Clinics and Research in Hepatology and Gastroenterology (2016) xxx, xxx–xxx

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MINI REVIEW

Non-alcoholic fatty liver disease and flavonoids: Current perspectives

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Summary Non-alcoholic fatty liver disease (NAFLD) is an accumulation of fat in the liver despite a low level of alcohol intake, with signs of hepatomegaly. Although in the past, NAFLD was predominantly viewed as an aspect of metabolic syndrome, it is now considered that it should be classified as an independent condition similar to obesity, diabetes, and hypertension. Therefore, new treatment strategies, not based on correcting insulin resistance, are needed for NAFLD. This work analyzes methods of prevention, therapeutic approaches, and mechanisms involved in NAFLD, focusing on the use of flavonoids (epigallocatechin-3-gallate, resveratrol, anthocyanins, and isoflavones) with high antioxidant capacity. In addition, the mechanisms of cholesterol accumulation in the liver are identified as potential avenues for entirely new approaches to NAFLD treatment, contrasting the well-known relation between neutral fat and NAFLD.

Introduction

Recently, non-alcoholic fatty liver disease (NAFLD) has received increasing attention [1,2]. In NAFLD, liver hypertrophy is caused by the accumulation of fat despite low alcohol intake. NAFLD can be divided into simple steatosis and non-alcoholic steatohepatitis (NASH). Simple steatosis is observed as lipid accumulation in hepatocytes with little or no inflammation and fibrosis. NASH includes inflammation and fibrosis [3,4]. From the histologic point of view, NAFLD comprises diverse liver ailments, including simple steatosis, steatohepatitis, hepatic fibrosis, and cirrhosis.

Abbreviations: ABCA1, ATP-binding cassette sub-family A member 1; AMPK, adenosin monophosphate-activated protein kinase; EGCG, epigallocatechin gallate; GPx, glutathione peroxidase; GSH, glutathione; HDL, high density lipoproteins; HMGCoA-r, hydroxymethyl glutaryl-coenzyme A reductase; NAFLD, non-alcoholic fatty liver diseases; NASH, non-alcoholic steatohepatitis; SOD, superoxide dismutase; SREBP2, sterol regulatory element-binding proteins 2; VLDL, very low density lipoproteins.

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http://dx.doi.org/10.1016/j.clinre.2016.07.001
2210-7401/

Please cite this article in press as: Shin JH, Jung JH. Non-alcoholic fatty liver disease and flavonoids: Current perspectives. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.07.001

Mild steatosis is not considered a serious health problem. However, approximately 10% of fatty cirrhosis diseases are diagnosed as steatohepatitis including inflammation. Moreover, 20—30% of steatohepatitis cases progress to cirrhosis and liver cancer. It is well known that NAFLD is closely related with central obesity. Surprisingly, however, 20—40% of NAFLD patients are not obese. This shows that NAFLD is not an aspect of the metabolic syndrome, but an independent disease.

Since resistance to insulin has been implicated in NAFLD, a great number of researchers have focused on treating NAFLD by improving insulin resistance [5]. However, diverse mechanisms have been shown to play a part in NAFLD as no histological improvements were detected in the liver despite the use of insulin sensitivity enhancers [6—8]. It is widely accepted that hyperlipidemia results in NAFLD. The accumulation of cholesterol is also a significant factor for lipotoxicity. We have studied the relation between cholesterol accumulation in the liver and NAFLD and researched the effects of natural foods in order to improve it [9]. Cholesterol accumulation was observed in the liver of laboratory rats with induced NALFD. In addition, increased levels of inflammatory cytokines were detected. These symptoms decreased in rats on black soybean-rich diet. Recently, various therapeutic approaches have been examined, including antioxidants and drugs for cholesterol control and regulating fat oxidation. This work describes the recent data on the relationship between NAFLD and cholesterol accumulation, focusing on preventive and therapeutic effects of flavonoids found in natural foods. Prominent current studies on dietary flavonoids in NAFLD have been summarized in Table 1.

