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REVIEW

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The role of FGF21 in the interplay between obesity and non-alcoholic fatty liver disease: a narrative review

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Abstract

Obesity poses a significant and escalating challenge in contemporary society, increasing the risk of developing various metabolic disorders such as dyslipidemia, cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and certain types of cancer. The current array of therapeutic interventions for obesity remains insufficient, prompting a pressing demand for novel and more effective treatments. In response, scientific attention has turned to the fibroblast growth factor 21 (FGF21) due to its remarkable and diverse impacts on lipid, carbohydrate, and energy metabolism. This comprehensive review aims to delve into the multifaceted aspects of FGF21, encompassing its discovery, synthesis, functional roles, and potential as a biomarker and therapeutic agent, with a specific focus on its implications for NAFLD.

Keywords: FGF21, obesity, NAFLD, fatty liver disease.

Introduction

The prevalence of obesity has risen sharply in recent years, driven by dietary changes and increasingly sedentary lifestyles [1]. While overeating and storing energy as fat was once essential for survival, it has become a significant disadvantage in today's society, where food is abundant. Our tendency to overeat and the body's ability to store energy has led to many health problems [2]. Obesity is a complex and multifactorial disease that lifestyle changes often fail to combat [1].

Non-alcoholic fatty liver disease (NAFLD) was initially identified in 1980, marking a significant milestone in our understanding of this condition. In recent decades, this has emerged as the most prevalent form of liver disease, coinciding with the increasing global prevalence of obesity [1]. The rising prevalence and severity of NAFLD have been attributed to the escalating rates of obesity [2]. NAFLD represents a spectrum of liver conditions, including simple steatosis (SS) and non-alcoholic steatohepatitis (NASH). If left unaddressed, these conditions can progress to more severe outcomes, such as liver cirrhosis and hepatocellular carcinoma (HCC) [2]. It is estimated that around 25% of the world's population may develop NAFLD [3]. The complex pathophysiology of NAFLD and its increased prevalence have led to research and development programs on possible treatments. Currently, there is no treatment available for NAFLD [4].

Aim

This review aims to explore NAFLD, commencing with examining obesity and adipose tissue, with a particular focus on fibroblast growth factor 21 (FGF21). The discussion will encompass the synthesis of FGF21, its mode of action, and the stimuli that elevate its secretion. Emphasis will be placed on its impact on various organs such as the central nervous system (CNS), liver, adipose tissue, kidney, muscle tissue, and pancreas. Due to its myriad pleiotropic effects, FGF21 has garnered escalating attention as a potential therapeutic target for metabolic disorders associated with obesity, notably NAFLD.

Adipose tissue from normal to pathological

Adipose tissue is a remarkably complex tissue with a role in energy homeostasis, serving as a storehouse of nutrients and a source of free fatty acids (FFAs) during periods of starvation; last but not least, it is a veritable endocrine organ that releases a series of adipokines [5]. Classically, adipose tissue is divided into white and brown adipose tissue. The brown adipose cell uses chemical energy to convert it into heat with the help of uncoupling protein 1 (UCP1). UCP1 is a protein that is specific to brown adipose tissue and is located at the inner mitochondrial (MT) membrane. Unlike adenosine triphosphate (ATP) synthase, which uses the proton gradient to form ATP, UCP1 uses it to create heat [5]. Beige fat cells have been found among white fat cells, which morphologically resemble brown fat cells but are derived from white fat cells [5].

A unique ability of adipose tissue is its ability to change its size depending on the body's caloric status, a

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characteristic not found in other non-neoplastic tissue [5]. This occurs either by increasing cell size (hypertrophy) or by increasing the number of cells (hyperplasia) [5]. Interestingly, once adipocytes appear, it is quite difficult to lose them, even after significant weight loss [5]. Both tumor and obese adipose tissues exhibit increased cell numbers, larger cell sizes, hypoxia, and the ability to enhance blood supply through angiogenesis. The comparison underscores intriguing similarities in the response to hypoxia, triggering adaptive mechanisms in both cancer and adipose tissues to cope with oxidative stress and improve vascularization for sustained growth [5]. In addition to the extracellular matrix accompanying adipose tissue, adipocytes are accompanied by various cells, such as endothelial cells, immune cells, fibroblasts, and stem cells. Adipocyte cells represent 20–40% of all cells, although they account for more than 90% of adipose tissue volume [6]. In individuals with normal weight, M2-type macrophages are predominant, contributing to tissue remodeling, wound healing, and secretion of anti-inflammatory cytokines. On the other hand, in obese individuals, M1-type macrophages are predominant, invading tissues and contributing to the progression of insulin resistance [7].

Adipose tissue in people with obesity is marked by inflammation with increased infiltration of macrophages as weight increases [8]. Adipocytes undergo a change in their secretions as they start producing small amounts of tumor necrosis factor-alpha (TNF-α), a substance that can trigger preadipocytes to generate monocyte chemoattractant protein-1 (MCP-1) [8]. In response to cytokines, endothelial cells also have the capacity to secrete MCP-1. Once macrophages are recruited and activated, they release more cytokines, and thus, a vicious circle of self-sustaining inflammation. Figure 1 schematizes the transition from healthy lean adipose tissue to obese adipose tissue.

