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The Role of Genomic Sequencing in Diabetes Mellitus

Yanne Pradwi Efendi[1,2*], Alexander Kam[1,2], Eva Decroli[1,2], Dinda Aprilia[1,2], Syafril Syahbuddin[1,2]

[1.] Metabolic Endocrinology and Diabetes Division, Internal Medicine Department, Medical Faculty, Universitas Andalas, Padang, West Sumatera, Indonesia
[2.] Metabolic Endocrinology and Diabetes Division, Internal Medicine Department, M. Djamil General Hospital, Padang, West Sumatera, Indonesia
Email: yanne.rama17@gmail.com

Abstract

Diabetes Mellitus is a chronic metabolic disorder caused by impaired insulin secretion and/or insulin resistance. Genetic testing through genomic sequencing is one of the modalities available for diabetes mellitus. Genomic sequencing is the process of analysing DNA obtained from a blood sample (or alternatively from tissue samples). Broadly, genomic sequencing plays two major roles in diabetes mellitus: supporting diagnosis and guiding therapeutic approaches. In its development, genomic sequencing has proven valuable for diagnostic investigation in type 1 diabetes and maturity-onset diabetes of the young (MODY), as well as for assessing the polygenic risk score (PRS) in type 2 diabetes. Establishing a definitive diagnosis allows for the selection of individualised therapy. Several randomised controlled trials have demonstrated that the risk of developing diabetes can be reduced by up to half if detected at an earlier stage. Moreover, genomic sequencing can identify genetic variants that influence responsiveness to antidiabetic treatments. At present, several potential antidiabetic agents targeting novel pathways are under development and in various stages of clinical trials. The application of genomic sequencing thus facilitates the implementation of individualised therapy, ultimately contributing to the realisation of precision medicine.

Keywords: Genomic sequencing, diabetes Mellitus, diagnosis, therapy

Abstrak

Diabetes Melitus adalah gangguan metabolisme kronis yang disebabkan oleh gangguan sekresi insulin dan/atau resistensi insulin. Pengujian genetik melalui pengurutan genom merupakan salah satu modalitas yang tersedia untuk diabetes melitus. Pengurutan genom adalah proses analisis DNA yang diperoleh dari sampel darah (atau dari sampel jaringan). Secara umum, pengurutan genom memainkan dua peran utama dalam diabetes melitus: mendukung diagnosis dan memandu pendekatan terapeutik. Dalam perkembangannya, pengurutan genom telah terbukti berharga untuk investigasi diagnostik pada diabetes tipe 1 dan diabetes onset maturitas pada usia muda (MODY), serta untuk menilai skor risiko poligenik (PRS) pada diabetes tipe 2. Menetapkan diagnosis definitif memungkinkan pemilihan terapi individual. Beberapa uji coba terkontrol acak telah menunjukkan bahwa risiko diabetes dapat dikurangi hingga setengahnya jika terdeteksi pada tahap awal. Lebih lanjut, pengurutan genom dapat mengidentifikasi varian genetik yang memengaruhi respons terhadap pengobatan antidiabetik. Saat ini, beberapa agen antidiabetik potensial yang menargetkan jalur baru sedang dikembangkan dan dalam berbagai tahap uji klinis. Penerapan pengurutan genom dengan demikian memfasilitasi penerapan terapi individual, yang pada akhirnya berkontribusi pada terwujudnya pengobatan presisi.

***Kata Kunci**: Pengurutan genomik, diabetes melitus, diagnosis, terapi*

I. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by impaired insulin secretion and/or insulin resistance. The prevalence of diabetes continues to rise globally, posing a major public health concern and contributing substantially to the worldwide disease burden.[1-3] Diabetes is categorised into four groups: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), specific types such as monogenic diabetes, exocrine pancreatic disease, drug-induced diabetes, and gestational diabetes.[4]

