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REVIEW

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Effects of metformin on fibroblast growth factor 21 in patients with type 2 diabetes mellitus: faraway but so close

Hayder M. Al-kuraishy[1*], Ali I. Al-Gareeb[1], Majid S. Jabir[2] and Salim Albukhaty[3,4*]

Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance (IR) and hyperglycemia. The development of inflammatory disorders in T2DM triggers the activation of different growth factors as a compensatory mechanism to reduce IR and adipose tissue dysfunction in T2DM. Fibroblast growth factor 21 (FGF21) which is involved in the regulation of glucose homeostasis is attractive to be a novel therapeutic target in the management of T2DM. FGF21 has poor pharmacokinetic profile as it rapidly degraded; therefore, FGF21 analogs which are more stable can be used in T2DM patients. However, FGF21 analogs are tested pre-clinically but not approved in clinical settings. Therefore, searching for anti-diabetic agents who enhance FGF21 expression is mandatory. It has been shown that metformin which used as a first-line in the management of T2DM can positively affect the expression of FGF21, though the underlying mechanisms for metformin-induced FGF21 expression are not fully elucidated. Therefore, this review from published studies aimed to find how metformin improves insulin sensitivity through FGF21-dependent pathway in T2DM. In conclusion, metformin improves FGF21 signaling in T2DM, and this could be a novel mechanism for metformin in the amelioration of glucose homeostasis and metabolic disorders in T2DM patients.

Keywords Type 2 diabetes mellitus, Fibroblast growth factor 21, Metformin

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance (IR) and hyperglycemia [1]. T2DM is linked with inflammatory disorders and end-organ injury due to hyperglycemia-induced oxidative stress and the release of pro-inflammatory cytokines [2]. IR and relative insulin deficiency due to pancreatic β cell dysfunction is the major feature of T2DM [3]. Activation of inflammatory disorders in T2DM occurs due to immune cell deregulation and infiltration of immune cells into adipose tissue that advances the expression of pro-inflammatory cytokines with the development of systemic inflammation [3]. Extended low-grade inflammation in T2DM by hyperglycemia and adipose tissue activation increases the development of IR and associated complications [4]. Inflammatory disorders participate in the progression of IR, T2DM, and systemic complications [5]. It has been revealed that hypoglycemia and hyperglycemia as well as glucose variability activate oxidative stress which enhances inflammatory disorders [6]. Furthermore, environmental and genetic factors such as stress, diet, and smoking are affianced with the activation of

*Correspondence:
Hayder M. Al-kuraishy
haydermutter@uomustansiriyah.edu.iq
Salim Albukhaty
albukhaty.salim@uomisan.edu.iq
[1] College of Medicine, Al-Mustansiriyah University, P.O. Box 14132, Baghdad, Iraq
[2] Department of Applied Science, University of Technology-Iraq, Baghdad, Iraq
[3] Department of Chemistry, College of Science University of Misan, Maysan, Iraq
[4] College of Medicine, University of Warith Al-Anbiyaa, Karbala, Iraq

chronic inflammation in T2DM [7]. These inflammatory changes trigger the activation of different growth factors as a compensatory mechanism to reduce IR and adipose tissue dysfunction in T2DM [8]. One of the most important growth factors is fibroblast growth factor 21 (FGF21) which is involved in the regulation of glucose homeostasis by increasing insulin sensitivity [9]. Of note, the insulin-sensitizing drug metformin which is used as a first-line in the management of T2DM can positively affect the expression of FGF21 [10]. Therefore, this review of published studies aimed to find how metformin improves insulin sensitivity through the FGF21-dependent pathway in T2DM.

