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Review Article

New Targets for Drug Therapy in Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is becoming more prevalent at an alarming rate. With a better understanding of its pathophysiology, new treatment alternatives directed to different critical targets in T2DM have been created and studied. The development of novel therapeutics using various methods, such as novel medication combinations, changed drug molecules, and enhanced delivery systems, can eliminate some of the side effects of old drugs while also improving their efficacy. Newer pharmacological targets such as protein kinase B (Akt/PKB), AMP-activated protein kinase (AMPK), sirtuin (SIRT), and others are effective through different processes. They can be used to treat T2DM of various types and etiologies. Other medicines, such as end barrier, gene therapy, and stem cell technology, employ advanced ways to treat T2DM, and their promise remains untapped. Molecular targets in T2DM are also extensively evaluated because of their capacity to target problems at the molecular level. Antibody treatments and immunizations against T2DM are also investigated in this area. However, there are few current clinical studies, and development progress is modest. There are numerous medicines available to treat T2DM, each with its own set of benefits and drawbacks. The treatment plan that the patient prefers is usually determined by the patient's health and the treatment aim. Many aspects should be considered before choosing an ideal treatment option. Patient compliance, therapeutic efficacy and potency, bioavailability, and other pharmacological and nonpharmacological features are only a few examples.

Keywords: T2DM, oral antidiabetics, new targets, novel therapies

أهداف جديدة للعلاج الدوائي للنوع الثاني من مرض السكري

الخلاصة

مرض السكري من النوع الثاني أصبح أكثر انتشارا بمعدل ينذر بالخطر. مع فهم أفضل للفيزيولوجيا المرضية، تم إقتراح ودراسة بدائل علاجية جديدة موجهة إلى أهداف حرجة مختلفة في تطوير علاجات جديدة باستخدام أساليب مختلفة، مثل تركيبات الأدوية الجديدة، والجزيئات الدوائية المتغيرة، وتعزيز أنظمة التسليم، وأمكانية تجنب بعض الآثار الجانبية للأدوية القديمة مع تحسين فعاليتها. تم ابتكار أهداف علاجية حديثة مثل البروتين كاينيز ب، كاينيز البروتين المنشط، السيرتوين، وغيرها ثبتت فاعليتها من خلال عمليات مختلفة. ويمكن استخدامها لعلاج النوع الثاني من داء السكري. تستخدم أدوية أخرى، مثل حاجز النهاية والعلاج الجيني وتكنولوجيا الخلايا الجذعية كطرائق متقدمة للعلاج، ولا يزال معضمها غير مستغل. كما يتم تقييم الأهداف الجزيئية في المرض على نطاق واسع بسبب قدرتها على استهداف المشاكل على المستوى الجزيئي. كما يتم التحقيق في استخدام الأجسام المضادة والتحصين ضد المرض. ومع ذلك ، هناك عدد قليل من الدراسات السريرية الحالية. عادة ما يتم تحديد خطة العلاج التي يفضلها المريض من خلال صحة المريض وهدف العلاج. وينبغي النظر في العديد من الجوانب قبل اختيار العلاج المثالي. امتثال المريض، والفعالية العلاجية، والتوافر البيولوجي، وغيرها من الميزات الدوائية وغير الدوائية ليست سوى أمثلة قليلة.