According to the American Diabetes Association (ADA) 2025, genetic testing is recommended in adults newly diagnosed with diabetes when T1DM is suspected, particularly to investigate monogenic diabetes.[2,3] Genomic sequencing has emerged as an important tool in this context, as it enables the simultaneous analysis of multiple genes, allowing for accurate identification of MODY (maturity-onset diabetes of the young) subtypes, which are often misdiagnosed as T1DM. Furthermore, genomic sequencing also contributes to the assessment of polygenic risk scores in individuals at risk of T2DM.[4,5]

Despite the availability of oral hypoglycaemic agents and insulin, current pharmacological therapies face significant limitations, including inter-individual variability in drug response, failure to achieve durable glycaemic control, and adverse drug effects. A considerable proportion of patients fail to maintain optimal glycaemic outcomes even after long-term therapy exceeding ten years. In response, both the ADA and the European Association for the Study of Diabetes (EASD) advocate for the adoption of individualised therapy and precision medicine in diabetes management.[1,2]

Pharmacogenomics, supported by genomic sequencing, represents a promising approach to optimise diabetes therapy by tailoring treatment according to patients' genetic profiles. Variations in drug efficacy, side effects, and metabolism are strongly influenced by genetic polymorphisms, and genomic sequencing has facilitated the identification of specific variants associated with these differences.[3,5] In addition, this approach holds potential for the discovery of novel antidiabetic agents. Thus, the integration of genomic sequencing into clinical practice provides a pathway towards individualised therapy and the advancement of precision medicine in diabetes care.

II. GENOMIC SEQUENCING OVERVIEW

The genome is the genetic material composed of DNA or RNA, with DNA serving as the long-term repository of genetic information. DNA consists of nucleotide bases: adenine (A), thymine (T), guanine (G), and cytosine (C) where A pairs with T and G with C. Determining the sequence of these bases is known as genomic sequencing.[6-8] This process analyses DNA, commonly obtained from blood or tissue samples, following informed consent, isolation, and preparation. Results require subsequent patient counselling and therapeutic planning.[6,9,10]

Genomic sequencing is performed using whole genome sequencing (WGS) and next generation sequencing (NGS). NGS enables rapid, parallel sequencing of large DNA fragments, while WGS employs NGS to generate a complete genomic sequence.[8] Sequencing involves fragmenting DNA, adding markers, amplifying fragments, and reading nucleotides with fluorescent signals, followed by bioinformatic analysis to identify genetic variants.[7,11]

Clinically, genomic sequencing supports understanding of genetic diseases, detection of pathogenic mutations, outbreak tracing, and therapeutic planning.[6] Its main applications include: (1) calculating

polygenic risk scores (PRS) to estimate disease susceptibility in complex conditions such as type 2 diabetes mellitus,[8,9] (2) identifying small variants (missense, indels, nonsense, short tandem repeats) relevant to monogenic diseases, pharmacogenetics, and actionable cancer drivers,[8,9] (3) detecting structural variants such as copy number variants, translocations, and inversions, and (4) recognising mutation signatures in cancer genomes to guide targeted therapies.[8,9]

In Indonesia, genomic sequencing is available through initiatives such as My Indosequence and the Biomedical and Genome Science Initiative (BGSi), which focus on cancer, infectious diseases, neurodegenerative disorders, metabolic conditions, genetic syndromes, and ageing.[10]

III. The Role of Genomic Sequencing in Diabetes Mellitus

The application of genomic sequencing in diabetes was first introduced in 2007 through genome-wide association studies (GWAS), which identified a large number of genes associated with common diseases, including diabetes mellitus (DM). Applied to millions of individuals, this method has successfully identified several genetic variants related to type 2 diabetes mellitus (T2DM).[11,12] Genomic sequencing has since been shown to be valuable in type 1 diabetes mellitus (T1DM) and maturity-onset diabetes of the young (MODY) for diagnostic purposes, and in T2DM for the assessment of polygenic risk scores (PRS) and the selection of individualised therapies.

