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Review Article

Roles of PPARα and HNF4α in the Emergence Of Fatty Liver Disease Pathophysiology

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Abstract

Globally, Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent forms of persistent liver disease. It is regarded as a constituent of the metabolic disease, which additionally comprises diabetes, overweight, resistance to insulin, hypertension, and dyslipidemia. The most common reason for NAFLD is disturbed whole-body energy balance brought on by consuming more calories than burning them. The extra energy is subsequently deposited in an aberrant fat stores. Alterations to the hepatic metabolic system are the hallmark of this disease. The characteristic feature underlying NAFLD is liver lipid accumulation in deficient excessive alcohol intake. PPARα is ligand-induced synthesis molecules that regulate the transcription of several processes primarily expressed in hepatic tissue, where it is involved in the fatty acid oxidation, regulation of many pathways implicated in metabolism, and regulates the energy and lipid balance. HNF4α is a multi-gene master regulator, that are involved in gluconeogenesis, and lipid homeostasis. Liver HNF4α not only controls VLDL secretion but also has a crucial influence in controlling liver lipolysis.

Key words: metabolic disease, excess calories, overweight, mechanisms.

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The liver is a specialized organ that, in addition to degrading down several drugs and xenobiotics, supporting immune system, fatty acid and cholesterol regulation, shares in macronutrient processsing. It is the human body's biggest solid endocrine tissue. Because of its many endocrine and metabolic roles, the liver is essential for metabolism .[1]

It's anatomical framework is extremely uniform and is made up of a typical arrangement of lobules, which are the liver's functioning unit. Hepatocytes, the most common cells in the liver, are composed of the base of each lobule; they are arranged among sinusoids along the portal-central axis, and they vary in terms of their physiological and biological functions. Other specialized kinds of cell found in the liver include cholangiocytes, Kupffer cells, stellate cells, and endothelial cells. [2]

Cell organelles are added to the liver to help it carry out its metabolic tasks. It is among the organs with the greatest density and quantity of mitochondria, which communicate with lysosomes, lipid deposits (LDs), and the endoplasmic reticulum (ER). As food is broken down in the digestive tract, metabolic substrates such as glucose, fatty acids, and amino acids are produced. These are then taken up by the bloodstream and transported to the liver via the portal vein circulatory system. Following a meal, glucose is stored as glycogen inside the liver, where any excess is used for de novo lipogenesis (DNL). DNL converts acetyl-CoA or malonyl-CoA into new triacyl glycerol (TAG). [3]

Non-alcoholic fatty liver disease (NAFLD) is a prevalent cause of long-term liver disease across the globe. NAFLD is a category of the disease that progresses to cirrhosis as well as fibrosis. It has characteristics of hepatic steatosis, which occurs when no other causes for secondary fat accumulation in the liver (e.g., excessive alcoholic consumption) can be identified. NAFLD can range from non-alcoholic fatty liver, a less harmful condition, to the condition known as non- alcoholic steatohepatitis (NASH), which is at the most serious portion of the spectrum. [4]

Increased intrahepatic fat buildup in the lack of additional danger elements for liver illness, like alcohol misuse, steatogenic drugs, and chronic liver disease, is known as the most common chronic hepatic illness worldwide. It is named non-alcoholic fatty liver disease (NAFLD). [5]

NAFLD is characterized by fatty deposits in the liver without valuable alcohol consumption. NAFLD is a benign condition, but it may lead to liver inflammation which is defined through abnormal collection of triglycerides within liver cells and inflammation among the liver, with or without fibrosis. Progress to cirrhosis and hepatocellular cancer is more likely as a result of this condition. [6]

NAFLD is categorized as a component of metabolic abnormalities, which also includes insulin resistance, diabetes, obesity, hypertension, and dyslipidemia. The most common reason for NAFLD is disturbed whole-body energy balance brought on by consuming more calories than burning them. The extra energy is subsequently deposited in an aberrant fat stores in the skeleton, pancreas, and liver as fats from visceral adipose tissue without esterification. [7]

Non-alcoholic fatty liver disease Pathophysiology

The development and occurrence of non-alcoholic fatty liver disease (NAFLD) are linked to increased fat intake, genetic predisposition seen in metabolic disorder, and excessive lipid accumulation in the liver. The so-called Western diets' high fat content has been linked to resistance to insulin, dyslipidemia, and metabolic or cardiovascular disorders. Although the exact mechanisms of NAFLD pathogenesis are yet unknown, the double-hit hypothesis provides a general idea for how NAFLD progresses. Insulin resistance is the main insult that leads to steatosis because it causes decreased fatty acid (FA) transport and hepatic de novo lipogenesis (DNL). The second hit includes, among many other things, increased inflammatory responses, endoplasmic reticulum stress, disruption of autophagy, mitochondrial failure, and hepatocellular apoptosis [8] as shown in figure [1].

