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Insulin resistance and clinical aspects of non-alcoholic steatohepatitis (NASH)

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Abstract

Non-alcoholic steatohepatitis (NASH) is one of the most common liver disorders. This is highly prevalent in obese and diabetic subjects. Persons with central obesity are at particular risk. Other clinical predictors are age more than 40–50 years and hyperlipidemias, but none of these factors is invariable for causation of NASH. Other reported associations are, celiac disease, Wilson's Disease and few other metabolic diseases. Drugs, particularly amiodarone, tamoxifen, nucleoside analogues and methotrxate have also been linked to NASH. The disease is evenly distributed in both sexes but advanced disease is more common in women. Ethnic variation exists and African Americans are less affected than Hispanic Americans. Specific clinical features of NASH are infrequent. Patients usually come to clinical attention by elevated liver enzymes found on routine evaluation but on history, about two third of patients will admit to have mild fatigue and about half will report right upper quadrant pain. Rarely, patient may present with a complication of cirrhosis. Physical examination may reveal hepatomegaly and splenomegaly. Research in last few years has stressed that development of steatosis, stetohepatitis, fibrosis with subsequent cirrhosis are most probably the result of insulin resistance. Therefore, clinical features may reflect existence of insulin resistance. Obesity, particularly central obesity is most important of these. Patients may have sleep apnea syndrome. Hypertension and manifestations of diabetes mellitus like polyuria, polydypsia, and neurological deficits may occur. Patients may have varying combination of obesity, diabetes, hyperlipidemia, hypertension and impaired fibrinolysis (syndrome X). Children with insulin resistance may show acanthosis nigricance. Patients with polycystic ovary syndrome, which consists of insulin resistance, diabetes, obesity, hirsutism, oligo or polymenorrha and hyperlipidemia may have NASH. Other rare manifestations of insulin resistance, which can be seen in patients of NASH are lipomatosis, lipoatrophy/lipodystrophy and panniculitis. Most other rare conditions known to cause NASH like peroxisomal diseases, mitochondialpathies, Weber–Christian disease, Mauriac syndrome, Madelung's lipomatosis and abetaliopprotenemia also have insulin resistance. This is believed that primary defect underlying insulin resistance is impairment in postreceptor pathways (through tyrosine kinase activity) of insulin action. Primary defect in insulin receptors appear uncommon. This results in down regulation of insulin receptor substance 1 (IRS-1) signaling by excess free fatty acids. In muscle, activated IRS-1 promotes translocation of glucose transporter protein 4 (GLUT4) to cell membrane. As a result, monocyte glucose uptake by GLUT4 increases glucose disposal from blood and reduced need for insulin. PKC-0 is a likely candidate as serine kinase in muscle regulated by fatty acids that can impair the activation of IRS-1.

Insulin resistance is usually evaluated by fasting insulin levels, Quantitative Insulin Check Index (QUICKI) and Homeostasis Model Assessment of Insulin Resistance (HOMA), C-peptid/insulin ratio oral glucose tolerance test and hyper insulinemic euglycemic clamp. The clamp technique is considered the gold standard.

Keywords: Non-alcoholic fatty liver; Steatosis; Obesity; Hyperlipidemia; Diabetes; Hyperinsulinemia

1. Introduction

Excessive fat accumulation in the liver is most common liver disorder. Although, the most common cause of fatty liver is alcohol, many patients have fatty liver in the absence of significant alcohol intake and this pathological state has been referred to as "non-alcoholic fatty liver disease (NAFLD)". NAFLD has been widely described in the recent literature and is now one of the hottest areas in liver research, particularly because of its potential to progress to a spectrum comprising steatohepatitis, fibrosis and cirrhosis with subsequent portal hypertension. For cases having significant inflammation

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associated with fatty liver, term "non-alcoholic steatohepatitis (NASH)" has been used. This term was first used by Ludwig et al. [1].

Fatty liver is defined when deposition of fat in the liver accounts for more than 5% of liver weight or when more than 5% of hepatocytes are affected [2]. Histologic picture of NASH resemble liver injury caused by alcoholic abuse.

