Review Article

Tyrosine Kinase Targeting: A Potential Therapeutic Strategy for Diabetes

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Abstract

Tyrosine kinase inhibitors (TKIs) have been studied extensively in cancer research, ultimately resulting in the approval of many drugs for cancer therapy. Recent evidence from reported clinical cases and experimental studies have suggested that some of these drugs have a potential role in diabetes treatment. These TKIs include imatinib, sunitinib, dasatinib, erlotinib, nilotinib, neratinib, and ibrutinib. As a result of promising findings, imatinib has been used in a phase II clinical trial. In this review, studies that used TKIs in the treatment of both types of diabetes are critically discussed. In addition, the different molecular mechanisms of action of these drugs in diabetes models are also highlighted to understand their antidiabetic mode of action.

Keywords: Diabetes, insulin, imatinib, mechanism of action, treatment, tyrosine kinase, tyrosine kinase inhibitors

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INTRODUCTION

Protein tyrosine kinases (PTKs) promote the addition of phosphate groups to target proteins, thus modulating their activity. Downregulation of PTK activity by various mechanistic alterations has implications for cellular proliferative activity, especially during malignant transformation.[1] Activation of PTKs results in increased cancer cell growth, induces anti-apoptotic actions, and promotes angiogenesis.[2] Specific tyrosine kinase inhibitors (TKIs) have been developed as a result of the deep understanding of the enzyme network activity. Several cases of improvement in patients with type 1 (T1D) and type 2 diabetes (T2D) during TKI treatment have been documented. These observations have also been supported by *in vivo* studies, which have uncovered the mechanism of action of these agents, and have resulted in the entry of imatinib into a clinical trial for the treatment of early onset T1D.[3]

Diabetes mellitus is a metabolic disease resulting from chronic elevation of blood glucose levels due to impairment in insulin secretion and activity. T1D is initiated as a result of an autoimmune system that destroys pancreatic β cells in combination with immune cell infiltration and cytokine and reactive oxygen species (ROS) secretion, ultimately causing β-cell apoptosis.[4] In this type of diabetes, the disorder usually progresses for years before chronic hyperglycemia is noticed.[4]

T2D is a complicated disorder characterized by a decrease in the sensitivity of the target tissue towards insulin action. This results in chronic hyperglycemia and hyperinsulinemia,

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and ultimately pancreatic β-cell exhaustion and dysfunction. Resistance to insulin action is strongly correlated with obesity, especially in the visceral region, and chronic inflammation from the adipose tissue of the abdomen.[5] In adipose tissue, macrophages produce cytokines, such as interleukin-6 and tumor necrosis factor-alpha, which augment inflammation and adipocyte impairment, resulting in the release of free fatty acids and inhibition of adiponectin production.

As a result of this scenario, kinases, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and c-Jun N-terminal kinase (JNK) are upregulated. These enzymes induce phosphorylation of the insulin receptor and insulin receptor substrate (IRS) on serine residues, thereby inhibiting their phosphorylation on tyrosine residues, which results in the inhibition of insulin signaling and maintenance of high glucose levels in the bloodstream.[6] However, β cells respond to insulin resistance by increasing insulin production; subsequently, they become exhausted and impaired. There is a multifactorial etiology behind the inability of β cells to overcome insulin resistance. Free fatty acid release, proinflammatory mediators, oxidative stress, and chronic hyperglycemia all contribute to the gradual damage of β cell activity.[6]

Insulin replacement therapy is the only therapy available for patients with T1D; no other safe interventions may be used for stopping immune destruction or regeneration of β-cells.[4] In addition, the current anti-diabetic drugs for T2D do not prevent or ameliorate β-cell dysfunction.[7] Thus, there is a demand for new intervention models that solve the etiology of T1D and T2D. In this review, the anti-diabetic effects of TKIs from available studies on humans and animals in both types of diabetes are critically discussed. In addition, the possible mode of action of TKIs on diabetes will be analyzed considering studies conducted in humans, *in vivo* animal models, and *in vitro* cell lines. The antidiabetic effects of TKIs have been reported from clinical observations and from studies in animals for both T1D and T2D, as shown in Table 1.

