Glucokinase Activators for Type 2 Diabetes: Challenges and Future Developments- A Review

Rutuja N. Bhadange[1], Shivani P. Wadichar[2], Vidya N. Bakan[3], Rewati H. Wanjari [4], Saurav V. Pathak[5], Pooja P. Darekar[6], Pratik D. Dhokne [7], Swapnil S. Tirmanwar [8]

[1]*Assistant Professor, Shree Sainath College of Pharmacy, Nagpur*

[2, 7]*Research Scholar, Priyadarshini J.L College of Pharmacy, Nagpur*

[3]*Assistant Professor, Department of Pharmacology, Durgamata Institute of Pharmacy Dharmapuri, Parbhani.*

[4, 5] *Research Scholar, Shri Ville Parle Kelavani Mandal's Institute of Pharmacy, Dhule*

[6] *Lecturer, Ravi Institute of Diploma in Pharmacy Koradi Nagpur*

[8]*Research scholar*

Abstract - Excessive hepatic glucose production is a key metabolic abnormality in Type 2 diabetes mellitus (T2DM) and remains inadequately addressed by most available glucose-lowering therapies, except metformin. This gap in treatment may be bridged by targeting glucokinase (GK), a crucial enzyme in the hexokinase family. GK acts as a "glucose sensor" in pancreatic β-cells, stimulating glucose-dependent insulin secretion, and as a "glucose gatekeeper" in hepatocytes, facilitating hepatic glucose uptake, glycogen synthesis, and storage. Pharmacological GK activation via small-molecule glucokinase activators (GKAs) offers an alternative approach to improving glycemic control in T2DM. GKAs can enhance insulin secretion from the pancreas, promote hepatic glycogen synthesis, and effectively reduce hepatic glucose output. While early GKAs faced setbacks due to concerns about hypoglycemia, hypertriglyceridemia, and loss of efficacy over time, recent advancements have renewed interest in this class. Notably, the development of dorzagliatin, a dual-acting full GKA, and TTP399, a novel hepatoselective GKA, has reinvigorated clinical research in this field. This article provides an in-depth review of the role, efficacy, safety, and future potential of GKAs in the management of T2DM, highlighting their mechanism of action, recent clinical findings, and prospects for integration into diabetes treatment strategies.

Keywords: Hepatoselective, Glucokinase, Glycogen, Type 2 Diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a multifaceted disease that presents significant challenges for patients, healthcare providers, and medical systems [1]. It arises from a combination of genetic and environmental factors, leading to chronic hyperglycemia and a cascade of inflammatory and oxidative processes. These mechanisms contribute to vascular complications, which remain the primary cause of morbidity and mortality in T2DM.

Our understanding of T2DM has evolved beyond the traditional view of the disease as merely a result of insulin deficiency and resistance. Instead, research now highlights the critical role of pancreatic islet cells (β-cells, α-cells, and others) and their interactions with the gut, brain, kidney, and liver in disease progression [2,3]. Given the rising global prevalence of T2DM, its progressive nature, and the substantial proportion of patients who fail to achieve optimal glycemic control [4], there is an urgent need for novel treatment strategies and therapeutic targets [5].

This growing need has driven the development of new therapeutic approaches aimed at more recently identified pathogenetic pathways. Notable advancements include glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter-2 (SGLT2) inhibitors, which primarily target mechanisms related to the gut, brain, and kidneys [6,7].

However, increased hepatic glucose production—one of the central metabolic abnormalities in T2DM—is not directly or effectively addressed by most current glucose-lowering therapies, except metformin [8]. A potential solution to this unmet need lies in targeting glucokinase (GK), a key enzyme in the hexokinase family. This article explores the role of GK activators (GKAs) and their potential future impact on T2DM management.

Role of Glucokinase (GK) in Glucose Homeostasis

Glucose homeostasis is primarily regulated by the balance between insulin and glucagon. Glucagon, secreted by pancreatic α-cells, maintains blood glucose levels during fasting by stimulating gluconeogenesis (glucose production from amino acids and fat) and glycogenolysis (breakdown of glycogen in the liver), ensuring a continuous energy supply. Additionally, free fatty acids released from adipose tissue provide an alternative energy source.

In contrast, insulin, secreted by pancreatic β-cells, lowers blood glucose levels after meals by facilitating glucose uptake in peripheral tissues (mainly skeletal muscle and adipose tissue) and promoting glycogen synthesis in the liver. Elevated glucose levels in the fed state also inhibit gluconeogenesis and glycogenolysis, further supporting glucose regulation [9].

