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# Physiological and pathophysiological role of endocrine fibroblast growth factors

Review

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**Abstract**

The endocrine subfamily of *fibroblast growth factors* (*FGF*) includes three factors: FGF19, FGF21, FGF23. They act on distal tissues through FGF receptors (FGFRs). The FGFR activation requires two cofactors: *α*- and *β*-Klotho, which are structurally related single-pass transmembrane proteins. The endocrine FGFs regulate various metabolic processes involved in the regulation of glucose and lipid metabolism as well as bile acid circulation, vitamin D modulation, and phosphate homeostasis. The FGF-FGFR dysregulation is widely implicated in the pathogenesis of various disorders. Significant alterations in plasma FGF concentration are associated with the most prevalent chronic diseases, including dyslipidemia, type 2 diabetes, cardiovascular diseases, obesity, non-alcoholic fatty liver disease, diseases of the biliary tract, chronic kidney disease, inflammatory bowel disease, osteomalacia, various malignancies, and depression. Therefore, the endocrine FGFs may serve as disease predictors or biomarkers, as well as potential therapeutic targets. Currently, numerous analogues and inhibitors of endocrine FGFs are under development for treatment of various disorders, and recently, a human monoclonal antibody against FGF23 has been approved for treatment of X-linked hypophosphatemia. The aim of this review is to summarize the current data on physiological and pathophysiological actions of the endocrine FGF subfamily and recent research concerning the therapeutic potential of the endocrine FGF pathways.

**Keywords**

fibroblast growth factors • endocrine • metabolic disorders • obesity • mineral balance

## 1. Introduction

The fibroblast growth factors (FGF) family is composed of 22 structurally related peptides, which have a wide spectrum of cellular functions, including cell growth, embryonic development, organogenesis, angiogenesis, regeneration, repair, and metabolism. They are expressed in nearly all tissues. Given the important role of FGFs in maintaining homeostasis, the dysfunction of FGF signaling is involved in the pathogenesis of numerous diseases [1]. These factors have been grouped into seven subfamilies according to their gene locus, mode of action, and phylogenetics. FGFs may be also classified into three groups based on their mechanism of action: canonical, intracellular, and endocrine FGFs [2]. The paracrine FGFs constitute the majority. They bind with high affinity to one of four FGF receptors (FGFR1-4) with tyrosine kinase activity. The FGFs require heparin or heparin sulfate as a cofactor in the interaction with FGFR. Heparin or heparin sulfate protect FGF from degradation and create its local reservoir. The FGFs/FGFR interaction results in dimerization and activation of the FGFR, initiating cytoplasmic signaling cascades [3]. Unlike canonical FGFs, intracellular FGFs including FGF11, FGF12, FGF13, FGF14 are not secreted and do not interact with FGFR. They interact with the voltage-gated sodium channels and other molecules, enabling the proper neuron development and influencing the ion-gating properties of the channel in mature neurons and other excitable cells such as cardiomyocytes [4].

Endocrine FGFs are members of the FGF15/19 subfamily composed of three factors: FGF19, FGF21, and FGF23 [4]. They are distinguished by a low affinity to heparin or heparin sulfate, which promotes their release from the tissue of origin into the blood circulation. They act on distal tissues through FGFR, but instead of heparin or heparin sulfate as cofactors for receptor binding and activation, endocrine FGFs require glycoproteins named α- and β-Klotho. The expression of α- or β-Klotho in their respective target tissues confers organ specificity for the FGF15/19 subfamily [5]. Klotho proteins are structurally related

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single-pass transmembrane proteins. $\beta$-Klotho is needed as a cofactor for FGF19 and FGF21, while FGF23 requires $\alpha$-Klotho for FGFR activation [4]. Members of the subfamily FGF15/19 participate in numerous endocrine pathways involving many organs. The endocrine FGFs regulate various metabolic processes that concern bile acids, lipids, and carbohydrate metabolism. They modulate calcium-phosphate balance, and participate in the maintenance of a stable bodyweight by controlling response to fasting. The FGF-FGFR dysregulation is widely implicated in the pathogenesis of various diseases. Alterations in FGF concentrations are associated with the most prevalent chronic diseases, such as obesity, type 2 diabetes, cardiovascular diseases, and malignancies. Therefore, the endocrine FGFs may serve as predictors and biomarkers for numerous disorders [5].

The aim of this review is to summarize the data on the physiological role of FGF19, FGF21, and FGF23 and discuss possible pathophysiological links between circulating concentrations of these factors and chronic diseases, as well as the results of current research investigating the therapeutic potential of the endocrine FGF pathways.

## 2. FGF19

### 2.1 Identification

FGF19 was identified for the first time in 1999 by Nishimura et al. [6] in the human fetal brain. This indicates that FGF19 participates in brain development during embryogenesis. The FGF15 present in rodents is an orthologue of the human FGF19. Both factors have comparable structure, tissue distribution, and mode of actions [7].

### 2.2 Expression

FGF19 is mainly produced in enterocytes of the terminal ileum in response to the farnesoid X receptor (FXR) activation. Bile acids (BAs) bind to FRX in enterocytes and induce expression and secretion of FGF19 [5]. However, BAs are not the only factor associated with FGF19 synthesis. Vergnes et al. [8] demonstrated that Diet1 expression levels in the small intestine regulate the production of FGF19. Diet1 is a protein produced only in epithelial cells lining the small intestinal villi and kidney proximal tubules [9]. Moreover, expression of FGF19 is also regulated by

