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Insulin Resistance, Reason or Consequence Nonalcoholic Steatohepatitis (NASH).

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ABSTRACT

Now a day's nonalcoholic fatty liver (NAFLD) is one of the most prevalent disease in children and adult people in all around the world. In some developed countries, it is the root cause of cryptogenic cirrhosis. NAFLD is a spectrum of lever disease that include simple steatosis or pathologic status such as steatohepatitis, fibrosis of cirrhosis. Nonalcoholic hepatitis (NASH) is a progressive type of liver disease witch refers to NAFLD and characterized with steatosis in hepatocytes, inflammation, necrosis and fibrosis and finally liver failure. The pathogenesis of NAFLD and NASH is closely associated with insulin resistance status. Insulin resistance may occur in peripheral or in liver. The resistance against insulin in hepatocytes is due to impaired function of insulin receptor substrate phosphorylation. Dysfunction of insulin receptor leads to failure to gluconeogenesis suppression. This impaired function of insulin receptors is seen in metabolic syndrome, diabetes type 2, obesity and some other condition. Regarding to high prevalence of NASH and it complications, in this review article, some aspect of NASH is studied.

Key words: NAFLD, NASH, Insulin resistance

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INTRODUCTION

Nonalcoholic Fatty Liver Disease (NAFLD) is defined as a wide spectrum of disorders related to fatty liver which is occurred without the presence of infection or considerable alcohol consumption. Most of patients with NAFLD have only increase in fat content of liver (simple steatosis) but others experience inflammation, hepatocellular damage, and fibrosis which is called Nonalcoholic Steatohepatitis (NASH). 20 percent of patients with NASH finally will suffer progressive hepatic disease in the form of cirrhosis and hepatic failure. Furthermore, the risk of hepatocellular carcinoma in NASH-induced cirrhosis is comparable with C hepatitis. NASH and NAFLD are related to metabolic syndrome, a group of disorders including central obesity, insulin resistance with or without type II diabetes, dyslipidemia, and hypertension in comparison with healthy people. Patients with Nonalcoholic Fatty Liver have decreased ability to produce insulin to suppress endogenous glucose and also have increased ability to absorb glucose by muscle and fat cells which demonstrates insulin resistance. NAFLD triggers to slowed trend of insulin suppression through dissemination of fatty acids from fat cells and also contribute to decreased oxidation of fatty acids [1].

The first induced damage in progression of Nonalcoholic Fatty Liver is steatosis mediated by fat deposition in hepatocytes in the form of triglycerides. This process is in relationship with invasion of fatty acids into the hepatocytes which is mediated by higher lipolysis rate in obesity and change in fatty hormones. For example, hyperlipidemia and hypoadiponectinemia which lead to increment in synthesis of triglycerides and decrement in fatty acid oxidation. Hyperinsulinemia in obese people contributes to increase in hepatic steatosis, simulation new lipogenesis, and inactivation of pathways related to fatty acid oxidation. The second step of NAFLD damage includes mechanisms of increasing inflammation and fibrosis. Increase in fatty acid level can trigger to production of cytokines an increase in peroxidation of lipids which contributes to hepatocellular damages, infiltration of inflammatory cells, activation of astrocytes, and physiologic reactions [1,2].

Although the relationship between NASH and insulin resistance has not been known yet, it is unknown that whether insulin resistance can leads to NASH. The prevalence of metabolic syndrome is much higher than NASH. Some of patients with NASH do not manifest symptoms of insulin resistance or other symptoms of metabolic syndrome. Furthermore, weight loss with diet and exercise promote sensitivity to insulin but moderately decrease fatty liver and serum transaminase level and do not eliminate NASH. However insulin sensitizers (such as Metformin and Thiazolindones) can decrease NASH-related fatty liver, inflammation, and fibrosis which demonstrate the vital role of this factor in insulin resistance. In the study of OTA et al, the relationship between insulin resistance and NASH with feeding mice with methionine-choline deficient (MCD) diet was assessed. MCD diet contribute to steatosis, steatohepatitis, and fibrosis which its' exact mechanism is unknown. However using S-adenosine methionine supplements prevents changes induced by MCD diet which demonstrates the key role of methionine in pathogenesis of steatohepatitis. However, MCD diet in mice can confront with weight loss and incompatible effects on insulin sensitivity. In contrast, Ota et al demonstrated that MCD diet contributes to NASH without considerable effect on weight. They examined the hypothesis that obesity, insulin resistance, and steatosis contribute to NASH which was conducted on two generation of OLETF and LETO mice with different metabolic features [1,3].