GK acts as a "glucose sensor" in pancreatic β-cells, triggering insulin secretion, and as a "gatekeeper" in hepatocytes, facilitating glucose uptake and storage as glycogen. Upon activation, GK phosphorylates glucose into glucose-6-phosphate (G6P), which not only serves as a substrate for glycogen synthesis but also activates glycogen synthase [11].

The unique biochemical properties of GK enable this dual function [12]. Its low affinity for glucose (K0.5 of ~7–8 mmol/L) ensures that GK activity remains restrained under normal physiological conditions [13]. Unlike other hexokinases, GK is not inhibited by its product, G6P, and follows a sigmoidal saturation curve with glucose (non-Michaelis–Menten kinetics), reaching an inflection point at 4–5 mmol/L—close to the insulin secretion threshold. This allows for a graded response to fluctuations in blood glucose levels, with GK activity plateauing as glucose approaches 5 mmol/L [13].

In the liver, GK exists in an inactive complex with glucokinase regulatory protein (GKRP) when glucose levels are below ~10 mM. This reduces GK's affinity for glucose in hepatocytes compared to pancreatic β-cells, ensuring activation predominantly in the postprandial state to support hepatic glucose uptake [14,15]. GKRP acts as a competitive inhibitor by sequestering GK in low-glucose conditions and releasing it when glucose concentrations rise.

Beyond pancreatic β-cells and hepatocytes, GK is also expressed in enteroendocrine cells, neurons, pancreatic α- and δ-cells, and the anterior pituitary [16]. However, its primary role in glucose homeostasis is regulating insulin secretion and hepatic glucose metabolism.

By enhancing GK activity, blood glucose levels can be lowered through both direct (insulin-mediated) and indirect mechanisms. This has led to the hypothesis that GK activation may offer a novel therapeutic approach for glucose regulation, especially in individuals with type 2 diabetes mellitus (T2DM), where GK activity is diminished [17].

This concept is supported by studies on maturity-onset diabetes of the young type 2 (MODY2), a monogenic form of diabetes caused by inactivating mutations in the GK gene. Individuals with MODY2 typically exhibit mild fasting hyperglycemia and a low risk of microvascular complications due to impaired glucose sensing [18,19]. More severe cases, with compound heterozygous or homozygous mutations, can lead to permanent neonatal diabetes [20]. On the other hand, activating GK mutations is rare but can result in congenital hyperinsulinemic hypoglycemia with variable clinical severity [21].

Animal and human studies [22–26] have confirmed GK's critical role in glucose regulation and demonstrated the feasibility of pharmacological activation. In T2DM, progressive β-cell dysfunction and increased hepatic glucose output are key pathological features that could potentially be addressed by GK activation, providing a compelling rationale for targeting this enzyme therapeutically.

Overview of Glucokinase Activators (GKAs)

Since the introduction of the first GK activator in 2003 [29], numerous GKAs have been developed and tested [27,28]. These small molecules bind to an allosteric site on the enzyme, stabilizing its high-affinity conformation and enhancing GK activity—interestingly, the same region where most activating GK mutations cluster.

GKAs can be categorized based on their chemical structure (carbon-, urea-, aryl-substituted, etc.) [13] or their site of action. Hepatoselective GKAs primarily target the liver, either by disrupting or preserving the GK-GKRP interaction [30,31], whereas systemic GKAs (e.g., piragliatin, dorzagliatin) affect both pancreatic and hepatic GK activity. Additionally, GKAs are classified as full activators or partial activators (e.g., PF-04937319), depending on their potency.

Despite significant research, only a few GKAs have advanced to clinical trials, as detailed in the following sections and summarized in Table 1.