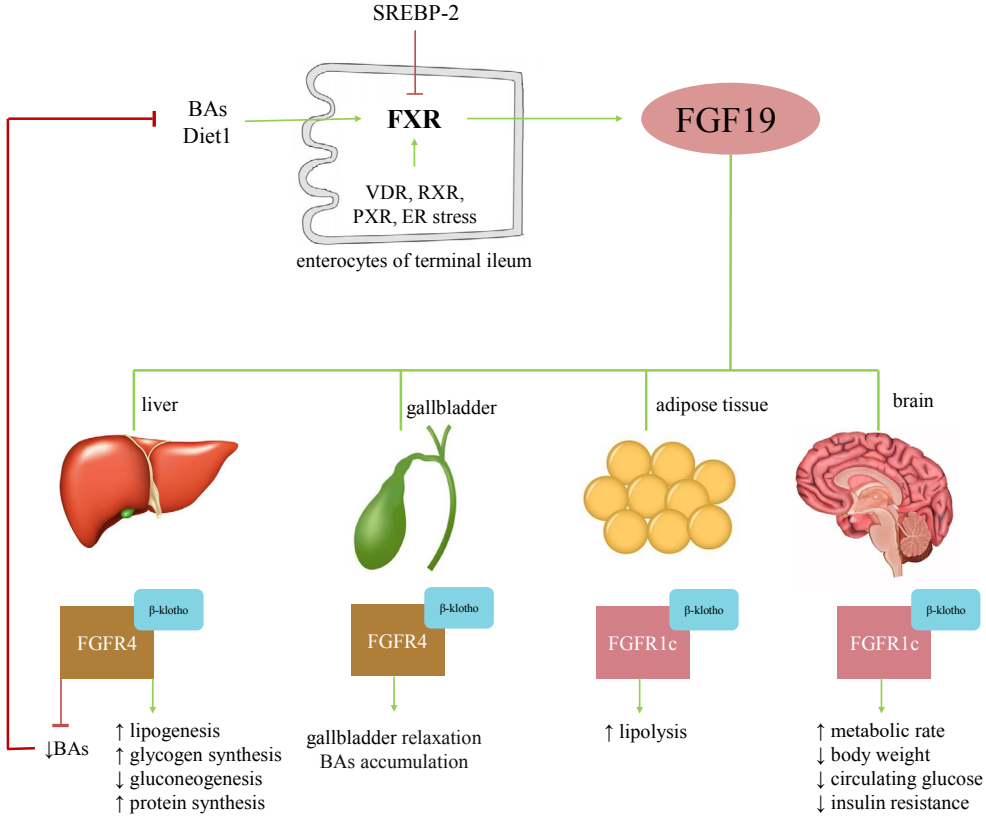


*Fig. 1. Regulation of Fibroblast Growth Factor 19 (FGF19) expression and the main functions of FGF19; FGF19 is produced in the enterocytes of the terminal ileum in response to the farnesoid X receptor (FXR) activation. Bile acids (BAs), Diet1, the vitamin D receptor (VDR), retinoid X receptor (RXR), pregnane X receptor (PXR), and endoplasmic reticulum (ER) stress induce expression of FGF19. Sterol regulatory element-binding protein 2 (SREBP-2) inhibits transcription of FGF19. FGF19 interacts with various organs including the liver, gallbladder, adipose tissue and the brain through fibroblast growth factor receptors (FGFR) and β-Klotho protein. The effects of action in particular organs are presented in the figure. Based on [5, 10]*

the vitamin D receptor, retinoid X receptor, and the pregnane X receptor, as well as endoplasmic reticulum stress molecules [5, 10]. Furthermore, in intestinal cancer cells sterol regulatory element-binding protein 2 (SREBP-2) has been indicated as a transcriptional regulator of FGF19. It inhibits FXR binding to the FXR responsive element in the FGF19 promoter [11]. The regulation of FGF19 expression and its main functions are presented in Figure 1.

### 2.3 Physiological role

FGF19 is secreted into the enterohepatic circulation, subsequently reaches the liver, and then circulating plasma. FGF19 interacts with various organs such as the liver, gallbladder, adipose tissue, and the brain. FGF19 can activate FGFR1c, FGFR2c, FGFR3c, and FGFR4, in the presence of β-Klotho [4]. FGF19 interacts mainly with the surface hepatic FGFR4 and stimulates various metabolic signaling cascades to modulate bile acid, lipid, glucose, and protein metabolism.

The FGFR4/FGF19/β-Klotho interaction participates in the negative feedback control of BA synthesis and secretion inducing a mitogen-activated protein kinase (MPKA) cascade that represses the activity of cholesterol-7α-hydroxylase (CYP7A1). Subsequently, it contributes to a decreased hydroxylation of BAs resulting in the reduction of BA synthesis [10]. BAs are produced in the liver and accumulated in the gallbladder. FGF19 interacts with FGFR4 and β-Klotho in the gallbladder, causing its relaxation and promoting BA accumulation [10]. After each meal, BAs are secreted to the intestine, where they are responsible for fat and oil digestion and absorption [12]. The overexpression of FGF19 disturbs lipid assimilation, thereby protecting from hyperlipidemia. Moreover, the direct interaction of FGF19 with FGFR4 induces lipogenesis after food intake. During starvation, FGF19 promotes lipolysis via FGF1Rc activation in adipose tissue [13]. FGF19 also has an insulin-like effect. Enhanced glycogen synthesis, inhibition of gluconeogenesis, and increase in glucose uptake to adipocytes are the FGF19-mediated effects. However, the pathways which are related to the FGF19 actions are independent of insulin. In animal studies, FGF15-knockout, which is an orthologue of the human FGF19, leads to lower glycogen concentration in the liver and glucose intolerance. Hepatic protein synthesis is also stimulated by FGF19 [14].

Furthermore, FGF19 acts in the central nervous system modulating glucose homeostasis, and β-Klotho and FGFR1c are expressed in the mediobasal hypothalamic areas and the hindbrain. The FGFR1c activation in the central nervous system increases metabolic rate, decreases body weight, reduces glucose level, and improves insulin resistance [15, 16].

## 3. FGF19 signaling in diseases

### 3.1 Metabolic syndrome

FGF19 being involved in glucose and lipid metabolism may significantly contribute to the development of metabolic syndrome (MS). A lower plasma FGF19 level was observed in obesity [17], dyslipidemia [18], and type 2 diabetes [19] compared to healthy controls. This is consistent with the results reported by Barutcuoglu et al. [20], where a negative correlation between FGF19 and body mass index, triglycerides, and glycated hemoglobin level was revealed in diabetic patients with MS. It has been shown that the administration of FGF19 in rodents reduces weight and plasma lipids level, improves diabetes, and accelerates metabolic rate [21]. Another interesting study performed by Perry et al. [22] explored intracerebroventricular (ICV) injections of the FGF19 recombinant in a rat model of type 1 diabetes. The central action of FGF19 resulted in inhibition of the hypothalamic–pituitary–adrenal axis with subsequently reduced glucose plasma level, suppressed lipolysis, decreased hepatic acetyl coenzyme A concentration, lowered pyruvate carboxylase activity and hepatic glucose synthesis.

### 3.2 Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is another commonly investigated disorder associated with dysregulation of the FGF19 signaling. Reduced concentrations of FGF19 were detected in obese adolescents suffering from NAFLD [23], and in adults with biopsy-proven NAFLD [24]. Overweight and obese NAFLD patients showed impaired FGF19 release in fasting and postprandial states [25]. The reduction in the FGF19 level leads to increased BA production, which is correlated with higher NAFLD fibrosis score [24]. Studies showed that low FGF19 level is associated with an increase in hepatic lipid accumulation, focal necrosis, and elevated plasma aspartate and alanine aminotransferase activities and triglyceride concentration [23, 26]. The FGF19 depletion in mice fed a high-fat diet leads to increased weight gain and exacerbated non-alcoholic steatohepatitis (NASH). The treatment with FXR agonists protects mice from the diet-induced hepatic steatosis, promotes fatty liver regeneration, reduces the accumulation of hepatic triglycerides and free fatty acids, and reduces hepatic inflammation [27, 28]. Currently, NGM282, an analogue of FGF19, is in clinical trials for treating patients with NAFLD. The administration of NGM282 contributes to a significant reduction in fat content in the liver with an acceptable safety profile in randomized, double-blind, placebo-controlled study [29]. The 12-week treatment with NGM282 in biopsy-proven NASH led to remarkable histological improvement, reduction in aspartate and alanine aminotransferase activities and noninvasive serum fibrosis biomarkers [30].

