5.6 mmHg vs. 12.3 ± 5.2 mmHg; $p < 0.0001$; average reduction, 10.7 %), Indeed, 42 % of patients had a HVPG reduction greater than 10 %. Although a linear correlation between weight loss and HVPG decrease was not observed, a greater HVPG decrease was observed in those patients with more than 10 % of body weight decrease.

Interestingly, no safety problems were observed during lifestyle intervention. Moreover, a slight increase in indocyanine green fractional clearance was observed as well as an improvement in metabolic profile and quality of life. The main conclusion of this proof-of-concept study indicates that an intensive short-term lifestyle intervention safely decreases HVPG in patients with compensated cirrhosis and portal hypertension.

This study clearly indicates the need to evaluate in appropriately designed clinical trials the effect of weight reduction on clinical end points in patients with compensated cirrhosis.

In patients with decompensated cirrhosis, maintenance of adequate nutrition is important to avoid loss of muscle mass which can also contribute to development of hepatic encephalopathy [20].

Other Interventions

Vaccination against hepatitis A and B viruses, influenza virus, and pneumococcus should be offered as early as possible, because the antigenic response becomes weaker as cirrhosis progresses, limiting the likelihood of effective protection.

Cigarette smoking has specific deleterious effects and is associated with more severe fibrosis in patients with different etiologies of liver disease [21], including viral hepatitis, primary biliary cirrhosis, and NASH. In patients with chronic hepatitis B, the risk of HCC is higher among heavy smokers [22]. In addition, daily cannabis is associated to worsening steatosis in HCV patients [23]. Therefore, smoking cessation strategies may have additional benefits in patients with chronic liver disease, which should be evaluated in cirrhosis.

Coffee consumption has been associated with a significant reduction in risk of fibrosis in NASH [24], as well to a reduction in the risk of HCC [25].

Table 13.1 Summary of lifestyle recommendations

Lifestyle recommendations	Rationale	References
Alcohol abstinence	Decreases HVPG. Decreases liver stiffness. Improves survival	[1, 3, 4]
Weight loss	Decreases HVPG. Decreases inflammation. Decreases steatosis	[15, 19]
Tobacco smoking cessation	Tobacco increases liver fibrosis and risk of HCC	[21, 22]
Cannabis smoking cessation	Cannabis increases steatosis in CHC	[23]
Coffee consumption	Decreases fibrosis in NASH. Decreases risk of HCC	[24, 25]
Antioxidant-rich food	Decreases HVPG	[26, 27]

Abbreviations: *HVPG* hepatic venous pressure gradient, *HCC* hepatocellular carcinoma, *NASH* nonalcoholic steatohepatitis, *CHC* chronic hepatitis C

Furthermore, the use of antioxidants, dark chocolate [26], and ascorbic acid [27] is associated to improvement of intrahepatic circulation in patients with cirrhosis by improving flow-mediated hepatic vasorelaxation and decreasing HVPG.

Summary and Conclusions

Besides specific therapies aimed to controlling etiological factors and to treating cirrhosis complications, simple lifestyle interventions have a relevant impact in pathogenically relevant events (i.e., portal pressure) and should be included as potential therapeutic tools to be evaluated in the future (Table13.1).

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