According to the American Diabetes Association (ADA) 2025, in adults with suspected T1DM, autoantibody testing is recommended. If the results are negative, and the individual is younger than 35 years, presents with clinical features suggestive of monogenic diabetes (such as renal cysts, partial lipodystrophy, maternally inherited deafness, or severe insulin resistance without obesity), and has a C-peptide level >200 pmol/L, then genetic testing should be pursued if available.[4] Genomic sequencing plays a crucial role in diagnosing and understanding MODY, enabling gene analysis to identify specific subtypes.[5,12]

In individuals at risk of T2DM, genomic sequencing can be used to calculate PRS, thereby informing appropriate management strategies. Since 2013, pharmacological interventions for T2DM have been directed towards both prevention and treatment; however, drug responses vary significantly between patients. To address this variability, individualised therapy also referred to as personalised diabetology and precision medicine are recommended. Precision medicine tailors treatment to patients based on genetic, environmental, and lifestyle factors.[1,3,13]

Genomic sequencing further enables the identification of genetic variants that influence response to antidiabetic drugs. Numerous studies have demonstrated such associations. For example, Maruthur et al. (2014) conducted an observational study evaluating the pharmacogenetics of metformin, sulfonylureas, repaglinide, thiazolidinediones, and acarbose in patients with diabetes. Significant gene drug interactions affecting glycaemic outcomes were observed, including loci *SLC22A1*, *SLC22A2*, *SLC47A1*, *PRKAB2*, *PRKAA2*, *PRKAA1*, and *STK11* with metformin, and *CYP2C9* and *TCF7L2* with sulfonylureas.[14]

IV. The Role of Genomic Sequencing in Diabetes Mellitus Diagnosis

Type 1 diabetes (T1D) may occur as part of autoimmune polyendocrine syndromes, such as IPEX, caused by FOXP3 mutations, or less commonly by AIRE mutations. Clinical studies have explored strategies for prevention and delay of T1D in individuals with islet cell autoimmunity. Stage 1 T1D is defined by the presence of ≥2 autoantibodies

with normoglycaemia, carrying a five-year progression risk of approximately 44%, while stage 2, characterised by multiple autoantibodies and dysglycaemia, carries a two-year risk of 60% and a five-year risk of 75%.[1]

Genetically, T1D shows strong associations with HLA haplotypes DQB1 and DRB1. Specific alleles confer susceptibility (e.g. DRB1*0301-DQB1*0201/DR3-DQ2, DRB1*0401-DQB1*0302/DR4-DQ8), while others are protective (e.g. DRB1*1501 and DQA1*0102-DQB1*0602).[1] Monogenic defects causing β-cell dysfunction, such as maturity-onset diabetes of the young (MODY), account for <5% of diabetes cases.[4] Monogenic defects involve a single gene mutation (Figure 1).

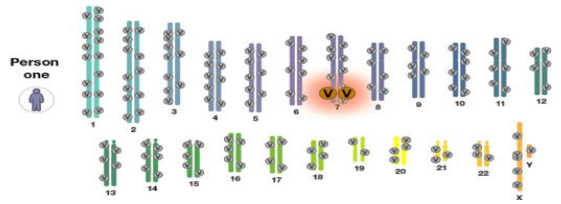

Figure 1. Monogenic defects associated with a single gene.
Source: National Human Genome Research Institute. Polygenic Risk Scores. 2024.

Genetic testing should be considered in children or young adults without classical T1D or T2D features and with successive generations affected, indicating autosomal dominant inheritance. MODY typically presents with hyperglycaemia before the age of 25 years, impaired insulin secretion with minimal or no insulin resistance, and autosomal dominant transmission involving at least 14 genes. The most frequently reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), HNF4A-MODY (MODY1), and HNF1B-MODY (MODY5), whereas MODY4 is rare and caused by PDX1 mutations.[3,14,15] Accurate diagnosis is essential to avoid misclassification as T1D or T2D, which may lead to suboptimal or harmful therapy and delayed recognition in relatives. Once diagnosed, personalised therapy can be implemented.[4]

By contrast, type 2 diabetes (T2D) is a polygenic disorder resulting from multiple genetic variants and environmental factors.[4,9] Polygenic defects involve numerous variants, some disease-associated and others benign (Figure 2).