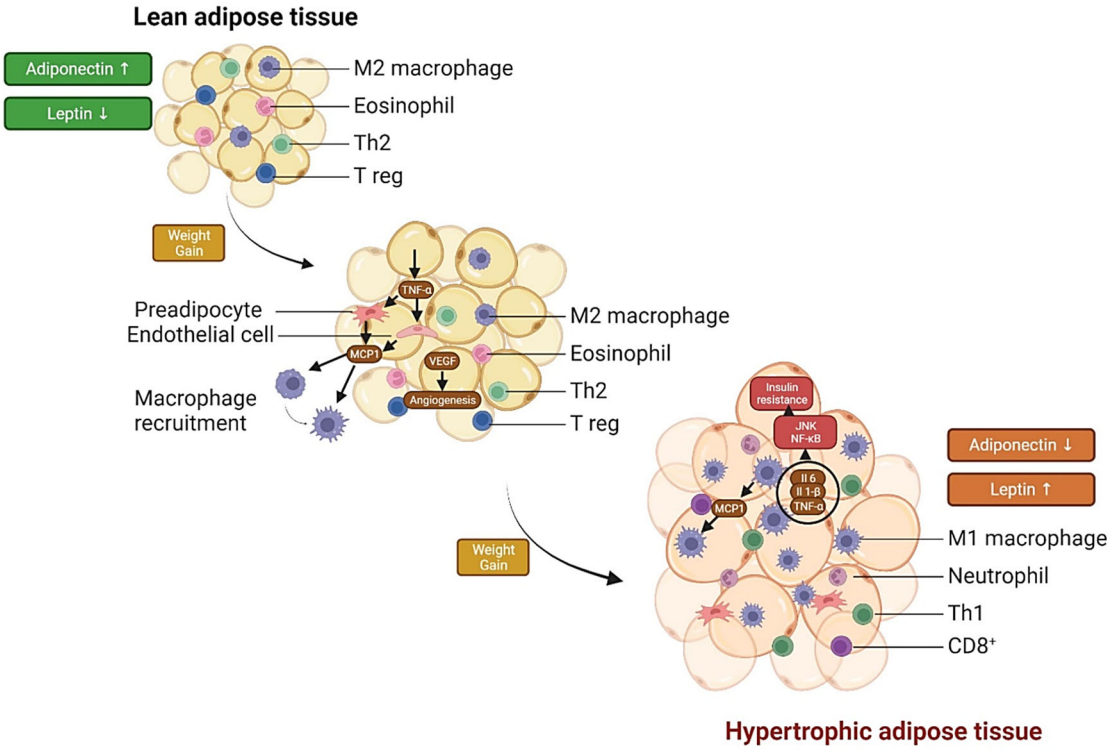

Figure 1 – ***Adipose tissue from normal to pathological. The metabolic changes that occur in obesity are the result of dysfunctional adipose tissue. In addition to adipocyte cells in adipose tissue, there are other cells: progenitor cells, endothelial cells, and immune cells. While in normal weight individuals, these cells are mainly represented by M2 macrophages, eosinophils, Th2 and CD4$^+$ T-lymphocytes, in obese individuals, these cells are replaced by M1 macrophages, neutrophils, Th1 lymphocytes, and CD8$^+$ T-lymphocytes. As a result of cellular hypertrophy and adipose cell hyperplasia in obesity, a state of hypoxia results in adipose tissue. Adipocytes begin to secrete inflammatory cytokines, one of which is TNF-α, which induces the release of MCP-1. MCP-1 attracts M1-type macrophages and causes the conversion of M2 macrophages to M1, which will, in turn, release more inflammatory cytokines. Thus, inflammation will self-perpetuate in obesity. CD4/8: Cluster of differentiation 4/8; IL-1β/-6: Interleukin-1beta/-6; JNK: c-Jun N-terminal kinase; MCP-1: Monocyte chemoattractant protein-1; NF-κB: Nuclear factor-kappa B; T reg: Regulatory T-cells; Th1/2: T-helper 1/2; TNF-α: Tumor necrosis factor-alpha; VEGF: Vascular endothelial growth factor.***

Obesity leads to NAFLD

Understanding the pathophysiology of NAFLD and its development involves considering the interplay of genetic and environmental factors [2]. These factors include genetic and epigenetic polymorphism [9], diet and lack of exercise [10], obesity and insulin resistance [11], abnormal adipokine secretion [12], lipotoxicity [13], endoplasmic reticulum (ER) stress and oxidative stress [14], gut flora dysbiosis [15, 16]. The interaction of these factors leads to the initial accumulation of lipids in hepatocytes, ultimately resulting in hepatic steatosis (HS). If HS is not managed promptly, it can lead to infiltration of immune cells in the liver, contributing to the inflammatory process seen in NASH [2]. If inflammation continues, NASH progresses to liver fibrosis [2].

Obesity seems to contribute to both the onset of SS and the progression to NASH [2]. Hepatocytes have been found to exhibit an adipocyte-like function. When the capacity to accumulate surplus energy is compromised, such as in cases of obesity or lipodystrophy, hepatocytes tend to accumulate triglycerides (TGs) [2]. Hepatocyte TG accumulation is due to excess FFAs, which either comes from diet (about 15%), adipose tissue lipolysis (60%), or *de novo* lipogenesis (about 25%), with carbohydrates being the preferred source [17]. Fatty acid esterification is linked to an increased release of TGs into the bloodstream as very-low-density lipoprotein (VLDL) [18]. Chronic storage of FFAs within the liver leads to an elevated rate of *β*-oxidation, which is a crucial process for energy production and overall metabolic health. Thus, the energy intake from the oxidation of FFAs exceeds the energy demand, generating reactive oxygen species (ROS) and thereby inducing oxidative stress [18]. This oxidative stress harms hepatocytes and triggers the transcription and secretion of FGF21, which seems to act on hepatocytes in a paracrine or autocrine fashion [19].

Recent studies have demonstrated that the extent of adipose tissue inflammation is directly linked to the severity of NAFLD [20]. Lipotoxicity and glucotoxicity present in patients with obesity have a significant impact on the development of SS and subsequent processes [2]. When the SS process is not controlled, liver inflammation occurs. This process is similar to that found in adipose tissue in obese people. The liver undergoes a gradual infiltration of various immune cells, such as neutrophils, monocytes, macrophages, T-lymphocytes, stellate cells, and dendritic cells, leading to their activation [2, 21]. Inflammatory cells, in turn, secrete a series of cytokines that promote inflammation. Fibrosis occurs due to an unsuccessful effort by the body to repair liver damage [2]. Stellate cells are the main cells responsible for fibrogenesis [2].

Obesity also contributes to liver pathology *via* adipokines (leptin, adiponectin, visfatin, and resistin) [22]. Adipokine secretion is different in normal weight *versus* obese patients. In obese individuals, the adipokine profile changes with increasing leptin concentration and decreasing adiponectin concentration, thus steatosis, inflammation, and liver fibrosis are stimulated. Also, inflammatory cells that infiltrate adipose tissue in obese people (macrophages, lymphocytes, neutrophils) generate a sequence of inflammatory cytokines [interleukin (IL)-1, IL-6, TNF-*α*], contributing to the advancement of liver damage [2]. Figure 2 shows the role of adipose tissue in the pathophysiology of NAFLD.