To extract relevant articles for this review, PubMed searches were carried out between March 2020 until the beginning of 2021 using the following keywords: <Diabetes, tyrosine kinase inhibitor>; <diabetes, treatment, tyrosine kinase inhibitor>; <Type 1 diabetes, tyrosine kinase inhibitor>; <Type 2 diabetes, tyrosine kinase inhibitor>; <Insulin, tyrosine kinase inhibitor>; <Hyperglycemia, tyrosine kinase inhibitor>; < Insulin resistance, tyrosine kinase inhibitor>; <Insulin secretion, tyrosine kinase inhibitor>.

TYPE 1 DIABETES

Clinical evidence

Many lines of evidence reveal that TKIs have antidiabetic properties in patients with T1D. In a patient with chronic myeloid leukemia (CML) who had T1D and was taking imatinib, the quantity of regular insulin intake decreased and a significant improvement in blood glucose concentrations was observed.[8] In addition, administration of sunitinib to a patient with pancreatic tumor who had T1D resulted in a reduction of his diabetic condition, such that he stopped insulin treatment for 12 weeks after starting sunitinib therapy[9] and improvement in glucose and hemoglobin A1c (HbA1c) levels was observed. In addition, diabetes improvement has been observed in patients with T1D diagnosed with renal cell carcinoma (RCC).[26] The patient started treatment with sunitinib for 8 months, after which insulin therapy was reduced.

Blood glucose levels and HbA1c were normal without antidiabetic drugs for approximately 7 months [Table 1]. A more selective TKI, ibrutinib, which targets Bruton's tyrosine kinase, shows an antidiabetic effect in two reported cases with chronic lymphocytic leukemia and T1D. Doses of insulin injection are lowered after administration of ibrutinib as a result of severe hypoglycemia and decreased levels of circulating insulin antibodies.[47]

Evidence from experimental studies

There is evidence from animal and *in vitro* studies supporting clinical observations of the antidiabetic effects of TKIs in T1D treatment.

Imatinib has shown antidiabetic action in nonobese diabetic (NOD) mice that are genetically similar to T1D, and also in diabetic mice induced by streptozotocin (STZ). The onset of diabetes was prevented in prediabetic NOD mice, partially prevented in mice that received STZ after administration of imatinib, and showed some protection of human pancreatic β cells through reduction of nitric oxide (NO).[9] These findings were confirmed by another study that found imatinib administration to a group of prediabetic NOD mice provided protection from diabetes onset.[10] However, a few mice progressed to diabetes after treatment termination, while diabetes reappeared in two-thirds of diabetic NOD animals after imatinib withdrawal. Nonetheless, imatinib withdrawal after extended administration led to prolonged diabetes reduction. In addition, imatinib has also been shown to induce insulin synthesis from NOD animals and protects human pancreatic β cells [Figure 1].[11,12]

Table 1: Tyrosine kinase inhibitors that have been studied in clinical and experimental models of type 1 diabetes and type 2 diabetes

