Commentary

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Abnormal Glucose Metabolism in Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic Fatty Liver Disease (NAFLD), a common cause of chronic liver disease, represents a spectrum of histopathologic abnormalities. NAFLD is often associated to the typical components of the metabolic syndrome (MS), with characteristics including abdominal obesity, type 2 diabetes, Insulin Resistance (IR), hypertension, and Hypertriglyceridemia, and has seriously threatened human health. IR, a crucial element of MS, is the fundamental contributor in the process of NAFLD. Therapy strategies are finite and, for now, are basically concentrated on weight reduction and utilization of insulin sensitizing agents. Recent literature indicated IR related to the abnormal glucose metabolism play a pivotal role in the development of NAFLD. Moreover, glucose resistance, glucocorticoid hormones, leptin, et al are also associated with glucose metabolism dysfunction in NAFLD. We highlight the mechanisms of these components in NAFLD, and our work might be beneficial for comprehending the mechanism and treatment of abnormal glucose metabolism in patients with NAFLD.

Keywords: NAFLD; Abnormal glucose metabolism; IR

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease characterized by hepatic steatosis. The disease includes simple steatosis, Nonalcoholic Steatohepatitis (NASH), fibrosis, cirrhosis and, in severe cases, hepatocellular carcinoma. The multiple-hit hypothesis defines insulin resistance (IR) as a key contributor in the pathogenesis of NAFLD because of its impact on increases in *de novo* lipogenesis and dysfunction in the release of Free Fatty Acids (FFAs) and triglycerides from the liver, which also plays a central role in metabolic syndrome (e.g., obesity, type 2 diabetes mellitus, dyslipidemia, hypertension). IR arises from the inability of

insulin to act normally in regulating nutrient metabolism in peripheral tissues. However, the role of IR on the progression of NAFLD has not been fully defined. Recent studies show that a NAFLD patient with type 2 diabetes mellitus prevalence rate was 30%-50% [1]. Consistently, a study described that the prevalence of NAFLD increased with increasing fasting plasma glucose levels. It is seen that NAFLD was independently associated with impaired glucose metabolism [2].

NAFLD and Abnormal Glucose Metabolism

NAFLD is closely linked with hepatic and adipose tissue IR, as well as a reduction of whole-body insulin

sensitivity. Insulin is the main hormone secreted from the pancreatic β cells, and could stimulate synthesis of glycogen, lipogenesis and lipoprotein, and suppressing gluconeogenesis/glycogenolysis in glucose and lipid homeostasis [3]. Its possible mechanisms include the following: (1) IR may conduce to hepatic steatosis by excessive FFAs accumulation in the liver. Patients with NAFLD demonstrated a decrease in FFA oxidation, showing reduced uptake and utilization of glucose as an energy source [4]. (2) Hepatic diacylglycerol level is increased due to impaired FFAs β -oxidation, as a consequence of systemic and hepatic IR; namely, that there is failure of phosphorylation of the insulin receptor that in turn fails to phosphorylate the insulin receptor substrate 2 (IRS-2). The pathophysiologic consequences include decreased glycogen synthesis due to glycogen synthase kinase-3 (GSK3) dephosphorylation, the failure of Forkhead box O (FOXO) phosphorylation results in nuclear translocation, up-regulation of Phosphoenolpyruvate Carboxy Kinase (PEPCK), export of glucose by the glucose transporter type 2 (GLUT2), and further aggravate systemic and hepatic IR [5]. (3) Endoplasmic Reticulum (ER) stress could exacerbate hepatocyte IR [6]. Many factors could result in ER stress such as excess FFA stores, and further lead to phosphorylation of transcription factors associated with ER stress in hepatocytes, including c-jun N-terminal Kinase (JNK), translation initiation factor 2, and pancreatic ER Kinase [7][8]. JNK appears to result in phosphorylation of IRS-1, with the effect on suppression of insulin receptor signaling, and thus aggravates hepatocyte IR.

