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Fibroblast growth factor 21 and its novel association with oxidative stress

Miguel Ángel Gómez-Sámano, Mariana Grajales-Gómez, Julia María Zuarth-Vázquez, Ma. Fernanda Navarro-Flores, Mayela Martínez-Saavedra, Óscar Alfredo Juárez-León, Mariana G. Morales-García, Víctor Manuel Enríquez-Estrada, Francisco J. Gómez-Pérez, Daniel Cuevas-Ramos*

Department of Endocrinology and Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

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ABSTRACT

Fibroblast growth factor 21 (FGF21) is an endocrine-member of the FGF family. It is synthesized mainly in the liver, but it is also expressed in adipose tissue, skeletal muscle, and many other organs. It has a key role in glucose and lipid metabolism, as well as in energy balance. FGF21 concentration in plasma is increased in patients with obesity, insulin resistance, and metabolic syndrome. Recent findings suggest that such increment protects tissue from an increased oxidative stress environment. Different types of physical stress, such as strenuous exercising, lactation, diabetic nephropathy, cardiovascular disease, and critical illnesses, also increase FGF21 circulating concentration. FGF21 is now considered a stress-responsive hormone in humans. The discovery of an essential response element in the *FGF21* gene, for the activating transcription factor 4 (ATF4), involved in the regulation of oxidative stress, and its relation with genes such as *NRF2*, *TBP-2*, *UCP3*, *SOD2*, *ERK*, and *p38*, places FGF21 as a key regulator of the oxidative stress cell response. Its role in chronic diseases and its involvement in the treatment and follow-up of these diseases has been recently the target of new studies. The diminished oxidative stress through FGF21 pathways observed with anti-diabetic therapy is another clue of the new insights of this hormone.

1. Introduction

Fibroblast growth factor 21 (FGF21) is a 209 amino acid protein in humans [1]. Its main actions are to regulate glucose and lipid metabolism, and energy balance [1]. It is synthesized mainly in the liver [2,3], but it is also expressed in white adipose tissue (WAT), brown adipose tissue (BAT) [4], pancreas [5], skeletal muscle [6], cardiac endothelial cells [7], and hypothalamus [8]. The main actions of circulating FGF21 are to increase glucose uptake in adipose tissue [5], augment lipolysis, enhance production of ketone bodies in the liver [9,10], and to regulate energy balance and physical stress responsiveness in humans [11]. FGF21 plasma concentration may increase with intense physical activity [12], after growth hormone treatment [13], during lactation [14], and after cold exposure [15]. Pathological physical stress conditions like obesity [16], anorexia nervosa [17], skeletal muscle autophagy deficiency [18], critical illness [19], hypothermia [20], amino acid deprivation or undernutrition [21], and nephropathy [22], also induce FGF21 expression (Fig. 1).

Many intracellular disturbances are associated with an increased expression of FGF21. Mitochondrial disorders that impair the oxidative phosphorylation (OXPHOS) and cause a diminished production of ATP [23], induce elevation of FGF21 serum concentration [24], thus it has been proposed as a serological marker in mitochondrial diseases [24]. Other kinds of intracellular stressors such as autophagy deficiency [18], disruption of the endoplasmic reticulum (ER) calcium homeostasis, and alteration of the ER redox balance [25,26] could induce FGF21 expression. Although the mechanisms by which FGF21 responds to oxidative stress are still subject of research, it is currently considered an important stress response hormone [9]. This review aims to summarize the role of FGF21 in the regulation of oxidative cell damage and the action of proteins and transcription factors involved in these pathways.

* Correspondence to: Department of Endocrinology and Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga # 15, Sección XVI, Tlalpan, 14000 Mexico City, Mexico.

E-mail addresses: miguelangelgomezsamano@gmail.com (M.Á. Gómez-Sámano), marianagrago@gmail.com (M. Grajales-Gómez), juliazuarth@gmail.com (J.M. Zuarth-Vázquez), fer.navarroflores@gmail.com (M.F. Navarro-Flores), mayela.saa@gmail.com (M. Martínez-Saavedra), oajl09@gmail.com (Ó.A. Juárez-León), marianaguadalupe.morales@upaep.edu.mx (M.G. Morales-García), vicmanuel280@gmail.com (V.M. Enríquez-Estrada), gomezperezfco@gmail.com (F.J. Gómez-Pérez), ceptamim@gmail.com (D. Cuevas-Ramos).