Fibroblast growth factor 21

FGF21 is a peptide hormone released from the liver as a member of different hormones called hepatocytes [11]. FGF21 is extremely expressed in the liver, pancreas, and adipose tissues [12]. Skeletal muscles and other tissues also produce FGF21 via a phosphoinositide 3 kinase (PI3K)-mediated pathway [13]. Expression of FGF21 differs by diverse pathophysiological conditions, fasting, and exercise which increases FGF21 expression in the liver and muscles correspondingly [14]. In addition, satiety and cold exposure augment FGF21 expression in the pancreas and adipose tissue correspondingly [15]. Different cellular signaling affects FGF21 expression like liver X receptor (LXR) which inhibits FGF21 expression [16]. FGF21 expression is also induced by thyroid hormones and fructose [17]. A chronic low-protein diet promotes FGF21 expression which improves the metabolic profile [18]. Hepatic FGF21 expression is induced by peroxisome proliferator activator receptor alpha (PPAR-α), and adipose tissue FGF21 expression is induced by PPAR gamma (PPAR-α) [19]. However, mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2) and sirtuin-1 (SIRT1) specifically induce FGF21 expression [20]. FGF21 binds four types of FGF receptors 1–4. Interaction of FGF21 with its receptor is improved by β-Klotho which is a transmembrane protein that acts as a co-receptor for FGF21 [15]. FGF21 augments glucose uptake and gluconeogenesis [21]. FGF21 has many beneficial effects on different body systems (Fig. 1).

Pharmacology of metformin

Metformin is an insulin-sensitizing agent reduces IR [22, 23]. Metformin is 3-(diaminomethylidene)-1,1-dimethylguanidine [24] (Fig. 2).

Metformin is an orally active drug, absorbed from the small intestine via plasma membrane monoamine transporter (PMAT) expressed in the enterocytes [25]. Organic cation transporter 2 (OCT2) which is expressed on the brush border of enterocytes is concerned with the uptake of metformin [26]. Hepatic uptake of metformin is mostly by OCT1 and less by OCT3. The uptake of metformin by the renal epithelial cell is mediated by

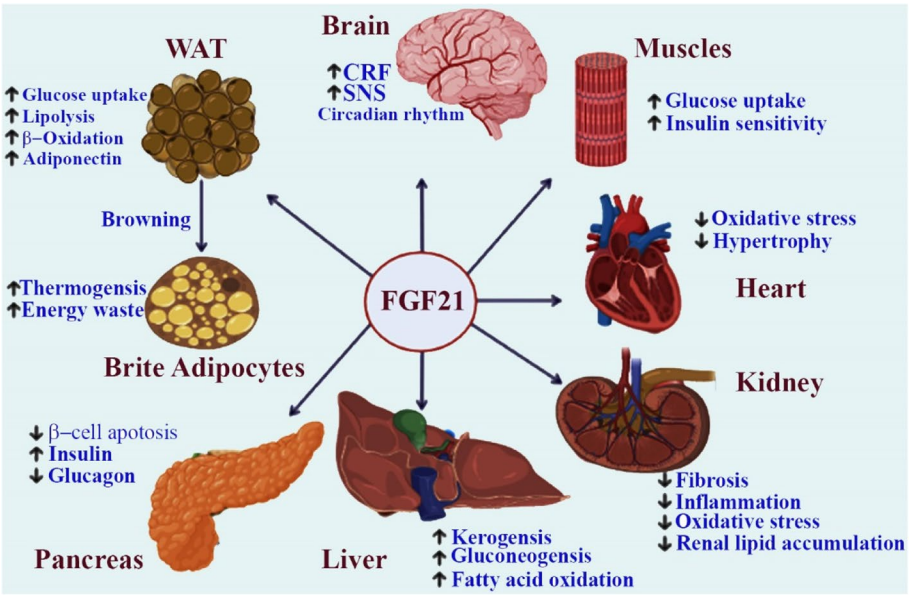
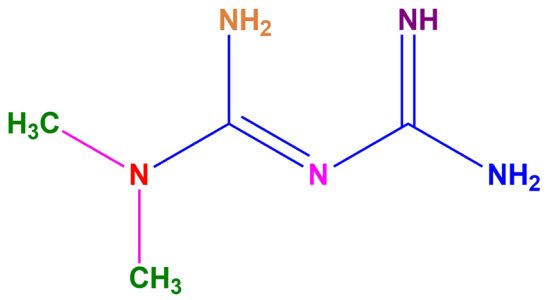