Drug	T1D		T2D	
	Clinical data	Experimental data	Clinical data	Experimental data
Imatinib	The amount of insulin was reduced after the drug administration in a patient with T1D[8]	Diabetes was prevented in NOD mice that received the drug[9] Protection of β cells from NO[9] Protected NOD mice from diabetes[10] Induced insulin production from NOD mice[11,12] Induces antiapoptotic activity in β cells[13] Modulated B lymphocyte activity led to β cells improvement and glucose normalization in NOD mice[14] Protected NOD mice from diabetes[15,16]	39 patients showed reduction in blood glucose[17] The drug ameliorated diabetes in 7 patients and blood glucose levels[18] Controlled blood glucose and HbA1c in T2D patient[19] The drug administration caused Insulin therapy cession[20] 106 patients who received the drug showed reduction in blood glucose and HbA1c[21]	The drug ameliorated diabetes, increased β cells size and insulin secretion in db/db mice[22] Increased insulin sensitivity, and decreased glucose levels in diabetic rats[23,24] Decreased inflammatory markers, insulin resistance in ob/ob mice[17] Induced glucose metabolism in HFD mice[22]
Sunitinib	Stopping insulin therapy after the drug administration[25] Insulin therapy was reduced after the drug administration[26]	Ameliorated diabetes in NOD mice[10] Decreased blood glucose after the drug in T1D mice[27] Increased insulin secretion from β cells[28] Decreased glucose levels, and reduced immune cell infiltration in β cells[29]	It reversed T2D in a patient, and caused withdrawn antidiabetic drug[30] 27 patients administrated the drug showed decrease in blood glucose levels[31] 19 patients treated with the drug showed a decrease in blood glucose[32]	Nonobese rat treated with the drug showed a significant reduction in glucose levels[33]
Dasatinib	43 patients treated with the drug showed adverse effects on glucose levels[34]		Blood glucose of a patient treated with the drug was reduced, and c-peptide elevated[35] Diabetes ameliorated in a patient after the drug treatment[36] A patient treated with drug resulted in normalization of blood glucose, and metformin withdrawn[37]	
Erlotinib		The drug attenuated diabetic cardiomyopathy in T1D mice model[38]	2 patients treated with drug showed a reduction in blood glucose levels[39]	db/db mice treated with drug showed improvement in glucose tolerance and insulin action, with less diabetic complications[40]
Nitolinib	102 patients treated with drug showed increasing in blood glucose levels[34]	The drug protected and preserved β cells function in T1D animal model[41]	Treated patients showed a decrease in insulin levels that led to insulin injection in T2D[42] The drug increased T2D incidence[43] Patients treated with the drug showed increase in blood glucose levels[44]	HFD mice treated with drug increased insulin sensitivity[45]
Neratinib		Improved β cells survival and activity in diabetic mice induced by STZ[46]		Improved β cells survival and activity in HFD diabetic mice[46]
Ibrutinib	Two cases of CLL and T1D, the drug administration resulted in decreasing insulin doses as a result of sever hypoglycemia and reduction the circulating in insulin antibodies[47]	The drug reduced glucose levels in diabetic rats induced by STZ, and improvement in foot ulcers[47]		The drug improved insulin action and lowered glucose[48]

T1D – Type 1 diabetes; T2D – Type 2 diabetes; NOD – Nonobese diabetic; NO – Nitric oxide; HbA1c – Hemoglobin A1c; STZ – Streptozotocin; HFD – High-fat diet; CLL – Chronic lymphocytic leukemia

A previous study has tested the potential anti-apoptotic action of imatinib and two other TKIs (GNF-2 and GNF-5) in STZ-induced diabetic animals;[13] all three TKIs have anti-apoptotic activity for β cells *in vitro*. Moreover, blood glucose levels were maintained within the normal range in STZ-induced mice after GNF-2 administration, whereas the effect was milder in mice that received GNF-5 [Table 1]. In addition, pancreatic tissue of STZ-induced diabetes animals treated with imatinib mesylate has low levels of oxidative stress and high antioxidant capacity.[15] The study also showed lower levels of tissue injury and higher insulin content in the treated animals.[15]