Possible mechanisms accused in NAFLD

To diagnose nonalcoholic fatty liver disease (NAFLD) histologically, hepatic steatosis must be present. Increases in fat supplies, such as those resulting from high-fat diets and excessive adipose tissue lipolysis, decreases in fat export in the form of very low density lipoprotein-triglycerides, decrease oxidation of liberated fatty acids , and increases in de novo lipogenesis (DNL) can all contribute to steatosis as shown in figure. [1]

Certain cytokines generated at sites of inflamemation, particularly from extra hepatic adipose tissues, can trigger the accumulation of fat in the liver, even if the molecular mechanisms behind this procedure are not fully known. [9]

- **Inflammation of Adipose Tissue**

Hypoxia and the degeneration of rapidly developing adipocytes are likely to be important causes, however the precise etiology of adipose tissue inflammation in obesity remains uncertain. Adipocytes experiencing inflammation release a variety of cytokines and chemokines, including interleukin-6 (IL-6), CC-chemokine ligand-2 (CCL2), and tumor necrosis factor-α (TNF-α). Through the signaling pathways of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC), circulating adiponectin controls hepatic fatty β-oxidation. When combined, these anomalies increase ectopic storage of fat and highlight adipocyte loss of fat. [10]

- **De Novo Lipogenesis (DNL)**

It is believed that the steatotic characteristic of NAFLD may enhance lipogenesis in the liver. It has been shown in earlier studies that diets high in simple sugar and saturated fat raise the risk of developing hepatic steatosis, at least partially, due to increased DNL. Another study that looked at individuals with metabolic syndrome and high liver fat content offers more proof that DNL plays a role in the onset of hepatic steatosis. De novo fatty acid synthesis happens three times faster in these individuals. Furthermore, distinct food components may have different effects. Because they are substrates, the quantity of carbohydrates in the diet will essentially have a positive effect on the amount of DNL in the liver. [11]

- **Insulin resistance in HFD-induced NAFLD**

To regulate the production of glucose, insulin stimulates lipogenesis and the formation of glycogen while inhibiting gluconeogenesis and glycogenolysis. It is essential for the metabolism of lipids because it binds to receptors and promotes the esterification of fatty acids, stores them in lipid droplets, and prevents lipolysis. Therefore, hepatic insulin signaling plays a crucial role in preserving the equilibrium of energy by regulating glucose and the metabolism of lipids. [12]

- **Increased stress of endoplasmic reticulum**

The crucial intracellular organelle known as the endoplasmic reticulum (ER) is in responsibility for calcium regulation, lipid production, and the secretory and generative folding of transmembrane proteins. As metabolic needs rise, the emergency room's workload also rises. By altering lipid disorders in the ER that result in lipid components of the organelle walls and inciting the so-called ER stress reaction, which activates several transcription factors, abnormally high levels of FFA disturb ER homeostasis. [12]

- **Oxidative Stress**

Oxidative stress can be caused by elevated levels of reactive oxygen/nitrogen species (ROS/RNS) and lipid peroxidation, which are produced during the breakdown of liberated fatty acids in microsomes, the peroxisomes and mitochondria, when hepatocytes are supplied with more fatty acid. [13]

- **Impaired autophagy is implicated in HFD-induced NAFLD**

Because autophagy helps maintain energy homeostasis and cytoplasmic quality control by removing misfolded proteins, destroyed organelles, and droplets of lipid it serves as a defense mechanism for maintaining cellular homeostasis. As a result, when autophagy is reduced, cells are more vulnerable to external stimuli that can cause death. [14]

- **Mitochondrial dysfunction contributes to HFD-induced NAFLD**

The urea cycle, fat metabolism and energy production, amino acids and iron metabolism, and signal transduction pathways involved in these activeties are all dependent on mitochondria, which are vital organelles. Liver disorders may arise as a result of changes in these mechanisms. NAFLD was linked to lower respiratory chain complex action, changed mitochondrial dynamics, ultrastructural mitochondrial abnormalities, and poor adenosine triphosphate synthesis capabilities. [15]

