Current status of liver disease in Korea: Nonalcoholic fatty liver disease

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Abstract

Recently, obesity (BMI ≥ 25 kg/m²) and type II diabetes mellitus have reached epidemic proportions in Korea, and rates of nonalcoholic fatty liver disease (NAFLD) are between 10% and 25% of the general population. NAFLD in Korea is as closely associated with several components of metabolic syndrome including obesity, hypertension, diabetes, and dyslipidemia as it is in Western countries. Insulin resistance and hyperinsulinemia may play a role in the pathogenesis of fatty liver in patients with normal body weight as well as in patients with obesity. And, obesity induced accumulation of fat in the adipose tissue leads to an imbalance in the regulation of adipokines, such as downregulation of adiponectin and upregulation of retinol-binding protein 4 (RBP4) and ghrelin. High BMI, the AST/ALT ratio, and ALT levels could be used to distinguish NASH from simple steatosis in Korean patients. In large number of NAFLD patients who underwent a voluntary medical checkup, even a small weight reduction was associated with improvements in their hepatic steatosis grade on ultrasonography, serum aminotransferase levels, and related metabolic abnormalities. Subjects with fatty liver disease should be advised to lose weight through lifestyle modifications. Small animal and human studies of treatment with PPAR agonists and betaine have been reported in the Korean literature. It is now acknowledged that NAFLD is the most common liver disease in Korea, largely due to the considerable increase in metabolic abnormalities such as obesity and diabetes. Future studies should continue to focus both on the pathogenesis and the treatment of NAFLD in order to accumulate more of our own data.

Key words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Prevalence; Korea
Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PPAR, peroxisome proliferator-activated receptor; AOX, acyl-CoA oxidase; HOMA-IR, homeostasis model assessment of insulin resistance; RBP4, retinol-binding protein 4; SOD, superoxide dismutase; OGTT, oral glucose tolerance test; IMT, intima-media thickness

Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by a wide spectrum of liver damage which includes steatosis, nonalcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma. In the last few years, active investigation has been focused on NASH, a relatively aggressive form of NAFLD. One of the main reasons for the explosion of information provided by clinical and basic studies is the high prevalence of risk factors, such as obesity, type II diabetes mellitus, and dyslipidemia. Recently, obesity (BMI ≥25 kg/m²) and type II diabetes mellitus have reached epidemic proportions in Korea and the incidence of NAFLD is between 10% and 25% in the general population.1-4

In this review, we examined the English and Korean literature on NAFLD in Koreans, to clarify the differences in NAFLD between Korea and Western countries.

Risk factors for NAFLD

NAFLD is closely associated with several components of the metabolic syndrome including obesity, hypertension, diabetes, and dyslipidemia.2,3,5-7 Several intriguing studies suggest that NAFLD is a hepatic manifestation of the metabolic syndrome and insulin resistance is a key factor in its pathogenesis, even in the normal-weight population.8-10 Distribution of fat may be more important than the total adipose mass. Central obesity is correlated with visceral adiposity and is more closely linked to insulin resistance.11-14 In addition to metabolic disorders, a number of other risk factors for NAFLD have been identified in Koreans. These include gender, higher serum alanine aminotransferase (ALT) level, low femoral subcutaneous fat amount, and reduced physical activity.12,15-17 Other studies suggest that increased peripheral iron overload and the hemochromatosis gene (H63D heterozygote) could be risk factors for NAFLD.18,19

Pathogenesis of NAFLD

Insulin resistance and hyperinsulinemia may play a role in the pathogenesis of fatty liver in patients with normal body weight as well as in patients with obesity.4,10,20,21 There are two important animal studies on the pathogenesis of NAFLD in Korea. One study observed the role of peroxisome proliferator-activated receptor-α (PPAR-α) and acyl-CoA oxidase (AOX), and the other investigated the role of a naturally occurring antioxidant, alpha-lipoic acid (ALA) in the development of NAFLD.22,23 Serum adipocyte fatty acid-binding protein (A-FABP) is significantly associated with NAFLD in type 2 diabetes, independent of BMI, waist circumference,
HOMA-IR, and triglycerides. Obesity induced accumulation of fat in the adipose tissue and imbalance in the regulation of adipokine, specifically downregulation of adiponectin and upregulation of retinol-binding protein 4 (RBP4) and ghrelin.

Predicting factors for NASH
(risk factors for advanced fibrosis in NAFLD)

High BMI, serum AST/ALT ratio, and serum ALT level could be used to distinguish NASH from simple steatosis in Korean patients. In addition, high BMI and a high serum AST/ALT ratio may be useful as predictors for severe liver fibrosis in NASH. Hepatic iron deposition or overload does not correlate with hepatic injury in patients with NAFLD. Leptin, one of the well-known adipokines, was not a significant predictor of NASH. The activity of superoxide dismutase (SOD) and catalase in serum were lower in the NASH than in controls. The disturbed metabolism of superoxide due to the decreased activities of SOD and catalase seem to be important in the pathogenesis of NASH.

NAFLD related diseases

Although the association between the metabolic syndrome and NAFLD is well known, the causative role between the development of metabolic syndrome and steatosis is not fully understood. In several studies, a considerable proportion of non-diabetic NAFLD patients produced an abnormal oral glucose tolerance test (OGTT), and were associated with increased rates of microalbuminuria independent of other risk factors. They recommended OGTT for NAFLD patients in order to predict the risk of type 2 diabetes. NAFLD was associated with an increased risk of chronic kidney disease (CKD) even in non-diabetic, non-hypertensive Korean men, irrespective of metabolic syndrome. The patients with NAFLD had greater carotid IMT (intima-media thickness) than those without NAFLD and their 10-year risk of developing coronary heart disease (CHD) as estimated by using Framingham risk scores (FRS) was higher in these patients. These results suggest that NAFLD is independently associated with carotid atherosclerosis and CHD, regardless of classical risk factors or other components of metabolic syndrome. Therefore, NAFLD is not only one of the hepatic manifestations of metabolic syndrome, but could also directly promote the occurrence and development of metabolic-related problems.

Management of NAFLD

A subset of patients with NAFLD has progressive liver fibrosis, which eventually progresses to liver cirrhosis, hepatic failure or hepatocellular carcinoma. Thus, treatment is warranted to prevent progression to those dismal conditions. In a large number of NAFLD patients, even a small weight reduction was associated with improvements in their hepatic steatosis grade on ultrasonography, aminotransferases, and related metabolic abnormalities. Subjects with fatty liver disease should be advised to lose weight through lifestyle modifications. The prevalence of NAFLD was lower in physically active individuals independent of metabolic abnormalities. Several
studies demonstrated that a higher level of habitual physical activity was associated with lower steatosis, and suggested that this relationship may be due to the effect of exercise per se. Treatment with PPAR agonists (α or γ), especially PPAR-α agonist, improved the histological and biochemical parameters in the rat models. Betaine supplementation protects the liver from nonalcoholic steatosis and oxidative stress, most likely via its effects on the trans-sulfuration reactions in high fat diet NAFLD rats.

Future directions

Even the prevalence of NAFLD is difficult to assess, since epidemiologic studies have several limitations. With the considerable increase in the metabolic abnormalities such as obesity and diabetes, it is now acknowledged that NAFLD is the most common liver disease in Korea. Future studies should focus on both the pathogenesis and the treatment of NAFLD. Increasing our understanding of its pathogenesis, particularly the factors responsible for progressive liver injury, will enable better targeting of therapeutic agents in the near future.

References

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