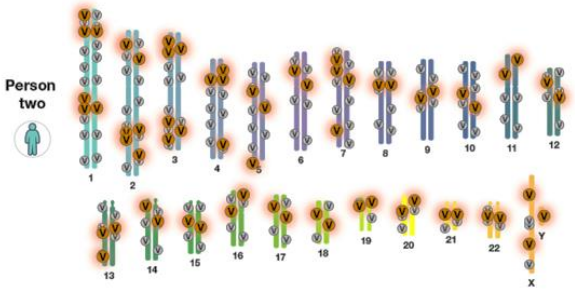

Figure 2. Polygenic defects associated with multiple genes.
Source: National Human Genome Research Institute. Polygenic Risk Scores. 2024.

Family history, particularly first-degree relatives, confers stronger predisposition than in T1D. Genomic sequencing in at-risk populations allows calculation of polygenic risk scores (PRS), providing a stratification tool for disease susceptibility (Figure 3).

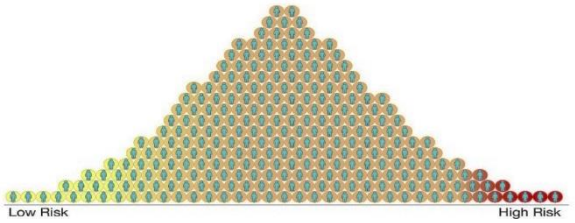

Figure 3. Bell-shaped distribution curve in polygenic risk score assessment.
Source: National Human Genome Research Institute. Polygenic Risk Scores. 2024.

PRS follows a bell-shaped distribution: most individuals have intermediate scores, while extremes represent low- and high-risk groups. Those at high risk may require earlier or more intensive interventions to prevent T2D progression.[9] Randomised controlled trials have shown that early detection and intervention can reduce progression risk by up to 50%.[3] Imamura et al. (2024) demonstrated that PRS derived from millions of variants in GWAS data (~450,000 European samples) accurately predicted early-onset T2D.[13] Similarly, Kim

et al. (2021) reported that patients with high genetic risk exhibited greater reductions in HbA1c after sulfonylurea therapy, highlighting the clinical utility of PRS.[14]

V. The Role of Genomic Sequencing in Diabetes Mellitus Therapy

The role of genomic sequencing is more closely linked to type 2 diabetes mellitus (T2DM). Variations in therapeutic response among individuals with T2DM arise from both genetic and non-genetic factors. T2DM is a polygenic disorder involving multiple loci responsible for insulin secretion, obesity, fasting glucose, body mass index, insulin resistance, and β-cell function. Genomic data not only aid early disease prevention but also help optimise pharmacological therapy, achieving glycaemic control and reducing the risk of complications.[3,15]

Biguanides

Metformin is the main biguanide used in T2DM. Its hypoglycaemic effect is not fully understood, but it is believed to reduce hepatic glucose output and enhance glucose uptake in peripheral tissues via AMP-activated protein kinase (AMPK). Metformin also acts on the intestine, reducing glucose absorption, altering bile acid metabolism, modulating gut microbiota, and increasing GLP-1 secretion, all contributing to lower glucose levels. It is excreted unchanged in bile and urine, primarily through transporters such as organic cation transporters (OCTs), multidrug and toxin extrusion transporters (MATEs), and plasma membrane monoamine transporters (PMATs).[2,12]

Metformin and Transporter Genes

After ingestion, metformin is absorbed into enterocytes by PMAT and OCT3, enters the circulation via OCT1, and is transported to the liver through OCT1 and OCT3. Hepatic excretion occurs via MATE1 (encoded by SLC47A1) and MATE2 (**S**LC47A2). Renal clearance is mediated by OCT2 (SLC22A2) and MATE transporters, while PMAT (SLC29A4) also contributes to intestinal absorption and renal reabsorption (Figure 4).[2,16]