Fig. 1 Endogenous FGF21 expression and interaction in metabolic organs. The liver, white and brown adipose tissue, skeletal muscle, the pancreas, and the heart are among the metabolic organs that express and secrete FGF21 in response to diverse stimuli [13, 15, 18, 20]. The FGFR1/KLB complex in the brain and white adipose tissue can be targeted by systemic FGF21, which is mostly produced by the liver. CRF, corticotropin-releasing factor; SNS, sympathetic nervous system; FGF21, fibroblast growth factor-21; WAT, white adipose tissue



(*E*)-2-carbamimidoyl-1,1-dimethylguanidine
Chemical Formula: $C_4H_{11}N_5$
Exact Mass: 129.10
Molecular Weight: 129.16
m/z: 129.10 (100.0%), 130.10 (6.2%)
Elemental Analysis: C, 37.20; H, 8.58; N, 54.22

Fig. 2 Chemical structure of metformin

OCT2, and its excretion by the kidney is through multidrug and toxin extrusion 1 (MATE1) [27]. Metformin is not metabolized and is excreted unchanged by the kidney. Metformin half-life is 5 h, highly distributed, and its plasma steady state ranged 54–4133 [28]. Metformin has an exclusive pharmacodynamic effect (Fig. 3); metformin is a positive charge molecule, extremely accumulated in the mitochondria because of the negative charge of the mitochondrial membrane [29].

Metformin inhibits ATP production through the inhibition of mitochondrial complex I leading to an increase AMP: ATP with increasing levels of adenosine monophosphate protein kinase (AMPK) [32]. AMPK inhibits gluconeogenesis and fat synthesis, decreases hepatic fat storage, and improves insulin sensitivity and anaerobic glucose metabolism in the enterocytes [30]. Metformin promotes glucose utilization by gut microbiota with the activation release of glucagon-like peptide 1 (GLP-1) from L cells in the intestine [33]. Furthermore, metformin improves peripheral glucose utilization by increasing the expression of glucose transporter type 4 (GLUT4) with subsequent improvement of insulin sensitivity [31]. Moreover, metformin has pleiotropic properties like anti-inflammatory and oxidant effects thereby reducing the risk of diabetic complications [34].

Prolonged use of metformin is linked with the development of various adverse effects counting gastrointestinal disorders like diarrhea, nausea, vomiting, abdominal pain, and loss of appetite [35]. Nevertheless, prolonged use of metformin is linked with the development of weight loss, B_{12}, and folate deficiency with a risk of