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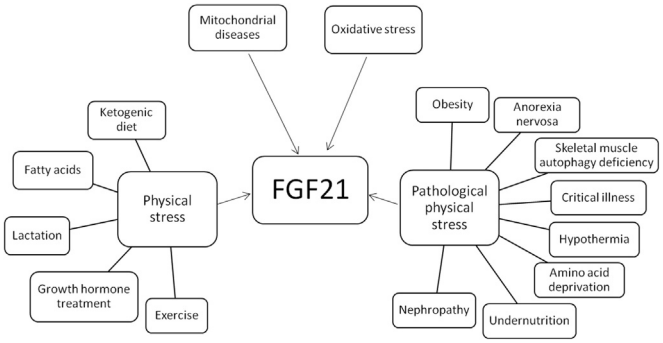

Fig. 1. Conditions associated with an increased FGF21 expression. FGF21 increases in four main circumstances: a) Mitochondrial diseases; b) oxidative stress, c) physical stress situations, such as ketogenic diets, free fatty acids release, lactation, treatment with exogenous growth hormone, and moderate to vigorous exercising; d) pathological physical stress such as obesity, anorexia nervosa, skeletal muscle autophagy deficiency, critical illness, hypothermia, amino acid deprivation, undernutrition, and diabetic nephropathy.

2. FGF21 and cellular oxidative stress

Oxidative stress is defined as an imbalance between pro-oxidant and anti-oxidant factors in favor of the former [27,28]. Pro-oxidants, such as reactive oxygen species (ROS), are chemically reactive molecules containing oxygen, hydroxyl radicals, hydroperoxyl, hydrogen peroxide, ketoaldehydes, and hydroxynonenal. ROS exert damage to DNA, proteins, and enzymes [29].

Human cells have defense mechanisms to protect against these harmful metabolites, for example, enzymes such as catalase and superoxide dismutase reduce oxygen radicals to H_2O_2 in the mitochondria [30,31]. In addition, dietary anti-oxidant molecules, like tocopherol or ascorbate, can donate hydrogen atoms to fatty acid radicals, stabilize cell membranes or change the function of enzymes like occurs with xanthine oxidase, alleviating oxidative stress [32].

Many chronic diseases are associated with an increased intracellular oxidative stress [33] (Fig. 2).

Recently, FGF21 has been considered a novel regulator of oxidative stress in humans. In cultured endothelial cells treated with oxidized low-density lipoproteins (oxLDL), an increased *FGF21* mRNA expression and protein concentration was observed [34]. The *FGF21* gene promoter has specific response elements (amino acid-responsive element [AARE1 and AARE2]) that are activated by the activating transcription factor 4 (ATF4), which is in turn, stimulated by ER stress produced by aminoacid deprivation or oxidative stress [25].

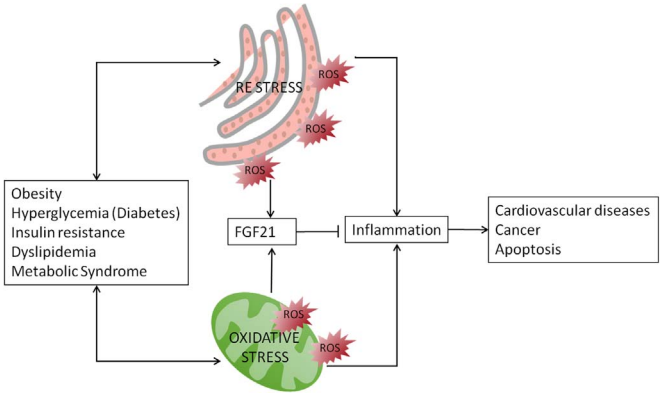

Fig. 2. FGF21 and its association with oxidative stress. Metabolic diseases, such as obesity, hyperglycemia, insulin resistance, dyslipidemia, and metabolic syndrome are in both-ways involved with the presence of endoplasmic reticulum stress and oxidative stress. Oxidative stress leads to inflammation responses that result in apoptosis and other pathologies like cardiovascular diseases and cancer. FGF21 inhibits inflammation in response to oxidative stress.

ER stress and oxidative stress is associated with the pathophysiology of metabolic disorders, contributing to insulin resistance, obesity, and type 2 diabetes mellitus (T2DM) [35–38]. ERS can be prompted by an increased unfolded protein load, altered calcium homeostasis or perturbed redox balance. If the homeostasis of the ER is altered, the unfolded protein response (UPR) is activated and in consequence FGF21 expression increases. (Fig. 2).