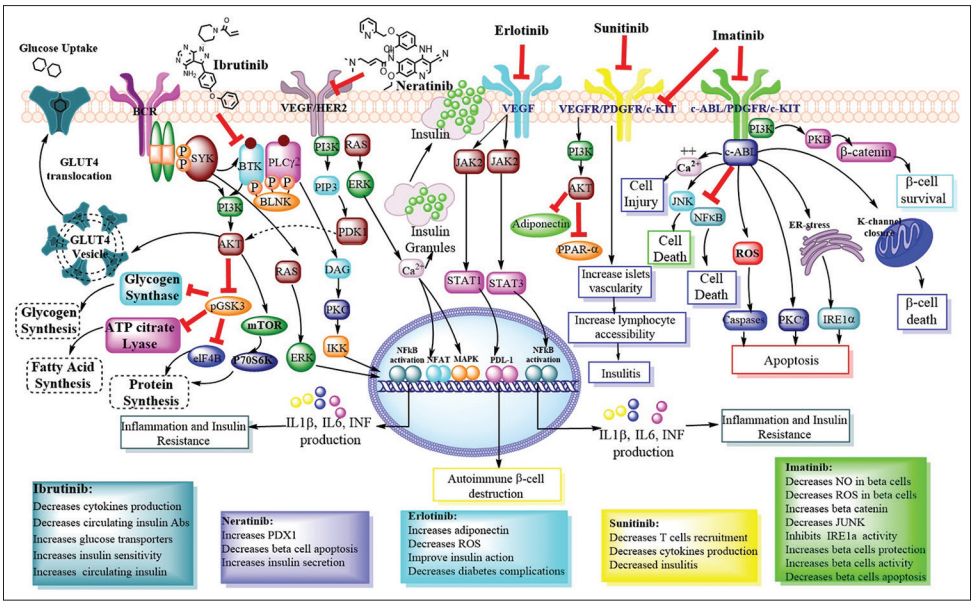

Figure 1: The potential mechanisms by which TKIs exert their effects as antidiabetic agents may vary and depend primarily on which TK is targeted. TKIs: Tyrosine kinase inhibitors

Another TKI drug, sunitinib, has been shown to ameliorate T1D in NOD animals in the first week of administration, and with diabetes reoccurring in only six mice, 9 weeks after drug injection.[10] In addition, T1D mice induced by alloxan have shown a decrease in blood glucose levels due to a single dose of sunitinib.[27] A more recent study that examined the mechanism by which sunitinib increases insulin secretion found that the drug directly stimulates glucose insulin secretion from pancreatic β-cells.[28]

Another study used a micelle polymer to encapsulate sunitinib, thereby increasing its release efficiency.[29] NOD T1D mice that received this formulation systematically showed a decrease in blood glucose levels. In addition, the diabetic animals responded rapidly to the drug, as determined by a glucose tolerance test, and the survival and activity of islet cells also increased in parallel with a reduction in immune cell infiltration.[29]

Erlotinib has also shown antidiabetic effects in mice treated with STZ; importantly, the treated mice showed less cardiomyopathy and less fibrotic tissue in the heart and decrease in the genes responsible for fibrosis and hypertrophy in cardiomyocytes.[38] However, it is not clear whether the later observations were from the antidiabetic effects of the drug.

These *in vivo* data confirmed that TKIs not only reverse T1D, but also prevent the onset of the disease. The possible proposed mechanism of their antidiabetic effect is possibly through protecting β cells from apoptosis and stimulation of insulin synthesis and secretion. Recently, imatinib reversed hyperglycemia in T1D NOD mice through B-lymphocyte modulation. Imatinib increases the antioxidant capacity of B lymphocytes and enhances ROS status in NOD mouse islet cells.[14] In fact, further work should focus on the mechanism of action of these drugs to identify any possible side effects.

As a result of the promising effect of TKIs on T1D, imatinib has been used in clinical trials. A phase II trial is underway for the treatment of early onset T1D. However, the trail has not proceeded to phase III, as no data on the pediatric population are available.[3]

TYPE 2 DIABETES

Clinical evidence

There is strong evidence of the antidiabetic role of TKIs in T2D. For example, patients with different cancer types who had T2D and were treated with imatinib or other TKIs showed a reduction in blood glucose levels, followed by a decrease or cessation of antidiabetic treatment.[17] Imatinib showed a long-acting antidiabetic action after the treatment session, while cessation of other TKIs led to diabetes reoccurrence. Similar findings were observed in seven patients with T2D who had CML and received imatinib; they showed diabetes amelioration and controlled blood glucose levels that resulted in a decrease in the dose of antidiabetic drugs.[18] Moreover, imatinib treatment in a patient with CML and T2D resulted in normalized blood glucose concentration and HbA1c levels,[19] while another patient with the same tumor type and T2D discontinued insulin replacement therapy, and blood glucose levels normalized.[20]

A recent study included 106 patients with CML or stromal cell cancer and T2D who were treated with imatinib and had a significant decrease in blood glucose and HbA1c levels at 1 and 6 months when using the drug.[21] These clinical data support the potential antidiabetic effect of imatinib.