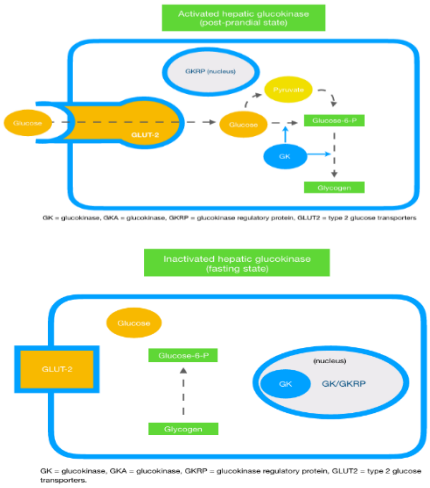

Fig. 1 Glucokinase activity in the hepatic cell

Table 1 Synopsis of the major clinical trials involving glucokinase activators

Molecule	Study	Total Study *N*	Dose (mg)	Duration (Weeks)	Background therapy	Primary effect notable findings	Major safety issues
RO4389620 (piragliatin)	Bonadonna et al.	15	25-100	10 h	None	Acute reduction of FPG PPG	None
RO4389620 (piragliatin)	Zhi et al.	59	10-200	1	None	Acute reduction of FPG PPG	Hypoglycaemia
MK-0941	Meininger et al.	587	10-40	30	Insulin glargine±metformin	HbA1c drop of 0.5 to−0.8% (not sustained), PPG	Hypoglycemia, hypertriglyceridemia hypertension, loss of efficacy
AZD1656	Wilding et al.	458	20-200	16+4	Add-on metformin/ glipizide	HbA1c drop of~0.6 to 1.2%, FPG	Increase in triglycerides
AZD1656	Kiyosue et al. [36]	224	100	16	Drug naïve or addon metformin/ sulfonylurea	Non-signifcant HbA1c drop of~0.2%, FPG	Hypoglycaemia, loss of efcacy
PF-04937319 A	Amin et al. [37] (B1621002)	304	100	12	Add-on metformin +/− glimepiride	HbA1c drop of ~0.5%, FPG	Hypoglycaemia
PF-04937319	Amin et al. [37] (B1621007)	335	150-100	12	Add-on metformin +/− sitagliptin	HbA1c drop of~0.7%, FPG	Hypoglycaemia
PF-04937319	Denney et al. [38]	33	200	2	Add-on metformin/ sitagliptin	FPG	None
AMG 151 (ARRY-403)	Katz et al. [39]	236	50-75	4	Add-on metformin	FPG	Hypoglycaemia, hypertriglyceridemia
Dorzagliatin (Sinogliatin, HMS5552)	Zhu et al. [40]	258	75	12	Drug naïve or addon metformin	PPG, HbA1c drop of~0.8 to 1.1%	None
Dorzagliatin (Sinogliatin, HMS5552)	Zhu et al. [41]	24	75	4	None	HbA1c drop of~0.8 to 1.0%	None
TTP399	Vella et al. [43]	190	400-800	4	Drug naïve or addon metformin	HbA1c drop of~0.9%	None

Clinically Tested GKAs: Pharmacodynamics and Safety

In a Phase Ib randomized, double-blind, placebo-controlled crossover trial involving 15 individuals with mild type 2 diabetes (T2DM), the GKA piragliatin (RO4389620) (25 mg or 100 mg) demonstrated a dose-dependent reduction in glucose levels in both fasting and fed states, primarily by enhancing β-cell function [32]. A similar short-term (8-day) dose-escalation study (up to 200 mg) in 59 patients with T2DM also reported a rapid, dose-dependent reduction in fasting and postprandial plasma glucose levels [33].

A double-blind study evaluating the efficacy and safety of the GKA MK-0941 (at doses of 10, 20, 30, or 40 mg three times daily) in 587 patients with T2DM treated with insulin glargine (mean baseline HbA1c of 9%) showed a significant 0.8% reduction in HbA1c by Week 14. Additionally, a notable decrease in 2-hour postprandial glucose (~40 mg/dL or 2.2 mmol/L) was observed. However, by Week 30, these improvements were not sustained [34]. MK-0941 was also linked to an increased incidence of hypoglycemia, hypertriglyceridemia (up to ~20% from baseline), and hypertension.

The efficacy and safety of AZD1656 were assessed in a dose-ranging, placebo-controlled study involving 458 patients with T2DM as an add-on to metformin. At four months, HbA1c reduction was comparable to glipizide; however, the glucose-lowering effect diminished over the subsequent two-month extension period, accompanied by an increase in triglycerides [35]. Similar results were found in a study involving 224 Japanese patients with T2DM, where the initial efficacy was not sustained, although no significant safety concerns were noted [36].

PF-04937319, a systemic partial glucokinase activator, was evaluated as an add-on therapy to metformin in dose-ranging randomized controlled trials (RCTs) involving 639 adults with T2DM [37]. Its glucose-lowering efficacy at three months was comparable to sitagliptin when administered as a single 100 mg dose. Subsequent studies exploring split-dose regimens demonstrated promising safety and tolerability outcomes [38].

AMG 151 (ARRY-403) was assessed in a randomized, placebo-controlled, 4-week Phase IIa study with 236 patients with T2DM on metformin. It significantly reduced fasting plasma glucose when administered twice daily but was associated with increased incidences of hypoglycemia and hypertriglyceridemia [39].

Dorzagliatin (Sinogliatin, HMS5552), a fourth-generation dual-acting systemic GKA, was developed based on piragliatin and later evaluated in a 12-week Phase II dose-ranging, randomized, double-blind, placebo-controlled study involving 258 Chinese patients with T2DM [40]. By Week 12, HbA1c reduction was −0.8% with 50 mg twice daily and ~1.1% with 75 mg twice daily compared to placebo. The drug primarily lowered 2-hour postprandial glucose rather than fasting glucose, with a more pronounced effect in drug-naïve patients, suggesting potential benefits for early intervention. Importantly, no serious adverse events or severe hypoglycemia were reported. A separate 4-week study in 24 patients with T2DM showed improvements in β-cell function [41]. Ongoing clinical trials (NCT03173391 and NCT03141073) aim to assess its long-term efficacy and safety [42].