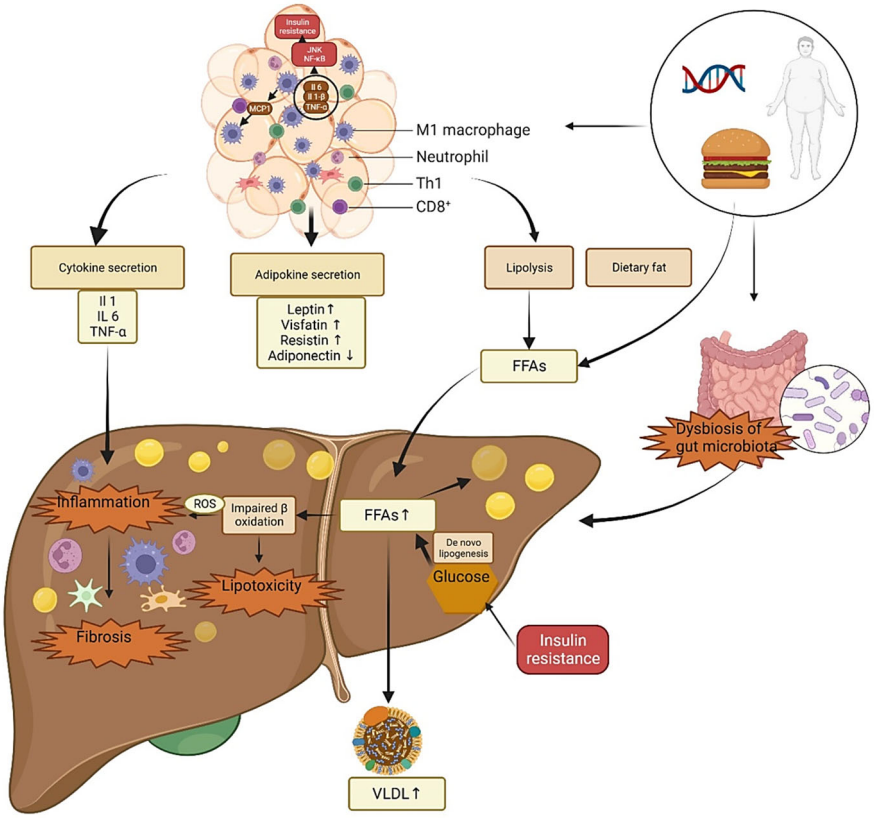

Figure 2 – ***From dysfunctional adipose tissue to NAFLD. Dysfunctional adipose tissue in obesity plays multiple roles in the pathophysiology of NAFLD through several mechanisms. First, dysfunctional adipose tissue in obesity is characterized by an increase in lipolysis. Thus, the amount of FFAs increases through lipolysis, but at the same time, as a result of increased dietary intake in obesity, FFAs may be exogenous in nature. Obesity is characterized by insulin resistance, with increased glucose levels that will stimulate de novo lipogenesis in the liver with additional hepatic FFAs. Excessive hepatic FFAs accumulation leads to impaired β-oxidation with the development of lipotoxicity. As a result of the increased amount of FFAs, altered β-oxidation, oxidative stress, and inflammation occur. Cytokines released by dysfunctional adipose tissue, as well as the adipokine profile of obesity, also contribute to inflammation. For example, it is well known that low levels of adiponectin play an inflammatory role and also promote fibrosis in the liver. CD8: Cluster of differentiation 8; FFA: Free fatty acid; IL-1β/-6: Interleukin-1beta/-6; JNK: c-Jun N-terminal kinase; MCP-1: Monocyte chemoattractant protein-1; NAFLD: Non-alcoholic fatty liver disease; NF-κB: Nuclear factor-kappa B; ROS: Reactive oxygen species; Th1: T-helper 1; TNF-α: Tumor necrosis factor-alpha; VLDL: Very-low-density lipoprotein.***

Introducing fibroblast growth factor 21

FGF21 belongs to the family of growth factors: fibroblast growth factors (FGFs). This family comprises a set of proteins consisting of 150–300 amino acids. They are structurally similar, with a common protein core of about 120 amino acids [23]. FGFs have multiple biological roles, including embryological development, tissue regeneration, and maintaining metabolic homeostasis.

Abnormalities in FGF signaling lead to neoplastic and metabolic pathologies [24]. The FGF superfamily comprises 22 members (FGF1–FGF23) grouped into seven subfamilies according to structure and function. FGF15 and FGF19 share the same gene in mice and humans [23].

FGF receptors and mechanism of action of FGF21

The fibroblast growth factor receptor (FGFR) is a membrane-bound protein with three extracellular immunoglobulin (Ig)-like domains and two intracellular tyrosine kinase-like domains [25]. The FGFR group comprises four members (FGFR1–FGFR4). Variants 'b' and 'c' arise from differences in domain III, influencing ligand specificity [24].

FGF21 depends on β-Klotho (KLB) as a cofactor to bind specifically to FGFR [26]. FGF21 acts on the following receptor types: FGFR1c, 2c, and 3c, but has a higher affinity for the FGFR1c isoform, which is mainly present in adipose tissue [18, 27]. Thus, adipose tissue plays a crucial role as one of the primary targets of FGF21. While receptors for FGF are ubiquitous in the organism, KLB is found in a more targeted distribution within the body. Thus, it is a limiting factor in the actions of FGF15/19 and FGF21 [28].

While adipose tissue, liver, and pancreas are traditionally recognized as the primary tissues expressing KLB [29], recent advancements in technology, such as ribonucleic acid (RNA) scope *in situ* hybridization, droplet digital polymerase cell reaction (PCR), and single-cell RNA sequencing, have revealed KLB expression in additional organs and cell types [28, 30]. This discovery underscores the role of FGF21 as a significant regulator of metabolism throughout the entire body.

The binding of FGF21 to the specific receptor along with the human leukocyte antigen (HLA)-B coreceptor leads to the activation of several signaling pathways, including the mitogen-activated protein kinase (MAPK)/p38 pathway, Akt pathway, nuclear factor-kappa B (NF-κB) pathway, and MAPK/extracellular signal-regulated kinase (ERK) pathway, triggering the activation of particular genes in the nucleus [25, 31].