### 3.3 Diseases of the biliary tract

Cholestatic disorders such as choledocholithiasis, primary biliary cholangitis, and primary sclerosing cholangitis are characterized by dysregulation of BA circulation and enhanced FGF19 synthesis [31, 32]. It has been demonstrated that in animal models NGM282 inhibits BA synthesis and protects from injury caused by BA accumulation in the liver [33]. It has been shown that 12-week treatment with NGM282 improves fibrosis biomarkers in patients with primary sclerosing cholangitis [34].

Since FGF19 induces gallbladder relaxation, enhanced FGF19 level impairs gallbladder contractility and increases cholesterol saturation and BA hydrophobicity, creating conditions for gallstone formation [35]. Patients after cholecystectomy are characterized by reduced FGF19 level and subsequently increased BA synthesis [36].

### 3.4 Cardiovascular diseases

FGF19 is implicated in the pathophysiology of cardiovascular disease (CVD), due to the alterations in the FGF19 level associated with MS, which is an important risk factor for CVD. Byun et al. [37] showed that hepatic FXR activation via FGF19 has a cholesterol-lowering effect and protects against atherosclerosis in mice. Another study revealed that loss of the FXR function in a mouse model increased total blood cholesterol, VLDL, LDL, and triglyceride, consequently resulting in more extensive degree of atherosclerotic formation, and in higher mortality [26]. Furthermore, the treatment of dyslipidemic mice with NGM282 resulted in reduced atherosclerotic lesion area in the aorta. The NGM282 application contributed also to the rise in HDL-C level in healthy volunteers [38]. Xu et al. [39] showed that treatment with FGF19 recombinant was associated with an improvement in cardiac function in diabetic rats. The 12-week therapy resulted in improvement of plasma glucose and lipid profile, decreased blood pressure, and amelioration of left ventricular function.

### 3.5 Malignancies

The FGFR4 activation by FGF19 is implicated in the development and progression of hepatocellular carcinoma (HCC) [4]. Patients with HCC have higher plasma FGF19 levels compared to healthy controls [40]. It has been shown that FGF19 is expressed in HCC cells, thereby formatting a feedback autocrine–paracrine loop, where FGF19 activates FGFR4 on HCC cells. The FGF19-mediated effect promotes HCC cell survival and proliferation via the stimulation of Ras-Raf-ERK1/2MAPK and phosphatidylinositol 3-kinase-protein kinase B (PI3K-Akt) pathways [41, 42]. The FGF19 expression in HCC cells is activated by endoplasmic reticulum stress, which commonly occurs in tumor cells, and promotes cell apoptosis. However, FGF19 provides cytoprotection to HCC cells, by decreasing endoplasmic reticulum stress-induced cell death. Moreover, the depletion of FGF19 reduces HCC cell survival and enhances apoptosis [43]. Therefore, FGF19/FGFR4 pathways are potential therapeutic targets in advanced HCC. Numerous FGFR inhibitors are in clinical and pre-clinical trials for treating HCC [42].

Moreover, FGFR4 expression has been identified as a significant independent prognostic biomarker in cholangiocarcinoma [44]. Upregulation of FGF19 was also reported in colorectal adenomas [45]. Another observation, confirming that FGF19 can promote tumor growth in various types of cancer, concerns lung cancer. It has been shown that FGF19 overproduction in lung squamous cell carcinoma cells markedly promotes cell growth, progression, and metastasis, while FGF19 downregulation effectively inhibits lung squamous cell carcinoma progression *in vitro* and *in vivo* [46].

### 3.6 Inflammatory bowel disease

Disturbances in FGF19 signaling may contribute to the pathogenesis of inflammatory bowel disease (IBD). Plasma FGF19 concentration is lower in IBD patients compared to healthy controls [5]. Patients with Crohn's disease have impaired reabsorption of BAs at the terminal ileum due to inflammation or resection of this part of the intestine. In consequence, the overload of unabsorbed BAs enters the colon lumen, evoking secretory effects and stimulating contractions. It may lead to diarrhea and abdominal pain afterwards. The BA malabsorption is associated with impaired FXR activation, subsequently leading to lower FGF19 expression. That results in increased production of BAs and diarrhea deterioration [47, 48]. Furthermore, patients with active ulcerative colitis have lower serum FGF19 level compared to patients with inactive ulcerative colitis, and FGF19 level negatively correlates with abdominal pain intensity, fecal calprotectin, and CRP level [49]. In mice with induced colitis, treatment with FXR agonist, which stimulates FGF19 production, leads to improvement of colitis symptoms, inhibition of epithelial permeability, and reduced proinflammatory cytokine production. These data suggest a novel target of treatment; however, further investigations are awaited to confirm its clinical application [50].

### 3.7 Chronic kidney disease

Hemodialyzed patients are characterized by higher plasma FGF19 levels compared to healthy subjects [51]. Marchelek-Myśliwiec et al. [52] studied alterations in FGF19 concentration in patients with chronic kidney disease (CKD) with and without hemodialysis and in patients after kidney transplantation. They observed the highest FGF19 concentration among non-dialysis patients with CKD. The results showed that hemodialysis and kidney transplantation reduce FGF19 concentrations. Furthermore, FGF19 level was conversely correlated with glomerular filtration rate (GFR) values. However, the clinical role of FGF19 in patients with CKD remains to be unraveled.

## 4. FGF21

### 4.1 Identification

FGF21 was first described in 2000 by Nishimura et al. [53] in mouse embryos. Later the human homolog, also termed as FGF21, was identified. It was observed that the human factor is in 75% identical to the mouse factor [54].

