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The Role of Pyruvate Dehydrogenase in Non-Alcoholic Fatty Liver Disease: Therapeutic Insights and Future Directions

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Abstract

Non-alcoholic fatty liver disorders (NAFLD) are defined by the accumulation of excess fat in the liver that has no other cause, such as drinking alcohol. Pyruvate dehydrogenase has been established as an alternative treatment for this disorder. NAFLD pathogenesis is complex and includes oxidative stress inflammatory processes and mitochondrial dysfunction. Impaired liver fatty acid oxidation and glucose oxidation are significant individuals in developing NAFLD, and strategies to reverse these defects can help alleviate the condition. A spectrum of liver diseases comprises NAFLD, which is currently referred to as metabolic dysfunction-associated liver disease (MASLD). The significant amounts of hepatocytes with minimal to no alcohol use hepatic steatosis disease indicates it. Over the next decade, NAFLD will overtake all other causes of cirrhosis due to its growing incidence, along with increased rates of obesity, metabolic syndromes, and, hence, prompting liver T2D transplantation. However, heart disease remains the leading cause of death, with a negligible proportion developing liver-related problems and fibrosis. To pathology, NAFLD is related to ergastoplasm stress, lipid toxicity, oxidative stress, and lipid depositions. Increased obesity and NAFLD, which is distinguished by the buildup of excess fat in the liver without alcohol abuse or other contributing factors like hepatitis C infection, are common in the public because of sedentary lifestyles and high-calorie consumption. Further, recent studies have demonstrated that, even while oxidative energy generation plays a minor role in the liver's total glucose/ pyruvate metabolism, defects in glucose oxidation may potentially be a portion of the mitochondrial dysfunction in NAFLD. Therefore, hepatic steatosis can be reduced, and glucose homeostasis can be improved by reducing the defect in glucose oxidation. In this review, we will discuss the data supporting the role of reduced liver glucose oxidation in NAFLD pathogenesis and investigate the possibility of specifically targeting pyruvate dehydrogenase (PDH), the enzyme that limits the rate of glucose oxidation in NAFLD. We will also go over possible MOA for how elevated hepatic PDH activity and consequent glucose oxidation might cure the pathophysiology of obesity-induced NAFLD, as well as ways to target this pathway with therapeutic drugs.

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INTRODUCTION

Hepatic steatosis, also known as NAFLD, is a disorder in which an individual's liver accumulates extra fat (triacylglycerol) over 5% of hepatocytes without any additional contributing factors, such as alcohol misuse or inflammation in the liver [1]. NAFLD is on the rise and has appeared as a leading basis of morbidity globally, impacting relatively one-third of adult western

populations [2]. Although non-alcoholic steatohepatitis (NASH), a more evolved form of the disorder that might raise the risk of hepatocellular cancer, may develop from the excess lipid/TAG accumulation in NAFLD, it does not always affect liver function in the presence of inflammation [3]. While NAFLD is frequently rather benign, as it progresses, it can raise the risk of T2D and cardiovascular diseases [4]. It also has a strong correlation with systemic insulin resistance. Also, NAFLD is caused by obesity. There has been a lot of research done to understand the processes causing the disease and its natural course. This research is important because it might result in the development of innovative therapeutics for the prevention of impaired insulin sensitivity and T2D [5, 6]. There is continuing research on the difficult question of whether NAFLD causes insulin resistance or T2D. NAFLD can also result from impaired insulin sensitivity [7]. With most of the research in this field concentrating on reduced fatty acid oxidation rates, mitochondrial dysfunction is another theory for why NAFLD occurs [8, 9]. When rates of oxidation of mitochondrial fatty aci1d drop in obesity, the liver accumulates more TAG because hepatic fatty acid absorption and supply overwhelm oxidation rates [10]. This process increases lipotoxic intermediates including ceramide and diacylglycerol (DAG). Increasing hepatic fatty acids oxidation rates has been demonstrated in several preclinical studies to prevent NAFLD and reduce the DAG buildup, all of which improve glucose homeostasis. and have a strong insulin-sensitizing impact. [11, 12]. Recent studies have demonstrated that lower rates of glucose oxidation in animal models of T2D and obesity may be a useful tactic to lessen the effects of obesity-related NAFLD. It is based on the Randle cycle, which was first reported by Philip Randle and colleagues in the 1960s. Boosting the oxidation of glucose should decrease the oxidation of fatty acids, which would promote the buildup of hepatic lipid/TAG [13, 14]. This may seem contradictory. This study is to investigate glucose oxidation as a potential therapeutic target considering these considerations and to characterize its involvement in the pathophysiological of NAFLD. Pyruvate dehydrogenase is the enzyme that reduces the rate at which glucose is oxidized. Glucose oxidation can improve glucose homeostasis and hepatic steatosis, which ultimately improves the pathophysiology of obesity-induced NAFLD [14, 15].