FGF21 discover

FGF21 was first identified in 2000 by Nishimura *et al.* [32], and the gene responsible for it was located on chromosome 19. This gene contains four exons encoding a 209 amino acid protein (pre-FGF21) [32]. Following the deletion of the first 28 amino acids→FGF21 mature sequence, a 181 amino acid protein with a molecular weight of approximately 20 kDa [24]. FGF21 can undergo cleavage and inactivation by fibroblast activation protein (FAP). FAP, an endopeptidase, plays a role in cleaving FGF21 at proline 171/serine 172 in the C-terminal region, which in turn impacts the ability of FGF21 to bind to its co-receptor [33]. FGF21 has been found to pass through the blood–brain barrier [34], and the clearance pathway is thought to be renal [35]. The half-life of intravenously injected recombinant human FGF21 in mice ranges from 0.5 to 2 hours [36].

FGF21 synthesis

FGF21 is synthesized in many cells in response to physiological and pathological stimuli, but the liver is the main tissue that expresses and synthesizes FGF21. Other sources are skeletal muscle, white adipose tissue, pancreas, brown adipose tissue, and many others [18, 37, 38]. These tissues are also sites of action for FGF21. Thus, FGF21 regulates metabolism in many organs, playing a favorable role in obesity, diabetes mellitus, dyslipidemia, and NAFLD.

FGF21 triggers

FGF21 synthesis is controlled by both internal and external factors, with metabolic stimuli being the most significant. Changes in the body's nutritional status, such as those induced by high-carbohydrate diets [39, 40], fasting or starvation [41, 42], or low-protein diets [43, 44], can affect its concentration. FGF21 is considered a stress hormone that responds to changes in metabolic status.

In each tissue, the secretion of FGF21 responds to various stimuli, which activate different signaling pathways, and there does not appear to be a detectable negative feedback loop [45]. Various stressors, including external factors such as hypoxia, oxidative stress, glucose or amino acid deficiency, and internal factors such as MT or ER stress, can induce the release of FGF21 in multiple tissues. After secretion, FGF21 engages in protective autocrine/paracrine pathways that enhance cellular resistance to stress. These mechanisms include promoting autophagy, increasing MT respiratory capacity, and initiating anti-inflammatory processes [45]. Systemically, FGF21 promotes β-oxidation of fatty acids, increases tissue glucose uptake, and stimulates adiponectin secretion, improving the body's adaptation to stress [45]. Figure 3 reviews the main triggers for FGF21 secretion.

FGF21 effects overview

FGF21 is involved in many metabolic processes, including increased insulin sensitivity, carbohydrate metabolism, lipid metabolism, and energy homeostasis. Figure 4 gives an overview of the effects of FGF21 on the whole body. The first function of FGF21 was described in 2005; it increases cellular glucose uptake [46].

Circulating FGF21 acts mainly on white adipose tissue and increases insulin sensitivity, glucose uptake, and adiponectin secretion [46–48]. FGF21 stimulates the browning of white adipose tissue and boosts thermogenesis in brown adipose tissue [49–51]. FGF21 has diverse effects on the CNS, including the augmentation of sympathetic nervous system activation, reduction in sweet preference, elevation in corticotropin-releasing factor release, and modulation of circadian rhythm [50]. Protein restriction is a crucial stimulus for FGF21 synthesis. FGF21 signaling in the brain plays a pivotal role in mediating metabolic

adaptive responses and influencing nutrient preferences during protein restriction [48, 52, 53]. A high-carbohydrate diet induces increased liver FGF21 expression [54]. FGF21 has been demonstrated to inhibit sugar intake in the CNS of mice and monkeys [55]. Clinical studies indicate elevated FGF21 levels in response to sweet products, potentially explaining the observed resistance to FGF21 in individuals with metabolic syndrome [56].

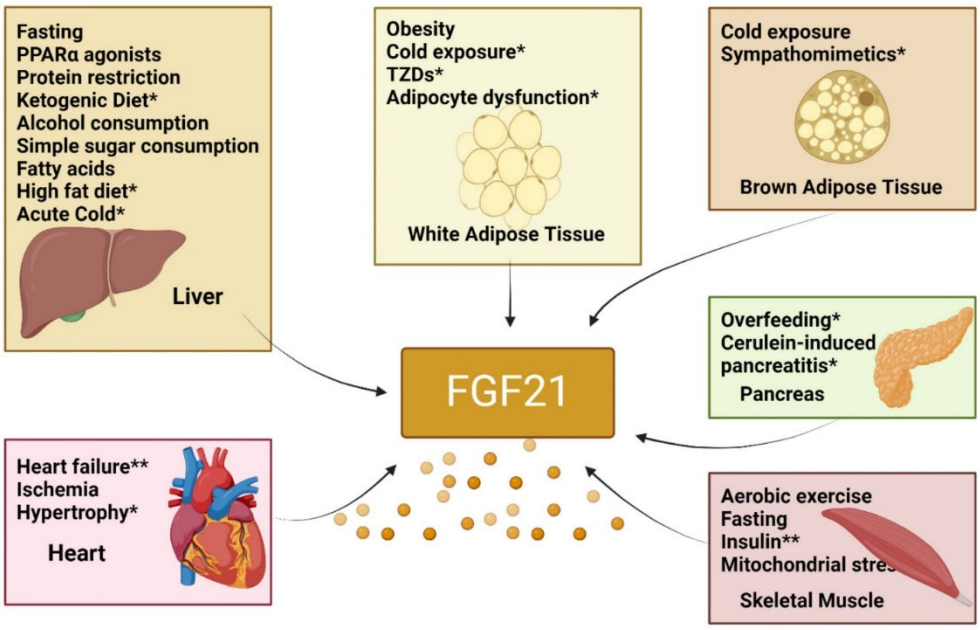

Figure 3 – ***Main triggers for FGF21 secretion. Modified after Spann et al. (2022) [38]. *: Studied in mice only; **: Studied in humans only; Without *: Studied in humans and mice. FGF21: Fibroblast growth factor 21; PPARα: Peroxisome proliferator-activated receptor alpha; TZDs: Thiazolidinedions.***