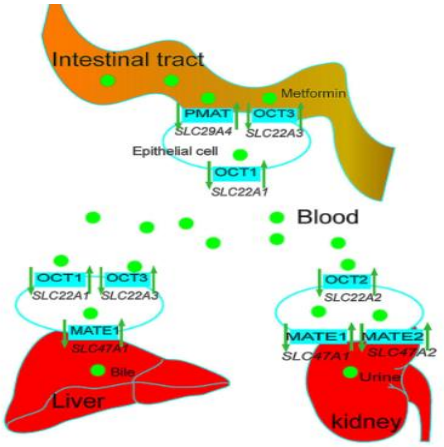

Figure 4. Pharmacokinetic process of metformin and transporter proteins responsible for its absorption and excretion.
Source: Zeng Z, Huang S, Sun T. Pharmacogenomic studies of current antidiabetic agents and potential new drug targets for precision medicine of diabetes. Diabetes Therapy. 2020;11:2521–38.

Polymorphisms in transporter genes significantly influence metformin efficacy, though results vary by ethnicity. For instance, SLC22A1 rs622342 was associated with improved HbA1c in South Indian and Mexican patients, but not in Iranian or Jordanian cohorts.[1,2,3,12] Similarly, SLC22A2 variants such as rs316019 and rs201919874 have shown variable effects across populations, enhancing HbA1c reduction in some groups but not others.[2,17] Variants in SLC22A3 (OCT3), including rs3088442 and rs12194182, were also linked to differential metformin response in Pakistani and Jordanian patients.[2,17]

MATE polymorphisms further impact therapy. SLC47A1 rs2289669 carriers (AG/AA) demonstrated greater HbA1c reduction, likely due to delayed elimination or increased GLP-1 secretion.[2] Patients with combined SLC22A2 rs316019 and SLC47A2 rs12943590 polymorphisms showed enhanced glycaemic improvement.[2,17-19] Finally, the PMAT gene

(SLC29A4) variant rs3889348 increased renal clearance of metformin in Korean patients.[2,20,21]

Sulfonylureas

Sulfonylureas help regulate blood glucose by enhancing insulin secretion from pancreatic β-cells. They are the first-line therapy for HNF1A-MODY and HNF4A-MODY. Sulfonylureas (and glinides) bind to the sulfonylurea receptor 1 (SUR1, encoded by *ABCC8*), thereby inhibiting the potassium channel encoded by *KCNJ11*. This leads to β-cell membrane depolarisation and opening of voltage-gated calcium channels. The resulting Ca^{2+} influx triggers insulin granule exocytosis and insulin secretion. Most sulfonylureas are metabolised by cytochrome P450 (CYP) enzymes in the liver. Mutations in genes encoding the receptor or metabolic enzymes may influence response to sulfonylureas (Figure 5).[2,3,16,12]

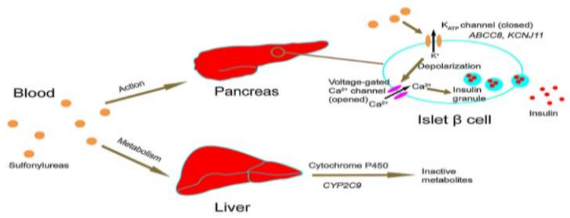

Figure 5. Mechanism of action and metabolism of sulfonylureas in relation to potential pharmacogenomic genes.
Source: Zeng Z, Huang S, Sun T. Pharmacogenomic studies of current antidiabetic agents and potential new drug targets for precision medicine of diabetes. Diabetes Therapy. 2020;11:2521–38.

Sulfonylureas and Target Genes

Sulfonylurea receptor 1 (SUR1), encoded by *ABCC8*, forms part of the KATP channel. A significant association has been demonstrated between the *ABCC8* Ser1369Ala polymorphism and sulfonylurea response. This variant may influence the therapeutic efficacy of sulfonylureas. Polymorphisms in *ABCC8* exons 16 and 31 have also been linked to HbA1c and triglyceride levels in patients with type 2 diabetes treated with sulfonylureas. Conversely, some studies have reported that the Ser1369Ala variant (*rs757110*) is not associated with severe hypoglycaemia or with good glycaemic control in patients receiving glibenclamide.[2,3,12]