2. Etiopathogenesis

2.1. Risk factors

Obesity, diabetes mellitus and hyperlipidemia are most common risk factors for NASH. Obesity is the most common coexisting condition. The risk is particularly high with truncal obesity and when body mass index is more than 30 kg/m^2. In different reports, about one third to 100% of obese individuals have evidence of fatty liver. Interestingly, NASH has been reported in subjects with central obesity and normal BMI [3].

Diabetes is an independent risk factor and increases the risk and severity of NASH irrespective of body mass index. Type 2 diabetes is most common but few patients, particularly children may have insulin dependent diabetes. When both diabetes and obesity are present, they pose a combined risk. In a study, all such patients were found to have at least mild steatosis, 50% had NASH, and 19% has cirrhosis [4].

About half of patients with hyperlipidemia have fatty liver on ultrasound as reported in a recent series [5]. Most common form of hyperlipidemia is hyeprtriglyceridemia rather than hypercholesterolemia.

Apart from this, other risk factors are family history of fatty liver, cryptogenic cirrhosis and use of few drugs, particularly amiodarone, valproic acid, Vitamin A, tamoxifen and methotrexate [6].

3. Pathogenesis

3.1. Insulin resistance

Pathogenesis of NASH has not been fully understood. Why some patients develop only fatty liver and some progress to NASH is not known. However, all available evidences point towards metabolic defects. Abnormalities of lipid metabolism can happen anywhere between uptake, synthesis, degradation and secretion of lipids from the cells.

Insulin resistance has been found to be extremely common and reproducible in patients with NASH. This has been proposed as a primary pathogenic mechanism for causation of NAFLD. However, how important is insulin resistance for progression of fatty liver to NASH in unclear? Insulin resistance is also an important feature of diseases associated with NASH like diabetes, obesity and metabolic syndrome (syndrome 'X').

Insulin acts by phosphorylating intracellular tyrosine kinase. Primary defects of insulin receptors are uncommon. Instead, defects of post receptor pathways are thought to be primary abnormalities.

Insulin resistance leads to hyperinsulinemia which in turn is responsible for defects in lipid metabolism at mitochondrial level, leading to defective lipolysis. This results in accumulation of excessive fat in the liver cells (NAFLD) with subsequent hepatocytes damage by production of oxidative stress. Reactive oxygen species, secreted from mitochondrion, is mostly responsible for oxidative stress. Cytokines play an important role in liver injury and most important of these is TNF-α [7]. TNF-α is secreted mainly from adipose tissue and its levels correlate with body mass index (BMI).

Insulin resistance can be diagnosed by measuring insulin resistance index, estimation of insulin levels 2 h after giving oral glucose and performing glucose tolerance test.

4. Liver histology

Liver biopsy findings are the basis of diagnosis of NASH. The Histologic picture is various combinations of fat accumulation, inflammation, fibrosis and cirrhotic changes. These determine the clinical spectrum of the disease.

Histology may reveal steatosis, which may be microvescicular or macro-vesicular, lobular inflammation with mixed cells infiltration, but predominantly with PMN cells, ballooning and necrosis of hepatocytes, Mallory's hyaline, fibrosis and cirrhotic. Perivenular areas are most commonly involved and portal areas are usually spared. However, in children with NASH, portal area involvement may be the predominant finding on histology. In addition, children only rarely show Mallory hyaline [8].

An NAFLD classification has been proposed [9]:

Class 1: Steatosis
Class 2: Steatosis + lobular inflammation
Class 3: Class 2 + ballooned hepatocytes
Class 4: Either Mallory's hyaline or fibrosis

In different studies, varying degree of fibrosis was present in 2/3rd of patients, severe fibrosis in 1/4th patients and cirrhosis in 1/6th of the patients. Presence of fibrosis and cirrhosis represent severe form of disease spectrum. As the Histologic severity increases, features of steatosis and inflammation gradually decrease. The term NASH is used when biopsy show fatty liver cells, inflammatory infiltrates, ballooning and necrosis of hepatocytes.

5. Clinical aspects

5.1. Symptoms and signs

Incidence of NASH has been increasingly reported in literature. NAFLD is reported to be present in 10–24% of