Otsuka mouse are susceptible to obesity, insulin resistance, diabetes, and steatosis which is similar to patients with metabolic syndrome. But non-Otsuka mouse are sensitive to insulin and less susceptible to steatosis after 2 week feeding with MCD diet which contributes to inflammation and fibrosis after 4 week and 8 week, respectively. A high fat (western) diet can contribute to increase in insulin resistance and development of NASH in Otsuka mice. MCD diet-induced NASH leads to rapid increase in hepatic glycerides due to expression of SREBP-1C fat producing gene, production of fatty acids, COA estriol, and esterase. In contrast, MCD diet in non-Otsuka mice contributes to increase in plasma Interleukin-6, hepatic tumor necrosis factor, activation of astrocytes, and fibrogenesis. Non-Otsuka mice present higher sensitivity to insulin and lighter response to MCD and high fat diets.

The relationship between insulin and MCD-mediated NASH was assessed by measuring adiponectin level and testing with Pioglitazone treatment. Adiponectin is secreted from fat cells and regulate the metabolism of fat and glucose (through suppressing gluconeogenesis and stimulating the consumption of glucose and fatty acid oxidation). Thiazolidinone-induced sensitizing feature to insulin is mediated through activation of adiponectin. Ota et al observed decrease in adiponectin in Otsuka mice feeding with MCD diet. Pioglitazone treatment triggers to increase in adiponectin simultaneously through insulin sensitizing effect and

decreasing NASH in MCD-OLETF mice. This lack of insulin sensitizing can be interpreted as causal relationship between insulin resistance and NASH [1,3].

The study of Ota et al presented new information regarding NASH in animal models and supports the relationship between obesity and insulin resistance and NASH [3]. However, using insulin and glucose tolerance test can determine better how insulin resistance is created and synthesis of glucose in liver and glucose consumption mediated by insulin sensitivity in skeletal muscles and adipose tissue are assessed more efficiently. However, adiponectin increase in non-Otsuka mice fed by MCD and treated with pioglitazone demonstrates promotion in insulin resistance and NASH which needs more experiments to determine the underlying mechanisms. Probably, other adipokines and hormonal factors are involved in NASH pathogenesis(3). Another deficiencies of Ota et al study is that MCD diet did not affect plasma level of lipids in Otsuka and non-Otsuka mice (in comparison with humans in which NAFLD is observed with dyslipidemia). Furthermore, diacylglycerol contents and various metabolites of lipids (such as ceramide) which interferes with insulin signaling in liver and other tissues were not measured. MCD model used in the current study is related to human NASH and should be used in treatment and assessment of this disease although it is deficit. This study apparently demonstrated that mice with more genetic susceptibility to metabolic syndrome are more at risk of NASH. Particularly it demonstrated that sensitivity promotion with thiazolidinone treatment can alleviate NASH in sensitive mice. This model is beneficial to present those molecular mechanisms involved in manifesting renal symptoms of NASH including steatosis, inflammation, and fibrosis [1].