- **The impact of gut microbiota in HFD-induced NAFLD**

An "invisible organ" of the body, the gut microbiota is necessary for healthy immunological function and metabolism. Numerous microorganisms, including facultative anaerobes, aerobes, viruses, and stringent anaerobe bacteria, cohabit in this complex ecosystem. About 90% of all

bacteria are found in the two major bacterial phyla that make up the gut microbiota: Firmicutes and Bacteroidetes. Through their metabolites (ethanol, short-chain fatty acids, etc.), endotoxemia from increased permeability of the gut, hormonal alterations, and bile acid signaling, the altered composition of the gut microbiota may control the onset and course of non-alcoholic fatty liver disease. [16]

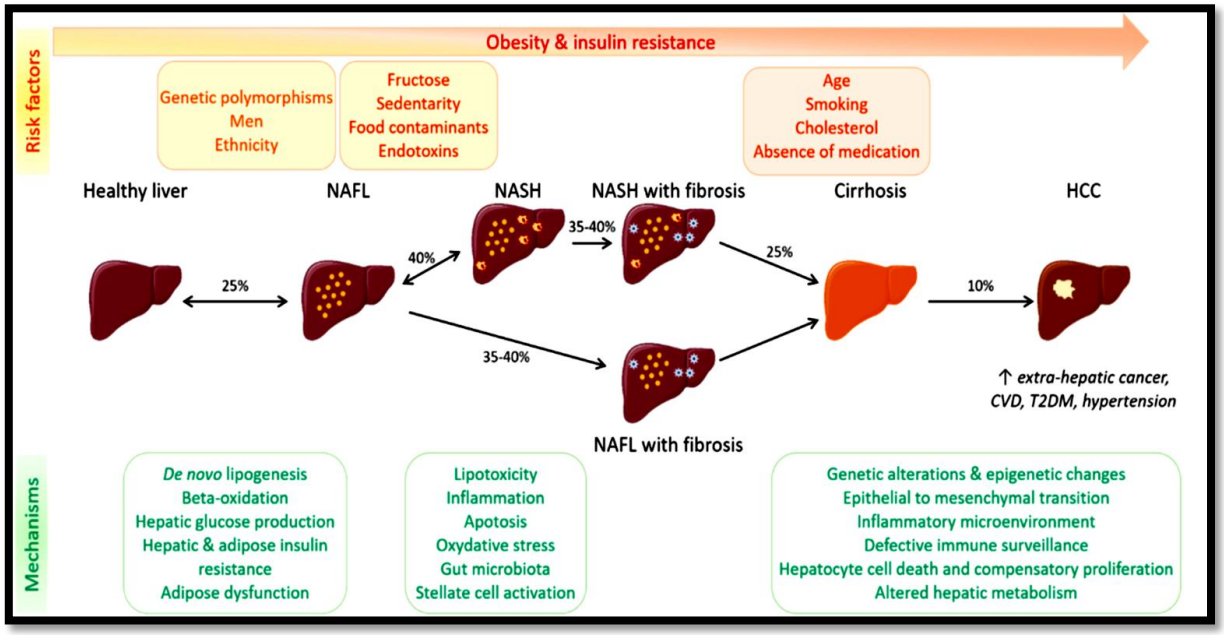

Figure 1: NAFLD progression and mechanisms [17].

Altered metabolic pathways in NAFLD

NAFLD begins with alterations to the hepatic metabolic system. At the transcriptional level, it is mostly controlled. PPARs are nuclear receptor family transcription factors that are ligand-activated. The primary modulator of hepatic fatty acid catabolism is PPARα. Through transcriptional up-regulation of fatty acid transport proteins, PPARα increases mitochondrial delivery of fatty acids generated from adipose tissue lipolysis during fasting conditions. Moreover, it possesses anti-inflammatory properties. [18]

In the liver, hepatocyte nuclear factor 4α (HNF4α) is significantly concentrated. The main function of HNF4α is regulation of several hepatic metabolic pathways and liver gene expression. When mature mice were subjected to a liver-specific deletion of HNF4α, there was a significant steatosis and disturbance of VLDL secretion. [19]

PPARs

The peroxisome proliferator-activated receptors (PPARs), which belong to the nuclear receptor superfamily, are ligand-induced synthesis molecules that regulate the transcription of several processes such as lipid metabolism, normal glucose levels, energy balance, inflammatory processes, and atherosclerosis [20].