In consequence of ER stress many pathways are activated. Firstly, a transient protein synthesis arrest is observed; then, the ER increases its capacity to handle unfolded proteins, and the UPR target genes are activated [39]. This step restores the translational pathway. When the UPR is activated, three pathways are switched on: 1) the activating transcription factor 6 (ATF6), 2) the inositol-requiring enzyme 1 (IRE1), and 3) the protein kinase-like endoplasmic reticulum kinase (PERK). These ER membrane proteins are sensors of the ER that bind to the luminal chaperone and then, the immunoglobulin protein (BiP) GRP78 binds too [39,40] (Fig. 3).

However, when cells are exposed to ER stress, BiP separates from these sensors leading to their activation [41]. ATF6 increases chaperones and foldases expression as well as unfolded proteins degradation [42]. As part of the UPR, IRE1 increases ER folding capacity by detecting misfolded ER proteins and activates the transcription factor, X-box-binding protein 1 (XBP1). The activation of IRE1 induces site-specific splicing of XBP1 mRNA. The genes upregulated by XBP1 mRNA improve clearance of unfolded proteins and are associated with the increase of pro-survival functions, [43] besides, XBP1 binds to the endoplasmic reticulum stress elements (ERSE), that promote the expression of FGF21 [44,45]. When all these protective steps are unable to control the injuring stimulus, intracellular death pathways are activated [46,47].

PERK works as a protein sensor that mediates translational inhibition. During ER stress, PERK is activated and promotes the phosphorylation of serine 51 (Ser 51) of the eukaryotic initiation factor 2 alpha (eIF2 alpha). The eIF2 alpha inactivates protein synthesis in order to decrease the ER stress load [37,48,49]. Furthermore, eIF2 alpha phosphorylation prompts simultaneous induction of ATF4 [50], initiating the expression of its target gene, transcription factor C/EBP homologous protein (*CHOP*) [51,52].

This association has been demonstrated in CHOP−/− mouse primary hepatocytes. When exposed to TG-induced ER stress, *FGF21* transcriptional activation was impaired. On the other hand, overexpression of ATF4 and CHOP are related to *FGF21* promoter activation, in a time and dose-dependent manner [26].

ATF4 is a transcription factor that promotes the expression of FGF21 when ER stress is present [25]. It acts as a regulator of genes involved in redox homeostasis and amino acid metabolism [53]. ATF4 also up-regulates the expression of beta-Klotho, the co-receptor of FGF21 [54]. The common endpoint of these pathways is the inhibition of protein synthesis, increasing the translation of full-length ATF4, which in turn, regulates expression of DNA damage gene 34 (*GADD34*).

GADD34 is a subunit of the protein phosphatase complex that dephosphorylates eIF2 alpha, allowing the resumption of protein synthesis and translation of the UPR reprogrammed mRNA pool [55]. This gene is also involved in gene expression and amino acid metabolism related to antioxidant defense.

These pathways aim to restore protein synthesis, activate kinases and transcription factors to diminish ROS, NFkappaB action, apoptosis, and subsequently oxidative stress. FGF21 helps to diminish importantly the oxidative stress inducing three antioxidant mechanisms:1) activation of the uncoupling protein 3 (UCP3), and superoxide dismutase-2 (SOD2) that decrease ROS [7], 2) ERK (extracellular signal-regulated kinase), which induces activation of CREB (cAMP responsive element binding protein), repressing NFkappaB, that acts as a pro-inflammatory factor [56], and 3) activation of MAPK and p38, activates AMPK and decrease the apoptosis [4,57]. This evidence