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INTRODUCTION

Diabetes mellitus is a global public health issue that contributes significantly to morbidity and mortality [1]. The disease's name is derived from a Greek term that means "passing through" and a Latin word that means "honey" or "sweet" [2]. It is distinguished by the discharge of a high urine volume with a honey-like flavor [3]. Diabetes mellitus is a systemic disease that is both complex and chronic. Hyperglycemia, hyperinsulinemia, and hypertriglyceridemia are examples of metabolic disorders. Diabetes mellitus can damage many organs (e.g., heart, blood vessels, kidney, neurons, and eye) and lead to various life-threatening consequences or even death if not addressed [4]. Diabetes mellitus (DM) is becoming more common all over the world. In 2015, it has been estimated that 246 million individuals globally have DM, with around 80% of them living in developing nations [5]. According to the World Health Organization (WHO), over 1.1 million people died of diabetic complications in 2010, with the death rate anticipated to rise to 50% by 2030 [6]. Increased urbanization, aging, changed lifestyle patterns (lack of exercise and awareness, smoking), and obesity are linked to an increased prevalence of DM in emerging and developed countries [7]. Type 1 diabetes mellitus (T1DM) (insulin-dependent) and type 2 diabetes mellitus (T2DM) (insulin-independent) are the two predominant kinds of DM, with T2DM accounting for roughly 95% of patients [8]. T1DM is defined by absolute insulin shortage and pancreatic cell death [9], whereas T2DM is characterized by insulin resistance (IR) and is occasionally accompanied by insulin secretion abnormalities [10]. DM is characterized by many common signs and symptoms. Polyuria, polyphagia, polydipsia (increased thirst), and weight loss are all symptoms of extensive protein oxidation and glycation. Gestational DM [11] is another mild kind of DM. Insulin mimickers, insulin secretagogues, insulin sensitizers, and carbohydrate absorption blockers are the medications utilized to treat T2DM on a mechanistic basis [12]. Previously, treatment options for T2DM included lifestyle changes, metformin, sulphonylureas, and insulin. Nowadays, there are many different types of antidiabetic drugs. This method of treatment appears to be reasonable. T2DM is associated with two outcomes: insulin resistance, which is indicated by increased hepatic glucose synthesis and impaired glucose utilization from tissues, particularly muscles, and decreased insulin secretion from β-cells [13]. Many details about the role of β-cells, incorrect glucagon secretion, and incretins in the pathogenesis of T2DM are now known. Other problems, such as increased glucose reabsorption from the kidneys and neurotransmitter dysfunction [14], immune system dysregulation/inflammation, increased rate of glucose absorption from the digestive tract, and aberrant microbiota [15], are also gaining attention. There are also new medication classifications introduced. Although there are several antidiabetic medications available in the market, the majority of them are associated with side effects. Off-target effects, contraindications, sustainability, safety, and tolerance are all linked to them [16]. The incremental modification of current therapeutic classes, such as antidiabetic medicines, has yielded promising results [16]. It can be done with new combinations of medications or pharmaceuticals with altered structures. Gene therapy and molecular technologies are examples of novel non-drug therapies. Even more remarkable, the use of nanotechnology in T2DM ensures that medications are delivered to their intended targets [17]. This review article aims to provide a comprehensive assessment of the newly found biological targets for antidiabetic drugs used to treat T2DM, as well as the molecular mechanisms involved in their actions. This paper will also provide an overview of novel and traditional techniques for T2DM management.

NOVEL DRUG TARGETS (Oral Agents) FOR T2DM TREATMENT

Protein Kinase B (Akt/PKB) Modulation

Glucose transport into skeletal muscle is regulated by two different, but interconnected mechanisms. The insulin-dependent Akt/PKB pathway and the contraction-stimulated adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)-dependent pathway are two among them [18]. There are just a few new medications that target the Akt/PKB pathway. IP7, a result of IP6K1-induced phosphorylation, inhibits the Akt/PKB pathway in muscles, suggesting that blocking IP6K1 could activate the Akt/PKB pathway for anti-diabetic benefits [19]. N2-(m-(trifluoromethyl) benzyl) N6-(p-nitrobenzyl) purine (TNP), on the other hand, inhibits insulin release in pancreatic cells via reducing IP6Ks, implying an opposite role in different organs [20]. Newly developed agents such as N, N-dimethyl phenylenediamine (DMPD)-derivatized nitrilotriacetic acid vanadyl complexes and zinc allixin-complexes are at the preclinical stage. They targeted the Akt/PKB pathway and have shown anti-diabetic properties [21]. Targeting the Akt/PKB pathway has been shown to have anti-diabetic benefits in several natural products [22].

Activation of 5' Adenosine Monophosphate-Activated Protein Kinase (AMPK)

Because of its energy sensing ability, AMPK is essential for maintaining metabolic homeostasis, and its absence is linked to insulin resistance [23]. Activating the AMPK system in the liver inhibits gluconeogenesis and lipogenesis by downregulating certain genes [24]. Meanwhile, AMPK activation enhances glucose uptake, mitochondrial genes, lipid oxidation, and sirtuin 1 (SIRT1) activity in muscles [22]. Most antidiabetic medicines, including the well-known metformin, are indirectly implicated in AMPK activation [25]. The activation of AMPK has been linked to AS160, SREBP, and other proteins involved in the pathogenesis of T2DM [26]. MK-8722, a powerful AMPK activator, has recently been found to improve glucose homeostasis while also causing ventricular hypertrophy [27]. In comparison to A769662 and AICAR.47, Merck's product, ex229, has shown greater AMPK activation in skeletal muscle, which enhances glucose uptake and fatty acid oxidation [28]. Furthermore, Pfizer's lead chemical, PF-06409577, has been described as a possible agent to protect against diabetic nephropathy and has

entered Phase 1; however, the underlying mechanism has yet to be elucidated [29].