PHASES OF NON-FATTY ACIDS LIVER DISEASES

NAFLD, or non-alcoholic fatty liver disease, is used to explain a group of problems that occur in those who consume alcohol in more quantity and currently have an excess of fat accumulated in their livers. Lower or no fat should be present in healthy liver cells [16, 17]. A steatoses liver may arise from the overconsumption of fat, as more than 5% accumulated in liver cells. (NAFLD) is divided into four phases [18].

1. Simple fatty liver or steatosis.
2. Non-alcoholic steatohepatitis (NASH).
3. Fibrosis.
4. Cirrhosis.

Fatty Liver (Steatosis)

This is the initial phase in which fat is accumulated by liver cells without causing inflammation or damage. In this, they do not show any symptoms, and many individuals may have no idea they have fatty livers [19, 20]. A nutritious diet and regular exercise can help remove extra fat in liver cells, which prevents fatty livers from developing further.

Non-alcoholic steatohepatitis (NASH)

This phase is characterized by inflammation and fat accumulation in the liver cells. This stage has a high impact on UK citizens [21]. The livers repair damaged tissue, which results in the liver to heal it, leaving the inflammatory areas as a scar.

Fibrosis

This develops when the liver and the blood vessels around the liver have a chronic accumulation of scar tissue [22, 23]. At this point, the liver can still operate normally and treating or eliminating the

inflammatory process may stop the damage from getting worse or even reverse part of it. The liver's ability to function is compromised if, over time, scar tissue begins to replace a large portion of the healthy liver tissue. Cirrhosis might result from this [24].

Cirrhosis

At this point, liver cirrhosis stops functionally normally, and symptoms like yellowing of the skin and colors of eyes become white and a dull ache in the lower right side of the ribs begins to show [25, 26]. It is hard to remove the scar tissue from liver cirrhosis, but if the underlying cause of the damage to the liver is found and treated, the disease can stop proceeding [27]. And further, the phases of NAFLD are explained in Figure 1.