Encouraging findings have also been reported for TTP399, a novel hepatoselective GKA. This molecule was screened for hepatic activity (glycogen and lactate production) while ensuring no pancreatic stimulation (insulin secretion) at high glucose concentrations (15 mM). It binds directly to GK in a glucose-like manner and reduces glucose levels without affecting GK translocation [31]. The Phase IIb AGATA trial, a 6-month RCT, assessed TTP399 (400 mg and 800 mg) against sitagliptin and placebo in 190 patients with T2DM on stable metformin doses [43]. The 800 mg dose led to a placebo-adjusted HbA1c reduction of −0.9% (−1.5 to −0.3) by six months, with effects becoming evident only after three months. This delayed onset differed from a previous Phase Ib/IIa study, where hypoglycemic effects appeared earlier [31]. TTP399 exhibited a strong safety profile, with very low symptomatic hypoglycemia (comparable to sitagliptin, with just one event). Additionally, treatment led to a significant increase in HDL cholesterol, a neutral effect on triglycerides and cholesterol, and notable weight loss in patients weighing over 100 kg.

Several other GKAs, including ADV-1002401, TMG-123, and LY2608204 (globalization), have entered clinical trials, though published results are still awaited.

Challenges Associated with GKAs

The use of older-generation GKAs has been accompanied by significant concerns related to both efficacy and safety. The most notable issues include the risk of hypoglycemia, fatty liver development, dyslipidemia, and a decline in long-term efficacy. Early in the development of GKAs, the potential for hypoglycemia and dyslipidemia was identified due to excessive stimulation of pancreatic and hepatic glucokinase, respectively [12, 44]. Acute insulin release, disproportionate to glucose levels, was recognized as a plausible risk of GK activation, with hypoglycemic episodes particularly reported in association with piragliatin and MK-0941. To mitigate this risk, partial activators that maintained a greater dependence on glucose levels were designed to reduce activation at low glucose concentrations [27]. Additionally, hepatoselective agents were developed and tested, with partial GKA PF-04937319 demonstrating a lower incidence of hypoglycemic events [37].

Regarding the mechanisms linking GK activation to dyslipidemia, it has been suggested that excessive hepatic glucokinase activity leads to an accumulation of glucose-6-phosphate (G6P), subsequently triggering glycolysis through fructose 2,6-bisphosphate-mediated allosteric activation. This metabolic shift results in increased production of acetyl-CoA, fueling fatty acid and triglyceride synthesis through malonyl-CoA and hepatic de novo lipogenesis [12]. This aligns with early-stage non-alcoholic fatty liver disease (NAFLD), which may progress from simple steatosis to steatohepatitis [45]. Although chronic exposure may be required for more severe manifestations, hypertriglyceridemia was acutely observed with MK-0941. Despite triglyceride increases being less than 20%—a level considered modest in comparison to high-carbohydrate, low-fat dietary effects [12]—such elevations remain undesirable in type 2 diabetes patients already predisposed to dyslipidemia, hypertension, and NAFLD [42].

Another major concern has been the transient nature of glucose-lowering efficacy observed with GKAs. Initial promising effects, often seen within the first few weeks of treatment, were followed by a rapid decline in efficacy over prolonged exposure, as demonstrated with MK-0941 and AZD1656 after approximately four months. The clinical evaluation periods for PF-04937319 and AMG 151 were limited to three and one month, respectively. The reasons behind this secondary failure remain unclear. In the case of MK-0941, the patient cohort may have had an insufficient residual β-cell mass for GKA action, given their long-standing diabetes and prior insulin therapy. However, this explanation does not apply to AZD1656. Some hypotheses suggest that hepatic de novo lipogenesis or plasma hyperlipidemia might contribute to GKA failure, though this remains a topic of debate [12]. Interestingly, hepatoselective GKA TTP399 exhibited a delayed onset of glucose-lowering efficacy, only becoming apparent after three months of treatment in the AGATA trial, in contrast to early-phase trials.

Potential β-cell toxicity of GKAs has also been proposed, with histological findings in murine models indicating double-strand DNA breaks, activation of the p53 tumor suppressor, and subsequent β-cell apoptosis following GK activation [13, 46]. These findings mirror the observed clinical trajectory of an initial drop in blood glucose followed by a loss of efficacy. Another hypothesis, as proposed by Agius [12], suggests that GKA exposure leads to an initial insulin-mediated correction of the insulin/glucagon ratio, resulting in hepatic GK activation. However, over time, accumulated G6P and downstream phosphate-ester intermediates suppress GK gene expression [47], negating the stimulatory effects of GKAs [48]. Regardless of the precise mechanism, this diminishing efficacy presents a significant challenge to the long-term viability of GKAs in clinical practice, potentially limiting their future development and approval.