Activation of SIRT1 Gene Isoforms

The sirtuin-1 (SIRT1) gene is the founding member of the mammalian sirtuin family. In diabetic mice, SIRT1 activity has been shown to lower the incidence of DM, β-cell damage, atherosclerosis, bone marrow, and autonomic neuropathy [30]. SIRT1 expression is inversely linked with advanced glycation end-products (AGEs) in T2DM, implying that SIRT1 plays a role in diabetic nephropathy prevention [31]. Calorie restriction enhances glucose homeostasis and insulin sensitivity via upregulating class 3 NAD^+-dependent histone deacetylase. In both in vitro and in vivo tests, Sirtris Pharmaceuticals' main compounds SRT1460, SRT1720, and SRT2183 appeared to be significantly more effective than resveratrol, another recognized SIRT1 activator [33]. Meanwhile, only a few data have looked at the role of SIRT2 as a metabolic target [34]. While it has been reported that inhibiting SIRT1 and SIRT3 has adverse effects on insulin signaling and sensitivity, a different study found that downregulating SIRT2 has the opposite impact on skeletal muscles [35]. SIRT2 expression is reduced in diabetic neuropathy and is required for axon regeneration, according to another study [36]. SIRT2 has also been linked to Akt/PKB activation; it increases insulin sensitivity and cures AGE-induced diabetic cardiomyopathy in multiple cells [37]. Overall, the vast majority of research found that upregulating SIRT2 has a favorable effect on T2DM. Downregulation of this gene, on the other hand, maybe helpful in other tissues.

G Protein-Coupled Receptors (GPCRs)

Insulin resistance is insufficient to develop T2DM since pancreatic β-cells can regulate blood glucose levels through compensatory hyperinsulinemia [38]. The majority of mediators that promote or inhibit glucose-stimulated insulin secretion (GSIS) worked through G protein-coupled receptors (GPCRs) [39]. G*s*, G*i*, G*q*, and G_{12} are the four major types of G-proteins known to be involved in the signaling pathways that affect insulin production [40]. The intracellular second messenger cAMP is modulated by G*s* and G*i*, whereas G*q* works through the IP3 pathway. G*s* and G*q* increase insulin secretion, whereas G*i* has the reverse effect [41]. Meanwhile, the function of G_{12} in β-cells remains a mystery.

Activation of GPR119 Receptor

GPR119 is primarily located in the pancreas and gastrointestinal tract of an adult human [42]. It is an orphan GPCR of class A (rhodopsin-type) that controls insulin and incretin production [43]. It raises intracellular cAMP concentration after activation, triggering GSIS in β-cells and releasing gut peptides as GLP1 and GIP [44]. Ex vivo testing of GPR119 activity on insulin secretion revealed that a GPR119 agonist, AR231453, significantly boosted insulin release [45]. Apart from insulin secretion, GPR119 agonist-induced incretin secretion may have additional benefits on blood glucose management due to the production of other hormones secondary to incretin action [46]. AR231453 was unable to improve insulin secretion directly in perfused islets in both in vivo and in vitro studies. Instead, in wild-type and β-cells inactivated mice, it improves glucose tolerance, GLP1, and insulin secretions [47]. The exceedingly low risk of hypoglycemia with GPR119 agonists is one of their benefits [48].

Activation of MT1/MT2 Receptors (Melatonin Receptors)

Melatonin is well known for its involvement in the control of the circadian rhythm. Melatonin receptors, MT1 and MT2, are present in human tissues in two isoforms [49]. Melatonin receptors have been connected to glucose homeostasis and insulin release in recent investigations [50]. In hepatocytes and pancreatic cells, both MT1 and MT2 are expressed. The glucose metabolism is controlled by these receptor-linked pathways [51]. Melatonin binding to these melatonin receptors has been shown in numerous investigations to improve both local and systemic insulin sensitivity and reduce gluconeogenesis [52]. Even though melatonin and its agonists have insulin-sensitizing activity, the coupling to G*i* protein lowers insulin release and leads to hyperglycemia [53]. Melatonin is thought to protect β-cells from functional overstrain by slowing insulin output [54]. Despite the lack of clinical support for risk of tolerance, a few long-lasting high-affinity MT1/MT2 receptor agonists such as Tasimelteon (Hetlioz®), Ramelteon (Rozerem®), Piromelatine (Neu-P11), and IIK7 have been produced, unlike over-the-counter melatonin. Ramelteon was found to be ineffective at lowering HbA1c levels in recent research [56]. The innovative medicine Piromelatine, on the other hand, has a longer half-life than melatonin. It has outstanding anti-diabetic benefits through a variety of mechanisms, including reduction of 11-hydroxysteroid dehydrogenase 1 (11-HSD1) and enhanced GLUT4 expression [57]. Tasimelteon is safe for individuals with non-24-hour sleep-wake disorder and insomnia, according to six clinical investigations [58].

Free Fatty Acid Receptors (FFAR)

FFAR1 (GPR40), FFAR2 (GPR43), FFAR3 (GPR41), and FFAR4 (GPR120), GPR42, and GPR84 were identified as FFARs. Only the first four FFARs have been widely researched as potential targets for anti-diabetic drugs. Long-chain free fatty acids (FFA) activate FFAR1 and FFAR4, while short-chain FFAs activate FFAR2 and FFAR3. Medium-chain FFAs, on the other hand, activate GPR84 [59]. Currently, antidiabetic effects can be found in a variety of agonists and antagonists that interact with distinct FFARs. The developed FFAR-targeting medicines are still in the early development stages, ranging from preclinical to phase 2 [60]. FFAR1 and FFAR4 agonists have been shown to increase insulin and incretin productions [61].