KCNJ11, located adjacent to *ABCC8*, encodes the Kir6.2 protein, another subunit of the KATP channel.[2,3] Variants most frequently studied are *rs5219* (E23K) and *rs5215*. In Caucasian patients with type 2 diabetes, carriers of the K allele of *KCNJ11 rs5219* showed greater HbA1c reduction after gliclazide therapy. However, *KCNJ11 rs5219* and *rs5215* have not been associated with hypoglycaemia risk in patients treated with sulfonylureas. *KCNJ11 rs5219* has instead been linked to increased sulfonylurea treatment failure, though not to therapeutic efficacy in Caucasian or Korean populations.[2,17,21]

Unlike metformin, which is excreted renally, sulfonylureas are metabolised in the liver and thus influenced by genetic variants of their metabolising enzymes.[23,24] The *CYP2C9* gene encodes a cytochrome P450 enzyme involved in sulfonylurea metabolism. Loss-of-function alleles (*CYP2C9* *2/*3) have been associated with higher sulfonylurea levels and a reduced risk of treatment failure. Maruthur et al. (2014) reported that the interaction between *CYP2C9* SNP *rs1057910* and sulfonylurea use produced greater mean reductions in HbA1c from baseline over six months of therapy. More recently, the *CYP2C9**3 polymorphism has been linked to improved glycaemic control in type 2 diabetes patients treated with glibenclamide.[2,17,23]

Glinides

Glinides are absorbed into the circulation and bind to the KATP channel, composed of SUR1 (encoded by *ABCC8*) and Kir6.2 (encoded by *KCNJ11*). Patients with the CT genotype of *ABCC8* SNP *rs1801261* show significant reductions in FPG and HbA1c

compared with those with the CC genotype. Homozygous CC carriers of the exon 16-3 T/C variant (*rs1799854*) in *ABCC8* exhibit decreased HOMA-IR, indicating that repaglinide enhances insulin sensitivity. Furthermore, patients carrying the K allele of the *KCNJ11* E23K (*rs5219*) variant display greater reductions in HbA1c and postprandial glucose (PPG) compared with EE homozygotes, suggesting that E/K and K/K genotypes are associated with a better response to repaglinide in stimulating insulin secretion. Other studies have reported significant changes in HbA1c and PPG, but not in FPG, after six months of therapy in patients with the *KCNJ11 E23K* genotype, reflecting the role of repaglinide binding to β-cell receptors in inhibiting potassium channels.[2,12]

Thiazolidinediones

Thiazolidinediones, a class of peripheral insulin sensitisers including pioglitazone and rosiglitazone, activate peroxisome proliferator-activated receptor-γ (PPARG) in peripheral tissues. This receptor regulates the expression of genes essential for insulin sensitivity. By mediating transcription of glucose metabolism-related genes, thiazolidinediones enhance peripheral tissue sensitivity to insulin, thereby lowering blood glucose.[1,2,12,25] PPARG is a nuclear hormone receptor encoded by the *PPARG* gene. The Pro12Ala (*rs1801282*) polymorphism is the most common variant and has also been linked to type 2 diabetes risk. Associations between Pro12Ala and improved therapeutic response to pioglitazone have been consistently reported across different populations, including South Indians, Chinese, Iranians, and postmenopausal Mexican women.[2,3,12]

Other Antidiabetic Agents and Related Genes

Other antidiabetic agents, including α-glucosidase inhibitors, GLP-1 receptor agonists, DPP4 inhibitors, and SGLT2 inhibitors, currently lack strong pharmacogenomic evidence. α-Glucosidase inhibitors act in the gastrointestinal tract by delaying the absorption of complex carbohydrates through inhibition of α-glucosidase. Acarbose reduces intestinal glucose absorption by inhibiting brush-border enzymes that hydrolyse carbohydrates. It is mainly excreted in the faeces and appears to lack well-defined pharmacokinetic and pharmacodynamic targets. Interactions have been reported between acarbose response and variants in *PPARA* (2 of 11 SNPs), *HNF4A* (2 of 6 SNPs), *LIPC* (single SNP), and *PPARGC1A* (single SNP).[3]