Future Directions

For a new-generation GKA to be considered a viable therapeutic option, it must demonstrate clinically meaningful and sustained glycemic efficacy while minimizing the risk of adverse effects, particularly hypoglycemia, hepatic steatosis, and hypertriglyceridemia. The ideal agent would not only address chronic hyperglycemia but also modify the natural progression of diabetes. Among emerging GKAs, dual-acting dorzagliatin and hepatoselective TTP399 exhibit promising characteristics.

Scheen conducted an indirect comparison of dorzagliatin's efficacy with older GKAs, indicating a superior HbA1c reduction relative to piragliatin, AZD1656, and PF-04937319 [42]. The placebo-

adjusted HbA1c reduction of approximately −0.8% with 75 mg dorzagliatin BID was comparable to that of MK-0941, which was discontinued due to safety concerns. The efficacy of AMG151 remains uncertain due to its limited one-month evaluation period [39]. Notably, dorzagliatin's glucose-lowering effect became progressively more pronounced over two to three months, suggesting a sustained benefit—contrasting with the transient efficacy seen in previous GKAs. Similarly, TTP399 achieved a ~0.9% placebo-adjusted HbA1c reduction, with effects persisting for at least six months. While the observed reductions (~0.8%–0.9%) may be modest, they are within the range of other antidiabetic therapies and could be clinically relevant for patients requiring treatment intensification.

From a safety perspective, dorzagliatin demonstrated a lower incidence of hypoglycemia, with no significant changes in triglycerides or transaminase levels over three months of treatment (except for one case of eyelid edema). TTP399 also exhibited a favorable safety profile, with no reports of symptomatic hypoglycemia. Moreover, TTP399 appears to exert a beneficial effect on lipid metabolism, including a modest but statistically significant increase in HDL-C—an outcome not observed with earlier GKAs. Additionally, unlike some GKAs that have been associated with weight gain, dorzagliatin appears to be weight-neutral, and TTP399 may even promote weight loss in certain subsets of patients, although the underlying mechanism remains unclear.

However, long-term data beyond the current three-month period for dorzagliatin and the six months for TTP399 are lacking. Critical uncertainties remain regarding their impact on microvascular complications, cardiovascular health, and renal outcomes. Given concerns that common GKRP gene variants may have adverse cardio-renal implications, these long-term evaluations are eagerly awaited [49]. At this stage, defining GKAs' precise role in the therapeutic landscape is premature, particularly considering the growing emphasis on cardiovascular and renal protection in diabetes management [50]. Nevertheless, given their reliance on a minimum functional β-cell mass and their primary impact on postprandial hyperglycemia, GKAs may be better suited as an early addition to therapy. Whether they can supplant established second or third-line agents will likely depend on demonstrating a distinct therapeutic advantage. The observed reduction in fasting glucagon with TTP399 may represent one such benefit. Furthermore, GKAs might hold promise for specific patient subgroups yet to be identified.

Ultimately, further research is required to determine the long-term efficacy, safety, and clinical positioning of GKAs. Large-scale clinical trials with extended follow-up periods, robust statistical power, and carefully selected comparators will be necessary to ascertain their therapeutic potential and long-term benefits.

CONCLUSION

Targeting glucokinase (GK) represents a promising therapeutic approach to addressing increased hepatic glucose output, a key metabolic defect in Type 2 diabetes mellitus (T2DM). While glucokinase activators (GKAs) initially faced setbacks due to concerns over hypoglycemia, loss of efficacy, and metabolic side effects, recent advancements have renewed interest in this class. The development of dorzagliatin, a dual-acting full GKA, and TTP399, a hepatoselective GKA, highlights the potential of GK activation in improving glycemic control while mitigating previous safety concerns. As research progresses, optimizing the efficacy, safety, and durability of GKAs will be essential for their integration into T2DM treatment regimens. If successfully developed, these novel agents could complement existing glucose-lowering therapies, offering an innovative strategy to improve metabolic control and reduce diabetes-related complications.

REFERENCES

[1] Konstantinos A. Toulis, Krishnarajah Nirantharakumar, Chrysa Pourzitaki, Anthony H. Barnett, Abd A. Tahrani. Glucokinase Activators for Type 2 Diabetes: Challenges and Future Developments Springer Nature Switzerland, August 2020. https://doi.org/10.1007/s40265-020-01278-z

[2] Tahrani AA, Barnett AH, Bailey CJ. Pharmacology and therapeutic implications of current drugs for type 2 diabetes mel litus. Nat Rev Endocrinol. 2016;12(10):566–92. https ://doi. org/10.1038/nrendo.2016.86.