Activation of Glucokinase (GKAs)

Glucokinase activators are substances that stimulate the production of the enzyme glucokinase. Glucokinase (GK) is a phosphorylation-activated enzyme that catalyzes the rate-limiting step in the conversion of glucose to glucose-6-phosphate in numerous organs [62]. Because glucose is used in glycolysis and glycogenesis, glucose levels will fall. GK activators (GKAs) are small molecules that attach to GK

allosterically and increase enzyme activity directly. They can also do so by causing the glucokinase regulatory protein (GKRP) complex to become unstable [63]. One of these molecules was discovered in a series of 2,5,6-trisubstituted indole compounds with great potency and the ability to reduce blood glucose levels in mice with a very low dosage [64]. The majority of GKAs have been shown to raise hepatic triglycerides, resulting in hepatic steatosis [65]. Pfizer completed phase 2 trials of one of its pipelines, PF-04991532, which revealed that it increases plasma triglyceride levels rather than hepatic triglyceride levels. Studies have shown that PF-04937319 can be used in conjunction with metformin to increase safety and tolerability, particularly when employing a split-dose strategy [66].

Inhibition of the Sodium-Glucose Cotransporter 2 (SGLT-2)

The main distinction between sodium-glucose cotransporter 1 (SGLT1) and sodium-glucose cotransporter 2 (SGLT2) is that the former transports both glucose and galactose in the small intestinal lumen, whilst the latter solely transports glucose in the kidney [67]. It's a cotransporter with a sodium-transporting N-terminus and a monosaccharide-transporting C-terminus. In the kidney, SGLT2 reabsorbs up to 90% of the filtered glucose [68]. As a result, SGLT2 inhibitors are classified as glycosuric medications because they can lower blood glucose levels by increasing glucose excretion in urine. SGLT2 inhibitors appeared to be a strong glucose-lowering medication whether administered alone or in combination with other treatments like insulin [69]. In comparison to monotherapy, the therapeutic benefits of SGLT2 inhibitors and GLP1 agonists are highly favorable in a variety of measures such as body weight, cardiovascular risk, glycemic management, and blood pressure [70]. There have been numerous reports of SGLT2 inhibitor-related adverse effects. Hypoglycemia, hypovolemia, genital mycotic infections, genital tract infections, and euglycemic ketoacidosis are just a few of the conditions [71].

Inhibition of the 11-Hydroxysteroid Dehydrogenase-1 (11-HSD1)

11-hydroxysteroid dehydrogenase 1 (11-HSD1) is an NADPH-dependent reductase that transforms inert cortisone to its active form cortisol in the endoplasmic reticulum [72]. Cushing's syndrome is linked to high levels of glucocorticoids like cortisol. Based on observations from 11-HSD1-transgenic mice and 11-HSD1 knockout mice, subsequent research concluded that 11-HSD1 contributes to the pathogenesis of T2DM [73]. As a result, 11-HSD1 inhibition has been proposed as a therapeutic target. INCB13739, an 11-HSD1 inhibitor developed by Incyte Corporation, has completed phase 2 testing for safety and efficacy when taken in conjunction with metformin [74].

Imeglimin as Insulin sensitizer

Imeglimin is a novel tetrahydro triazine-containing family of chemicals created by Poxel for the treatment of T2DM that just completed a Phase 2 trial in Japan with promising findings [75]. Its therapeutic potential stems from its ability to sensitize insulin-resistant tissues like muscle and the liver. It also boosts insulin secretion and decreases apoptosis in β-cells [76]. It has been studied as a supplement to metformin and sitagliptin, with the findings indicating that Imeglimin is likely to have complementary effects with other medications [77]. Its efficacy is comparable to metformin, and it has a favorable safety profile [78]. Imeglimin appears to be a promising antidiabetic treatment based on the results of animal trials and human investigations, regardless of whether it is used as a monotherapy or in combination with other drugs [79].

Conclusions

The development of new targets for pharmacological therapy in T2DM is critical to give clinicians a variety of alternatives. Treatment could be more effective, safe, and cost-efficient than present options.

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Conflicting interests

The authors declared no conflicting interests.

Data sharing statement

N/A

REFERENCES

1. Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. *Nat Rev Endocrinol*. 2016;12(10):616-622. doi:10.1038/nrendo.2016.105

2. Porth CM, (Ed.), Essentials of Pathophysiology: Concepts of Altered Health States, (3rd ed.) Wolters Kluwer, The Netherlands, 2010.

3. Timper K, Donath MY. Diabetes mellitus type 2: The new face of an old lady. *Swiss Med Wkly*. 2012;142:13635. doi: 10.4414/smw.2012.13635.