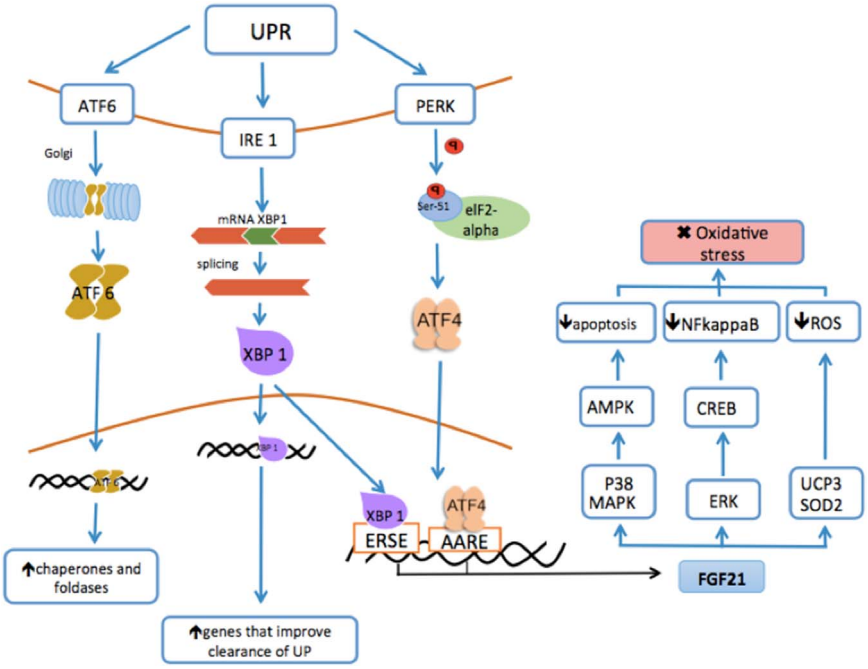

Fig. 3. Activation of FGF21 by the endoplasmic reticulum stress. Three pathways are induced by ER (Endoplasmic reticulum) stress: 1) the activating transcription factor 6 (ATF6), 2) the inositol-requiring enzyme 1 (IRE1), and 3) the protein kinase-like endoplasmic reticulum kinase (PERK). **ATF6** increases the expression of chaperones and foldases promoting the degradation of unfolded proteins. **IRE1** increases ER folding capacity by detecting misfolded ER proteins and inducing the site-specific splicing of X-box-binding protein 1(XBP1). **XBP1** activation up-regulates genes that improve clearance of unfolded proteins and enhance cell survival and binds the endoplasmic reticulum stress element (**ERSE**) to enhance the expression of FGF21. The **PERK** activation leads to the phosphorylation of serine-51 (Ser-51) of eukaryotic initiation factor 2 alpha (EIF2 alpha), a transcription factor that catalyzes the first step in the beginning of protein synthesis, in order to decrease the ER load. Furthermore, EIF2 alpha phosphorylation prompts simultaneous induction of ATF4 (activating transcription factor 4), which initiates the expression of its target gene, transcription factor C/EBP homologous protein (**CHOP**). Three antioxidant mechanisms are activated when FGF21 is expressed due to ER stress: 1) **UCP3** (uncoupling protein 3) and the **SOD2** (superoxide dismutase-2), decreasing the action of **ROS** (reactive oxygen species). 2) **ERK** (extracellular signal-regulated kinase) induces the activation of **CREB** (cAMP responsive element binding protein) repressing **NFkappaB** that works as a pro-inflammatory factor, and 3) **MAPK** (mitogen-activated protein kinase) and **p38** that activate **AMPK** (adenosine monophosphate kinase)**,** decreasing the apoptosis. Finally, oxidative stress is diminished.

strongly indicates that ER stress increases FGF21 synthesis as a protective event.

3. FGF21 and transcription factors related to oxidative stress (Table 1)

The hepatic expression of FGF21, induced by protein restriction, may act as an endocrine signal of low-protein intake. This augmented expression correlates with a phosphorylation of eIF2 alpha in the liver [58], which stimulates ATF4 [50]. FGF21 KO mice are fully resistant to low protein-induced changes in food intake, energy expenditure (EE), body weight gain, and metabolic gene expression. This has been confirmed in an experimental study performed for 6 months [59].

Nrf2 (nuclear factor E2-related factor 2) is another transcription factor related to oxidative stress that promotes diverse antioxidant genes. Nrf2 is a key redox regulator in many organs and also it has been involved in cardiovascular diseases [60]. In the pancreatic beta cells it induces the expression of glutathione-related genes in order to reduce apoptosis mediated by nitric oxide [61]. Its functions have been described under basal and stress conditions [62]. Nrf2 is negatively regulated by an adaptor protein Keap1 (Kelch-like ECH-associated protein 1) [63].

