International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1415-1417 www.ijprajournal.com ISSN: 2249-7781

New Therapy for Nafld: Targetting Pdh

Dr. Syed Abdul Jabbar Basha*, K.Narendra Naidu[2], MD.Apsar Pasha[3], Dr.Ch.Madhu[4].

*Associate professor, Sana College of pharmacy, Kodad**
Assistant professor, Sana College of pharmacy[2, 3], Kodad
Associate professor, Pratishta institute of pharmaceuticals, Durajpally, Suryapet[4]

Submitted: 25-11-2023 Accepted: 05-12-2023

ABSTRACT
Sedentary life style and excess calorie intake has greatly increased obesity and Non alcoholic fatty liver disease (NAFLD), Defined as accumulation of excess fat in absence of alcohol with high risk of other infections like HEP-C. NAFLD increases the risk for insulin resistance, type 2 diabetes (T2D), and cardiovascular disease, while currently having no approved therapy to counteract its pathology. Thus, increasing efforts to understand the mechanisms responsible for NAFLD have been pursued in preclinical studies, in the hopes of developing novel therapies that can prevent the progression of insulin resistance and/or T2D. The pathology of NAFLD is multifactorial, with proposed mechanisms including inflammation, oxidative stress, and mitochondrial dysfunction to name a few. To overcome this situation a potential target for NAFLD is pyruvate dehydrogenase (PDH) a rate limiting enzyme of glucose oxidation by increasing the activity of PDH can revrse the situation of fatty liver
Key words: NAFLD, PDH, Oxidation

INTRODUCTION

Fatty liver disease means that you have fat inside your liver that can, over time, affect liver function and cause liver injury. People who drink too much alcohol may also have fat in their liver, but that condition is different from fatty liver disease.

Types of fatty liver disease

Health care providers divide fatty liver disease into two types. If you just have fat but no damage to your liver, the disease is called nonalcoholic fatty liver disease (**NAFLD).** If you have fat in your liver plus signs of inflammation and liver cell damage, the disease is called nonalcoholic steatohepatitis (**NASH**).
About 10% to 20% of Americans have NAFLD. About 2% to 5% have NASH.

Symptoms

Fatty liver disease is sometimes called a silent liver disease. This is because it can happen without causing any symptoms. Most people with NAFLD live with fat in their liver without developing liver damage. A few people who have fat in their liver develop NASH.

If you have NASH, you may have symptoms that could take years for them to develop. If liver damage from NASH leads to permanent scarring and hardening of your liver, this is called cirrhosis.
Symptoms from NASH may include:

- Severe tiredness
- Weakness
- Weight loss
- Yellowing of the skin or eyes
- Spiderlike blood vessels on the skin
- Long-lasting itching

NASH that turns into cirrhosis could cause symptoms like fluid retention, internal bleeding, muscle wasting, and confusion. People with cirrhosis over time may develop liver failure and need a liver transplant.

Who's at risk

Health care providers don't know the exact cause of fatty liver disease. But they think that obesity is the most common cause. Obesity in the U.S. has doubled in the last decade, and health care providers are seeing a steady rise in fatty liver disease. Although children and young adults can get fatty liver disease, it is most common in middle age.

Risk factors include:

- Being overweight
- Having high blood fat levels, either triglycerides or LDL ("bad") cholesterol
- Having diabetes or prediabetes
- Having high blood pressure

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1415-1417 www.ijprajournal.com ISSN: 2249-7781

Diagnosis

Fatty liver disease can happen without causing any symptoms. It's usually diagnosed when you have routine blood tests to check your liver. Your health care provider may suspect fatty liver disease with abnormal test results, especially if you are obese.

Imaging studies of your liver may show fat deposits. Some imaging tests, including special ultrasound and MRI scans can help diagnose the disease and spot scar tissue in the liver. But the only way to be certain that fatty liver disease is the only cause of liver damage is with a liver biopsy. A liver biopsy involves getting a tissue sample of your liver with a needle. The needle removes a small piece of liver tissue that can be looked at under a microscope. Here's how your health care provider makes the diagnosis:

- If you have fat but no inflammation or tissue damage, the diagnosis is NAFLD.
- If you have fat, inflammation, and liver damage, the diagnosis is NASH.
- If you have a type of scar tissue in your liver called fibrosis, you may be developing cirrhosis.

Treatment

If you have NAFLD without any other medical problems, you don't need any special treatment. But making some lifestyle changes can control or reverse the fat buildup in your liver. These may include:

- Losing weight
- Lowering your cholesterol and triglycerides
- Controlling your diabetes
- Avoiding alcohol

` If you have NASH, no medication is available to reverse the fat buildup in your liver. In some cases, the liver damage stops or even reverses itself. But in others, the disease continues to progress. If you have NASH, it's important to control any conditions that may contribute to fatty liver disease. Treatments and lifestyle changes may include:

- Losing weight
- Medication to reduce cholesterol or triglycerides
- Medication to reduce blood pressure
- Medication to control diabetes
- Limiting OTC drugs
- Avoiding alcohol
- Seeing a liver specialist

Some medications are being studied as possible treatments for NASH. These include antioxidants like vitamin E. Scientists are also studying some new diabetes medications for NASH that may be given even if you don't have diabetes. However, you should only take these medicines after consulting with a liver specialist.

Complications

The main complication of fatty liver disease is the progression of NASH to cirrhosis. Cirrhosis means permanent scarring and hardening of the liver.