4. Mirmiran P, Bahadoran Z, Azizi F. Lipid accumulation product is associated with insulin resistance, lipid peroxidation, and systemic inflammation in type 2 diabetic patients. *Endocrinol Metab (Seoul)*. 2014;29(4):443-449. doi: 10.3803/EnM.2014.29.4.443.

5. Tabish SA. Is diabetes becoming the biggest epidemic of the twenty-first century? *Int J Health Sci (Qassim)*. 2007;1(2):V-VIII. PMID: 21475425.

6. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. *Oman Med J*. 2012;27(4):269-273. doi: 10.5001/omj.2012.68.

7. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. *Phys Ther*. 2008;88(11):1254-1264. doi: 10.2522/ptj.20080020.

8. Thomas CC, Philipson LH. Update on diabetes classification. *Med Clin North Am*. 2015;99:1-16. doi: 10.1016/j.mcna.2014.08.015.

9. Chillarón JJ, Flores Le-Roux JA, Benaiges D, Pedro-Botet J. Type 1 diabetes, metabolic syndrome and cardiovascular risk. *Metabolism*. 2014;63(2):181-187. doi:10.1016/j.metabol.2013.10.002

10. De Fronzo RA. Pathogenesis of type 2 diabetes mellitus. *Med Clin North Am*. 2004; 88:787-835. doi: 10.1016/j.mcna.2004.04.013.

11. Kohei KA. Pathophysiology of type 2 diabetes and its treatment policy. *J Med Assoc J*. 2010;53(1):41-46.

12. Raptis SA, Dimitriadis GD. Oral hypoglycemic agents: insulin secretagogues, alpha-glucosidase inhibitors and insulin sensitizers. *Exp Clin Endocrinol Diabetes*. 2001;109(Suppl. 2):S265-287. doi: 10.1055/s-2001-18588.

13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2009;32(Suppl 1):S62-S67. doi: 10.2337/dc09-S062.

14. De Fronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58(4):773-795. doi: 10.2337/db09-9028.

15. Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR, Aguilar RB. The time is right for a new classification system for diabetes: Rationale and implications of the β-cell-centric classification schema. *Diabetes Care*. 2016;39(2):179-186. doi:10.2337/dc15-1585.

16. Guthrie RM. Evolving therapeutic options for type 2 diabetes mellitus: an overview. *Postgrad Med*. 2012; 124:82-89. doi: 10.3810/pgm.2012.11.2614.

17. Chellappan DK, Yenese Y, Wei CC, Gupta G. Nanotechnology and diabetic wound healing: A review. *Endocr Metab Immune Disord Drug Targets*. 2017;17(2):87-95. doi:10.2174/1871530317666170421121202

18. Mackenzie RW, Elliott BT. Akt/PKB activation and insulin signaling: a novel insulin signaling pathway in the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes*. 2014;7:55-64. doi: 10.2147/DMSO.S48260.

19. Larner J, Brautigan DL, Thorner MO. D-chiro-inositol glycans in insulin signaling and insulin resistance. *Mol Med*. 2010;16:543-552. doi: 10.2119/molmed.2010.00107.

20. Wang N, Wang Z, Niu X, Yang X. Synthesis, characterization and anti-diabetic therapeutic potential of novel aminophenol-derivatized nitrilotriacetic acid vanadyl complexes. *J Inorg Biochem*. 2015;152:104-113. doi: 10.1016/j.jinorgbio.2015.07.012.

21. Padmanabhan U, Dollins DE, Fridy PC, York JD, Downes CP. Characterization of a selective inhibitor of inositol hexakisphosphate kinases: use in defining biological roles and metabolic relationships of inositol pyrophosphates. *J Biol Chem*. 2009;284(16):10571-10582. doi:10.1074/jbc.M900752200.

22. Lima CR, Vasconcelos CF, Costa-Silva JH, Maranhão CA, Costa J, Batista TM, et al. Anti-diabetic activity of extract from *Persea americana* Mill. leaf via the activation of protein kinase B (PKB/Akt) in streptozotocin-induced diabetic rats. *J Ethnopharmacol*. 2012;141(1):517-525. doi: 10.1016/j.jep.2012.03.026.

23. Hardie DG. AMPK: a key regulator of energy balance in the single-cell and the whole organism. *Int J Obes*. 2008;32(Suppl 4):S7-12. doi: 10.1038/ijo.2008.116.

24. Horike N, Sakoda H, Kushiyama A, Ono H, Fujishiro M, Kamata H, et al. AMP-activated protein kinase activation increases phosphorylation of glycogen synthase kinase 3beta and thereby reduces cAMP-responsive element transcriptional activity and phosphoenolpyruvate carboxykinase C gene expression in the liver. *J Biol Chem*. 2008;283(49):33902-10. doi: 10.1074/jbc.M802537200.