Nrf2 increases hepatic *FGF21* expression and plasma FGF21 concentration in diabetic db/db and high-calorie-diet-induced obesity mice models [64]. When Keap1 is exposed to oxidative stimuli, Nrf2 is protected against the proteasome-mediated degradation [65], translocates and accumulates in the nucleus and forms an heterodimer with small Maf proteins, then it binds to the antioxidat/electrophile responsive element (ARE/EpRE). This oxidative stress-response system is called the Keap1-Nrf2 system [66]. Besides the important functions of antioxidance and detoxification, the Keap1–Nrf2 system is involved in the regulation of metabolically stressed conditions [67–69]. Keap1 knock-out mice show an increase in FGF21 plasma concentration and *FGF21* hepatic expression, by Nrf2 induction. Also FGF21 increases when Nrf2 is induced by oleanolic triterpenoid 1-[2-cyano-3,12-dioxooleane-1, 9(11)-dien-28-oyl] imidazole in diabetic db/db and high-calorie-diet-induced obesity mice models [64]. Thus, FGF21 is a biomarker of the activation of the Keap1-Nrf2 system [64].

Thioredoxin binding protein-2 (TBP-2), also known as thioredoxin-interacting protein, is an alpha arrestin protein that binds to thior-

Table 1
Relationship between FGF21 and key transcription factors associated with oxidative stress.

Transcription factor	Association with FGF21	Bibliography
Nrf2	When Nrf2 is induced, *FGF21* gene expression and FGF21 plasma concentration increases in db/db diabetic mice	[64]
ATF4	It has been linked to the adaptive response to oxidative stress and identified as a clear FGF21 expression inductor The promoter region of FGF21 has specific binding sites for ATF4	[25,26,54]
TBP-2	Mice with liver deletion of Tbp-2 show enhanced insulin sensitivity as well as an increased expression of FGF21	[72]

Nrf2: nuclear factor erythroid-derived 2; ATF4: activating transcription factor 4; TBP2: thioredoxin binding protein-2.

edoxin, an antioxidant protein involved in redox signaling, essential for cell growth and survival [70]. The over-expression of TBP-2 causes impairment of insulin sensitivity and insulin secretion, leading to beta cell apoptosis [71]. It has also been involved in the regulation of transcription factors associated with G protein-coupled receptors involved in metabolic homeostasis and cancer suppression [70].

Mice with liver deletion of TBP-2 showed an enhanced insulin sensitivity with improvement in glucose-induced insulin secretion related with higher expression of PPAR alpha target genes such as *FGF21* [72].

Autophagy is a cellular process that transports cytoplasmic constituents to lysosomes for degradation of proteins and recycling of organelles or nutrients [73]. Autophagy defects have been associated with altered insulin secretion [74] and insulin resistance [75]. Since skeletal muscle accounts for 80% of whole-body insulin-mediated glucose utilization [76], a mice model with skeletal muscle autophagy-deficiency with a deletion of autophagy related 7 (Atg7) transcription factor showed altered mitochondrial function. Interestingly, induction of FGF21 by the ATF4 pathway was reported, exerting a decrease in fat mass, improving insulin sensitivity, and showing resistance to diet-induced obesity [18].

4. FGF21 and diseases with an increased oxidative stress

Mitochondrial DNA mutations cause elevation of FGF21 [24]. Recently, it was shown that preprogeroid polymerase gamma mutator (*POLG*) mouse that accumulates point mutations and deletions in their mitochondrial genome, produced an increment in FGF21. When challenged with a high fat diet, these mice were resistant to diet-induced obesity, highlighting a metabolically favorable synergy between mitochondrial stress and FGF21 [77].

Critical illnesses are also characterized by mitochondrial damage and FGF21 elevation [24,78]. In a cross-sectional study of 405 critically ill subjects, serum FGF21 concentration was 8-fold higher than in control subjects ($P < 0.0001$). In a rabbit model of critical illness, hepatic FGF21 expression was correlated with mitochondrial dysfunction and an integrated stress response (ISR) markers ($r^2=0.48$, $p < 0.0006$; and $r^2=0.73$, $p < 0.0001$ respectively) [19]. Also, the correction of hyperglycemia decreased FGF21 concentrations. Noteworthy, elevated serum FGF21 concentration was higher in the sickest patients who did not survive ($p < 0.006$), suggesting that FGF21 is a stress or cell damage-induced response [19]. As described above, the ISR activation in critical illness phosphorylates eIF2 alpha which blocks the activation of protein translation, and promotes the translation of transcription factor ATF4, regulating FGF21 expression [79].