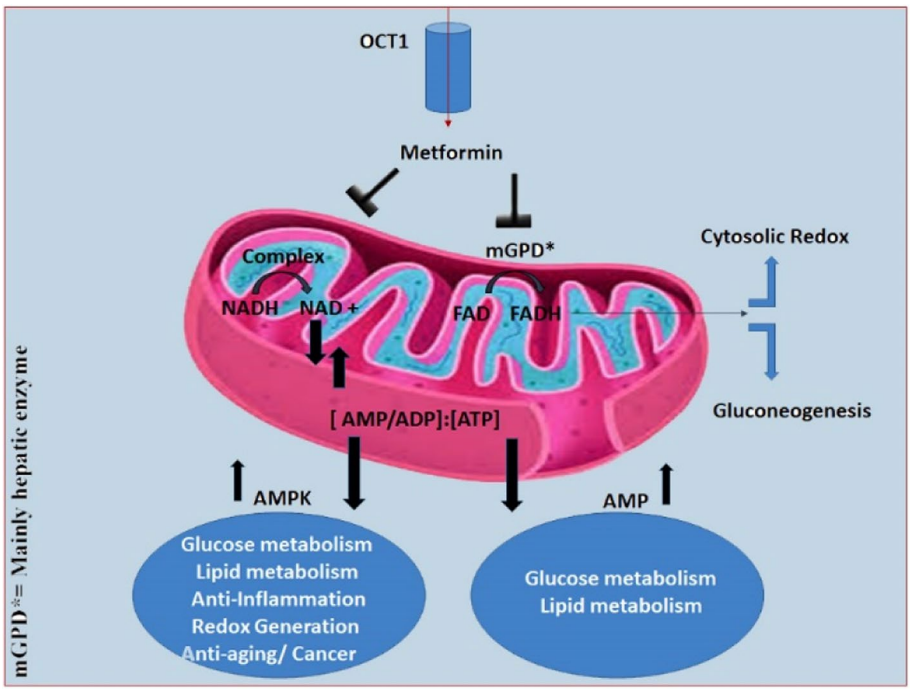


Fig. 3 Metformin's pharmacodynamics pathway. Cells have been stylized to show how metformin works. Metformin appears to elevate insulin sensitivity and AMPK levels, which improves glucose transport [30, 31]. AMP, adenosine monophosphate; AMPK, adenosine monophosphate-activated protein kinase; mGPD, mitochondrial glycerophosphate dehydrogenase; OCT1, organic cation transporter 1; NAD, nicotinamide adenine dinucleotide; NADH, H for hydrogen; FADH, flavin adenine dinucleotide

peripheral neuropathy and cognitive impairment [36]. A rare but serious adverse effect related to metformin use is lactic acidosis which developed due to a reduction in the use of lactate by inhibited gluconeogenesis process [37]. Metformin toxicity due to overdosage leads to hypoglycemia and lactic acidosis; it is treated by hemodialysis [38].

Moreover, metformin had low interaction with other drugs as it was not metabolized and excreted unchanged by the kidney [39]. Aspirin and anti-diabetic agents increase the risk of hypoglycemia when used with metformin [40], though some drugs like cimetidine, topiramate, ranolazine, and cephalexin increase the risk for the development of lactic acidosis by competing with metformin renal excretions [39].

Effects of metformin on FGF21 in T2DM

FGF21 in T2DM

It has been reported that FGF21 plays a critical role in the regulation of glucose metabolism and can be used as a monotherapy in the management of T2DM [41]. FGF21 exerts a beneficial effect on T2DM and obesity by reducing blood glucose and restoring the function of adipose tissue respectively [42]. Of note, FGF21 expression is increased in T2DM patients as a compensatory mechanism to counteract inflammatory disorders and associated IR [43]. An experimental study illustrated that hepatic expression of FGF21 mRNA was increased in mice with a high-fat diet [44]. Obesity in children increases circulating FGF21 levels due to the development of FGF21, and weight loss decreases FGF21 levels [45]. It has been shown that FGF21 level is increased during fasting; however, this reaction is impaired in mice with experimental diabetes [46]. FGF21 analog LY2405319 was confirmed to improve blood glucose in streptozotocin-induced diabetes in mice through modulation metabolism of brown adipose tissue (BAT) [46]. Furthermore, there is a significant change in postprandial FGF21 level in diabetes according to preclinical and clinical findings [47, 48]. FGF21 level is higher in T2DM patients compared to controls due to the development of FGF21 resistance [47]. Chavez et al. [49] observed that circulating FGF21 level is increased in patients with impaired glucose tolerance and T2DM that correlated with IR. A population-based prospective study in China observed that higher FGF21 level in prediabetes subjects was a predictor for the development of T2DM within 5.4 years [50].