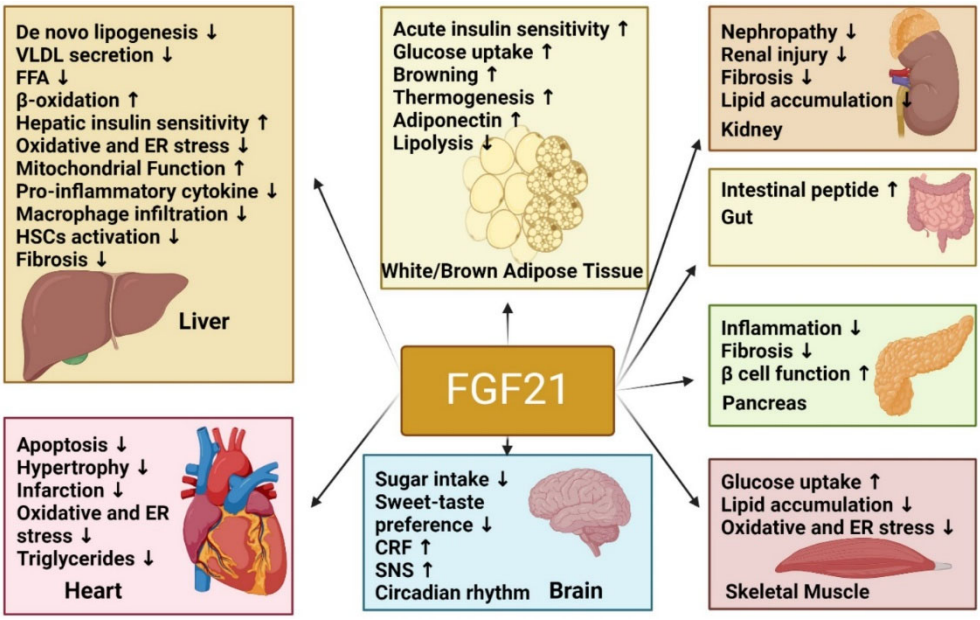

Figure 4 – ***Whole body effects of FGF21. Modified after Chen et al. (2022) [48]. CRF: Corticotropin-releasing factor; ER: Endoplasmic reticulum; FFA: Free fatty acid; FGF21: Fibroblast growth factor 21; HSCs: Hepatic stellate cells; SNS: Sympathetic nervous system; VLDL: Very-low-density lipoprotein.***

At the hepatic level, FGF21 enhances β fatty acid oxidation, reduces VLDL secretion, improves insulin sensitivity, and decreases *de novo* lipogenesis [50]. The liver is the main site of FGF21 production, contributing significantly to plasma levels [48]. Regulation of FGF21 in the liver involves the peroxisome proliferator-activated receptor alpha (PPARα) pathway activated by FFAs or protein deficiency and the exchange protein directly activated by cyclic adenosine monophosphate (EPAC)/protein kinase A (PKA) pathway activated by glucagon (GCG) receptor stimulation [57, 58]. During fasting, lipolysis triggers an increase in circulating FFAs, activating PPARα in the liver, leading to FGF21 synthesis. FGF21, in turn, promotes ketone body formation as an energy source in the absence of ingested carbohydrates [59, 60]. A common denominator among the effects of FGF21 is reduced lipotoxicity, decreased oxidative stress, decreased migration of inflammatory cells, and thus decreased inflammation and fibrosis [61, 62].

Initial studies showed that the KLB coreceptor is modestly expressed in the heart, and the effects of FGF21 on the heart are too small [29]. Recent studies unequivocally demonstrate that FGF21 plays an important role in cardiac remodeling, with the heart expressing FGFR1, KLB, and FGF21 [63]. FGF21 in mice protects against oxidative stress, cardiac hypertrophy, and myocardial infarction [64–66]. FGF21 reduces endothelial injury and apoptosis, thereby inhibiting the progression of atherosclerosis [65]. The levels of FGF21 in animal models started to increase significantly and rapidly within one hour of coronary artery occlusion and continued to rise after [67], so FGF21 can be used as a biomarker in myocardial infarction.

In general, the role of skeletal muscle tissue has been locomotion, but in 2000, the secretory function of this tissue was also recognized, IL-6 being the first myokine described [63]. FGF21 is also a myokine. Under basal conditions, FGF21 expression was undetectable or limited [63]. However, various physiological or pathological conditions, such as exercise and MT diseases, can induce FGF21 expression in muscles and its secretion into the bloodstream [63]. FGF21 directly enhances glucose uptake in skeletal muscle through a mechanism involving glucose transporter type 1/4 (GLUT1/4) and atypical protein kinase C-zeta (PKC-ζ) [68] and also improves insulin sensitivity by inhibiting phosphorylation of insulin receptor substrate 1 (IRS1), inhibiting mechanistic target of rapamycin complex 1 (mTORC1) [69]. FGF21 effectively lowered intramuscular TG levels in obese mice [70].

The pancreas is both a source and a target of FGF21 action. Acinar tissue expresses levels 20 times higher than pancreatic islets [71]. FGF21 in pancreatic tissue leads to phosphorylation of the ERK1/2 pathway [71]. Although FGF21 secretion is elevated in the pancreas, the functions of FGF21 in the pancreas are still unclear [48]. Studies indicate that FGF21 plays a regulatory role in lesions induced by pancreatitis. Thus, FGF21-deficient mice with induced pancreatitis showed more severe lesions than mice without FGF21 deficiency and induced pancreatitis [72]. Mice with increased FGF21 levels also showed an attenuated phenotype [72]. FGF21 has been demonstrated to enhance *β*-cell survival and provide protection against glucolipotoxicity and cytokine-induced apoptosis [73].

In diabetic nephropathy, FGF21 led to a significant decrease in urinary albumin excretion, alleviated mesangial expansion and inhibited fibrillar matrix synthesis and also reduced oxidative stress and enhanced lipid metabolism in the kidney [74].

Resistance to FGF21

Even though FGF21 has beneficial effects on carbohydrate, lipid, and energy metabolism, levels are paradoxically high in people with obesity [75–78], NAFLD [78–80], NASH [81], chronic kidney disease [82], coronary heart disease [83], diabetes mellitus [84], diabetic nephropathy [85], atherosclerosis [86, 87].

Higher levels of FGF21 present in people with obesity and those with obesity-related pathologies may result from FGF21 resistance, as seen in insulin and leptin [38]. This is supported by the decreased FGFR1c and KLB coreceptor in liver and white adipose tissue and the lack of efficacy of recombinant FGF21 administration in human and mouse studies [38]. In individuals with obesity, the generation of proinflammatory factors and microRNAs, along with other elements triggered by excess fat, is heightened [48]. For instance, TNF-*α* suppresses KLB expression by activating the c-Jun N-terminal kinase 1 (JNK1). Increased micro-ribonucleic acid-34a (miR-34a) in adipose tissue decreases KLB expression [48, 88]. The mechanisms that lead to the development of FGF21 resistance, as well as the effects of FGF21 resistance, are schematized in Figure 5.