Method

The available published journals were searched using PubMed and KSI KISS from January 2005 to March 2015. We used the keywords in our study using the following words: non-alcoholic fatty liver disease, treatment, and metabolism. We found 2522 published papers, however, counted most out as one of the related papers; because there was no specific focus of dietary treatment. In the end, we selected 50 papers in our study and summarized the studies in Table 1.

Cholesterol and NAFLD

Obesity and systemic insulin resistance are strongly associated with increased risk of fibrosis, nonalcoholic steatohepatitis (NASH), and the highest NAFLD activity scores [10]. Although many NAFLD patients have a tendency to overeat, are obese, and/or have insulin resistance, not all patients exhibit these features [11]. Interestingly, cholesterol intake was higher in non-obese than in obese NAFLD patients, although cholesterol intake in obese patients was also significantly higher than in healthy volunteers [12]. In the fatty liver, the ability of insulin to restrain the production of both glucose and VLDL cholesterol is impaired. This results in hyperglycemia, hyperinsulinemia, and hypertriglyceridemia, which, in turn, lead to lower HDL cholesterol concentration [13]. Hypertriglyceridemia and reduced HDL cholesterol levels are the types of dyslipidemia associated with NAFLD [14]. It is important to understand the mechanisms responsible for increased synthesis and low absorption of cholesterol in NAFLD. Cholesterol accumulates in the liver due to increased synthesis, absorption, and decreased effusion (Fig. 1).

Cellular cholesterol synthesis is regulated by activation of membrane-bound transcription factors designated SREBP2. SREBP2 act as regulators of hepatic cholesterol levels and activate genes involved in the synthesis of cholesterol [15]. However, in the context of NAFLD, the regulatory loop of SREBP2 is disturbed, even if the intracellular levels of cholesterol are high [16]. SREBP2 upregulate the gene expression of HMGCoA-r, the key enzyme of cholesterol synthesis, and the expression of LDL receptor protein, which results in increased cholesterol synthesis and absorption [13]. Additional mechanisms might involve bile acids; biologically active molecules that promote absorption of dietary lipids in the intestine and stimulate biliary excretion of cholesterol [17,18]; and miR-33, which decreases the expression of ABCA1, suppresses cholesterol elimination from the liver, and increases cholesterol accumulation [19]. Activated SREBP2 is overexpressed in NAFDL owing to feedback system dysfunction.

A recent study has shown that adiponectin is secreted from adipose tissue; low level of serum adiponectin is considered a factor in the development of insulin resistance underlying NAFLD [20]. In NAFLD, decreased adiponectin secretion results in decreased AMPK activation. Thus, fatty acid clearance in the liver is low and the fatty acid remnants can accumulate in hepatocytes or be released into the bloodstream [21]. Increased free fatty acid delivery to the liver is caused by insulin resistance. Insulin resistance increases the level of total serum free fatty acids through increased lipolysis in peripheral adipose tissues [22]. Therefore, low levels of adiponectin and AMPK and high levels of serum free fatty acids have been associated with obesity, insulin resistance, and NAFLD.

Another mechanism underlying the pathogenesis of NAFLD is oxidative stress [23]. In in vivo models of NAFLD, lipid peroxidation is induced because of increased formation of free radicals and decreased levels of hepatic antioxidants, such as SOD, GPx, catalase, and GSH [24]. Antioxidative enzymes are induced in response to oxidative stress and represent the primary cellular defense mechanism against free radicals and oxidative injury [25]. The use of complementary and alternative medicine approaches, such as natural antioxidants and hepatoprotective plant products, are gaining popularity in the last decade [26].

Given that this review focuses on the relation between cholesterol accumulation in the liver and NAFLD, a general discussion of NAFLD causes is outside its scope. Weight-loss and diet therapy are the most used methods to control NAFLD because the precise cause and therapy for NAFLD are still unidentified. Lately, diverse diet therapy programs have been explored for regulating NALFD. It is known that many food ingredients can reduce the symptoms of NAFLD. However, underlying mechanisms of NAFLD are still unknown. In this review, preventive and treatment effects in NAFLD are discussed according to the dietary ingredients associated with them.

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