Role of pyruvate dehydrogenase

The liver plays a major role in whole-body glucose homeostasis, with glucose transporter 2 serving as the primary transporter for hepatic glucose uptake.[18] Following transport into the liver, glucose is phosphorylated by glucokinase to glucose-6-phosphate and has a variety of metabolic fates. This includes

1. undergoing glycogenesis for storage as glycogen;
2. shuttling into the pentose phosphate pathway to generate reduced nicotinamide adenine dinucleotide phosphate for supporting DNL and the production of reduced glutathione; and
3. undergoing glycolysis to support small amounts of energy (ATP) production with the eventual generation of pyruvate

In order to maximize ATP production during glucose metabolism, glycolytically derived pyruvate is transported into the mitochondria via the mitochondrial pyruvate carrier (MPC), following which pyruvate is decarboxylated into acetyl CoA via the pyruvate dehydrogenase (PDH) complex (PDC).

It should be noted though that pyruvate oxidation only accounts for a minor fraction of glucose/pyruvate metabolism in the liver, even in the post-prandial state, as the vast majority of mitochondrial pyruvate is carboxylated into oxaloacetate via pyruvate carboxylase (PC), which contributes to supporting DNL.

Hepatic PDH Activity in NAFLD

While the previous section alluded to increases in muscle glucose oxidation representing the mechanism by which stimulating PDH activity imparts beneficial actions in obesity, the majority of these studies have not considered whether increases in PDH activity/glucose oxidation in other organs could be responsible. Reasons for

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1415-1417 www.ijprajournal.com ISSN: 2249-7781

hepatic PDH activity not being considered likely involve the minimal contribution that pyruvate oxidation has in terms of overall pyruvate metabolism in the liver.[19] Furthermore, liver-specific PDH deficient mice exhibit robust reductions in hepatic glucose production and an improvement in whole-body insulin sensitivity,[26] which would raise concern with regard to stimulating hepatic PDH activity in the setting of NAFLD. However, these studies were not performed in the context of HFD supplementation and obesity.

The prototypical pan-PDHK inhibitor is dichloroacetate,[32] but this agent is limited by a short half-life, and thus a series of novel PDHK inhibitors were recently developed by the Chuang laboratory, with the strongest candidate being 2-[(2,4-dihydroxyphenyl)sulfonyl]isoindoline-4,6-diol (PS10).[33] While acute treatment of mice with PS10 appears to stimulate PDH activity in multiple organs, prolonged PS10 treatment appears to harbor selectivity toward increasing hepatic PDH activity.[33] Moreover, treatment of male C57BL/6J mice fed a HFD (60% kcal from lard) for 14 weeks with PS10 (70 mg/kg once daily) during the final 4 weeks improved glucose tolerance, which was associated with a robust reduction in hepatic steatosis as indicated by decreased Oil Red O staining.[33,34] As NAFLD is a major risk factor for insulin resistance/T2D, this suggests that systemic activation of PDH to increase glucose oxidation rates may also improve glucose homeostasis via reductions in hepatic steatosis. Indeed, despite mangiferin treatment increasing muscle PDH activity/glucose oxidation in obese mice, it also caused marked reductions in adiposity,[28] suggesting that reductions in hepatic steatosis may have been present. Observations from Go et al. engendered further interest along this perspective, as mice with a whole-body PDHK2 deficiency demonstrated protection against insulin resistance when subjected to experimental obesity via chronic HFD (60% kcal from lard) supplementation, which they specifically attributed to a reduction in hepatic steatosis.[16] Furthermore, they observed that experimental obesity increased hepatic PDHK2 mRNA/protein expression, thereby decreasing hepatic PDH activity, whereas obese PDHK2 deficient mice exhibited normal hepatic PDH activity, which was associated with decreased liver weights and hepatic steatosis compared to their obese wild-type littermates. Because PDHK2 deficient mice also demonstrated reductions in adiposity in response to experimental obesity, the reductions in hepatic steatosis could once again be secondary to weight loss. However, liver-specific knockdown of PDHK2 via tail vein injection of an adenovirus also lowered hepatic TAG content and improved glucose tolerance, alluding to effects in the liver being a major driver of the phenotype observed in PDHK2 deficient mice.

Additional support for increasing hepatic PDH activity and subsequent glucose oxidation rates to mitigate obesity-related NAFLD have been observed with ranolazine, a second-line therapy used for the treatment of angina. While ranolazine's mechanism of action for improving angina stems from its ability to inhibit the late inward sodium current by blocking the voltage-gated sodium channel subunit 1.5,[35] ranolazine has also been demonstrated to increase glucose oxidation rates in both isolated working heart and muscle preparations.[36,37] Accordingly, male C57BL/6J mice fed a HFD (60% kcal from lard) for 10 weeks were subsequently treated with ranolazine (50 mg/kg daily) for 30 days while remaining on the HFD, which led to marked reductions in the liver weight/body weight ratio and hepatic TAG content, as well as an overall improvement in glycemia.[38] The ranolazine mediated improvement in hepatic steatosis was associated with decreased hepatic PDH phosphorylation (indicative of increased PDH activity), which may involve a direct effect, as ranolazine treatment of HepG2 cells also decreased PDHK4 mRNA expression and subsequent PDH phosphorylation. Importantly, reductions in hepatic steatosis are necessary for the glucose-lowering actions of ranolazine, as a single treatment of obese male C57BL/6J mice with ranolazine failed to lower hepatic TAG content and glucose levels during a pyruvate tolerance test. Conversely, a 1-week treatment of obese male C57BL/6J mice with ranolazine was sufficient to lower hepatic TAG content, which was now associated with improved glycemia during a pyruvate tolerance test. As obese individuals are often at risk for angina/ischemic heart disease, it may prove worthwhile for future studies to assess the prevalence of NAFLD in subjects treated with ranolazine in this patient population.

REFERENCES:

1.Pyruvate Dehydrogenase as a Therapeutic Target for Nonalcoholic Fatty Liver Disease…Christina T. Saed,†‡§ Seyed Amirhossein Tabatabaei Dakhili,†‡§ and John R. Ussher