25. Jäger S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. *Proc Natl Acad Sci U A*. 2007;104(29):12017-12022. doi: 10.1073/pnas.0705070104.

26. Steinberg GR, Schertzer JD. AMPK promotes macrophage fatty acid oxidative metabolism to mitigate inflammation: implications for diabetes and cardiovascular disease. *Immunol Cell Biol*. 2014;92(4):340-345. doi: 10.1038/icb.2014.11.

27. Moreno D, Knecht E, Viollet B, Sanz P. A769662, a novel activator of AMP-activated protein kinase, inhibits non-proteolytic components of the 26S proteasome by an AMPK-independent mechanism. *FEBS Lett*. 2008;582(17):2650-2654. doi: 10.1016/j.febslet.2008.06.044.

28. Lai YC, Kviklyte S, Vertommen D, Lantier L, Foretz M, Viollet B, et al. A small-molecule benzimidazole derivative that potently activates AMPK to increase glucose transport in skeletal muscle: comparison with effects of contraction and other AMPK activators. *Biochem J*. 2014;460(3):363-375. doi: 10.1042/BJ20131673.

29. Zhang HZ, Zhao ZL, Zhou CH. Recent advances in oxazole-based medicinal chemistry. *Eur J Med Chem*. 2018;144:444-492. doi: 10.1016/j.ejmech.2017.12.044.

30. Banks AS, Kon N, Knight C, Matsumoto M, Gutiérrez-Juárez R, Rossetti L, et al. SirT1 gain of function increases energy efficiency and prevents diabetes in mice. *Cell Metab*. 2008;8(4):333-341. doi: 10.1016/j.cmet.2008.08.014.

31. Cardellini M, Menghini R, Martelli E, Casagrande V, Marino A, Rizza S, et al. TIMP3 is reduced in atherosclerotic plaques from subjects with type 2 diabetes and increased by SirT1. *Diabetes*. 2009;58(10):2396-2401. doi: 10.2337/db09-0280.

32. Albiero M, Poncina N, Tjwa M, Ciciliot S, Menegazzo L, Ceolotto G, et al. Diabetes causes bone marrow autonomic neuropathy and impairs stem cell mobilization via dysregulated p66Shc and Sirt1. *Diabetes*. 2014;63(4):1353-1365. doi: 10.2337/db13-0894.

33. Liu R, Zhong Y, Li X, Chen H, Jim B, Zhou MM, et al. Role of transcription factor acetylation in diabetic kidney disease. *Diabetes*. 2014;63(7):2440-2453. doi: 10.2337/db13-1810.

34. Kitada M, Koya D. SIRT1 in Type 2 diabetes: Mechanisms and therapeutic potential. *Diabetes Metab J*. 2013;37:315-325. doi: 10.4093/dmj.2013.37.5.315.

35. Bordone L, Guarente L. Calorie restriction, SIRT1 and metabolism: understanding longevity. *Nat Rev Mol Cell Biol*. 2005;6:298-305. doi: 10.1038/nrm1616.

36. Heilbronn LK, Civitarese AE, Bogacka I, Smith SR, Hulver M, Ravussin E. Glucose tolerance and skeletal muscle gene expression in response to alternate day fasting. *Obes Res*. 2005;13(3):574-581. doi: 10.1038/oby.2005.61.

37. Milne JC, Lambert PD, Schenk S, Carney DP, Smith JJ, Gagne DJ, et al. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. *Nature*. 2007;450(7170):712-6. doi: 10.1038/nature06261.

38. Oh DY, Olefsky JM. G protein-coupled receptors as targets for anti-diabetic therapeutics. *Nat Rev Drug Discov*. 2016;15:161-172. doi: 10.1038/nrd.2015.4.

39. Ahrén B. Islet G protein-coupled receptors as potential targets for treatment of type 2 diabetes. *Nat Rev Drug Discov*. 2009;8:369-385. doi: 10.1038/nrd2782.

40. Denis C, Saulière A, Galandrin S, Sénard JM, Galés C. Probing heterotrimeric G protein activation: applications to biased ligands. *Curr Pharm Des*. 2012;18(2):128-144. doi: 10.2174/138161212799040466.

41. Kimple ME, Neuman JC, Linnemann AK, Casey PJ. Inhibitory G proteins and their receptors: emerging therapeutic targets for obesity and diabetes. *Exp Mol Med*. 2014;46(6):e102. doi: 10.1038/emm.2014.40.

42. Overton HA, Babbs AJ, Doel SM, Fyfe MC, Gardner LS, Griffin G, et al. Deorphanization of a G protein-coupled receptor for oleoylethanolamide and its use in the discovery of small-molecule hypophagic agents. *Cell Metab*. 2006;3(3):167-175. doi: 10.1016/j.cmet.2006.02.004.

43. Niazi AK, Niazi SH. A novel strategy for the treatment of diabetes mellitus - sodium-glucose co-transport inhibitors. *N Am J Med Sci*. 2010;2:556-560. doi: 10.4297/najms.2010.2556.