Under normal physiological conditions, glucose stimulates while insulin inhibits FGF21 secretion [51]. However, FGF21 secretion is mainly driven by blood glucose independent of insulin or glucagon-like peptide 1 (GLP-1) secretion in normal healthy subjects [51]. In addition, many studies reported that insulin did not affect FGF21 secretion [52, 53]. However, super-physiological insulin level enhances FGF21 secretion [54]. In addition, glucagon enhances FGF21 secretion independent of insulin level [55]. Similarly, glucagon promotes hepatic expression of FGF21 [56]. In T2DM, glucagon and insulin levels are augmented and implicated in the development of diabetic complications [57]. Therefore, increasing glucagon and insulin levels in T2DM together with FGF21 resistance may explain a higher level of FGF21 in T2DM patients.

Of note, FGF21 has a poor pharmacokinetic profile; it rapidly degraded in vitro and in vivo, so it has a short half-life [46]. Therefore, FGF21 analogs could be novel therapeutic agents for the management of T2DM and metabolic disorders [58]. Therefore, FGF21 analogs that are more stable can be used in T2DM patients. It has been shown that in two administrations of FGF21 analogs, mFGF21 was more effective than insulin glargine and GLP-1 receptor agonist liraglutide in the reduction of glycated hemoglobin level, improvement of insulin sensitivity, and lipid profile [59]. The half-life of mFGF21 is 20 times longer than FGF21, so it induces rapid and persistent reduction of blood glucose independent of insulin secretion without risk of hypoglycemia [58]. In addition, mFGF21 increases the expression of glucokinase (GK) and GLUT-1 leading to more reduction of blood glucose [59]. Additionally, FGF21 analogs AKR-001 improve insulin sensitivity and reduce metabolic complications in FGF21 analogs [60]. A previous clinical trial on the use of FGF21 variant LY2405319 (LY) compared to placebo in obese patients with T2DM revealed that LY use for 4 weeks improves dyslipidemia and insulin sensitivity with significant reduction of atherogenic risk [61]. These findings indicated that FGF21 analogs are highly effective in the management of T2DM.

The underlying mechanism for the reduction of blood glucose is related to the inhibition of G6Pase and activation of GK and GLUT-1 as illustrated in Fig. 4.

Metformin and FGF21

It has been reported from preclinical and clinical findings that metformin increases the expression of FGF21 [62–64]. In vitro and in vivo studies showed that metformin promotes the expression of FGF21 through AMPK dependent pathway [62]. In addition, metformin increases FGF21 expression through the induction of expression of activating transcription factor 4 (ATF4) [62]. Metformin therapy for 6 months in T2DM patients increased FGF21 circulating level through ATF4 [62]. ATF4 in addition to its neurological is also involved in the regulation of lipid and glucose metabolism through modulation of insulin secretion and sensitivity [65]. It has been shown that metformin has protected against

