

Possible Connection Between Non-Alcoholic Fatty Liver Disease and Type-2 Diabetes Mellitus

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Sir,

The aetiology of NAFLD remains mysterious. NAFLD is characterized by insulin resistance (IR) and sub-clinical inflammation. Enhanced growth in the number of available fatty acids (FFAs) to the liver induces fatty permeation in the hepatocytes, which causes hepatic impairment through lipid peroxidation along with mitochondrial dysfunction.^{1,2} De novo lipogenesis (DNL) is another supplier of fatty acids & intrahepatic triglycerides for NAFLD patients, even during fasting. Adipose tissue inflammation and increased FFA importation contribute to hepatocellular injury in obese people. Hyperglycemia contributes to the chronic glucotoxicity characteristic of type-2 diabetes. By triggering IR, DNL, and hepatocellular impairment, glucotoxicity may contribute to the development of NASH. A current animal analysis revealed that fructose, not glucose, impairs fat metabolism when combined with a high-fatty diet. NAFLD patho-

genesis involves gut, adipose, and liver mechanisms. They're called gut-fat-liver axis. Recent multi-omics research findings with gut bacteria profiling showed that metabolic endotoxemia leading to excessive gut permeability is closely tied to NAFLD. These mechanisms regulate apoptosis & cell stress. Lipotoxicity-stimulated hepatocyte ballooning leads to the down-regulation of caspase 9, the main player in the apoptotic pathway. This, together with reinforcement from such a hedgehog autocrine survival signalling pathway, produces an "undead hepatocyte" in which apoptosis is initiated but not executed, driving inflammation (NASH) and fibrosis.³ Fibrosis is the primary NASH histologic indicator of end-stage hepatic morbidity and death. Sedentary lifestyle, metabolic endotoxemia, as well as IR, are MetS and T2D hallmarks.⁴⁻⁶ Currently, that NAFLD induces the hepatic consequences of MetS, its magnitude can be better appreciated.^{7,8}

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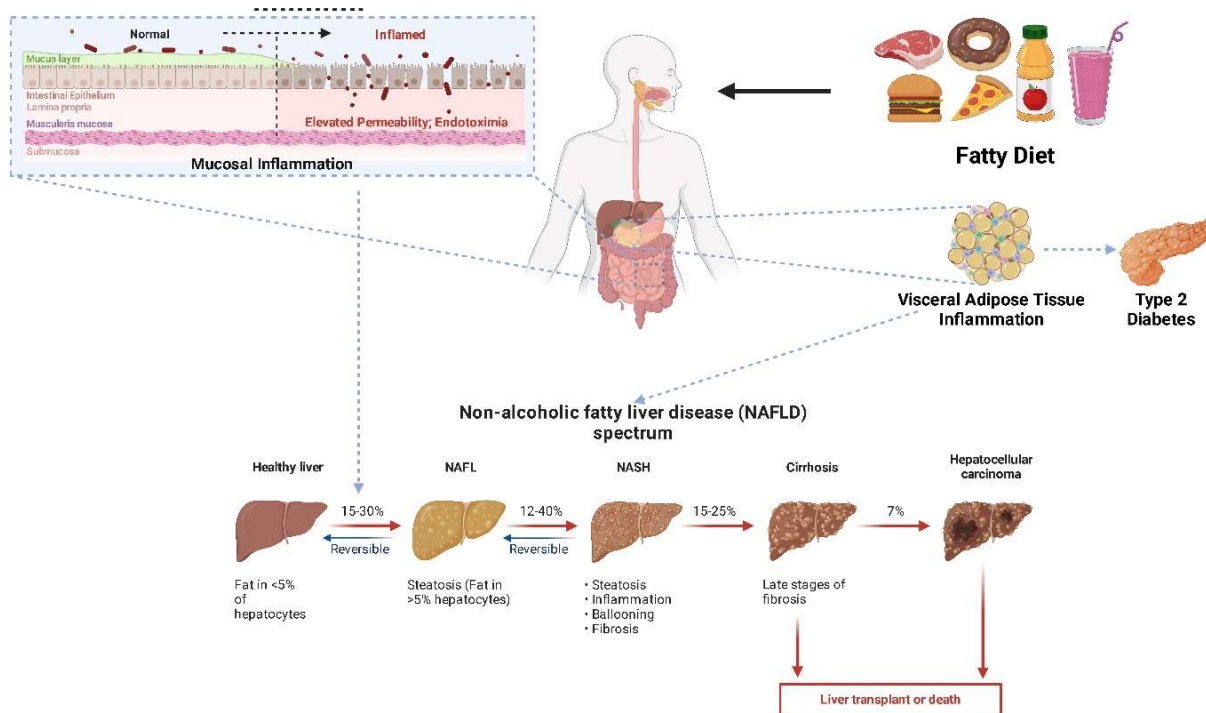


Figure 1: Probable mechanisms in the liver, adipose tissue, and gut contribute to the development of NAFLD/NASH (Created with BioRender.com)

[Image Description: The graphic above illustrates that non-alcoholic fatty liver disease is a progressive disease that advances through many stages. The final and fatal stage of this disease is known as cirrhosis and hepatocellular carcinoma. At that juncture, a liver transplant becomes imperative, as failure to do so will ultimately lead to death. By implementing lifestyle modifications and effectively managing diabetes, it is possible to control the initial two phases of this illness, namely non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH).

The image illustrates that consuming a diet high in fat, combined with type-2 diabetes, is the main cause of inflammation in the visceral adipose tissue and mucous membranes. Additionally, the image depicts the progression of non-alcoholic fatty liver disease, starting from a healthy liver and leading to the development of cirrhosis and hepatocellular carcinoma.]

NAFLD and T2D are related. NASH, HCC, and cirrhosis are all aided by diabetes (**Figure 1**). Type 2 diabetes is triggered by NAFLD.³ Ludwig et al. coined the term "non-alcoholic steatohepatitis" in 1980 after documenting 20 cases without alcoholism.⁹ Thus, the recent terminology of "non-alcoholic fatty liver disease" focuses on what "does not" cause it rather than what "may cause it." Due to information gaps in NAFLD's natural history, treating type 2 diabetics is difficult.¹⁰ NAFLD's inclusion among diabetes-related comorbidities is debatable and won't be settled minus mechanistic studies evaluating their relationship. Moreover, an analysis of how to explain NAFLD with pre-existing diabetes mellitus is needed.¹¹ Obesity, insulin resistance & subclinical inflammation are linked to both conditions, but the path is unclear.

Abbreviation:

- NAFLD – Non-alcoholic Fatty liver disease
- IR- Insulin resistance
- FFA -Free Fatty Acid
- DNL – De-novo lipogenesis
- NASH -Non-alcoholic Steatohepatitis

- Mets- Metabolic Syndrome
- T2D -Type 2 diabetes

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