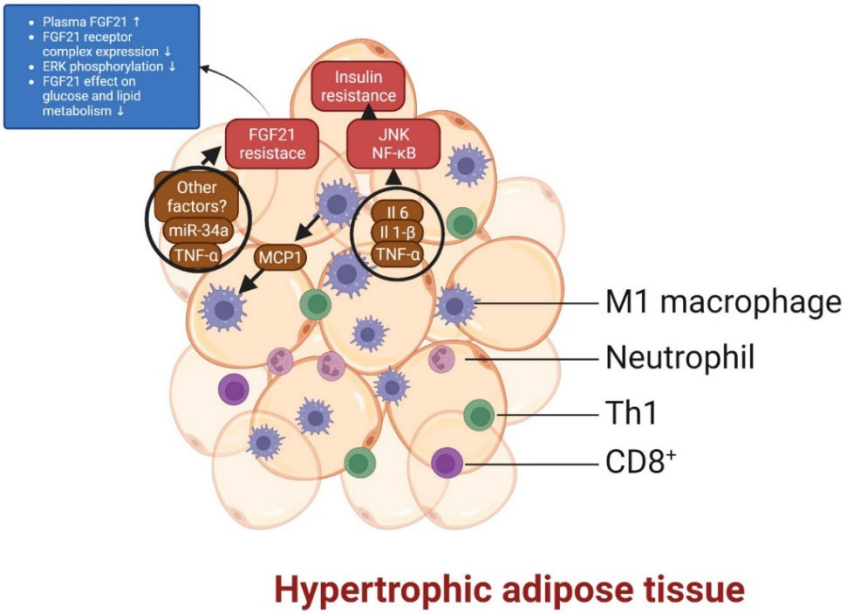

Figure 5 – ***Resistance to FGF21. In addition to insulin resistance in obesity, FGF21 resistance is also likely to occur. FGF21 resistance increases FGF21 levels, decreases FGFR–KLB complex expression, and decreases the effect of FGF21 on lipid and carbohydrate metabolism. CD8: Cluster of differentiation 8; ERK: Extracellular signal-regulated kinase; FGF21: Fibroblast growth factor 21; IL-1β/-6: Interleukin-1beta/-6; JNK: c-Jun N-terminal kinase; MCP-1: Monocyte chemoattractant protein-1; miR-34a: Micro-ribonucleic acid-34a; NF-κB: Nuclear factor-kappa B; Th1: T-helper 1; TNF-α: Tumor necrosis factor-alpha.***

However, this theory is not unanimously supported; another possible theory is that in obese people, dysfunctional adipocytes may secrete increased amounts of FGF21 [89]. The evidence strongly supports the idea that heightened FGF21 levels in individuals with alcoholic fatty liver are a direct result of metabolic stress [90].

FGF21 potential biomarker

FGF21 as a biomarker is not used in current practice; there are no accepted average values yet [91]. However, FGF21 may find its place in current clinical practice, at least in liver pathology.

Liver pathologies

Researchers have demonstrated that FGF21 can be used as a biomarker in liver pathologies:

Liver transplant

One study showed that FGF21 increases up to 25-fold after two hours in liver transplant patients, while transaminase levels peak at 24 hours. Thus, FGF21 may serve as a specific and sensitive biomarker for detecting ischemia–reperfusion damage in liver transplant subjects [92].

Acetaminophen poisoning

In Acetaminophen-induced acute liver failure, both liver and circulating FGF21 expressions were significantly increased within three hours, just before the rise in serum transaminases [93]. The lack of FGF21 in mice led to much more severe lesions, indicating the therapeutic potential of this molecule [93]. FGF21 decreased hepatotoxicity by acting on PPARα [93].

NAFLD

Previous studies have shown that the level of FGF21 is increased in the plasma of mice with NAFLD and increases directly proportional to the amount of intrahepatic fat [94]. A meta-analysis published in 2017 showed that FGF21 can easily distinguish NASH from HS [95].

Hepatitis

FGF21 levels have been found to positively correlate with the severity of chronic hepatitis C in affected patients [96]. In patients with acute hepatitis caused by the hepatitis B virus, FGF21 levels were elevated and returned to normal after treatment [97]. In patients who developed HCC, the FGF21 niche showed a dramatic increase and may be a marker for liver carcinogenesis [97].

Cachexia

Cachexia is a pathology characterized by a 5% decrease in body weight in the last three months and concurrent anorexia [98]. In a study by Franz *et al.*, values of FGF21 were increased [98]. These increased values are either the result of an adaptive response to nutrient deprivation or FGF21 contributes to the catabolic disease state [98].

Mitochondrial diseases

FGF21 level is increased in patients with MT diseases [99]. FGF21 has low sensitivity and high specificity [100] for MT diseases.

Metabolic syndrome

Metabolic syndrome is a combination of medical disorders that includes elevated blood pressure, impaired fasting glucose, abdominal obesity, dyslipidemia, and insulin resistance [101]. FGF21 may be a predictor for metabolic syndrome [101, 102].

Colorectal cancer

Serum FGF21 levels are linked to a higher risk of colorectal cancer, suggesting its potential as a biomarker for colorectal neoplasms [103].

Sepsis

Currently, there is no potential biomarker for the prognosis of patients with sepsis [104]. FGF21 may be such a biomarker, as shown by Li *et al.* in a study of 120 patients with sepsis [104]. Increased FGF21 levels correlated with higher mortality among patients with sepsis [104]. In sepsis's early stages, inflammatory and anti-inflammatory cytokines are elevated. FGF21 has an anti-inflammatory role in sepsis [31].

Kidney disease

A positive correlation was observed between renal dysfunction, albuminuria, and FGF21 [105], but a longitudinal analysis showed that FGF21 levels did not predict a decline in glomerular filtration rate [105].

Cardiac pathology

In patients with myocardial infarction, the expression of FGF21 greatly enhanced within the first 24 hours after the event and remained elevated for one week [106]. FGF21 levels correlate with systolic dysfunction [107]. Patients with elevated FGF21 levels have a higher risk of mortality than patients with low levels [107].

Heart failure is a significant health problem with an increasing prevalence due to the aging population. Despite improvements in heart failure therapy, mortality remains high. The emergence of cardiac biomarkers that improve heart failure prediction, diagnosis, and prognosis has received much attention in the last decade. Recent studies show FGF21 may be a promising biomarker in heart failure [108].