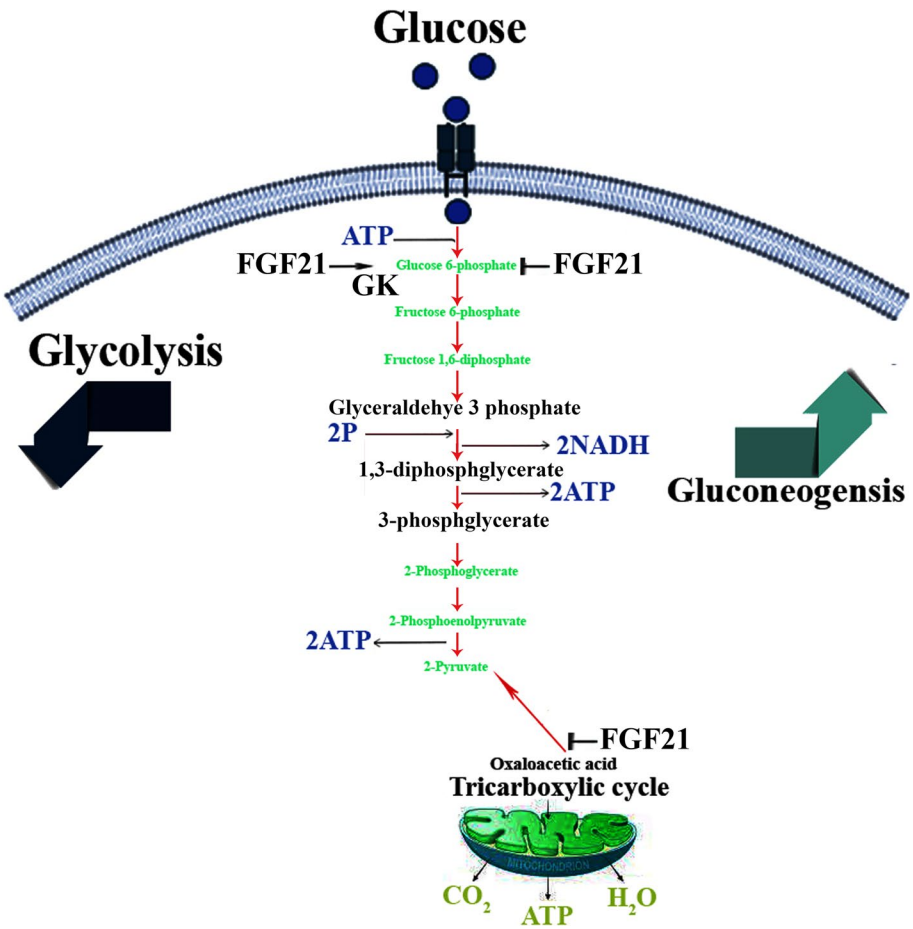


Fig. 4 The glucose-lowering effect of FGF21. FGF21, fibroblast growth factor-21; ATP, adenosine triphosphate; ADP, adenosine diphosphate

lipopolysaccharide (LPS)-induced inflammation by increasing the expression of FGF21 in rats [66]. Furthermore, metformin improves blood glucose and increases the expression of hepatic FGF21 via AMPK pathway [63]. Therefore, FGF21 seems to be a potential mediator for the action of metformin in the regulation of glucose homeostasis and metabolic adaptive response [67].

Moreover, metformin regulates metabolic balance through the induction expression of FGF21 in adipocytes and the liver [64]. Increasing expression of FGF21 by metformin not only regulates blood glucose but also contributes in the regulation of autoimmune response and atherogenic risk [68, 69]. Metformin through AMPK/FGF21 improves the differentiation of brown adipose tissue and regulates immune balance in obese mice [68]. In addition, metformin reduces the progression of atherosclerosis by increasing the expression of FGF21 [69].

Of note, β-Klotho which is a co-receptor for FGF21 [15] is also deregulated in T2DM [70]. Notoriously, β-Klotho/FGF21 complex seems to be an attractive target in the management of T2DM [70]. It has been observed that β-Klotho serum is reduced in T2DM [71], and this may explain the development of FGF21 resistance in T2DM patients. A case–control study involving 261 T2DM and 106 healthy controls observed that β-Klotho serum reduced as compared to controls [71]. Notably, β-Klotho is highly downregulated in T2DM patients, and downregulation induces the development of diabetic complications [70]. Therefore, amelioration of β-Klotho expression by anti-diabetic agents may reduce the risk of diabetic complications. Interestingly, metformin promotes β-Klotho expression thereby it acts as anti-aging agent [23]. In addition, metformin prevents diabetic nephropathy by increasing the expression of β-Klotho [72].

It has been shown that diabetic mice had low FGF21 sensitivity due to higher circulating miR34a levels [73]. Consequently, increasing of β-Klotho and its effectors SIRT1 and ERK by metformin was shown to improve FGF21 sensitivity [73], though over-expression of FGF21 in T2DM may lead to FGF21 resistance [74]. Furthermore, IR and high pro-inflammatory cytokines

like TNF-α repress the expression of β-Klotho leading to FGF21 resistance in adipocytes that further aggravate inflammatory disorders [75]. Thus, mitigation of IR by metformin can regulate β-Klotho expression and abrogate FGF21 resistance. These observations suggest that metformin via increasing β-Klotho expression can enhance the functional activity of FGF21.