### 4.2 Expression

FGF21 is produced mainly in the liver, adipose tissue, and the pancreas, but is also synthesized at lower concentrations in the thymus, skeletal muscles, heart, kidneys, and the testes. The main inducers of the FGF21 transcription include fasting state, overfeeding, ketogenic and high carbohydrate diets, protein restriction, free fatty acids, physical exercise, and nuclear receptor agonists. During starvation, the hepatic FGF21 expression is induced predominantly by the peroxisome proliferator receptor α (PPARα) agonists and the cyclic adenosine monophosphate (cAMP)-responsive element-binding protein H (CREBH). These two transmitters both control transcription of FGF21, via interaction with the promoter of FGF21, and also regulate the production of each other [55]. Fenofibrates, which are PPARα activators, induce FGF21 synthesis [56]. The production of FGF21 is also regulated by carbohydrate-responsive binding protein (ChREBP) in hepatocytes, which is related to the presence of carbohydrates in a meal. Protein deprivation is a state of nutrient stress in hepatocytes that induces integrated stress response, subsequently promoting the activating transcription factor 4 (ATF4). ATF4 arouses expression of FGF21. However, other pathways can be also activated by low protein intake, including PERK, NUPR1, IREa-XBP1, or PPARα [55]. Fatty acids increase hepatic FGF21 synthesis and secretion via activation of the PPARα [57]. The production of FGF21 in white adipose tissue (WAT) is induced by activation of PPARγ. Cold exposure is strongly related to FGF21 synthesis in WAT and also in brown adipose tissue [10]. FGF21 is synthesized in the exocrine part of the pancreas and in lower levels in the pancreatic islets. Refeeding and endoplasmic reticulum stress are main inducers of the FGF21 expression in the pancreatic acinar cells while fasting and pancreatitis inhibit the FGF21 expression. The FGF21 transcription is regulated by ATF4 [58]. In skeletal muscles, the FGF21 expression is induced by oxidative stress via ATF4 [5]. The summary of the regulation of FGF21 expression is presented in Figure 2.

### 4.3 Physiological role

FGF21 activates multiple FGFRs, including FGFR1c, FGFR2c, FGFR3c, and FGFR4, in the presence of β-Klotho. Nevertheless, FGF21 binds with the highest affinity to FGFR1c. The β-Klotho ex-

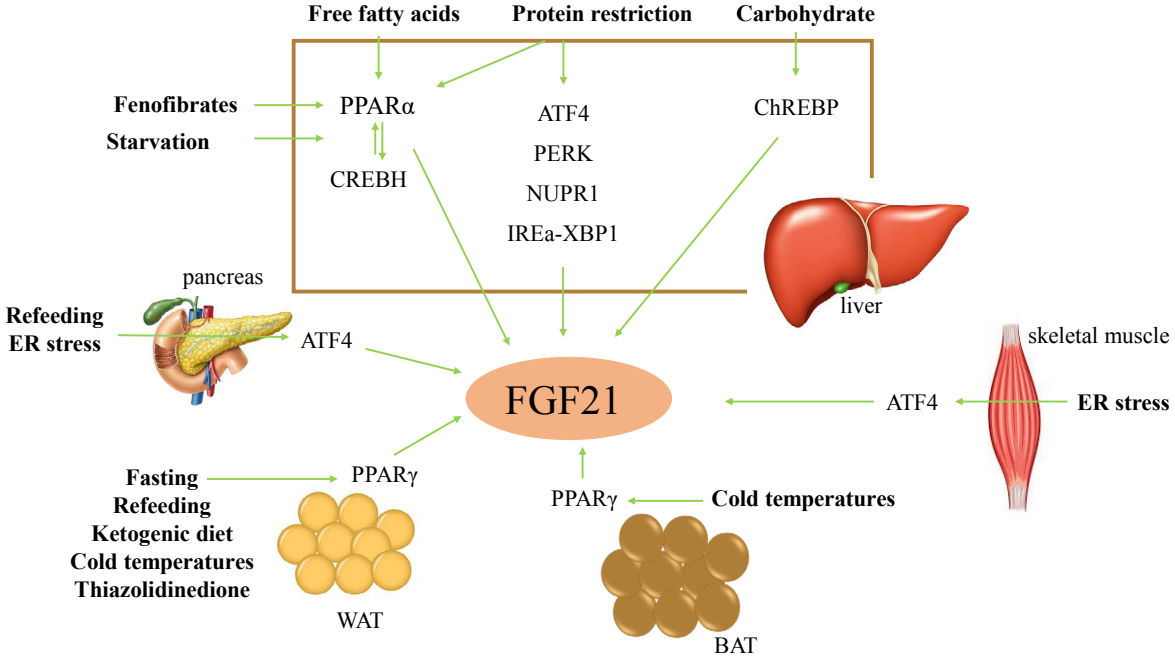


*Fig. 2. Regulation of Fibroblast Growth Factor 21 (FGF21) expression; FGF21 is mainly produced in the liver, white adipose tissue (WAT), brown adipose tissue (BAT), and the pancreas, but is also synthesized in lower level in the skeletal muscles. In the figure, inducers of FGF21 synthesis (marked in bold font) act on the particular organs and stimulate signaling cascades including peroxisome proliferator receptor α (PPARα), cyclic adenosine monophosphate responsive element-binding protein H (CREBH), carbohydrate-responsive binding protein (ChREBP). The activation of transcription factor 4 (ATF4), protein kinase R-like endoplasmic reticulum kinase (PERK), the liver-integrated stress response-driven nuclear protein 1 (NUPR1), inositol-requiring enzyme 1 - transcription factor X-box-binding protein 1 (IREa-XBP1), and PPARγ, consequently leads to FGF21 expression. Based on [10, 55]*

pression in target organs determines the tissue-specific action of FGF21. FGF21 has influence on the liver, adipose tissue, the pancreas, and the brain [59]. The mode of FGF21 action is considered not only endocrine but also paracrine and autocrine. FGF21 controls several pathways involved in the regulation of glucose and lipid metabolism. Moreover, it participates in insulin sensitivity regulation and the maintenance of a constant bodyweight [55].

FGFR1c is expressed predominantly in WAT, thus the adipose tissue is the main target organ of FGF21. The mode of FGF21 action synthesized in WAT is considered mainly autocrine. Activation of PPARγ via FGF21 contributes to an increase in glucose transporter 1 expression, and consequently stimulates glucose uptake in adipocytes. The FGF21-mediated PPAR-γ stimulation increases insulin sensitivity as well [57]. FGF21 can both inhibit and stimulate lipolysis in WAT, after meals and during fasting, respectively [3]. FGF21 chronic administration can induce fatty acid oxidation in WAT [55]. Another important role of FGF21 is the coordination of adipose tissue thermogenesis as a response to cold exposure. Heat production is stimulated by PPARγ coactivator protein-1α (PGC-1α) in WAT. Higher PGC-1α level activates PPARγ, that promotes browning of WAT in adaptive thermogenesis. In brown adipose tissue the thermogenesis effect is a result of the mitochondrial uncoupling protein 1 (UCP1) expression [57]. The FGF21 knockout mice showed reduction in all of the following: PPAR-γ activity, insulin sensitivity, browning of WAT, and adaptation to chronic cold temperatures [3].

During fasting, FGF21 arouses the expression of PGC-1α in the hepatocytes, stimulating gluconeogenesis, ketogenesis, and fatty acid oxidation. The loss of FGF21 function in mice is associated with impaired gluconeogenesis, and with ketone body formation in response to prolonged starvation [60]. The FGF21 application improves hepatic steatosis and insulin sensitivity in diet-induced obese mice [3].