[3] Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes

mellitus. Diabetes. 2009;58(4):773–95. https ://doi.org/10.2337/ db09-9028.

[4] Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR 3rd, Aguilar RB. The time is right for a new classification system for diabetes: rationale and implications of the beta-cell-centric classification schema. Diabetes Care. 2016;39(2):179–86. https ://doi.org/10.2337/dc15-1585.

[5] Khunti K, Ceriello A, Cos X, De Block C. Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract. 2018;137:137–48. https ://doi.org/10.1016/j.diabr es.2017.12.004.

[6] Altaf QA, Barnett AH, Tahrani AA. Novel therapeutics for type 2 diabetes: insulin resistance. Diabetes Obes Metab. 2015;17(4):319–34. https://doi.org/10.1111/dom.12400.

[7] Toulis KA, Hanif W, Saravanan P, Willis BH, Marshall T, Kumarendran B, et al. All-cause mortality in patients with diabetes under glucagon-like peptide-1 agonists: a population-based, open cohort study. Diabetes Metab. 2017;43(3):211–6. https ://doi. org/10.1016/j.diabet.2017.02.003.

[8] Toulis KA, Willis BH, Marshall T, Kumarendran B, Gokhale K, Ghosh S, et al. All-cause mortality in patients with diabetes under treatment with dapagliflozin: a population-based, open cohort study in the health improvement network database. J Clin Endocrinol Metab. 2017;102(5):1719–25. https ://doi.org/10.1210/ jc.2016-3446.

[9] Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. Lancet. 2011;378(9786):182–97. https ://doi.org/10.1016/S0140 -6736(11)60207-9.

[10] Rines AK, Sharabi K, Tavares CD, Puigserver P. Targeting hepatic glucose metabolism in the treatment of type 2 diabetes. Nat Rev Drug Discov. 2016;15(11):786–804. https ://doi.org/10.1038/ nrd.2016.151.

[11] Perseghin G. Exploring the in vivo mechanisms of action of glu cokinase activators in type 2 diabetes. J Clin Endocrinol Metab. 2010;95(11):4871–3. https://doi.org/10.1210/jc.2010-2049.

[12] Petersen MC, Vatner DF, Shulman GI. Regulation of hepatic glucose metabolism in health and disease. Nat Rev Endocrinol. 2017;13(10):572–87. https://doi.org/10.1038/nrendo.2017.80.

[13] Agius L. Lessons from glucokinase activators: the problem of declining efficacy. Expert Opin Ther Pat. 2014;24(11):1155–9. https://doi.org/10.1517/13543776.2014.965680 .

[14] Nakamura A, Terauchi Y. Present status of clinical deployment of glucokinase activators. J Diabetes Investig. 2015;6(2):124–32. https://doi.org/10.1111/jdi.12294.

[15] Choi JM, Seo MH, Kyeong HH, Kim E, Kim HS. Molecu lar basis for the role of glucokinase regulatory protein as the allosteric switch for glucokinase. Proc Natl Acad Sci USA. 2013;110(25):10171–6. https ://doi.org/10.1073/pnas.13004 57110 .

[16] Raimondo A, Rees MG, Gloyn AL. Glucokinase regulatory protein: complexity at the crossroads of triglyceride and glucose metabolism. Curr Opin Lipidol. 2015;26(2):88–95. https ://doi. org/10.1097/MOL.0000000000000155.

[17] Matschinsky FM, Wilson DF. The central role of glucokinase in glucose homeostasis: a perspective 50 years after demonstrating the presence of the enzyme in islets of Langerhans. Front Physiol. 2019;10:148. https://doi.org/10.3389/fphys.2019.00148.

[18] Agius L. Glucokinase and molecular aspects of liver glycogen metabolism. Biochem J. 2008;414(1):1–18. https ://doi. org/10.1042/BJ20080595.

[19] Chakera AJ, Steele AM, Gloyn AL, Shepherd MH, Shields B, Ellard S, et al. Recognition and management of individuals with hyperglycemia because of a heterozygous glucokinase mutation. Diabetes Care. 2015;38(7):1383–92. https ://doi.org/10.2337/ dc14-2769.

[20] Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, Hattersley AT. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. JAMA. 2014;311(3):279–86. https ://doi.org/10.1001/ jama.2013.283980.