GLP-1 is an incretin hormone degraded by DPP4; it stimulates insulin secretion, inhibits glucagon release, and delays gastric emptying. GLP-1 receptors are expressed in several organs, including the pancreas. GLP-1 receptor agonists such as exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, and semaglutide are resistant to DPP4-mediated degradation and are used in diabetes therapy. The drug target gene, *GLP1R*, has been the main focus of pharmacogenetic studies. Some studies suggest that carriers of the A allele of *GLP1R rs6923761* experience greater weight loss and prolonged gastric emptying following therapy. However, other studies have reported no significant association between *GLP1R* polymorphisms and therapeutic response to GLP-1 receptor agonists in patients with type 2 diabetes.[2,12,21]

SGLT2 inhibitors, including dapagliflozin, empagliflozin, ertugliflozin, and canagliflozin, act by blocking glucose reabsorption in the S1 and S2 segments of the proximal renal tubules, thereby reducing blood glucose levels. SGLT2 is encoded by *SLC5A2*; however, pharmacogenetic studies have shown no significant association between *SLC5A2* SNPs and therapeutic response to empagliflozin in terms of blood

glucose, insulin sensitivity/resistance, or insulin secretion.[1,21]

Emerging Antidiabetic Agents

Improving the therapeutic effects of antidiabetic drugs, reducing adverse events, and supporting the management of diabetes require the discovery and development of novel agents. Currently, several potential antidiabetic agents with new targets are under clinical investigation. These agents may represent new therapeutic approaches and provide more treatment options for patients with diabetes.[2]

Glucokinase Activators

Glucokinase (GK) is an enzyme predominantly expressed in pancreatic and hepatic cells. As a hexokinase, it phosphorylates glucose to glucose-6-phosphate (G6P), a rate-limiting step in glucose metabolism. In the pancreas, GK responds to blood glucose levels by enhancing insulin release and reducing glucagon secretion when glucose is high. In the liver, GK facilitates glucose uptake and glycogen synthesis, thereby lowering blood glucose. Hepatic GK activity is regulated by glucokinase regulatory protein (GKRP), which binds or releases GK depending on glucose concentrations to maintain glucose homeostasis. Overall, GK activation in both pancreas and liver contributes to lowering blood glucose, making GK modulation a potential therapeutic approach in diabetes.[2]

Glucokinase activators (GKAs) have been developed as candidate therapies. However, side effects such as hypoglycaemia and elevated triglycerides have hindered their progress. More recently, dual-acting full GKAs such as dorzagliatin (HMS5552) and liver-selective GKAs such as TTP399 have shown improved safety and tolerability, with no associated weight gain. Both agents have demonstrated success in phase II clinical trials. GKAs are therefore considered one of the most promising novel drug targets for diabetes.[2]

11β-hydroxysteroid dehydrogenase 1 inhibitors (11β-HSD1 inhibitors)

11β-HSD1 is an enzyme primarily expressed in the liver and adipose tissue, catalysing the conversion of inactive cortisone to active cortisol, which binds and activates the glucocorticoid receptor. Increased systemic glucocorticoid activity is associated with visceral obesity, insulin resistance, glucose intolerance, dyslipidaemia, hypertension, and heightened cardiovascular risk. Thus, 11β-HSD1 inhibitors may reduce cortisol levels and improve diabetes management.[2]

Examples include INCB013739, MK0916, the selective inhibitor PF-915275, and BI 135585, all of which have progressed to clinical trials and demonstrated safety and good tolerability in patients with diabetes. In mouse models, 11β-HSD1 inhibitors improved insulin sensitivity, reduced FPG, lowered body weight, and enhanced lipid profiles, highlighting their potential as candidate therapies for diabetes.[2]

G-Protein-Coupled Receptor 119 Agonists (GPR119)