The majority of PPARα is found in the liver. The liver's lipid and body energy balance are regulated by three fatty acid oxidative metabolic processes that are regulated by PPARα: oxidation in peroxisomes, mitochondria, and microsomes. Moreover, PPARα is crucial for lipoprotein production, the response to inflammation, with the emergence of liver cancer in rodents. [21]

PPARα is primarily expressed in hepatic tissue, where it is involved in metabolic processes, controls the in vivo lipid and energy balances, and regulates the synthesis of lipoproteins, inflammatory reactions and hyperinsulinemia. PPARβ may also prevent liver damage by improving the muscles of the body and visceral tissue's metabolism of fatty acid oxidation and energy uncoupling, as well as via taking part in the starvation-induced stress response of the liver, lowering the transmission of signals linked to inflammation, and storing energy in adipocytes. [22]

Ligands for PPAα

The ligand-activated nuclear transcription factor family includes PPARα. Its agonists can be divided into two groups: external ligands, which

are manmade compounds, and endogenous ligands, which are biomolecules. Various lipid-lowering medications, industrial phthalate monoester plasticizers, pesticides, herbicides, and other substances are examples of exogenous ligands, commonly referred to as peroxisome proliferators. [23]

Functions of PPARα in NAFLD development

• PPARα and energy metabolism

As regard to its capacity to coordinate the metabolism of fat and glucose, Maintaining the body's energy balances is mostly the responsibility of the liver. The three primary components of hepatic fat metabolism are lipid transport, fatty acid oxidation, and adipogenesis. Fatty acid synthesis and its subsequent transformation into triacylglycarnitines are the two steps that make up adipogenesis. In the liver, PPARγ, work to control adipogenesis. Among these, Sterol regulatory element binding protein (SREBP-1c) can influence hepatic lipogenesis through controlling the production of genes associated with glycolysis and lipid synthesis. [24]

In hepatic tissue , PPAR primarily controls energy consumption and the metabolism of fatty acid oxidation. The primary requisite for PPARα activation is energy deprivation. This causes the metabolism of intracellular energy to be upregulated, which in turn triggers the production of ATP by oxidative phosphorylation. PPARα deleted mice that are starving exhibit substantial low blood sugar, low body temperature, and elevated serum FFAs, suggesting the obstruction of absorption and burning of fatty acids [25].

- **PPARα and dyslipidemia**

NAFLD exhibits a low concentration of higher-density lipoprotein with elevated serum TGs. Numerous lipid metabolic activities involve PPARα. The first major mechanism is that PPARα enhances the acceptance of fatty acids or their change to acyl CoA by upregulating translocase for fatty acids and their transportation protein, which in turn boosts the production of acetyl CoA synthetase. Following the intake of FAs, PPARα controls the movement of fats to mitochondrial organelle by promoting the production of carnitine palmitoyl transferase (CPT1), a protein unique to the liver and muscles. Moreover, PPARα can control how lipids are metabolized in mitochondria by controlling the lipid transporters' expression and catalytic bases. [26]

Second, PPARα regulates a number of apolipoproteins. Activators of PPARα, like fibrates, increase the apolipoproteins mRNA expression, which in turn enters hepatocytes and results in increased HDL in the bloodstream. Third, PPARα can decrease the expression of the genes, concerned with decrease action of lipopolysaccharide (LPL) action, as well as encourage the expression of LPL genes. Lastly, by interfere with the breakdown of lipoprotein, PPARα modifies the transit of FA and lipids in circulation. The enzyme that controls the rate of production of oxidation is elevated by PPARα, which ultimately promotes FAs degradation. [27]

- **Role in insulin resistance (IR)**

NAFL linked to metabolic distress is a part of the IR-based metabolic syndrome and is inherited, environmental, and metabolic stress-related condition. IR may be a contributing factor to the buildup of fat in the liver. In some way, the insulin stabilizes blood glucose and encourages anabolism, both of which can prevent fat from breaking down and lower free fatty acid levels in the blood. After IR sets in, peripheral fat breakdown and blood FFA levels will rise. Fat deposits in hepatocytes and subsequently helps with the development of fatty liver when the liver's level of produced fat increases beyond the liver cell capacity to metabolize, use, and move lipoproteins around. Conversely, increased free fatty acid can result in resistance at the post-receptor or insulin receptor level. As an illustration, if the quantity of affinity . [28]

The pathophysiology of obesity and IR is intimately linked to the functional alterations of PPARα. In rats, PPARα activation prevents weight gain, whereas its inactivation causes a late-onset overweight. When rodents lacking PPARα are given food rich in calories, their body weight increases noticeably. The possibility that obesity and the PPARα gene are connected has been further established. According to recent research, PPARα has a significant role in controlling insulin sensitivity. When PPARα agents like fenofibrate are used, they can considerably reduce insulin resistance (IR), blood glucose levels, and decreased glucose tolerance in type 2 diabetic mice and obese rats, preventing the onset of diabetes.[29]