Glucose resistance is a state with impaired insulin-independent glucose homeostasis and suppressed hepatic glycogen production. Hyperglycemia could inhibit the export of hepatic glycogen and promote synthesis of hepatic glycogen. In other words, the levels of blood glucose not only depend on the regulation of insulin but also the feedback from blood glucose [9]. The above mechanism plays an important role in maintaining glucose homeostasis of NAFLD. A study demonstrated the variations in glucose metabolism of cirrhosis, including decreased insulin sensitivity and glucose availability, and an increased pancreatic β cell responsiveness to glucose, all resulting in hyperinsulinemia. Apart from decreasing insulin sensitivity, reduced glucose availability may play a significant role in impaired glucose tolerance, while no obvious deficiency in insulin degradation is discovered [10].

NAFLD is associated with glucocorticoid hormones as well. Glucocorticoid hormones, including

glucocorticoid, somatotropin, glucagon and prolactin, are crucial regulatory factors of hepatic glucose and lipid metabolism [11]. In addition to their role in energy homeostasis, glucocorticoid hormones are important regulatory factors of low-grade inflammation in the liver, a process conducting to metabolic disturbances [12]. In NAFLD patients, the destruction of liver cells may decrease the level of glucocorticoid hormones and the effect of glucagon on the liver and other target tissues, which cause hyperglycemia directly [13]. However, another study confirms a significant inverse result of somatotropin when compared with other glucocorticoid hormones, i.e., somatotropin was significantly increased in the progression of NAFLD [14].

Leptin, discovered as a factor produced by adipose tissue, has been implied to play a role in partitioning energy provision from glucose and lipid through regulating insulin sensitivity. Similar to insulin, leptin resistance might have an effect on exacerbating glucose intolerance and increasing FFAs intake in the liver. Leptin acts on the same target organs with insulin via a common signal transmission system. Under healthy conditions, leptin is thought to promote the combination of insulin substrates and insulin and improve insulin sensitivity to regulate of blood glucose with insulin. However, in NAFLD, leptin concentrations are increased but there is decreased responsiveness to leptin probably due to reduced leptin receptor expression, leading to leptin resistance [15].

Therapy for Abnormal Glucose Metabolism of NAFLD

Given the correlation of NAFLD with abnormal glucose metabolism, agents that targeting glucose are important to combat NAFLD. Because IR is considered to play a central role in the pathogenesis of NAFLD, insulin sensitizers have been thought as potential medical treatments. Metformin, an insulin sensitizing drug, was originally shown to ameliorate biochemical and histologic abnormalities of fatty liver in *ob/ob* mice [16]. In a clinical study, NASH patients received Metformin intervention for 6 months. Metformin was shown to reduce Transaminase levels and IR indices [17]. The Thiazolidinediones (TZDs), pioglitazone and rosiglitazone, increase insulin sensitivity via Peroxisome Proliferator Activated Receptor (PPAR)- γ signaling, and have been demonstrated to ameliorate blood glucose control, as well as NASH-related parameters in clinical research [18]. Glucagon-like peptide-1 (GLP-1), mainly secreted by the L cells of the intestine, has been demonstrated to ameliorate hepatic steatosis in parallel

with obesity and diabetes in several clinical studies [19]. In response to a meal, GLP-1 could be released, which causes incretin effects, such as insulin secretion and decrease of glucagon production. Recent studies on both human and obese animal have shown that GLP-1 receptor activation could decrease the fat content in the liver via regulating fatty acid oxidation, lipogenesis, insulin secretion from pancreatic β -cells and hepatic glucose metabolism [20] [21].

Conclusion

In summary, glucose metabolism played an important role in NAFLD pathogenesis, and the abnormal glucose metabolism could be resulted from IR, glucose resistance, leptin resistance and the elevated glucocorticoid hormones. Besides, the drug used in the NAFLD treatment, such as insulin sensitizers, had certain influence on glucose metabolism. Therefore, the abnormal glucose metabolism in the development of NAFLD should be paid attention, and the underlying mechanisms need to be further explored.

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