Kidney controls carbohydrate homeostasis which stores or releases glucose based on metabolic needs. Therefore any defect in kidney can contribute to abnormal metabolism of carbohydrates. NAFLD is referred to wide spectrum of hepatic diseases from a simple fatty liver to Nonalcoholic Steatohepatitis (NASH) which is accompanied with fibrosis and progression to cirrhosis. Dietary disorders such as calorie-protein malnutrition and methionine-choline deficient (MCD) diet are known as important factors affecting NASH. A MCD diet through inhibition biosynthesis of phosphatidylcholine leads to increase in fat contents of hepatocytes by preventing synthesis and exit of VLDL. Increasing intrahepatic fatty acid levels prepare a suitable environment for lipid peroxidation particularly under oxidative stress conditions [4].

These observations may be indicative of disease progression from steatosis to steatohepatitis and cirrhosis due to increase in peroxidation, cytokines, and induction of Fas ligand. In contrast, some evidences demonstrates that increase in fatty acid contents and NASH metabolism occurs through wrong phosphorylation of IRS1 and IRS1 insulin receptors, therefore cascade reactions of insulin are usually weakened despite higher insulin level [5].

Sings of NASH

NASH is accompanied with different clinical symptoms including type II diabetes, hyperlipidemia, hypertension, and obesity which is defined as metabolic syndrome or insulin resistance syndrome. NASH normally occurs in decades 4 or 5 of life. Studies demonstrates that insulin resistance in NAFLD patients is almost doubled in comparison with similar control group which is as a result of increase in insulin concentration and normal glucose levels [6]. Disturbed insulin signaling contributes to hyperinsulinemia and decreased insulin sensitivity apart from obesity and overt diabetes is defined as a cause for NASH. Fat aggregation in liver leads to production of cytokines such as TNFα and IL4 which affect lipid metabolism in liver and creates fatty liver. Interaction of these pre-inflammatory cytokines are increased in NASH and can contribute to necrosis and hepatic inflammation in early stages of NAFLD (steatosis) at finally can cause cirrhosis. TNFα is a pre-inflammatory agent involved in insulin resistance pathogenesis, over-releasing fatty acids from fat cells, decreasing adiponectins, and disturbance of insulin signaling [7]. Other studies demonstrated that TNFα activates stress-related kinases (such as JNK), inhibits Kappa B kinase, and causes insulin resistance in cells. Production and activity of TNFα is antagonized by adiponectin. In conducted studies demonstrates much higher levels of TNFα in NASH patients in comparison with control group which had lower levels of adiponectins [8].

Adiponectin (Acrp30-AdipoQ) is found in low levels in circulation of obese individuals with type II diabetes. Serum levels of adiponectin depends on visceral fat content. Increase in visceral fat content contributes to insulin resistance, decreasing adiponectin, and lipid aggregation in liver. However studies suggested that low serum levels of adiponectin is involved in NASH independent from insulin resistance. In

liver, adiponectin increases sensitivity of insulin to inhibit gluconeogenesis, regulates hepatic metabolism and free fatty acids, inhibits lipogenesis, and activates oxidation of free fatty acids. Adiponectin decrement plays an important role in developing steatosis independent from the amount of visceral fat. New findings demonstrate that adiponectin decrement is of early causes of NASH and can be the connection between disturbance of glucose homeostasis and hepatic diseases [8].

Insulin and carbohydrate

The concentration of plasma insulin in fasting condition in normal people in comparison with those with fatty liver and NASH, have step-by-step increase in baseline average (6SD). During two-satge assessments, the concentration of plasma insulin in patients with NASH in comparison with the mean increased based on the amount of injected insulin.

In each stage of assessment, a step-by-step decrease was observed in the amount of injected insulin. This decrement demonstrated that insulin sensitivity in individuals with fatty acid and patients with NASH is decreased. Although, this finding was more in NASH patients. Generally the amount of glucose injection has a reverse relationship with body fat percentage. However, the mean age of normal people was lower than study group. Age had no linear correlation with the rate of glucose injection. In contrast, hepatic sensitivity to insulin in individuals with fatty liver and NASH was similar. During injection of insulin, exist of hepatic glucose in patients with NASH decreased 54 percent in comparison with 18 ± 76 percent in people with fatty liver. In higher amounts of injected insulin, nearly total suppression of exited hepatic glucose was observed in groups with fatty liver and NASH [9].