FGF21: a potential pharmacological molecule? Exploring the therapeutic prospects and challenges

There are important differences between the physiological roles of FGF21 and the pharmacological effects of exogenous FGF21 [109].

Due to overeating and modern sedentary lifestyles, the global prevalence of metabolic diseases such as type 2 diabetes mellitus, obesity, and NAFLD is increasing [110]. There are currently no approved molecules for the treatment of NASH, with approximately 216 molecules under study [3]. Depending on the mechanism of action, these therapies can be broadly divided into five categories: (*1*) therapies targeting metabolism, (*2*) therapies targeting oxidative stress, (*3*) therapies targeting inflammation, (*4*) therapies targeting apoptosis, (*5*) therapies targeting fibrosis [111].

Most of these molecules aim to focus on metabolic

pathways, with some also addressing fibrosis and inflammation [3]. Major targets include metabolic enzymes acting on lipid metabolism: fatty acid synthase (FASN), acetyl-coenzyme A (CoA) carboxylase (ACC), with a role in HS, farnesoid X receptor (FXR), which affects bile acid signaling, PPARs, thyroid hormone receptor beta (THRb), GCG-like peptide-1 (GLP-1) receptors, GCG receptor, gastric inhibitory polypeptide (GIP) receptor, FGF19 and FGF21 receptors which have pleiotropic effects on steatosis, inflammation and liver fibrosis, amine oxidase copper containing 3 (AOC3) and chemokines [C–C motif ligand 2 and 5 (CCL2/5)], which influence inflammation, caspases which are key players in apoptosis and lysyl oxidase-like 2 (LOXL2), which acts on fibrosis [111]. Even with the many potential drugs and diverse substances, no clear frontrunner has emerged.

Following an analysis by Chen [3], which analyzed 33 clinical trials that also presented histological data, he made a top ranking of these molecules, considering the degree of hepatocyte ballooning, steatosis, fibrosis, inflammation, cirrhosis, duration of treatment as well as the safety of treatment. In first place are FGF21 analogs. Then followed FGF19 analogs, Obeticholic Acid, Pioglitazone, Semaglutide, Resmetirom. These substances are in stage II clinical trials, and Resmetirom even in stage III clinical trials [3].

Based on preclinical studies in mice showing a number of beneficial effects of FGF21 on metabolism, FGF21 appears to be the ideal treatment for metabolic pathology in humans. However, the results observed in mice could not be fully translated into humans. Studies show that treating obese mice with pharmacological doses of FGF21 lowers their blood sugar and insulin values during glucose tolerance testing [42, 46].

FGF21 has created new hope for treatment in patients with metabolic diseases

From a positive perspective, FGF21 has demonstrated favorable effects on lipid metabolism, including reducing TG levels, total cholesterol, and low-density lipoprotein-cholesterol (LDL-C), along with enhancing high-density lipoprotein-cholesterol (HDL-C) levels in clinical studies [112]. However, from the perspective that FGF21 analogs have failed to translate the observed benefits from preclinical studies into practice [113], some aspects raise questions about its actual effectiveness in treating certain conditions.

The most beneficial impacts of FGF21 treatment were seen in patients with non-alcoholic fatty liver. At the hepatic level, FGF21 inhibits *de novo* lipogenesis and stimulates β-oxidation, thus decreasing lipid accumulation [112]. FGF21 also reduces inflammation in the liver by reducing the level of inflammatory cytokines (IL-1β), limiting the NF-κB pathway, and decreasing intrahepatic oxidative stress [112]. Some data show that FGF21 decreases liver fibrosis by decreasing hepatic expression of alpha-smooth muscle actin (α-SMA), transforming growth factor-beta (TGF-β), and collagen I [112]. These mechanisms by which FGF21 acts at the hepatic level are illustrated in Figure 6.

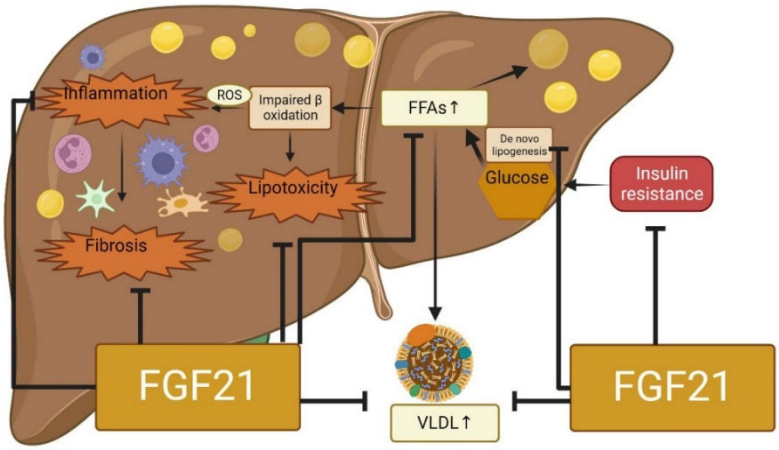

Figure 6 – ***FGF21 as a potential treatment in NAFLD. Stimulates β-oxidation and inhibits de novo lipogenesis, thereby reducing the accumulation of newly formed lipids in the liver. Additionally, FGF21 reduces inflammation and fibrosis in the liver, decreases insulin resistance, and lowers plasma VLDL levels. FFA: Free fatty acid; FGF21: Fibroblast growth factor 21; NAFLD: Non-alcoholic fatty liver disease; ROS: Reactive oxygen species; VLDL: Very-low-density lipoprotein.***

Endogenous FGF21 has a short lifespan, so FGF21 analogs used in clinical trials have been designed to have a longer duration of action [114]. In addition to the short half-life (0.5–2 hours), other obstacles were the poor bioavailability and instability of the molecule [115]. This led to the creation of analogs of FGF21 by polyethylene glycosylation (PEGylation) or by fusion with antibodies [116].

LY2405319

LY2405319 (LY) is the first FGF21 analogue to enter clinical trials in humans [117]. LY showed favorable effects in terms of lipid profile, with weight loss and increased adiponectin levels but no significant decrease in blood glucose [118]. Clinical development of this molecule has been discontinued due to its lack of effect on carbohydrate metabolism. This study paves the way for the development of a new class of drugs that seeks to find a solution [117].