Hepatocyte nuclear factor 4 α (HNF4α) and NAFLD:

The liver exhibits significant expression of HNF4α, a nuclear hormone receptor, while the pancreas, gut, and kidney exhibit reduced expression. The main action of HNF4α is regulation several genes in hepatocytes that are involved in metabolism of medications, glucose production, conjugation of bile acids, and lipids balance, in addition to hepatocyte differentiation and morphogenesis . [30]

Pathophysiology:

NAFLD patients as well as diabetic or high-fat diet-fed animals have a significant decrease in hepatic HNF4α expression. Hnf4α-/- animals that are specific to hepatocytes exhibit elevated hepatic neutral lipid accumulation and reduced levels of triglyceride in bloodstream. Acute HNF4α ablation causes a significant drop in serum lipids while increasing liver lipids fourfold. Given the significant decrease in hepatic expression of microsomal transfer protein and apo B, it is likely that the abrupt changes in plasma and hepatic lipid levels are the consequence of a dramatic drop in very low density lipoprotein (VLDL) secretion. [31]

Hepatocyte HNF4α not only controls VLDL secretion but also has a crucial influence in controlling liver lipolysis and FAO. It has been demonstrated that hepatic carboxylesterases (CES1 and CES2) promote the breakdown of liver triglycerides, which reduces TG concentrations in the liver. HNF4α directly targets both CES1 and CES2. Hepatocyte HNF4α overexpression stimulates lipolysis and FAO, while the opposite consequences occur when HNF4α is deleted. Accordingly, these enzymes could have a role through HNF4α-mediated control of lipolysis, FAO, and hepatic TG levels [32] as shown in figure(2)

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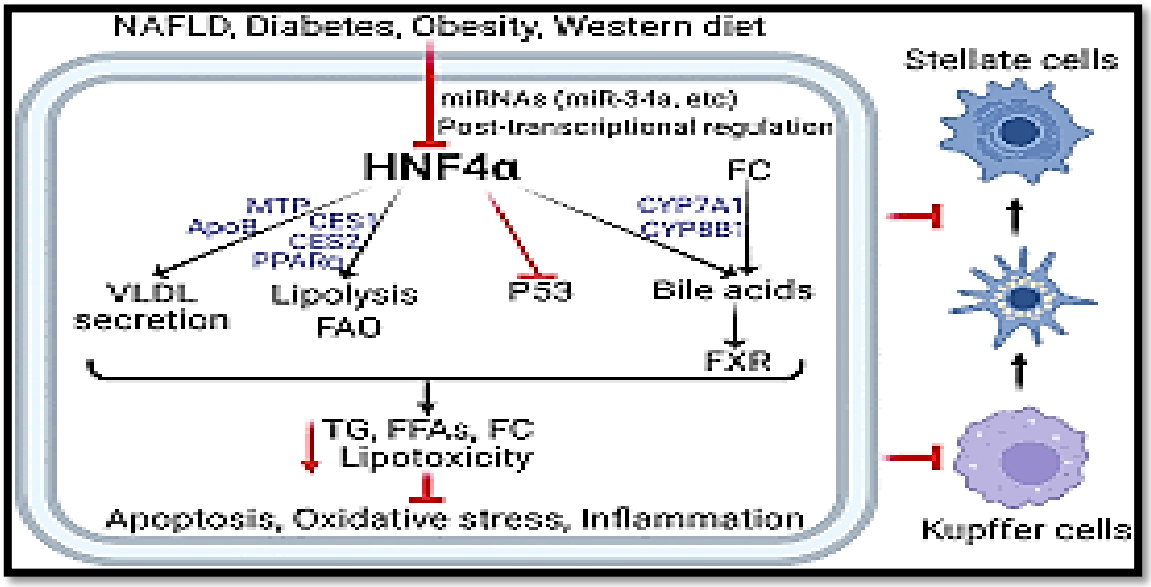

Figure.2 HNF4α influences the formation and advancement of fatty liver across various mechanisms [30] .

Conclusion

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent forms of persistent liver disease. Many risk factors are involved in NAFLD pathogenesis. Altered metabolic pathways are an emerging instant items. Ppar and its target genes promotes fatty acid oxidation and protects against fatty liver. HNF4α promotes lipid exportation from the liver and is involved in many metabolic processes acting against fat accumulation in the lver.

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