

Review Article

Lifestyles and Diseases of the Liver

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Abstract: Liver diseases are a major health burden globally. The sharp increase in obesity has led to a greater prevalence of nonalcoholic liver diseases. NAFLD may progress to NASH, cirrhosis of the liver, and even hepatocellular carcinoma. Alcoholic liver disease is also a common disorder, leading to alcoholic steatohepatitis and alcoholic cirrhosis. Alcohol abuse is a risk factor in about 50% of cases of cirrhosis. Cirrhotic patients may present with ascites, portal hypertension-related bleeding, or hepatic encephalopathy. They are also at a higher risk of developing hepatocellular carcinoma. Hepatic viral infections are also rampant. Hepatitis B viral infection is common, with almost 30% of the world's population showing serological evidence of exposure. These patients can progress to hepatocellular carcinoma. HCV infections also can lead to cirrhosis and hepatocellular carcinoma. Chronic HCV infection is often the primary reason for having a liver transplant. It is estimated to affect over 58 million worldwide and is a major cause of liver disease-related death. No vaccination is available for HCV. Hepatocellular carcinoma is the sixth most common malignant tumor in the world. It is also the fourth leading cause of cancer-related death worldwide. It usually occurs in patients with a history of viral hepatitis, alcoholic hepatitis, or nonalcoholic fatty liver disease. Since its diagnosis is often made at late stages, mortality is high. Given the ominous nature of these liver diseases, prevention and management via lifestyle modification is an important option. This manuscript discusses five major modifiable lifestyle behaviors that can significantly impact liver diseases.

Keywords: Liver diseases, smoking, alcohol, diet, obesity, exercise.

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INTRODUCTION

The common liver diseases are nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease, and hepatocellular carcinoma [1]. NAFLD is due to lipid accumulation in the hepatocyte (steatosis) [2]. The estimated worldwide prevalence of NAFLD is 25% [3], and is projected to increase to 33.5% by 2030 [4]. NAFLD may progress to more severe stages such as non-alcoholic steatohepatitis (NASH), which is characterized by lipid-derived inflammation, hepatocellular ballooning, and fibrosis [5]. NASH may progress to liver cirrhosis [6]. Cirrhosis is an ominous disease, affecting over 122 million individuals in 2017 [7]. Besides NASH, cirrhosis may be caused by chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, and alcohol-related liver damage [7]. NAFLD also increases the risk for hepatocellular carcinoma (HCC) [8-10]. Other risk factors for HCC are chronic viral infections [11] and alcohol [12]. The liver can also be damaged because of traumatic injuries [13], drugs [14], and heart failure [15]. Lifestyles play an important role in all aspects of these diseases.

DISCUSSION

Healthy lifestyles include non-smoking, low to moderate alcohol intake, a normal body mass index, regular exercise, and a prudent quality of diet [16].

Smoking

Smoking is a major cause of preventable morbidity and mortality globally [17]. Smoked tobacco products include, besides cigarettes and cigars, water pipes [18], electronic cigarettes [19], bidis [20], and krekets [21]. Tobacco smoke has several thousand chemicals, and many of them are carcinogenic [22]. Smoking has been causally related to several major diseases [23], including cardiovascular diseases [24], COPD [25], and cancer [26]. Smokers age faster, and premature wrinkles attest to this [27]. Smoking during pregnancy not only causes complications in the mother [28], but also increases the risk of diseases such as asthma and obesity in the offspring [28]. Children who are exposed to secondhand smoke are at increased risk for several diseases, including, sudden infant death syndrome [29]. Smoking cessation reduces

the risk of major chronic diseases [30]. Cessation also helps reduce the severity of these diseases [31], improves the quality of life [32], increases disease-free life [33], and augments life expectancy [34]. Smoking is the leading preventable cause of death worldwide [35].

Smoking damages the liver via three mechanisms: toxic (both direct and indirect), immunologic, and oncogenic [36]. Kim *et al.*, studied 160,862 patients found that of current smokers, former smokers, and nonsmokers, 42%, 39%, and 18%, respectively, had evidence of NAFLD on liver ultrasound [37]. They concluded that current smoking is an independent risk factor for NAFLD [37]. Smoking also subjects these individuals to worse including increased rates of liver transplantation and a higher long-term overall mortality [38]. Smoking also increases the severity of hepatic lesions in patients infected with HBV [39] or HCV [40]. Smoking has been linked with an increased risk of hepatocellular carcinoma in patients with chronic liver disease [41-44]. Lee *et al.*, calculated that the relative risk ratio was 1.51 for current smokers and 1.12 for former smokers for increased incidence, after conducting a meta-analysis of 38 cohort studies and 58 case-control studies, and after adjusting for HBV infection, HCV infection, and alcohol consumption [45]. Smoking also increases HCC related mortality [46]. Cigarette smoke has a known HCC carcinogen, 4-Aminobiphenyl [47]. P53, a tumor-suppressing gene is also reduced in smokers [48]. Smokers may have poor lung function that may preclude liver transplantation [49]. Tobacco smoking is also harmful to liver transplant patients, increasing complications [50]. Smokers also face an increased risk of de novo malignancy [51], and non-graft-associated mortality after liver transplantation [52]. Further, chronic smokers are more likely to drink alcohol in excess [53], and the harmful effects of alcohol on the liver are well known [54].