Chau et al. [76] illustrated that FGF21 regulates energy metabolism by increasing the expression of PGC-1α, SIRT1, and AMPK. Inhibition of PGC-1α, SIRT1, and AMPK reduces the effect of FGF21 on gene expression and oxygen consumption by adipocytes with the development of FGF21 resistance [76]. Of note, metformin activates PGC-1α, SIRT1, and AMPK [77, 78]. Metformin attenuates pancreatic β cell apoptosis and prevents IR via the activation of PGC-1α, SIRT1, and AMPK [77]. In addition, metformin prevents gluconeogenesis through increasing the expression of hepatic PGC-1α [78]. Henceforth, metformin through modulation of PGC-1α, SIRT1, and AMPK improves FGF21 signaling and reduces FGF21 resistance.

Moreover, metformin increases the production of GLP-1 from L cells with significant protection of GLP-1-producing cells [79]. Analysis from clinical trials illustrated that metformin increases the release of GLP-1 [80]. GLP-1 acts additively with FGF21 against the development of T2DM in mice [81]. Genetic ablation of glucagon receptor increases FGF21 expression [81]; therefore, increasing GLP-1 by metformin reduces glucagon and improves the release of FGF21. Remarkably, GLP-1 blocks hepatic glucose output through increasing expression of FGF21 [82]. Therefore, glucose homeostasis induced by GLP-1 is mediated by FGF21 signaling. Supporting this notion, the inhibition of FGF21 receptors by antibodies reduced the inhibitory effect of GLP-1 on hepatic glucose output [82]. Thus, metformin improves FGF21 by increasing the expression of GLP-1 in patients with T2DM.

Furthermore, metformin augments the expression of anti-inflammatory growth differentiation factor 15 (GDF15) which reduces body weight and improves insulin sensitivity [24, 83]. GDF15 improves the expression of β-Klotho in experimental acute kidney injury [84]. Fasting promotes the expression of FGF21 which enhances the release of GDF15 which in turn enhance the release of FGF21 [85]. In addition, both of FGF21 and GDF15 are augmented in response to mitochondrial dysfunction [86]. Of note, cold exposure activates sympathetic drive which promotes release of GDF15 though FGF21 [87]. Therefore, metformin through activation of GDF15 improves the expression and release of FGF21. Regarding role of inflammatory disorders in T2DM and their effects on the expression on GDF15 and FGF21, it has been shown that pro-inflammatory cytokines, p53, and angiotensin II promote the expression and release of GDF15 [88, 89]. Besides, proinflammatory cytokines attenuate the metabolic effect of FGF21 leading to FGF21 resistance [90]. Therefore, increasing of GDF15 by metformin can mitigates the inflammatory disorders in T2DM and enhances FGF21 action. In addition, FGF21 is anti-inflammatory by inhibiting the inflammatory signaling pathway NF-κB and increasing expression of anti-inflammatory nuclear factor erythroid 2-related factor 2 (Nrf2) [91]. Therefore, the anti-inflammatory effects of metformin might be mediated by FGF21. In this state, there is a complex interaction between GDF15 and FGF21 during inflammatory reactions in T2DM.