Insulin lipogenesis

In basic fasting condition, the average amount of serum FFA and glycerol in patients with NASH is higher than healthy people and individuals with fatty liver. Insulin injection leads to decrement in serum concentration of FFA and glycerol. However, this decrement in patients with NASH and in normal people is the lowest and highest amount, respectively. This finding was observed in two stages of the study. There is a tendency toward analysis of fat (producing glycerol) in patients with NASH. Furthermore, based on obtained information from this study, those people with fatty liver and NASH are also resistant to peripheral insulin in skeletal muscle (glucose disposal) and adipose tissue (fat decomposition) [9].

Pre-inflammatory effects

Fat can contribute to insulin resistance in various sensitive cells through activation off serine kinases. Alone or in combination, these Phosphoinositide pyruvates regulates residual serine in RS1 and RS2 receptors of insulin which leads to phosphoropyruvation of produced tyrosine or insulin and interference with physiologic response of insulin. The casual relationship between fat-mediated activation in serine kinase and insulin resistance in adipose tissue, muscle, and liver is proved which occurs in body in rapid response to intravenous fat injection and high fat diets. Saturated and unsaturated fatty acids can activate serine kinase which contributes to insulin resistance. It seems that saturated long-chain fatty acids are the most powerful model in liver [10,11].

Three serine kinase which are strongly involved in insulin resistance pathogenesis mediated by fat includes JNK and NFKB kinase, IKK, and PKC. Of these serine kinases, JNK and IKK are important pre-inflammatory signaling molecules. In obesity, activation of this kinase probably occurs through various mechanisms which are signified in the figure. In one scenario, PKC is produced with the mediation of diacylglycerol in the metabolism of fats and JNK and LKK are produced as a part of cascade in lower region [11].

In the second pathway, intracellular fat produce these kinases independent from PKC as a part of response to ER endoplasmic network stress. In the third pathway in which activated oxygen is produced in oxidation of fatty acids, are as inductors of JNK and IKK. Fourth, extracellular fatty acids; due their resemblance to Lipopolysaccharide of fat; can connect IKK and JNK to create relationship between insulin resistance and inflammation in the context of obesity. The complexity of this relationship increases when produced inflammatory cytokines from JNK and IKK pathways can amplify insulin resistance and inflammatory signaling.

The vital role of inflammatory pathways in pathogenesis of insulin resistance is proved by studies of suppression with drugs, genetics, or inflammatory signaling which promote insulin sensitivity. The role of inflammatory pathways in NAFLD disease is under study which with available data, inflammation has etiologic role in insulin resistance in liver, hepatic steatosis, and steatohepatitis [11].

In several conducted studies; regarding BMI, baseline adipose tissue insulin resistance (adipo), type of treatment, and ethnicity of study people; there was no significant relationship between Adipo changes during 16 weeks and change in liver tissue in baseline status and after 96 weeks in ALT (neither in week 16 nor in week 96). However, there was no significant relationship between change in adipo after 96 weeks and consequences of primary histology in PIVENS experiment and change in ALT. There existed a significant relationship between Adipo promotion after 96 weeks and findings of histology [12].

CONCLUSION

Lipid accumulation in hepatocytes causes variable degrees of NASH. High lipid level concentration in the liver produces reactive oxygen species that lead to oxidative damages. Thus antioxidant agents have an important therapeutic role in these patients (5). When insulin resistance occurs, more insulin is requiring stimulating phosphorylation in receptor substrate. While these mechanisms frequently took place in obesity, diabetes and metabolic syndrome and lead to NAFLD and NASH, some studies show that insulin resistance may presents in absence of underlining causes (9). Bell and colleagues confirmed the association between NASH and insulin resistance, but this relation was independent of degree of obesity (12).

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