Alcohol

Alcohol is protective for some diseases if it is taken in moderation – not to exceed two standard drinks a day for men and one standard drink a day for women [55]. The American Heart Association defines one drink as one 12-ounce regular beer, 5 ounces of wine or 1.5 ounces of 80-proof spirits, such as bourbon, vodka or gin [56]. Heavy drinking is defined as, high-dose intake, of >60 g/day in men and >40 g/day in women, usually taken over the long term [57]. Binge drinking is considered as 4 or more drinks for women and 5 or more drinks for men over 2-hours or in one sitting [58, 59]. Compulsive excessive alcohol intake leads to alcohol use disorder (AUD) [60]. Besides several health issues, including liver problems mentioned below, AUD is also associated with violence, accidents, suicide, and higher mortality [61, 62]. Alcohol can damage the liver and result in alcoholic liver disease (ALD), which includes alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis [63]. They are also more prone to

develop HCC [64, 65]. About 90% of alcoholics develop alcoholic fatty liver (steatosis), about 25% develop alcoholic hepatitis, about 15% develop alcoholic cirrhosis, and about 10% develop HCC [66, 67]. Continued alcohol consumption usually in those with ALD leads to progression to end-stage liver disease [68]. Alcohol abstinence markedly reduces mortality [69], and the only definitive treatment for end-stage ALD is liver transplantation [70, 71]. Alcohol-related liver injury may be potentiated by chronic viral hepatitis, both HBV and HCV [72-74]. Other factors such as genes [75], metabolic syndrome [76], and iron overload [77] may also play a role.

Obesity

A body mass index (BMI) between 20 and 24.9 kg/m² is normal, a BMI between 25 and 29.9 kg/m² is considered overweight, while a BMI of >30 kg/m² represents obesity [78]. Asians have a high risk of type 2 diabetes and CVD at a lower BMI, and the norms are different for them [79]. Obesity has been further divided as follows: class 1, BMI >30 and <34.9; class 2, BMI >35 and <39.9; class 3, BMI >40 [80]. Obesity is prevalent all over the world [81-87]. In the USA in 2017-2018, 42.2% of all adults were found to be obese [81]. Excess body weight is reported in over 30% of Europeans [82]. China, India, and Brazil have also seen a major rise in the prevalence of obesity [83-86]. It is also increasing rapidly in most African countries [87]. Besides estimation of BMI, diagnosing visceral fat deposition, or visceral obesity is also important [88]. Compared with subcutaneous fat, white visceral fat secretes free fatty acids and adipocytokines [89] and is associated with significant cardiovascular disease, type 2 diabetes, cancer, and mortality, even if the BMI is normal [90, 91]. Visceral obesity can be measured by several anthropometric measurements: waist circumference <102 cm in males and <88 cm in females; waist-hip ratio 0.9 or less in males and 0.85 or less in females; weight height ratio < 0.5 [92]. Obesity increases the incidence of NAFLD by 3.5-fold [93]. It is estimated that 30% to 37% of patients with obesity have NAFLD [94-96]. In those who have undergone bariatric surgery, the prevalence rises from 84% to 96% [95]. Pang *et al.*, in a meta-analysis, found that for each 1 unit increase in waist circumference, the odds ratio of NAFLD increased by 1.07, and for each 1 unit increase in BMI, the odds ratio increased by 1.25 [97]. Weight loss is a viable option in the treatment of NAFLD and fibrosis [98]. Histological improvements are noted with as little as 3-5% weight loss in these patients [98, 99]. Further reduction in weight loss is helpful, but greater weight loss (>10%) is associated with the highest rates of NAFLD/NASH resolution and fibrosis regression [100]. The presence of obesity is ominous for patients with alcoholic hepatitis, and they are twice as likely to die in the short term, compared to those who are nonobese [101]. HCV infected individuals also face a poor prognosis if they are obese, with frequent complications and early death [102, 103]. Obesity is

also a risk factor for hepatocellular carcinoma [104, 105].