Of note, liver X receptor (LXR) inhibits FGF21 expression [16]. High-cholesterol fed promotes expression of LXR which reduces expression of FGF21 expression [16]. Likewise, LXR agonists TO-901317 reduce expression of FGF21 to protect the liver from cholesterol accumulation and intrahepatic lipolysis [16]. In addition, fasting-induced expression of FGF21 is inhibited by LXR agonists via the activation of histone deacetylase 3 (HDAC3) co-repressor in mice [92]. LXR is involved in lipid and glucose homeostasis, and dysregulation of LXR is involved in the pathogenesis of T2DM. Genetic variation of LXR is implicated in T2DM as confirmed in a clinical study [93]. Dysregulation of LXR in T2DM increases the risk for the development of nonalcoholic fatty liver disease (NAFLD) [94]. Different studies illustrated that metformin is effective against the development NAFLD in T2DM by various molecular mechanisms inclusion repression expression of LXR [95, 96]. It has been shown by many studies that metformin can reduce the expression of LXR [97, 98]. Metformin attenuates the development of NAFLD by downregulating the expression of LXR in mice [97]. Similarly, metformin reduces the hypothalamic pituitary adrenal axis in T2DM through induction phosphorylation of LXR in the pituitary [98]. Therefore, metformin through modulation of LXR can improve FGF21 expression.

Furthermore, hepatic FGF21 expression is induced by PPAR-α [19]; thus, PPAR-α agonists can enhance FGF21 expression [99]. Interestingly, metformin induces expression of GLP-1 independent of AMPK pathway but through activation of PPAR-α in mice [100]. In addition, metformin reduces the risk of atrial fibrillation in T2DM patients through induction expression of PPAR-α which regulates lipid metabolism in the atria [101]. Herein, metformin through induction of PPAR-α improves FGF21 expression.

Taken together, metformin improves FGF21 signaling in T2DM, and this could be a novel mechanism for

metformin in the amelioration of glucose homeostasis and metabolic disorders in T2DM patients.

Conclusions

T2DM is a chronic metabolic disorder characterized by IR and hyperglycemia. Commencement of inflammatory disorders in T2DM occurs due to immune cell deregulation and infiltration of immune cells into adipose tissue that advances the expression of pro-inflammatory cytokines with the development of systemic inflammation. These inflammatory changes stimulate the activation of different growth factors as a compensatory mechanism to reduce IR and adipose tissue dysfunction in T2DM. One of the most important growth factors is FGF21 which is concerned with the regulation of glucose homeostasis by increasing insulin sensitivity. Of note, the insulin-sensitizing drug metformin which is used as a first-line in the management of T2DM can positively affect the expression of FGF21. FGF21 plays a critical role in the regulation of glucose metabolism and can be used as a monotherapy in the management of T2DM. FGF21 expression is increased in T2DM patients as a compensatory mechanism to counteract inflammatory disorders and associated IR. Glucagon promotes hepatic expression of FGF21 and in T2DM; glucagon and insulin levels are augmented and implicated in the development of diabetic complications. Therefore, increasing glucagon and insulin levels in T2DM together with FGF21 resistance may explain a higher level of FGF21 in T2DM patients. FGF21 has a poor pharmacokinetic profile; it rapidly degraded, so it has a short half-life. Thus, FGF21 analogs could be novel therapeutic agents for the management of T2DM and metabolic disorders. FGF21 analogs which are more stable can be used in T2DM patients. However, FGF21 analogs are tested preclinically but not approved clinical settings. Therefore, searching for anti-diabetic agents who enhance FGF21 expression is mandatory.

Metformin increases expression of FGF21 through AMPK dependent pathway. In addition, metformin increases FGF21 expression via induction of expression of different signaling pathways including PGC-1α, SIRT1, GDF15, PPAR-α, and GLP-1. In addition, β-Klotho which is a co-receptor for FGF21 is also deregulated in T2DM. Interestingly, metformin promotes β-Klotho expression. Therefore, mitigation of IR by metformin can regulate β-Klotho expression and abrogate FGF21 resistance. Henceforth, metformin improves FGF21 signaling in T2DM, and this could be a novel mechanism for metformin in the amelioration of glucose homeostasis and metabolic disorders in T2DM patients. Clinical trials and large-scale clinical studies are recommended in this regard.

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Authors' contributions
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