Sunitinib has been shown to reverse T2D. There are documented cases of patients with RCC and T2D, whose blood glucose levels normalized after 2 weeks of sunitinib therapy, leading to the withdrawal of prescribed antidiabetic medicine.[30] Ten patients with RCC and T2D who were treated with sunitinib demonstrated a significant decrease in blood glucose levels, followed by decreasing or even cessation of antidiabetic therapy.[31] In contrast, after 2 weeks of treatment cessation, blood glucose levels rose. The same results were observed in 19 patients with RCC with T2D;[32] 1-month after treatment with sunitinib, blood glucose levels were reduced and then elevated after drug withdrawal.

Regarding another TKI, dasatinib, a case study showed that it normalized blood glucose levels in a patient with CML and T2D, and resulted in insulin therapy cessation and increased C-peptide in the blood.[35] Another study also found that dasatinib administration in a patient with CML and T2D ameliorated diabetes.[36] In addition, a study reported that a patient with T2D, who had been treated with metformin, was later diagnosed with CML. Subsequently, dasatinib was introduced as a therapy for the cancer, and later, glucose levels improved and HbA1c levels became more controlled.[37]

Finally, erlotinib is another TKI showing an effect on T2D by exhibiting an antidiabetic effect in two patients with T2D and non-small cell lung cancer.[39,49] In these patients, erlotinib caused a clear reduction in blood glucose levels, leading to the discontinuation of regular diabetes treatment.[39]

However, there are reported cases of the opposite effects of TKIs on diabetes. For example, use of nilotinib has shown the opposite effect in many reported studies. Nilotinib treatment in patients with CML showed a reduction in insulin secretion, leading to the introduction of insulin therapy until termination of the nilotinib therapy.[42] In addition, a recent retrospective analysis of the incidence of T2D in patients who had CML and were treated with nilotinib showed a higher incidence rate of diabetes. However, the study assessed the risk of developing T2D, including different age groups rather than the antidiabetic potential of the drug, and the patients treated with nilotinib and erlotinib were compared.[43] A prospective study on patients with CML who were treated with nilotinib for 12 months showed a significant increase in blood glucose levels.[44]

Evidence from experimental studies

There is evidence of the effect of TKIs in *in vivo* and *in vitro* models of T2D. Db/db mice, a genetic model of T2D, treated with imatinib normalize blood glucose levels by increasing β cell size and improving insulin action on the target tissue.[43] Moreover, addition of imatinib has been found to abolish the induction of insulin resistance and high glucose levels in rats.[23] The antidiabetic effect of imatinib has been reported in another study; it decreases random blood glucose in parallel with insulin resistance and inflammatory biomarkers in ob/ob mice.[24] A subsequent study showed that imatinib exerts positive effects on the metabolism of glucose and fat, resulting in improved insulin signaling.[22] Spontaneously diabetic Torii rats, a non-obese model of type 2 diabetes, treated with sunitinib show a remarkable reduction in blood glucose levels.[33]

In addition, erlotinib has been shown to have antidiabetic effects in db/db mice. Treated mice have shown lowered blood glucose, improved glucose tolerance and insulin action, and increased adiponectin levels compared to controls.[40] In addition, the treated animals presented fewer diabetic complications compared with the untreated mice. Interestingly, treatment of high-fat diet mice with nilotinib increases insulin sensitivity and decreases fat mass,[45] which contradicts the clinical data of the adverse effects of nilotinib on glucose impairment. One possible explanation is that clinical observations[42,44] have focused on insulin secretion rather than insulin action. Another probable reason is that nilotinib may have off-target effects that may include dual effects of insulin.