GPR119 is highly expressed in pancreatic β-cells and intestinal endocrine cells. Activation of GPR119 stimulates glucose-dependent insulin secretion from β-cells, enhances GLP-1 release in the gastrointestinal tract, and improves glycaemic control. GPR119 agonists may help preserve or enhance β-cell function in type 2 diabetes. One such agent, DS-8500a, has completed phase II clinical trials, showing greater reductions in FPG and PPG compared with placebo. Additionally, total cholesterol, LDL-C, and triglycerides were significantly reduced in the DS-8500a group. DS-8500a enhanced insulin secretory capacity from β-cells and was well tolerated without major adverse effects or

hypoglycaemia. Thus, GPR119 agonists provide effective glycaemic control through dual mechanisms and hold potential for preserving β-cell function.[2]

Glucagon Receptor Antagonists

Glucagon, secreted by pancreatic α-cells, promotes gluconeogenesis and glycogenolysis while inhibiting glycogen synthesis in the liver, thereby raising blood glucose levels. Suppressing glucagon lowers hyperglycaemia. In animal models with insulin deficiency or resistance, glucagon receptor inhibition normalised blood glucose levels. The antagonistic effects of glucagon include reduced insulin requirements, decreased risk of long-term diabetic complications, and lower risk of other metabolic syndromes. Phase II trials of PR-06291874 and LGD-6972 have been completed, and no hypoglycaemia was reported, suggesting glucagon receptor antagonists may be an effective therapy for type 2 diabetes.[2]

KIF11 Inhibitors

Kinesin family member 11 (KIF11) is a kinesin protein essential for cell division. Its inhibition has been implicated in the development of various diseases, including diabetes. Current findings suggest that although KIF11 inhibitors are not primary therapies for diabetes, they may have potential in managing diabetes-related complications, particularly in retinal pathology and cell cycle regulation. Further research is required to better understand the role of KIF11 in diabetes.[26,27]

GSK3β Inhibitors

Glycogen synthase kinase-3β (GSK3β) is a key enzyme in insulin signalling and glycogen synthesis. Its inhibition has shown promising effects in diabetic animal models. GSK3β inhibitors are under investigation as potential therapies for diabetes due to their ability to enhance insulin sensitivity and improve glucose metabolism.[28]

The inhibition of GSK3β plays several important roles in diabetes management. Firstly, it enhances insulin sensitivity, as GSK3β inactivates insulin receptor substrate-1 (IRS-1), a crucial mediator of insulin signalling, thereby contributing to insulin resistance; its inhibition can help restore insulin responsiveness. Secondly, GSK3β inhibition promotes glycogen synthesis by relieving the suppression of glycogen synthase, resulting in increased glycogen synthase activity and greater glycogen formation. Finally, in animal models, GSK3β inhibition has been shown to lower fasting hyperglycaemia and improve oral glucose tolerance, highlighting its therapeutic potential in improving glucose metabolism.[29]

AP-1 Inhibitors

Activator protein-1 (AP-1) is a transcription factor regulating genes involved in inflammation and endothelial dysfunction, both of which contribute to diabetic complications. AP-1 inhibition is being studied as a potential therapeutic approach, particularly for diabetic atherosclerosis. AP-1 inhibitors bind to DNA, modulating gene expression, thereby reducing inflammatory molecule production and improving endothelial function. In animal studies, AP-1 inhibition reduced atherosclerosis in diabetic mice. Preclinical studies suggest that AP-1 inhibitors hold promise as novel antidiabetic therapies. Examples include T-5224, a selective AP-1 inhibitor tested in preclinical studies, and curcumin, which has shown the ability to inhibit AP-1 and potentially reduce TGF-β1–induced hyperglycaemia.[30]

VI. Conclusion

Genomic sequencing's role in type 1 diabetes and MODY is for diagnostic evaluation, while in type 2 diabetes is for assessing polygenic risk score (PRS).

Genomic sequencing also helps identify genetic variants that influence drug response, so this can help to reach therapeutic optimization. Alongside the development of novel antidiabetic agents currently in clinical trials, the application of genomic sequencing is expected to enable individualised therapy and support the advancement of precision medicine. Further research and implementation are still needed. Integration into routine screening, ethical and cost-effectiveness challenges, need for local genomic databases.

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