Prolonged starvation induces growth hormone resistance, which is a subsequent metabolic effect of FGF21. The overexpression of FGF21 is associated with impaired somatic growth, reduced IGF-1, and increased growth hormone concentration [61].

FGF21 acts in an autocrine/paracrine mechanism on the pancreatic acinar cells, resulting in increased digestive enzyme secretion through intracellular calcium release. It was observed that FGF21 concentration is decreased in pancreatitis [58]. FGF21 has a protective role against damages during experimental pancreatitis. The administration of FGF21 reduces pancreatic edema, and decreases serum amylase level and activation of proinflammatory mediators [58]. FGF21 ameliorates β-cell function and survival, having protective effects against stressor factors such as glucolipotoxicity and cytokine-induced apoptosis under diabetic conditions. The glucose-lowering effect of FGF21 is a result of increased insulin secretion from β-cells and decreased glucagon secretion from α-cells [10]. Reduced glucose and free fatty acids concentration protect from glucolipotoxicity and cytokine-induced apoptosis, as well as activation of Akt, which is induced by FGF21 [5].

Similarly to FGF19, FGF21 crosses the blood-brain barrier and acts in the central nervous system. The central effects of FGF21 are related to glucose homeostasis and bodyweight regulation [15]. The metabolic effects of FGF21 are determined by the presence of FGFR1c and β-Klotho in the brain. The deletion of β-Klotho in the central nervous system impairs FGF21-mediated effects. Direct ICV injection of FGF21 into the brain promotes weight loss, reduces glucose level, and improves hepatic insulin sensitivity [15]. FGF21 stimulates sympathetic nerve activity, and then metabolism of the brown adipose tissue. Furthermore, FGF21 induces the production of corticotropin-releasing hormone activating the hypothalamic–pituitary–adrenal axis to increase gluconeogenesis in the liver during prolonged starvation [59].

## 5. FGF21 signaling in diseases

### 5.1 Obesity

In obesity, the FGF21 level is increased [62]. The administration of recombinant FGF21 protein contributes to weight reduction. Overproduction of FGF21 in transgenic rodents protects from diet-induced obesity [63]. Jimenez et al. [63] conducted a long-term study investigating administration of a gene therapy using adeno-associated viral vector encoding FGF21 in mouse models. A single application resulted in FGF21 overexpression in the liver which contributed to constant elevation of plasma FGF21 concentration, causing bodyweight reduction. It suggests that FGF21 gene therapy is a possible procedure to cure obesity in the future.

### 5.2 Diabetes

FGF21 has glucose-lowering effects, thus improves diabetic condition. Elevated FGF21 concentrations are observed in type 2 diabetes compared with weight-matched control participants [64]. However, in patients with type 1 diabetes, serum FGF21 concentration is decreased. Insulin deficiency in T1D patients is probably associated with lower FGF21 level, because insulin is an inducer of FGF21. These data suggest that FGF21 level may serve as a biomarker for predicting diabetes [64, 65]. Treatment with LY2405319, a FGF21 analogue, in obese patients with type 2 diabetes improves glucose level, enhances insulin sensitivity, induces a significant improvement in dyslipidemia, and reduces the body mass. These outcomes indicate the potential role of FGF21-based therapies in the treatment of metabolic disorders [66].

### 5.3 Non-alcoholic fatty liver disease

Shen et al. [67] observed a significant elevation of serum FGF21 levels in patients with NAFLD, compared to subjects without this condition. Excess of fatty acids in hepatic steatosis disturbs PPARα signaling and results in FGF21 overexpression. Elevated FGF21 concentration may be a consequence of FGF21 resistance in obesity as well, because it was observed that decreased β-Klotho in the NAFLD liver was correlated with high plasma FGF21 levels [68, 69]. Moreover, in obese patients with NAFLD, FGF21 serum level was significantly higher in patients with more advanced steatosis (grade 2 and 3) compared to those without or with mild steatosis (grade 0 and 1) [70]. Also, in another study, positive correlation between serum FGF21 level and progression of NAFLD was observed, while the highest FGF21 concentration was found in patients with NASH [71]. It indicates the potential role of FGF21 as a biomarker of NAFLD advancement and NASH development. Chronic administration of FGF21 analogues enhances fatty acid oxidation and suppresses expression of lipogenic genes in the liver, causing reduction of triglyceride content and improvement of fatty liver in obese mice [72]. Conversely, knockout of hepatic FGF21 in mice on a ketogenic diet contributes to hepatic steatosis and hyperlipidemia [73]. Pegbelfermin, a FGF21 analogue, thas been investigated in NASH. The previous study with that analogue showed relevant reduction in fat content in the liver, decrease in serum alanine aminotransferase and aspartate aminotransferase activities, and improvement in non-invasive fibrosis markers [74].

### 5.4 Cardiovascular diseases

Another condition that enhances FGF21 concentration is atherosclerosis. The impact of FGF21 level on atherosclerosis is associated with the abundant presence of FGFR1c and β-Klotho in the aorta and arterial vessels, which are considered targets for FGF21 [65]. Deficiency in FGF21 aggravates atherosclerotic plaque development, inducing aortic thickening in mice. Studies in animal models demonstrated that application of the FGF21 analogue is associated with anti-atherosclerotic effects, due to reduction of lipids levels, vascular inflammation, and oxidative stress. The administration of FGF21 improves high blood pressure as well [75]. Patients with atherosclerosis have elevated FGF21 levels, probably in the course of adaptive response. Furthermore, FGF21 is elevated in atherosclerosis-associated disease including type 2 diabetes, dyslipidemia, obesity, and hypertension [76]. These diseases and atherosclerosis increase risk of cardiovascular events. Serum FGF21 concentration was identified as a risk factor of coronary heart disease development [67]. While FGF21 may be considered as a biomarker for predicting early stages of atherosclerosis and cardiovascular events, it may also have a therapeutic potential to prevent atherosclerosis [67, 76].

### 5.5 Inflammatory bowel disease

Liu et al. [77] investigated the impact of FGF21 in experimental colitis on body weight and lipolysis in WAT. They demonstrated that plasma FGF21 concentration is higher in mice with colitis compared to control mice. They examined the FGF21 level in humans with IBD as well. In fact, IBD patients have higher plasma FGF21 concentrations compared to healthy control subjects. Also, in children with IBD, the acute phase of the disease was found to be associated with a significant increase in serum FGF21 level [78]. Low body weight in IBD has multifactorial pathogenesis, but one of the causes may be elevated FGF21 level. Feingold et al. [79] demonstrated that FGF21 is increased by inflammatory stimuli. Colitis is a stressor factor that induces FGF21 expression. Subsequently, it activates lipolysis in WAT and weight loss. However, further studies are needed to clarify the pathophysiological link between IBD and FGF21.