Recently, neratinib has demonstrated antidiabetic activity. Neratinib improves β-cell proliferation and activity *in vitro*.[46] Neratinib decreased blood glucose levels and improved β cell activity and size after STZ injection as well as in obese mouse models. Gefitinib, which targets receptor-interacting serine/threonine-protein kinase-2, also decreases glucose levels in a glucose tolerance test in an insulin-resistant animal model by increasing insulin action.[50] Another recent example of a TKI with antidiabetic activity is ibrutinib. *In vitro*, ibrutinib increases glucose transportation inside cells and decreases the production of inflammatory cytokines from treated cells.[48]

Previous studies in experimental models of T2D [Table 1] have emphasized the clinical evidence of the potential role of TKIs as antidiabetic agents by increasing β cell

mass and activity, decreasing inflammatory responses, and enhancing insulin sensitivity, which subsequently improved blood glucose levels.

MECHANISM OF ACTION OF TKIs AS ANTIDIABETIC DRUGS

The potential mechanisms by which TKIs exert their effects as antidiabetic agents may vary and depend primarily on which TK is targeted [Figure 1]. Alternatively, for some TKIs, such as imatinib, the mechanism of its antidiabetic activity is not fully understood.

Abelson non-receptor tyrosine kinase (c-Abl) pathway

c-Abl is a non-receptor tyrosine kinase that activates β cell apoptosis when it becomes active.[9] It contributes to the control of cellular cytoskeleton functions, such as cell shape, cell cycle upregulation, and movement.[51] However, when cells are under stress from oxidation, for example, c-Abl activity is induced, resulting in cell cycle regression and apoptosis,[52] by upregulating JNK[53] and downregulating NF-κB activity.[9] Therefore, imatinib, when targeting c-Abl, may prevent β cell apoptosis in diabetic conditions. In addition, a study shows that imatinib and two other c-Abl molecule inhibitors (GNF-2 and GNF-5) protect β cells from death due to STZ.[13] Targeting c-Abl reduces JNK, caspase-3, and protein kinase C γ levels, which are known to promote β cell apoptosis. Furthermore, another study showed that c-Abl induces β cell apoptosis in NOD mice by binding to inositol-requiring transmembrane kinase/endoribonuclease 1α (IRE1α), which damages the endoplasmic reticulum to induce apoptosis. Imatinib reduces c-Abl and IRE1α binding diminishes IRE1α action, which subsequently protects and reverses β cell T1D.[16]

C-Abl modulates insulin synthesis and secretion, demonstrating the inhibitory effect of c-Abl on insulin secretion from β cells.[54] The negative role of c-Abl in insulin secretion is through downregulation of NK2 homeobox 2 and glucose transporter 2, which normally induce insulin production in glucose-positive conditions.[11] In parallel, targeting c-Abl increased insulin secretion by β cells.

Another finding proposes that imatinib targeting c-Abl activity increases *in vitro* human β cell growth and survival.[12] The study also shows that imatinib activates phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), protein kinase B, and β-catenin signaling, which is essential for β cell activity.[12] In fact, β-catenin is a central modulator of the Wnt and protein kinase B pathways, and upregulation of β-catenin increases survival and growth of different cells, including β cells.[55] C-Abl phosphorylates SH2-domain-containing inositol phosphatase 2 (SHIP2) and inhibits PI3K and β-catenin activity. This subsequently decreases the capacity of β cells for proliferation and activity.[12] In this event, c-Abl inhibition by imatinib reverses its negative role in β cell survival and proliferation through activation of SHIP2 and PI3K.

Adiponectin, a positive modulator of insulin sensitivity, increases after imatinib treatment.[56] *In vitro* studies have shown that the drug accelerates adipocyte differentiation and elevates adiponectin production. Platelet-derived growth factor receptor (PDGFR), a downstream target of c-Abl, has been shown to be an important effector.[57] Lastly, antidiabetic properties of c-Abl downregulation may be linked to activation of low-density lipoprotein receptor-related protein 1, which transduces extracellular signal-regulated kinase activation.[56]

PDGFR pathway

PDGFR is another PTK that may be targeted for therapeutic purposes.[57] It not only has proliferative and growing effects under physiological conditions, but is also involved in the progression of many chronic disorders, such as atherosclerosis and pulmonary and renal fibrosis.[58]