[21] Amed S, Oram R. Maturity-onset diabetes of the young (MODY): making the right diagnosis to optimize treatment. Can J Diabetes. 2016;40(5):449–54. https://doi.org/10.1016/j.jcjd.2016.03.002

[22] Ping F, Wang Z, Xiao X. Clinical and enzymatic phenotypes in congenital hyperinsulinemic hypoglycemia due to glucokinase activating mutations: a report of two cases and a brief overview of the literature. J Diabetes Investig. 2019. https ://doi.org/10.1111/ jdi.13072 .

[23] Doliba NM, Fenner D, Zelent B, Bass J, Sarabu R, Matschin sky FM. Repair of diverse diabetic defects of beta-cells in man and mouse by pharmacological glucokinase activation. Diabetes Obes Metab. 2012;14(Suppl 3):109–19. https ://doi.org/10.111 1/j.1463-1326.2012.01652.x.

[24] Lu M, Li P, Bandyopadhyay G, Lagakos W, Dewolf WE Jr, Alford T, et al. Characterization of a novel glucokinase activator in rat and mouse models. PLoS One. 2014;9(2):e88431. https ://doi. org/10.1371/journal.pone.0088431.

[25] Nakamura A, Shimazaki H, Ohyama S, Eiki J, Terauchi Y. Effect of long-term treatment with a small-molecule glucokinase activator on glucose metabolism, lipid profiles and hepatic function. J Diabetes Investig. 2011;2(4):276–9. https://doi.org/10.111 1/j.2040-1124.2011.00104.x.

[26] Nakamura A, Terauchi Y, Ohyama S, Kubota J, Shimazaki H, Nambu T, et al. Impact of small-molecule glucokinase activator on glucose metabolism and beta-cell mass. Endocrinology. 2009;150(3):1147–54. https://doi.org/10.1210/en.2008-1183

[27] Nakamura A, Togashi Y, Orime K, Sato K, Shirakawa J, Ohsugi M, et al. Control of beta cell function and proliferation in mice stimulated by small-molecule glucokinase activator under various conditions. Diabetologia. 2012;55(6):1745–54. https ://doi. org/10.1007/s00125-012-2521-5.

[28] Filipski KJ, Pfefferkorn JA. A patent review of glucoki nase activators and disruptors of the glucokinase–glucoki nase regulatory protein interaction: 2011–2014. Expert Opin Ther Pat. 2014;24(8):875–91. https ://doi.org/10.1517/13543 776.2014.918957

[29] Sarabu R, Berthel SJ, Kester RF, Tilley JW. Novel glucokinase activators: a patent review (2008–2010). Expert Opin Ther Pat. 2011;21(1):13–33. https ://doi.org/10.1517/13543 776.2011.54241 3.

[30] Grimsby J, Sarabu R, Corbett WL, Haynes NE, Bizzarro FT, Cof fey JW, et al. Allosteric activators of glucokinase: potential role in diabetes therapy. Science. 2003;301(5631):370–3. https://doi. org/10.1126/science.1084073.

[31] Pfefferkorn JA. Strategies for the design of hepatoselective glucokinase activators to treat type 2 diabetes. Expert Opin Drug Discov. 2013;8(3):319–30. https ://doi.org/10.1517/17460 441.2013.748744.

[32] Egan A, Vella A. TTP399: an investigational liver-selective glucokinase (GK) activator as a potential treatment for type 2 diabetes. Expert Opin Investig Drugs. 2019;28(9):741–7. https ://doi. org/10.1080/13543784.2019.1654993.

[33] Bonadonna RC, Heise T, Arbet-Engels C, Kapitza C, Avogaro A, Grimsby J, et al. Piragliatin (RO4389620), a novel glucokinase activator, lowers plasma glucose both in the postabsorptive state and after a glucose challenge in patients with type 2 diabetes mellitus: a mechanistic study. J Clin Endocrinol Metab. 2010;95(11):5028–36. https://doi.org/10.1210/jc.2010-1041.

[34] Zhi J, Zhai S. Effects of piragliatin, a glucokinase activator, on fasting and postprandial plasma glucose in patients with type 2 diabetes mellitus. J Clin Pharmacol. 2016;56(2):231–8. https :// doi.org/10.1002/jcph.589.

[35] Meininger GE, Scott R, Alba M, Shentu Y, Luo E, Amin H, et al. Effects of MK-0941, a novel glucokinase activator, on glycemic control in insulin-treated patients with type 2 diabetes. Diabetes Care. 2011;34(12):2560–6. https://doi.org/10.2337/dc11-1200.

[36] Wilding JP, Leonsson-Zachrisson M, Wessman C, Johnsson E. Dose-ranging study with the glucokinase activator AZD1656 in patients with type 2 diabetes mellitus on metformin. Diabe tes Obes Metab. 2013;15(8):750–9. https ://doi.org/10.1111/ dom.12088 .