### 5.6 Renal diseases

Alteration of FGF21 concentration is observed also in CKD and acute kidney disease [80]. As with FGF19, the level of FGF21 increases along with reduction of GFR. Hemodialysis and kidney transplantation are associated with lower FGF21 concentrations among patients with CKD [52]. CKD leads to changes in the metabolic profile, inflammation, and accumulation of toxins, which as stressor factors may induce the FGF21 production. Insulin resistance and cardiovascular diseases commonly coexist among CKD patients. These disorders are associated with higher FGF21 concentration as well [81]. Kohara et al. [82] demonstrated that elevated plasma FGF21 level predicts a high mortality rate in patients with end-stage renal disease. Thus, circulating FGF21 levels may serve as a predictive biomarker for mortality associated with kidney disease.

### 5.7 Psychiatric disorders

Centrally FGF21-mediated modes of action may play a role in mood regulation. Chang et al. [83] demonstrated the association between FGF21 level and the depression severity measured by Hamilton Depression Rating Scale among patients with bipolar disorder. Higher plasma FGF21 concentration was observed after treatment with mood stabilizers, indicating that FGF21 could be a common regulator of the mood. Furthermore, another investigation demonstrated a significant negative correlation between cerebrospinal fluid FGF21 concentration and the Beck Depression Inventory scores in male Chinese subjects [84]. In addition, a recent study showed that FGF21 had an antidepressant effect in lipopolysaccharide-induced depression [85]. Its action was associated with the suppression of the proinflammatory cytokine expression [85].

## 6. FGF23

### 6.1 Identification

Yamashita et al. [86] in 2000 isolated the mouse cDNA encoding FGF23 for the first time in the ventrolateral thalamic nucleus of the brain. Subsequently, the human cDNA encoding FGF23 was also isolated, and the factor was homological in 72% to the mouse one.

### 6.2 Expression

FGF23 is predominantly synthesized by differentiated osteoblasts and osteocytes. It is also produced by the salivary glands, the stomach, and at lower levels by other tissues, including skeletal muscles, the brain, mammary gland, liver, and the heart [87]. Parathyroid hormone (PTH), 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$), dietary phosphate, calcium, iron deficiency, and inflammation are the main stimulators of FGF23 production [88]. The effect of PTH is to enhance FGF23 production in the bone tissue, and it is mediated by the protein kinase A (PKA) activated via forskolin. PKA has positive direct impact on FGF23 expression and indirect effect through inhibition of Wnt pathway [89]. $1,25(OH)_2D_3$ directly induces FGF23 expression through binding to the vitamin D receptor, which is the transcription factor regulating gene expression in various cell types, including osteoblasts and osteocytes. $1,25(OH)_2D_3$ may also reduce dentin matrix acidic phosphoprotein 1 (DMP1) expression, an inhibitor of FGF23 production, thereby enhancing FGF23 synthesis in an indirect way [90]. The phosphate-mediated mechanism in induction of FGF23 synthesis has not been clearly described so far. However, it has been indicated that oral phosphate load induces FGF23 expression by stimulating NADPH-induced reactive oxygen species production and the MEK-ERK pathway [90]. An increased activity of hypoxia inducible factor 1α (HIF1α) is one of the mechanisms through which inflammation stimulates the FGF23 transcription. HIF1α is the transcription factor that regulates gene expression by binding to the promoters of target genes. Inflammation induces HIF1α expression and leads to iron deficiency. Iron depletion stabilizes HIF1α [88]. Inflammation is associated with elevated interleukin-1β (IL-1β) and IL-6 levels, which are also stimulators of FGF23 [91]. IL-1β increases HIF1α expression. IL-6 binds with soluble IL-6 receptor and activates the signal transducer and activator of transcription 3 (STAT3), and contributes to increased transcription of FGF23 [91, 92]. Aldosterone is another potent stimulator of FGF23 synthesis via increasing cytosolic calcium concentration [93]. In turn, hyperinsulinemia is associated with a decreased FGF23 synthesis. Insulin inhibits the transcription factor FOXO1 through PI3K/PKB/Akt signaling, resulting in the down-regulation of FGF23 gene transcription [94]. Three other

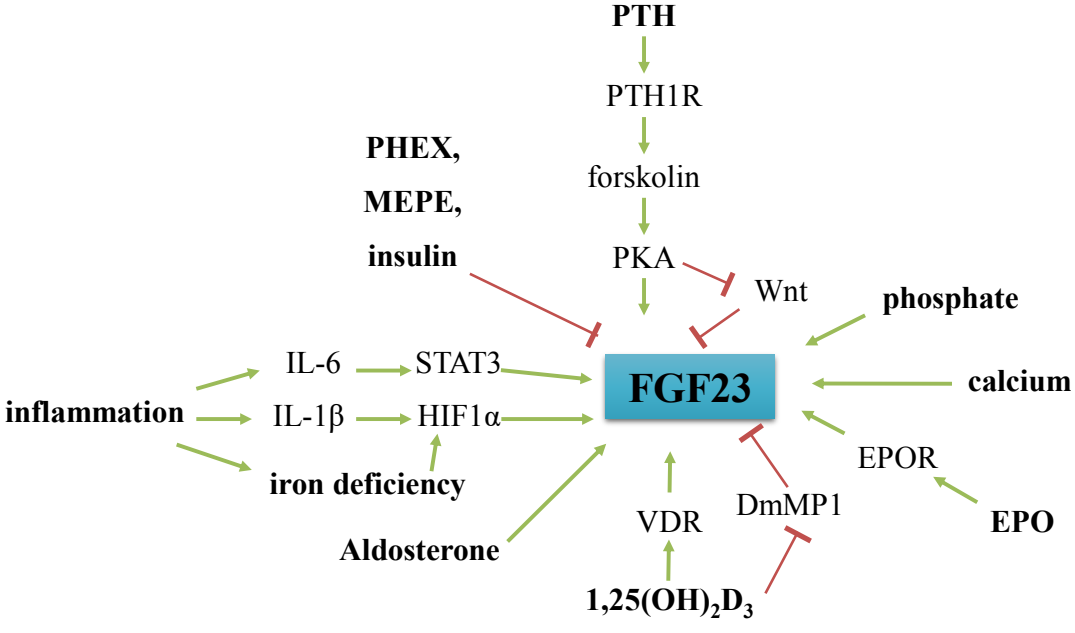


*Fig. 3. Regulation of Fibroblast Growth Factor 23 (FGF23) expression; FGF23 is predominantly synthesized by osteoblasts and osteocytes. Parathyroid hormone (PTH), phosphate, calcium, erythropoietin (EPO), 1,25- dihydroxyvitamin D (1,25(OH)2D3), aldosterone, iron deficiency, and inflammation are stimulators of FGF23 production (marked in bold font). Mode of their action is presented in the figure. Phosphate-regulating gene with homologies to endopeptidase on the X chromosome (PHEX), matrix extracellular phosphoglycoprotein (MEPE), insulin, Wnt pathway, and dentin matrix acidic phosphoprotein 1 (DMP1) are inhibitors of the FGF23 expression.*
*PTH1R – Parathyroid hormone receptor, PKA – protein kinase A, EPOR – erythropoietin receptor, VDR – vitamin D receptor, IL-1β – interleukin-1β, IL-6 – interleukin 6, STAT 3– signal transducer and activator of transcription 3, HIF1α – hypoxia inducible factor 1α. Based on [5, 89]*

factors also inhibit FGF23 synthesis: the phosphate-regulating gene with homologies to endopeptidase on the X chromosome (PHEX), DMP1, and matrix extracellular phosphoglycoprotein (MEPE) [90]. The recent study conducted by Toro et al. [95] revealed that erythropoietin and subsequent erythropoietin receptor activation enhanced serum FGF23 concentration among patients with AKI. A summary of the regulation of FGF21 expression is presented in Figure 3.