44. Shah U, Kowalski TJ. GPR119 agonists for the potential treatment of type 2 diabetes and related metabolic disorders. *Vitam Horm*. 2010;84:415-448. doi: 10.1016/B978-0-12-381517-0.00016-3.

45. Overton HA, Fyfe MC, Reynet C. GPR119, a novel G protein-coupled receptor target for the treatment of type 2 diabetes and obesity. *Br J Pharmacol*. 2008;153(Suppl. 1):S76-81. doi: 10.1038/sj.bjp.0707529.

46. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev*. 2008;60(4):470-512. doi: 10.1124/pr.108.000604.

47. Panaro BL, Flock GB, Campbell JE, Beaudry JL, Cao X, Drucker DJ. β-Cell Inactivation of *Gpr119* Unmasks Incretin Dependence of GPR119-Mediated Glucoregulation. *Diabetes*. 2017;66(6):1626-1635. doi: 10.2337/db17-0017.

48. Yoshida S, Ohishi T, Matsui T, Tanaka H, Oshima H, Yonetoku Y, et al. Novel GPR119 agonist AS1535907 contributes to first-phase insulin secretion in rat perfused pancreas and diabetic db/db mice. *Biochem Biophys Res Commun*. 2010;402(2):280-285. doi: 10.1016/j.bbrc.2010.10.015.

49. Reppert SM, Weaver DR, Ebisawa T. Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. *Neuron*. 1994;13:1177-1185. doi: 10.1016/0896-6273(94)90055-8.

50. Reppert SM, Godson C, Mahle CD, Weaver DR, Slaugenhaupt SA, Gusella JF. Molecular characterization of a second melatonin receptor expressed in human retina and brain: The Mel1b melatonin receptor. *Proc Natl Acad Sci USA*. 1995;92(19):8734-8738. doi: 10.1073/pnas.92.19.8734.

51. Cecon E, Oishi A, Jockers R. Melatonin receptors: molecular pharmacology and signaling in the context of system bias. *Br J Pharmacol*. 2018;175(16):3263-3280. doi: 10.1111/bph.13950.

52. She M, Laudon M, Yin W. Melatonin receptors in diabetes: a potential new therapeutical target? *Eur J Pharmacol*. 2014;744:220-223. doi: 10.1016/j.ejphar.2014.08.012.

53. Espino J, Pariente JA, Rodríguez AB. Role of melatonin on diabetes-related metabolic disorders. *World J Diabetes*. 2011;2(6):82-91. doi: 10.4239/wjd.v2.i6.82.

54. Forrestel AC, Miedlich SU, Yurcheshen M, Wittlin SD, Sellix MT. Chronomedicine and type 2 diabetes: shining some light on melatonin. *Diabetologia*. 2017;60(5):808-822. doi: 10.1007/s00125-016-4175-1.

55. Faria JA, Kinote A, Ignacio-Souza LM, de Araújo TM, Razolli DS, Doneda DL, et al. Melatonin acts through MT1/MT2 receptors to activate hypothalamic Akt and suppress hepatic gluconeogenesis in rats. *Am J Physiol Endocrinol Metab*. 2013;305(2):E230-242. doi: 10.1152/ajpendo.00094.2013.

56. Karamitri A, Renault N, Clement N, Guillaume JL, Jockers R. Toward the establishment of a link between melatonin and glucose homeostasis: association of melatonin MT2 receptor variants with type 2 diabetes. *Mol Endocrinol*. 2013;27(8):1217-1233. doi: 10.1210/me.2013-1101.

57. Peschke E, Mühlbauer E. New evidence for a role of melatonin in glucose regulation. *Best Pract Res Clin Endocrinol Metab*. 2010;24:829-841. doi: 10.1016/j.beem.2010.09.001.

58. Peschke E. Melatonin, endocrine pancreas and diabetes. *J Pineal Res*. 2008; 44:26-40. doi: 10.1111/j.1600-079X.2007.00519.x.

59. Ichimura A, Hasegawa S, Kasubuchi M, Kimura I. Free fatty acid receptors as therapeutic targets for the treatment of diabetes. *Front Pharmacol*. 2014;5:236. doi: 10.3389/fphar.2014.00236.

60. Li Z, Qiu Q, Geng X, Yang J, Huang W, Qian H. Free fatty acid receptor agonists for the treatment of type 2 diabetes: drugs in preclinical to phase II clinical development. *Expert Opin Investig Drugs*. 2016;25(8):871-90. doi: 10.1080/13543784.2016.1189530.

61. Watterson KR, Hudson BD, Ulven T, Milligan G. Treatment of type 2 diabetes by free fatty acid receptor agonists. *Front Endocrinol (Lausanne)*. 2014;5:137. doi: 10.3389/fendo.2014.00137.