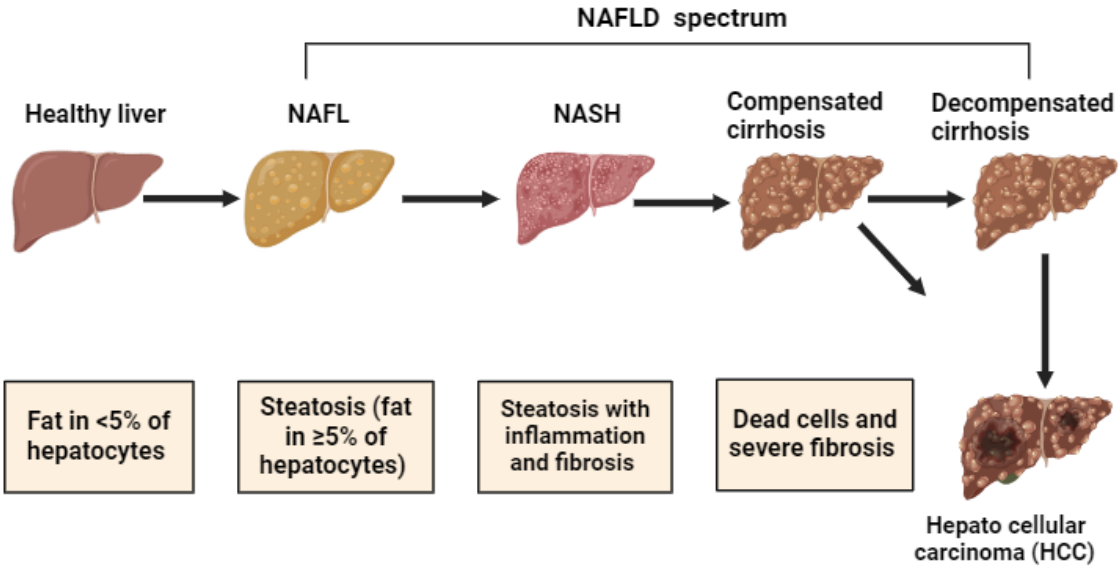

Figure 1. Different phases of NAFLD [28, 29].

MECHANISM OF ACTION OF PYRUVATE DEHYDROGENASE IN THE EVALUATION OF NON-FATTY HEPATIC DISEASES

The evaluation of non-alcoholic liver illness requires improved oxidation processes and glucose homeostasis, which are achieved via pyruvate dehydrogenase [30, 31]. The following steps are involved in (PDH) MOA in NAFLD.

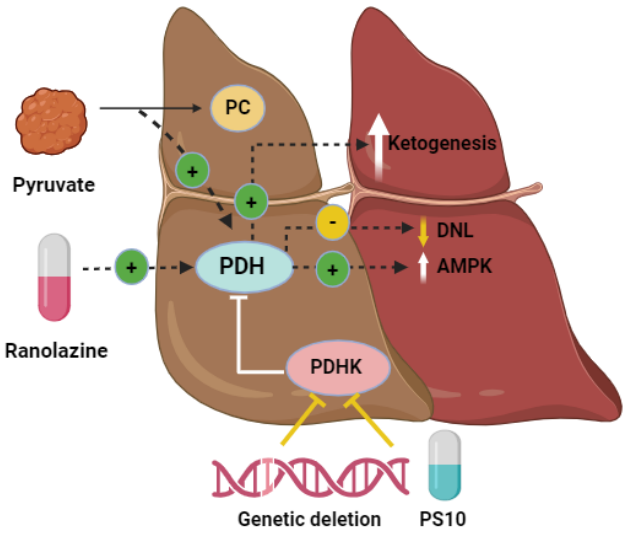

Figure 2. Pyruvate dehydrogenase's mode of action in the medication of non-fatty liver diseases [32, 33].

1. *Enhancement of glucose oxidation:* The enzyme PDH, which converts the pyruvate into acetyl coenzymes before it enters the curb's cycle [34, 35]. The enzyme that limits the pace at which glucose oxidation may occur. Elevated PDH activity promotes glucose oxidation, which lowers the hepatocytes, and triacylglycerol and improves glucose homeostasis.
2. *Decreases hepatic steatosis:* Raising PDH activity helps lessen lipid droplet buildup in the hepatic cell, which helps in the medication of NAFLD [36, 37].
3. *Enhancing the signaling of insulin:* Elevated PDH activity can reduce insulin resistance and the risk of T2D by enhancing insulin signaling [38].
4. *Balance of mitochondrial redox:* PDH and KGDH are important for preserving the redox equilibrium inside the mitochondria. Hydrogen peroxide (H_2O_2) generation is redox modified by PDH and KGDH through protein S-gluathionylation (PSSG) and S-nitrosylation (PSNO) adducts, acting as feedback inhibitors for the propagation of oxidative stress signals in many physiological situations [39].
5. *Fatty:* Acids regulation- By changing the PDH redox state, fatty acids can render it inactive by boosting the PDH activity by a variety of methods, including boosting the activity of PDK enzyme inhibitors [40]. Further mechanism of action PDC is explained below in Figure 2.

HEPATIC GLUCOSE OXIDATION AND PYRUVATE DEHYDROGENASE

PDH is an important enzyme in the oxidation of glucose, especially in the regulation of glucose metabolism [41].