### 6.3 Physiological role

FGF23 acts by binding to FGFR1c, FGFR3c, and FGFR4 in the presence of α-Klotho [3]. The α-Klotho cofactor was found in the kidneys and the parathyroid glands, indicating that they are FGF23 target organs [54]. The $\alpha$-Klotho gene is also expressed in the choroid plexus in the brain [4]. FGF23 plays an essential role in calcium-phosphate balance.

Kidneys are the main target organ for FGF23. FGF23 suppresses reabsorption of phosphates causing increase in urinary phosphate excretion, subsequently decreasing plasma phosphates level. Phosphates are reabsorbed almost exclusively in the renal proximal tubule through a transcellular pathway, involving sodium-dependent phosphate cotransporters: NPT1, NPT2a, NPT2b, NPT2c, PiT1, PiT2. It has been demonstrated that FGF23 inhibits the expression of NPT2a and NPT2c and consequently reduces phosphate reabsorption [87]. Moreover, FGF23 diminishes the activation of $25(OH)_2D_3$ by reducing expression of 1$\alpha$-hydroxylase. FGF23 induces also the catabolism of the active form of $1,25(OH)_2D_3$ by increasing 24-hydroxylase transcription. These two effects lead to lowering $1,25(OH)_2D_3$ levels and consequently reduce intestinal uptake of phosphate and calcium [90]. Depletion of FGF23 in mice results in severe hyperphosphatemia and ectopic mineralization, due to enhanced renal reabsorption in the presence of increased NPT2a expression in the proximal tubule. These mice are characterized also by enhanced serum $1,25(OH)_2D_3$ level as a result of increased expression of renal 1α-hydroxylase [96]. Inversely, FGF23 overexpression leads to hypophosphatemia and reduction of plasma $1,25(OH)_2D_3$level [97]. The biological actions of FGF23 are observed in proximal tubules, but α-Klotho is not expressed there. However, FGFR1, FGF3, FGFR4, and α-Klotho are highly expressed in distal tubules. That suggests that the mode of FGF23 action in proximal tubules is indirect. It is conceivable that activation of FGFR in distal tubules generates an unknown paracrine signal that stimulates proximal tubule function. Therefore, α-Klotho is considered as a contributor of paracrine signaling [87]. However, FGF23 may also have a direct impact on distal tubules. The FGFR stimulation in distal tubules leads to up-regulation of renal membrane sodium chloride cotransporter (NCC) expression via activation of extracellular signal-regulated kinase 1/2 (ERK1/2), serum/glucocorticoid-regulated kinase 1 (SGK1), and with-no lysine kinase-4 (WNK4). NCC mediates renal sodium reabsorption. The knockout of FGF23 and α-Klotho in mice lowered expression of NCC in renal distal tubules and reduced reabsorption of sodium. Inversely, injections with recombinant FGF23 in wild-type mice mediated the enhancing effect on expression of the NCC in distal tubules and increased reabsorption of sodium, consequently leading to plasma volume expansion, hypertension, and heart hypertrophy [98].

The parathyroid glands are characterized by the expression of FGFR1c and α-Klotho, hence they are capable of responding to FGF23. FGF23 inhibits the secretion of PTH via the MAPK pathway [89]. That has been confirmed by Ben-Dove et al. [99] in rat models. Furthermore, it has been identified that α-Klotho can independently suppress PTH secretion, via the calcineurin-mediated pathway [100].

Furthermore, excess of FGF23 inhibits erythropoiesis in the negative feedback loop. Depletion of FGF23 contributes to a relevant increase in erythropoiesis [90].

## 7. FGF23 signaling in diseases

### 7.1 Chronic kidney disease

In patients with CKD, up to 1000-fold elevation in FGF23 concentration may be observed. Impaired phosphate excretion in CKD is the main cause of increased FGF23 synthesis. Conditions related to CKD, including iron deficiency and tissue hypoxia secondary to anemia, may also lead to the elevation in FGF23 concentration [90]. Furthermore, under uremic conditions, α-Klotho is downregulated, which potentially causes FGF23 resistance. Disturbances in FGF23-induced suppression of PTH production lead to hyperparathyroidism, and subsequently enhance FGF23 synthesis [5]. Increased FGF23 secretion is an adaptive response in the early stages of CKD, which develops preceding hyperparathyroidism and the increase in phosphate concentrations. FGF23 can be used as a sensitive early biomarker to identify CKD in patients with normal serum phosphate levels [101]. It is also a pathogenic factor for the progression of CKD. FGF23 levels positively correlate with the degree of hyperphosphatemia. FGF23-mediated reduction of active vitamin D level results in diminished gastrointestinal absorption of calcium and phosphates and the development of secondary hyperparathyroidism [87].

### 7.2 Acute Kidney Injury

Rapid rise of serum FGF23 level is also observed in acute kidney injury (AKI), therefore plasma FGF23 can be considered as a diagnostic biomarker of AKI [102]. Serum FGF23 concentration is negatively correlated with the GFR values [102]. Elevated FGF23 level is associated with unfavorable prognosis in patients with AKI [103]. The pathway leading to excess of FGF23 in AKI is probably independent of PTH, $1,25(OH)_2D_3$, and phosphates. Increased expression of FGF23 in osteocytes is suggested as a main source of FGF23 in patients with AKI. Resection of the kid-

ney contributes to increased serum FGF23 concentration, thus suggesting the kidneys are not a source of FGF23 excess in AKI. Inflammation and anemia, characteristic features in CKD and AKI, associated with high IL-6 level, increased circulating erythropoietin, and iron deficiency may also contribute to elevated production of FGF23 [95, 104].