Diabetic nephropathy is an oxidative-stress related condition [80]. In previous studies with patients with T2DM and diabetic nephropathy, there was proof of higher serum concentration of FGF21, demonstrating a negative relationship between FGF21 and glomerular filtration rate [22]. In addition, FGF21 have shown a positive correlation with albuminuria [81]. The intraperitoneal administration of FGF21 in mice, exerted an improvement in albuminuria, reversing mesangial expansion, and reducing pro-fibrotic molecules such as inhibitor-1 plasminogen activator (PAI-1) and transforming growth factor beta 1 (TGF beta1). Moreover, FGF21 reduced the oxidative stress in the kidneys inhibiting the pro-inflammatory pathway of nuclear factor kappa beta (NF-kB) [82]. The association between diabetic nephropathy pathophysiology and FGF21 concentration plays an important role in the inhibition of oxidative stress and subsequent fibrosis [83], as well as its action in decreasing lipotoxicity damage and apoptosis.

5. Effect of FGF21 on anti-diabetic drugs and its relationship with oxidative stress

FGF21 appears to be a mediator of the therapeutic effects of drugs involved in the treatment of some metabolic diseases [84]. Metformin reduces the plasma glucose concentration through the inhibition of glucose absorption in the intestine, suppression of gluconeogenesis in the liver and the improvement of the insulin action in the periphery [85]. To suppress liver gluconeogenesis, metformin induces adenosine monophosphate kinase (AMPK) activation, which in turn inhibits transcription of hepatic gluconeogenic enzymes [86]. Some studies have shown increased FGF21 serum concentration after metformin treatment in hepatocytes in an AMPK activation-dependent manner [87]. Also, it has been suggested that the FGF21 upregulation by metformin depends on the elF2 alpha-ATF4 axis [88], which is involved in the oxidative stress response. Moreover, the increased expression of FGF21 in the liver may be associated with the gluconeogenic gene glucose 6-phosphatase (*G6Pase*) suppression, and the increased glucose uptake by GLUT1 [89,90]. Taking together, the increment of FGF21 serum concentration contributes to the beneficial metabolic effects of metformin [91].

Other drugs to treat diabetes and also related with increment of FGF21, are the glucagon like peptide-1 (GLP1) analogs. GLP1 is an incretin hormone released by L-cells at small intestine that enhances beta cells insulin release under hyperglycemia, and suppresses glucagon secretion by pancreatic alpha cells. In addition, GLP1 inhibits gastric emptying contributing to satiety sensation and reduction in food intake [92]. GLP1 analogs protect cardiomyocytes against apoptosis via inhibition of endoplasmic reticulum stress [93]. GLP1-derived nonapeptide GLP1(28-36) protected pancreatic β-cells from glucolipotoxicity in increased oxidative stress conditions, independently of the GLP1 receptor [94].

GLP1 analogs are also able to promote FGF21 expression. Especially, Liraglutide induce *FGF21* gene expression in the liver [95]. The administration of another GLP1 analog, Exendine-4, for 10 weeks augmented hepatic *FGF21* gene expression in mice fed with high fat diet compared to control [96]. However, opposite results were recently reported, where hepatic expression and FGF21 serum concentration were decreased with exedin-4 treatment in mice also fed with high fat diet for 4 weeks [84]. Therefore, more studies are needed to clarify FGF21 role using such drugs in patients with diabetes.

Also, the administration of FGF21 analogs in humans have demonstrated favorable effects on body weight, fasting insulin, and adiponectin when administered for 28 days in obese T2DM subjects [97]. Recently, in a phase I study, a long acting FGF21 analog produced a decrease in triglyceride concentration, as well as a reduction in total cholesterol and low-density lipoprotein cholesterol, and an increase in high-density lipoprotein cholesterol observed in the high-dose groups [98].

6. Conclusions

FGF21 is considered a new novel metabolic hormone related with glucose and lipid metabolism, insulin resistance, and obesity. Its role as an important regulator of mitochondrial and oxidative stress has been consistently demonstrated in experimental studies. Also the multiple beneficial effects on human disorders and its therapeutic potential by attenuating apoptosis, ER stress, inflammation, and its consequences have been studied recently. Therefore, FGF21 is a human stress-response hormone, synthesized and released in order to decrease cell damage. Prospective studies are required to address the questions if supra-physiological concentrations of FGF21 might improve the conditions associated with an increased oxidative stress, and to assess the effects of an increased oxidative stress in FGF21 knock-out mice.

Declaration of interest

The authors have no multiplicity of interest to disclose.

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Author contributions

All authors contributed equally to this work.

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