PDGFR activity is increased in diabetes through high blood glucose levels and low adiponectin and peroxisome proliferator-activated receptor (PPAR)-λ. These cause upregulation of the PDGFR pathway, leading to a decrease in insulin sensitivity in the target tissue.[59,60] Hence, it is possible that targeting PDGFR may increase insulin action and ameliorate diabetes. As stated previously, using imatinib, which targets a pathway that involves PDGFR, increases adiponectin through a mechanism that depends on PDGFR inhibition.[61] PPAR-λ is blocked after imatinib administration, which increases insulin sensitivity.[22]

Tyrosine-protein kinase KIT (c-Kit) pathway

c-Kit is another kinase targeted by imatinib and is less affected by sunitinib and dasatinib.[57] It is involved in the growth and differentiation of pancreatic cells, among other cells.[62] c-Kit upregulation in β cells increases their proliferation and activity and prevents the development of diabetes in animal models.[63] These results suggest that c-Kit performs a physiological function in β cells; thus, its targeting by TKIs may have adverse effects on diabetes. This concept has been confirmed by studies that reveal that c-Kit inhibition does not selectively normalize blood glucose in diabetic mice,[29] and amelioration *in vivo* by TKIs works independently of c-Kit.[64]

Vascular endothelial growth factor receptor pathway

This enzyme is targeted by sunitinib among other TKIs; targeting vascular endothelial growth factor receptor (VEGFR) has shown antidiabetic properties. VEGFR2 signaling controls angiogenesis, while VEGFR1 signaling performs opposite events.[65] VEGFR ligands play a role in inflammation and white blood cell recruitment by increasing the expression of cytokines and chemokines.[66,67] Blocking VEGFR2 signaling through TKIs normalized the blood glucose levels and ameliorated diabetes. In addition, it was shown that targeting VEGFR2 decreased T cell recruitment into β cells of the pancreas as well as inflammation. These findings have been documented in other studies, where VEGFR2 inhibition decreased insulitis.[33]

Epidermal growth factor receptor pathway

Epidermal growth factor receptor (EGFR) downregulation has been proposed to have antidiabetic properties. This finding is reported in db/db mice, where targeting EGFR improves blood glucose levels, and increases glucose tolerance and insulin action.[40] Moreover, EGFR decreases proinflammatory cytokines and immune cell recruitment in renal tissue, leading to less diabetic complications compared with controls.[40] EGFR-signal transducer and activator of transcription 3 (STAT3) signaling may play a role in diabetes. A study reporting *in vivo* and *in vitro* models of diabetes showed an interaction between EGFR and STAT3 in cardiomyopathy resulting from diabetes complications. Blocking EGFR inhibits STAT3 phosphorylation and decreases cardiomyopathy in diabetic mice, in parallel with genes that play a role in fibrosis and hypertrophy in cardiomyocytes.[38]

OFF-TARKET EFFECTS OF TKIs

Although TKI drugs have been designed to target and inhibit specific modulators of pathways, off-target effects are commonly seen in such therapies. There are some documented examples of TKI off-target effects in diabetes. A recent study showed the effects of neratinib, the drug that has been approved for metastatic human epidermal growth factor receptor 2-positive breast cancer,[68] and showed antidiabetic activity in T1D and T2D animal models. However, neratinib exerts this effect through different molecular mechanisms.[46] The use of a knockout mouse model showed that the drug worked mainly through blocking the activity of the transcription factor MTS1 in β cells. Therefore, some of the TKIs that have been discussed may show an antidiabetic effect through off-targeting effects. In the future, more precise methodology using knockout mouse models is required to illustrate the exact mechanism by which TKIs exert antidiabetic properties.

CONCLUSIONS

TKIs have been widely used as therapeutic regimens for different cancers. Accumulating evidence has proposed the antidiabetic actions of these TKIs in both types of diabetes. Clinical and experimental data showed that some of them have potent effects on T1D, while others affect T2D. In contrast, some TKIs, such as erlotinib, interestingly, induced or augmented diabetes in studies. Therefore, understanding the molecular mechanism of TKIs in diabetes is very important before proceeding with experimental data from clinical trials.

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