### 7.3 Nephrolithiasis

FGF23 increases urinary phosphate excretion. Renal phosphate leak is associated with hypophosphatemia, which consequently increases calcium excretion. Enhanced calcium urinary saturation rises the risk of calcium stones formation, therefore the FGF23 overproduction may lead to nephrolithiasis development [105]. Rendina et al. [106] demonstrated that 20% of renal stones are related to renal phosphate leak and enhanced serum FGF23 level.

### 7.4 Heart failure

High FGF23 levels are observed among patients with left ventricular hypertrophy. The FGF23-mediated hypertrophic action on cardiomyocytes is independent of α-Klotho expression in the myocardial tissue. Furthermore, high FGF23 concentration stimulates FGFR4 and subsequently reduces cardiomyocyte calcium levels impairing the contractile function of cardiomyocytes [4]. Left ventricular hypertrophy may be also a result of FGF23-mediated sodium reabsorption in the kidneys, afterwards leading to volume expansion [98]. Moreover, FGF23 may activate the renin–angiotensin–aldosterone system. FGF23 suppresses α-Klotho, while α-Klotho induces aldosterone secretion. FGF23 expression is induced by aldosterone in the positive feedback loop. Hyperaldosteronism is a common predictor of cardiac hypertrophy, fibrosis, and remodeling, that suggests the participation of FGF23 in the pathogenesis of the heart failure [81, 93].

### 7.5 Bone diseases

Increased FGF23 level contributes to hypophosphatemia and hypovitaminosis D, resulting in the development of rickets in children and osteomalacia in adults [90]. Studies with animal models showed that FGF23 overexpression promoted osteomalacia, short stature, and lower extremity deformities. Inversely, depletion of FGF23 leads to ectopic soft tissue calcification and poorly formed skeleton. It has been shown that FGF23 secreted from osteocytes may regulate mineralization by FGFR3 activation through an independent autocrine feedback loop [3]. Impaired function of FGF23 was described in many congenital diseases including X-linked hypophosphatemia, autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, hyperphosphatemic familial tumoral calcinosis, tumor-induced osteomalacia, and familial tumoral calcinosis [3, 90]. Recently, burosumab, a human monoclonal antibody against FGF23, has been approved for the treatment of X-linked hypophosphatemia [107].

### 7.6 Inflammatory bowel disease

Alterations in FGF23 concentration may be involved in the pathophysiology of IBD. El-Hodhod et al. [108] reported that a significant elevation of serum FGF23 was observed during flares in children with IBD with a reduction after remission induction. Moreover, IBD patients were characterized by higher FGF23 levels compared to healthy subjects. It was suggested that TNF-α, a cytokine implicated in the pathogenesis of IBD, reduces PHEX transcription, resulting in diminished degradation of FGF23. Interestingly, these patients had high $1,25(OH)_2D_3$ levels, which is a well-known stimulus of FGF23 synthesis. Elevated FGF23 level may contribute to increased risk of osteoporosis in IBD patients due to diminished bone mineral density observed in patients during flares [108]. Inflammation and iron deficiency are other common conditions among IBD patients, which can be related to elevated FGF23 level [109]. However, a study conducted by Oikonomou et al. [110] demonstrated that patients suffering from Crohn's disease had significantly lower serum FGF23 levels compared with healthy controls. These patients with Crohn's disease had low $1,25(OH)_2D_3$ levels, which can be associated with declining FGF23 levels. $1,25(OH)_2D_3$ has potential immunomodulating effects by inhibiting proinflammatory cytokines and stimulating anti-inflammatory pathways. Patients with IBD are more prone to develop vitamin D deficiency due to malabsorption of nutrients. It has been shown that vitamin D is involved in IBD pathogenesis and negatively correlated with the disease activity [111]. Due to the association between vitamin D and FGF23, further investigations are needed to establish relationships between alterations in FGF23 concentration and IBD.

## 8. CONCLUSION

The FGF15/19 subfamily is the group of three factors FGF19, FGF21, and FGF23, with mainly endocrine modes of action. They are involved in various metabolic functions including glucose, lipid, and protein homeostasis, BA circulation, and mineral balance. Alterations in the levels of these factors are observed in numerous diseases. Therefore, they are promising predictors and biomarkers in a wide spectrum of disorders. The signaling pathways of endocrine FGFs also constitute emerging therapeutic targets. Currently, the analogues of endocrine FGFs are under development for treatment of NAFLD, metabolic disorders, and primary sclerosing cholangitis. Moreover, numerous FGFR inhibitors are in clinical and pre-clinical trials for treating HCC, and recently, a human monoclonal antibody against FGF23 has been approved for treatment of X-linked hypophosphatemia. However, further investigations are required to implement other FGF-based therapies into clinical practice.

## Abbreviations

**1,25(OH)$_2$D$_3$** – 1,25-dihydroxyvitamin D, **AKI** – acute kidney injury, **ATF4** – activating transcription factor 4, **BA** – bile acid, **ChREBP** – carbohydrate-responsive binding protein, **CKD** – chronic kidney disease, **CREBH** – cyclic adenosine monophosphate responsive element-binding protein H, **CVD** – cardiovascular diseases, **CYP7A1** – cholesterol-7α-hydroxylase, **DMP1** – dentin matrix acidic phosphoprotein 1, **ERK1/2** – extracellular signal-regulated kinase 1/2, **FGF** – fibroblast growth factor, **FGFR** – fibroblast growth factor receptor, **FXR** – farnesoid X receptor, **GFR** – glomerular filtration rate, **HCC** – hepatocellular carcinoma, **HIF1α** – hypoxia inducible factor 1α, **IBD** – inflammatory bowel disease, **IL** – interleukin, **ICV** – intracerebroventricular, **MEPE** – matrix extracellular phosphoglycoprotein, **MPKA** – mitogen-activated protein kinase, **MS** – metabolic symndrome, **NAFLD** – non-alcoholic fatty liver disease, **NASH** – non-alcoholic steatohepatitis, **NCC** – sodium chloride cotransporter, **NPT1** – sodium-dependent phosphate cotransporters, **PGC-1α** – peroxisome proliferator receptor γ coactivator protein-1α, **PHEX** – phosphate-regulating gene with homologies to endopeptidase on the X chromosome, **PI3K-Akt** – phosphatidylinositol 3-kinase-protein kinase B, **PKA** – protein kinase A, **PPARα** – peroxisome proliferator receptor α, **PTH** – parathyroid hormone, **SGK1** – serum/glucocorticoid-regulated kinase 1, **SREBP-2** – sterol regulatory element-binding protein 2, **STAT3** – signal transducer and activator of transcription 3, **UCP1** – mitochondrial uncoupling protein 1, **WAT** – white adipose tissue, **WNK4** – with-no-lysine kinase-4.

## Authors' Contribution

**A.Ł.**: concept of the article, literature review, writing the paper; **A.M.**: concept of the article, revising the paper. **Both authors** have read and approved the final version of the manuscript.

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## Conflict of Interest

The authors have no potential conflicts of interest to declare.

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