PF-05231023

The second clinical trial involving FGF21 analogs uses PF-05231023 (CVX-343) [119]. PF-05231023 is an antibody

fused with an FGF21 analog. It has been demonstrated to lower body weight, enhance lipid profile, and increase adiponectin levels [119]. The use of PF-05231023 has been associated with increased heart rate and elevated blood pressure, which likely contributed to the decision to discontinue the drug [117].

MK-3655

MK-3655 (NGM313) is a monoclonal agonist antibody that specifically activates the β-Klotho/FGFR1c. A single dose of NGM313 improved insulin sensitivity and reduced liver fat content in obese subjects, leading to improved LDL-C, HDL-C, and TG levels [120].

LLF580

LLF580, later known as BOS-580, is another long-acting FGF21 [121]. LLF580 in patients with obesity decreased TG levels, led to improvement in liver markers of fibrosis, and enhanced adiponectin levels [121]. As with other FGF21 analogs, adverse effects consisted of gastrointestinal (GI) disturbances. Similarly to other FGF21 analogs, GI effects were significantly higher in the treatment group than in the placebo group [121].

Pegbelfermin

Pegbelfermin (BMS-986036) is a modified recombinant human FGF21 analog with an extended half-life, allowing up to one weekly dose [114]. Pegbelfermin was generally well tolerated by patients with obesity and type 2 diabetes and an increased prevalence of fatty liver. Adverse effects mainly occur in the GI area [114]. Treatment with Pegbelfermin for 12 weeks did not result in significant changes in hemoglobin A1C (HbA1C) or body weight. However, it did lead to improvements in metabolic parameters (HDL-C and TGs), fibrosis markers (PRO-C3), and increased adiponectin levels [114].

Efruxifermin

Another FGF21 analog is Efruxifermin, which was investigated in patients with NAFLD [113]. Efruxifermin is a fusion protein between IgG1 Fc and human FGF21, acting on FGFR1c, FGFR2c, and FGFR3c [113]. Efruxifermin has a half-life of 3–3.5 days [113]. All doses of FGF21 showed an improvement in liver parameters compared with placebo and also favorable effects on liver fibrosis [113]. Reported adverse effects of Efruxifermin were mild and included diarrhea, nausea, vomiting, abdominal pain, and fatigue [113].

In addition, multi-targeted fusion peptides appear, *e.g.*, GLP-1–FGF21, GLP-1–GCG–FGF21, and GLP-1–GIP–FGF21 [3]. The GLP-1–GIP combination reduces the GI effects caused by GLP-1; therefore, the GLP1–GIP–FGF21 combination may significantly impact both carbohydrate and lipid metabolism while minimizing GI discomfort. As we approach the end of the tunnel, it's important to stay cautiously optimistic while we await the results of the phase III trials for FGF21 [3].

These clinical trials of FGF21 analogs shown in Table 1 have demonstrated their potential use as therapeutic agents for metabolic and liver disorders. In addition, safety concerns, *e.g.*, cardiovascular side effects and possible loss of bone mass, generate questions about long-term treatment. Also, anti-drug antibodies may antagonize the biological impact of endogenous FGF21 [115]. Another challenge to FGF21 analogs is the endogenous FGF21 resistance in people with obesity and other related metabolic diseases. Therefore, more extensive and longer-term studies should be conducted to evaluate their safety and efficacy.

Table 1 – *FGF21 in clinical trials*

Drug	Reference	Results	Additional information
LY2405319	Gaich *et al.* (2013) [118]	Significantly improves lipid profile, favorable effects on insulin levels, adiponectin levels, and body weight.	LY2405319 is the first FGF21 analog to enter clinical trials in humans. Clinical development was discontinued due to its lack of effect on carbohydrate metabolism.
PF-05231023	Talukdar *et al.* (2016) [119]	Weight loss, lower TGs, total cholesterol, LDL-C, increased HDL-C, no effect on blood glucose, increased adiponectin.	PF-05231023 is an antibody fused with an FGF21 analog. Discontinued due to increased heart rate and elevated blood pressure.
MK-3655 (NGM313)	Depaoli *et al.* (2019) [120]	Decreased HbA1C, LFC, TG, LDL-C, increased HDL-C.	MK-3655 (NGM313) is a monoclonal agonist antibody that specifically activates the β-Klotho/FGFR1c.
LLF58 (BOS-580)	Rader *et al.* (2022) [121]	Reduction of LFC, improvement of liver function tests, no effect on body weight.	LLF580/BOS-580 is another long-acting FGF21 analog. The treatment group had significantly higher gastrointestinal effects than the placebo group.
Pegbelfermin (BMS-986036)	Charles *et al.* (2019) [114]	Reduction of LFC, improvement of liver function tests, decrease of fibrosis marker, adiponectin increase, no effect on body weight.	Pegbelfermin (BMS-986036) showed no significant changes in HbA1C or body weight but improved metabolic parameters and fibrosis markers.
Efruxifermin	Harisson *et al.* (2021) [113]	Reduction of LFC, improvement of liver function tests, no effect on body weight.	Efruxifermin is a fusion protein between IgG1 Fc and human FGF21, acting on FGFR1c, FGFR2c, and FGFR3c. All doses showed an improvement in liver parameters and favorable effects on liver fibrosis.

FGF1/21: Fibroblast growth factor 1/21; FGFR1c/2c/3c: Fibroblast growth factor receptor 1c/2c/3c; HbA1C: Hemoglobin A1C (glycated hemoglobin); HDL-C: High-density lipoprotein-cholesterol; IgG1: Immunoglobulin G1; LDL-C: Low-density lipoprotein cholesterol; LFC: Liver fat content; TGs: Triglycerides.

Conclusions

FGF21 emerges as a pivotal player in intricate metabolic regulation, demonstrating its therapeutic potential against various metabolic diseases. Its protective effects on organs such as the liver, pancreas, cardiovascular system, and kidneys underscore its significance in mitigating the inflammatory damage induced by obesity. Despite its diverse functions and sites of synthesis, FGF21 remains a subject of ongoing debate, reflecting the complexity of its actions. Preclinical models indicate its role in weight loss through enhanced energy expenditure and the induction of browning

in white adipose tissue, shedding light on potential avenues for combating obesity. However, challenges persist in translating these promising outcomes to human subjects. The prospect of FGF21 based therapies, including analogs, holds promise for NAFLD although further research is required to unlock their translational potential.

Conflict of interests

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Authors' contribution

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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