[37] Kiyosue A, Hayashi N, Komori H, Leonsson-Zachrisson M, Johnsson E. Dose-ranging study with the glucokinase activator AZD1656 as monotherapy in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2013;15(10):923–30. https ://doi.org/10.1111/dom.12100 .

[38] Amin NB, Aggarwal N, Pall D, Paragh G, Denney WS, Le V, et al. Two dose-ranging studies with PF-04937319, a systemic partial activator of glucokinase, as an add-on therapy to metformin in adults with type 2 diabetes.

Diabetes Obes Metab. 2015;17(8):751–9. https://doi.org/10.1111/dom.12474.

[39] Denney WS, Denham DS, Riggs MR, Amin NB. Glycemic effect and safety of a systemic, partial glucokinase activator, PF-04937319, in patients with type 2 diabetes mellitus inadequately controlled on Metformin-A randomized, crossover, Active-Controlled Study. Clin Pharmacol Drug Dev. 2016;5(6):517–27. https://doi.org/10.1002/cpdd.261.

[40] Katz L, Manamley N, Snyder WJ, Dodds M, Agafonova N, Sierra Johnson J, et al. AMG 151 (ARRY-403), a novel glucokinase activator, decreases fasting and postprandial glycemia in patients with type 2 diabetes. Diabetes Obes Metab. 2016;18(2):191–5. https://doi.org/10.1111/dom.12586.

[41] Zhu D, Gan S, Liu Y, Ma J, Dong X, Song W, et al. Dorzagliatin monotherapy in Chinese patients with type 2 diabetes: a dose ranging, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Diabetes Endocrinol. 2018;6(8):627–36. https ://doi. org/10.1016/S2213-8587(18)30105-0.

[42] Zhu XX, Zhu DL, Li XY, Li YL, Jin XW, Hu TX, et al. Dor zagliatin (HMS5552), a novel dual-acting glucokinase activa tor, improves glycaemic control and pancreatic beta-cell func tion in patients with type 2 diabetes: a 28-day treatment study using biomarker-guided patient selection. Diabetes Obes Metab. 2018;20(9):2113–200. https://doi.org/10.1111/dom.13338.

[43]. Scheen AJ. New hope for glucokinase activators in type 2 dia betes? Lancet Diabetes Endocrinol. 2018;6(8):591–3. https ://doi. org/10.1016/S2213-8587(18)30133-5.

[44] Vella A, Freeman JLR, Dunn I, Keller K, Buse JB, Valcarce C. Targeting hepatic glucokinase to treat diabetes with TTP399, a hepatoselective glucokinase activator. Sci Transl Med. 2019. https ://doi.org/10.1126/scitranslmed.aau3441

[45] Matschinsky FM. GKAs for diabetes therapy: why no clinically useful drug after two decades of trying? Trends Pharmacol Sci. 2013;34(2):90–9. https://doi.org/10.1016/j.tips.2012.11.007.

[46] Brouwers M, Jacobs C, Bast A, Stehouwer CDA, Schaper NC. Modulation of glucokinase regulatory protein: a double-edged sword? Trends Mol Med. 2015;21(10):583–94. https ://doi. org/10.1016/j.molmed.2015.08.004.

[47] Tornovsky-Babeay S, Dadon D, Ziv O, Tzipilevich E, Kadosh T, Schyr-Ben Haroush R, et al. Type 2 diabetes and congenital hyperinsulinism cause DNA double-strand breaks and p53 activity in beta cells. Cell Metab. 2014;19(1):109–21. https ://doi. org/10.1016/j.cmet.2013.11.007.

[48] Arden C, Petrie JL, Tudhope SJ, Al-Oanzi Z, Claydon AJ, Beynon RJ, et al. Elevated glucose represses liver glucokinase and induces its regulatory protein to safeguard hepatic phosphate homeostasis. Diabetes. 2011;60(12):3110–20. https ://doi.org/10.2337/ db11-0061.

[49] Arden C, Tudhope SJ, Petrie JL, Al-Oanzi ZH, Cullen KS, Lange AJ, et al. Fructose 2,6-bisphosphate is essential for glucose-regulated gene transcription of glucose-6-phosphatase and other ChREBP target genes in hepatocytes. Biochem J. 2012;443(1):111–23. https://doi.org/10.1042/BJ20111280.

[50] Simons P, Simons N, Stehouwer CDA, Schalkwijk CG, Schaper NC, Brouwers M. Association of common gene variants in glucokinase regulatory protein with cardiorenal disease: A systematic review and meta-analysis. PLoS One. 2018;13(10):e0206174. https://doi.org/10.1371/journal.pone.0206174.

[51] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018;61(12):2461–98. https ://doi.org/10.1007/s00125-018-4729-5