The Pyruvate Dehydrogenase Complex's (PDC) activity

The long-term impacts of lipid metabolism can decrease glucose oxidation by raising pyruvate dehydrogenase kinase's (PDK) specific activity, which results in increased PDC phosphorylation and inactivation [42]. PDC, the pyruvate dehydrogenase complex, is the primary factor that determines the rate at which glucose is oxidized.

Acute Pyruvate Dehydrogenase Activation

Acute PDH activation raises muscle glucose oxidation without modifying muscular glucose consumption. Pyruvate's transformation into acetyl-CoA for oxidation appears to be regulated by PDH activity [43]. In insulin-resistant muscle, this activation does not improve insulin-stimulated glucose uptake [44].

Role in Hepatic Glucose Production

Acute PDH activation in muscle does not alter the current at which glucose is infused, the rate at which glucose disappears, or the quantity of glucose produced in the liver [45, 46].

Therapeutic Goal

A PDK inhibitor to increase PDC activity can improve insulin activity by reducing blood glucose levels and boosting glucose oxidation [47, 48, 49].

PYRUVATE DEHYDROGENASE FUNCTIONS IN TREATING A RANGE ON ILLNESS AND UPCOMING PROMISES

The pyruvate dehydrogenase complex (PDC) is essential for treating several diseases [50].

Diseases Related to Metabolism

A significant regulator of metabolic balance is PDC. Obesity, diabetes, and heart failure are metabolic disorders linked to the activation of PDK isoforms, which impede PDH [51, 52]. PDC-modulating therapies, such as activating PDC with dichloroacetate (DCA), show advantages in certain metabolic circumstances [52].

Neurodegenerative Diseases

Alzheimer's and Parkinson's diseases are linked to PDC dysfunction, the malfunction of the mitochondria, and the resulting oxidative stress
that follows. In animal models, increasing pyruvate metabolism and PDC activity through treatments, such as pyruvate supplementation has shown neuroprotective benefits [53].

PDCD, or pyruvate dehydrogenase complex deficiency, is an uncommon metabolic disease brought on by insufficiencies in the PDC enzymes [54]. To maximize PDC activity, the mainstay of treatment is cofactor supplementation with thiamine, carnitine, and lipoic acid. The biochemical correction of PDC deficit has also been achieved by dichloroacetate, but with little success in reversing neurological symptoms (Table 1) [55, 56].

Table 1. The Role of pyruvate dehydrogenase in diagnosis of various diseases [57, 58].

S. No	Diseases	Mechanism of Action/Effects
1	Metabolic diseases	PDKS regulates the activity of PDC by phosphorylation inhibition of specific serine residue on the Eα subunit of pyruvate dehydrogenase.
2	Diabetes	PDK inhibitors can prevent increases in liver glucose levels.
3	Heart failure	PDK inhibition may reduce injury caused by myocardial ischemia.
4	Cancer	PDK inhibitors can induce apoptosis (cell death) in tumor cells.

CONCLUSIONS

Pyruvate dehydrogenase has been related to the pathogenesis of NAFLD and is essential for the metabolism of glucose. Pyruvate dehydrogenase kinase (PDK), which phosphorylates and inactivates PDH, controls the activity of PDH. PDH activity is lowered, and glucose oxidation is hampered in NAFLD due to elevated PDK activity.

Research has indicated that hepatic fat buildup and insulin resistance are linked to decreased glucose oxidation in NAFLD. PDK inactivates PDH, the enzyme that limits the rate at which glucose is oxidized, resulting in less glucose oxidation and more glucose produced in the liver. This may increase the build-up of triacylglycerol in hepatocytes, which may help in the treatment of this disease.

In NAFLD, DK4 is an essential regulator of glucose metabolism. Because it controls the metabolism of glucose and lipids in the liver, PDK4 is elevated in NAFLD and contributes to the pathophysiology of the ailment. PDH is phosphorylated and rendered inactive by PDK4, which impairs glucose oxidation and increases glucose synthesis in the liver.

In conclusion, the PDK, which is elevated in NAFLD, controls the action of PDH. This causes the liver to produce more glucose and oxidize less glucose, which furthers the development of NAFLD. In NAFLD, PDK4 is an essential regulator of glucose metabolism and is vital to the pathophysiology of the condition.

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