62. Matschinsky FM. A lesson in metabolic regulation inspired by the glucokinase glucose sensor paradigm. *Diabetes*. 1996;45:223-241. doi: 10.2337/diab.45.2.223.

63. Nakamura A, Terauchi Y. Present status of clinical deployment of glucokinase activators. *J Diabetes Investig*. 2015;6:124-132. doi: 10.1111/jdi.12294.

64. Xu J, Lin S, Myers RW, Addona G, Berger JP, Campbell B, et al. Novel, highly potent systemic glucokinase activators for the treatment of type 2 diabetes mellitus. *Bioorg Med Chem Lett*. 2017;27(9):2069-2073. doi: 10.1016/j.bmcl.2016.10.085.

65. De Ceuninck F, Kargar C, Ilic C, Caliez A, Rolin JO, Umbdenstock T, et al. Small molecule glucokinase activators disturb lipid homeostasis and induce fatty liver in rodents: a warning for therapeutic applications in humans. *Br J Pharmacol*. 2013;168(2):339-353. doi: 10.1111/j.1476-5381.2012.02184.x.

66. Erion DM, Lapworth A, Amor PA, Bai G, Vera NB, Clark RW, et al. The hepatoselective glucokinase activator PF-04991532 ameliorates hyperglycemia without causing hepatic steatosis in diabetic rats. *PLoS One*. 2014;9(5):e97139. doi: 10.1371/journal.pone.0097139.

67. Dominguez Rieg JA, Rieg T. What does sodium-glucose co-transporter 1 inhibition add: Prospects for dual inhibition. *Diabetes Obes Metab*. 2019;21(Suppl. 2):43-52. doi: 10.1111/dom.13630.

68. Novikov A, Vallon V. Sodium-glucose cotransporter 2 inhibition in the diabetic kidney: an update. *Curr Opin Nephrol Hypertens*. 2016;25(1):50-58. doi: 10.1097/MNH.0000000000000187.

69. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(1):73-79. doi: 10.1097/MED.0000000000000311.

70. Busch RS, Kane MP. Combination SGLT2 inhibitor and GLP-1 receptor agonist therapy: a complementary approach to the treatment of type 2 diabetes. *Postgrad Med*. 2017;129:686-697. doi: 10.1080/00325481.2017.1342509.

71. Ritz C, Jaafar J, Philippe J. The combination of GLP-1 analogs and SGLT2 inhibitors: new perspectives? *Rev Med Suisse*. 2017;13:1134-1139. PMID: 28639755.

72. Gathercole LL, Lavery GG, Morgan SA, Cooper MS, Sinclair AJ, Tomlinson JW, et al. 11β-Hydroxysteroid dehydrogenase 1: translational and therapeutic aspects. *Endocr Rev*. 2013;34(4):525-555. doi: 10.1210/er.2012-1050.

73. Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, et al. A transgenic model of visceral obesity and the metabolic syndrome. Science. 2001;294(5549):2166-2170. doi: 10.1126/science.1066285.

74. Ziouzenkova O, Orasanu G, Sharlach M, Akiyama TE, Berger JP, Viereck J, et al. Retinaldehyde represses adipogenesis and diet-induced obesity. *Nat Med*. 2007;13(6):695-702. doi: 10.1038/nm1587.

75. Perry RJ, Cardone RL, Petersen MC, Zhang D, Fouqueray P, Hallakou-Bozec S, Bolze S, et al. Imeglimin lowers glucose primarily by amplifying glucose-stimulated insulin secretion in high-fat-fed rodents. *Am J Physiol Endocrinol Metab*. 2016;311(2):E461-470. doi: 10.1152/ajpendo.00009.2016.

76. Vial G, Chauvin MA, Bendridi N, Durand A, Meugnier E, Madec AM, et al. Imeglimin normalizes glucose tolerance and insulin sensitivity and improves mitochondrial function in liver of a high-fat, high-sucrose diet mice model. *Diabetes*. 2015;64(6):2254-2264. doi: 10.2337/db14-1220.

77. Pacini G, Mari A, Fouqueray P, Bolze S, Roden M. Imeglimin increases glucose-dependent insulin secretion and improves β-cell function in patients with type 2 diabetes. *Diabetes Obes Metab*. 2015;17(6):541-545. doi: 10.1111/dom.12452.

78. Fouqueray P, Pirags V, Inzucchi SE, Bailey CJ, Schernthaner G, Diamant M, et al. The efficacy and safety of imeglimin as add-on therapy in

patients with type 2 diabetes inadequately controlled with metformin monotherapy. *Diabetes Care*. 2013;36(3):565-568. doi: 10.2337/dc12-0453.

79. Vuylsteke V, Chastain LM, Maggu GA, Brown C. Imeglimin: A potential new multi-target drug for type 2 diabetes. *Drugs RD*. 2015;15(3):227-32. doi: 10.1007/s40268-015-0099-3.