Exercise

Physical inactivity is becoming a major causal factor in several disorders [106, 107]. Exercise is safe in most chronic diseases [108] and has innumerable health benefits [109]. The World Health Organization recommends that adult men and women should accumulate at least 150 min of moderate-intensity physical exercise per week and young people aged 5–17 years should accumulate at least 60 min of physical exercise of moderate to vigorous intensity daily [110]. Exercise is beneficial in patients with NAFLD [111, 112]. Whitsett *et al.*, conducted a systematic review of 18 studies and concluded that exercise significantly reduced hepatic fat content [113]. The American Gastroenterological Association, the American Association for the Study of Liver Diseases, and the American College of Gastroenterology all recommend physical exercise as a treatment for NAFLD [114]. It has also shown benefits in patients with NASH [115]. Wong *et al* demonstrated in a randomized trial of 145 NASH patients, aerobic and resistance exercise along with dietary restriction resulted in a 64% remission rate compared to a 20% remission rate in the non-intervention control group [116]. Exercise in patients with NASH also decreases progression to hepatocellular cancer [117]. HCV patients exhibit lower physical activity than the general population [118] and are at an increased risk for cardiovascular diseases [119]. Exercise in these patients not only reduces the CVD risk [120]. HCV patients also have a poor quality of life [121], and this improves with exercise [122]. HCV infected patients frequently (30%-50%) cognitive dysfunction and exercise helps decrease cognitive dysfunction [123]. Exercise (personalized) is recommended in patients with cirrhosis by the American Association for the Study of Liver Diseases [124]. These patients have reduced exercise capacity and low VO₂ max [125, 126] and often develop sarcopenia [127, 128]. Exercise, both aerobic and resistance, helps improve cardiorespiratory fitness and preserve muscle mass and reverse sarcopenia in these patients [129, 130]. It is safe in patients with cirrhosis of liver [131, 132]. The improved endurance with exercise [133] contributes to the improved quality of life noted by these patients with exercise [134]. Liver transplant patients also benefit from exercise, while on the waitlist [135]. Following transplantation, exercise training is associated with a shorter length of hospital stay and a reduced 90-day readmission rate [136]. These patients often have a reduced exercise capacity and muscle strength [137], and exercise helps reduce these deficits. Exercise post-transplant also helps improve the cardiometabolic profile and the mental components of quality of life [138, 139]. Increasing physical activity may play a significant role in reducing the risk and decreasing the mortality of liver cancer [140, 141]. Two meta-analyses have found an inverse

relationship between physical activity and liver cancer risk [142], and liver cancer mortality [143]. In a recent analysis has confirmed these relationships, Lee found that in a meta-analysis of 10 prospective cohort studies, liver cancer risks and mortality were 26% and 25% lower with high amounts of physical activity (PA) and 23% and 19% lower in moderate amounts of PA, respectively, compared to low amounts of PA [144]. At the vigorous-intensity PA level, high and moderate amounts of PA reduced these risks by 54% and 45%, respectively [144].

Diet

Besides maintaining a healthy weight by exercise and calorie restriction, the quality of diet is important [145]. The dietary guideline for Americans recommends that the diet be well balanced, mostly plant-based, rich in fruits and vegetables, whole grains, fish, low in sugar and salt, and with the occasional intake of lean meat [146]. It should limit or eliminate trans-fats, saturated fats, fried foods, sodium, red meat, refined carbohydrates, and sugar-sweetened beverages [146]. The benefits of a plant-based diet have been confirmed in several studies [147-152]. DASH diet [153], Mediterranean diet [154] and Nordic diets [155] are healthy diets. A vegetarian diet is a plant-based diet and avoids meat [153, 154, 156, 157]. A quality diet, besides a diet that prevents excess body weight, is also important in patients with NAFLD [158-161]. These include Mediterranean, Paleolithic, ketogenic, high-protein, plant-based, low-carbohydrate diets [158]. Intermittent fasting has also shown beneficial health outcomes in these patients [158]. NAFLD patients do better with diets that incorporate soluble and insoluble fiber, monounsaturated or polyunsaturated fatty acids, micronutrients, vitamins E, C, and D, and polyphenols like resveratrol, curcumin, caffeine, quercetin [159, 160]. Fructose and saturated fatty acids contribute to the pathogenesis of NAFLD [161]. The role of alcohol in causing liver damage (ALD) has been discussed before. Abstinence from alcohol is critical in these patients [162]. ALD patients often suffer from malnutrition [163]. The American College of Gastroenterology and the American Association for the Study of Liver Diseases guidelines recommend 1.2 to 1.5 g/kg per day of protein intake and 35 to 40 kcal/kg per day of body weight for energy intake in patients with ALD [164]. Several micronutrients are also helpful in these patients and include minerals like zinc, magnesium, selenium [165-167], and vitamins such as vitamins D, vitamin E, folate, niacin, and thiamine [168-171]. ALD patients following a prudent diet have fewer infectious complications and improve their 1-year mortality [172, 173]. Diet plays an important role in the risk of hepatocellular carcinoma [174-176]. Besides a calorie-restricted diet to avoid obesity, diets rich in vegetables, poultry, fish, monounsaturated fats, whole grains, nuts, tea, and caffeinated coffee are helpful [177-185]. Micronutrients such as vitamin E, vitamin B9, β -carotene, manganese, and potassium are also HCC

preventive [186]. HCC harmful diets are rich in processed red meat consumption, high-fat dairy foods, sugar-sweetened beverages, and/or associated with heavy alcohol intake [187-191].

CONCLUSION

Liver diseases, especially NAFLD, hepatitis, and hepatocellular carcinoma are a major health burden globally. Many of these conditions are related to poor lifestyles, such as smoking, alcoholism, sedentary lifestyle, obesity, and a poor diet. These factors are modifiable. Following healthy lifestyle behaviors help reduce these major liver diseases. The effect is significant. The added advantage of following a healthy lifestyle is an improvement in other aspects of ill-health and a major increase in life expectancy.

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