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Comparison of Current Diabetes Medication Use, Efficacy and Side Effects

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Abstract. Since the discovery and use of insulin in the 1930s, our understanding of diabetes and its pathogenesis has continued to grow, leading to a wide variety of diabetes treatment options worldwide. Advances in pharmaceutical chemistry over the past 50 years have significantly enriched the range of diabetes medications. This article examines the advantages and disadvantages of different diabetes medications, as well as the timing of their use. This article compares the hypoglycemic efficacy, mechanism of action, side effects, and precautions of three major diabetes medications: biguanides, sulfonylureas, and glinides. It also addresses the selection of diabetes medications in specific circumstances. Biguanides and sulfonylureas have roughly equivalent hypoglycemic effects and can be used in combination with other medications. However, biguanides are more susceptible to gastrointestinal side effects, while sulfonylureas are more prone to hypoglycemia. While glinides are less effective than the biguanides, they also have a lower risk of hypoglycemia. This systematic comparison of various diabetes medications based on their mechanism of action, efficacy, safety, and additional benefits, such as cardiovascular protection and weight management, aims to provide clinicians with a basis for precise, personalized medication decisions, highlight research gaps, and promote new drug development and overall patient management.

Keywords: Diabetes, treatment methods, comparative analysis

1. Introduction

According to the latest data published by The Lancet on World Diabetes Day 2024, the number of adults with diabetes worldwide has exceeded 800 million, more than four times that of 1990. A research report published by the World Health Organization shows that the global diabetes prevalence has climbed from 7% to 14% between 1990 and 2022 [1]. In 2022, the number of untreated adults with diabetes aged 30 and above was nearly 450 million (approximately 59% of all adults with diabetes), a figure 3.5 times that of 1990, of which 90% lived in low- and middle-income countries. In 2021, diabetes directly caused 1.6 million deaths, of which 47% occurred before the age of 70. In addition, there were 530,000 deaths from kidney disease caused by diabetes. Although lifestyle adjustments are key measures for diabetes management, in many cases, it is difficult to effectively control blood sugar levels by relying solely on lifestyle changes, so drug treatment is

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indispensable. The core goal of drug treatment is to help patients maintain blood sugar levels within a reasonable range, thereby reducing the risk of diabetic complications.

Given the importance of medication for diabetic patients, this article summarizes the various types of medications used to treat type 2 diabetes, and their advantages and disadvantages. By systematically reviewing and thoroughly comparing the mechanisms of action, efficacy profiles, adverse reaction profiles, and clinical application scenarios of existing type 2 diabetes medications, this article aims to help healthcare professionals quickly distinguish the strengths and limitations of various medications amidst the growing array of treatment options, thereby enabling more precise and personalized medication decisions. Furthermore, by comparing the differences in cost-effectiveness, patient compliance, and long-term safety among various medications, this article reveals gaps and challenges in current research and application, providing guidance for future new drug development and clinical trial design, and hopefully promoting overall advancements in type 2 diabetes treatment and a sustained improvement in patients' quality of life.

2. Classification of diabetes medications

2.1. Insulin and its analogs

Long-acting insulin analogs are associated with a lower incidence of severe hypoglycemia. Patients treated with twice-daily insulin glargine are less likely to experience hypoglycemic events.

2.2. Oral hypoglycemic agents

2.2.1. Biguanides

Biguanides are a class of antidiabetic drugs derived from compounds in French cloves, a plant known since the Middle Ages for its hypoglycemic properties [2]. Phenformin (N-phenylethyl biguanide) is a biguanide used since the 1950s to treat type 2 diabetes, but was discontinued in the United States in the late 1970s due to the risk of lactic acidosis. In 1995, another biguanide with fewer side effects, metformin (dapoxetine), was approved in the United States and has become the most widely prescribed diabetes medication.

Mechanism of action of metformin: Complex I inhibition. Complex I inhibition underlies multiple mechanisms of action of metformin [3]. Upon inhibition of complex I, adenylate-activated protein kinase (AMPK) is activated due to elevated adenylate (AMP) levels, thereby inhibiting CRTC2 and preventing the formation of the CREB-CBP-CRTC2 complex. AMPK also phosphorylates and inhibits ACC1 and ACC2, thereby promoting fat oxidation and decreasing lipogenesis. Additionally, elevated adenylate levels are thought to inhibit hepatic gluconeogenesis independently of AMPK. High adenylate levels may prevent glucagon-stimulated cyclic adenosine monophosphate (cAMP) production, thereby counteracting the effects of hepatic glucagon. Adenylate also directly inhibits the gluconeogenic pathway by allosterically inhibiting fructose bisphosphatase 1 (FBP1). The cytoplasmic redox state is enhanced. Metformin inhibition of glyceraldehyde-3-phosphate dehydrogenase 2 (GPD2) decreases the conversion of glyceraldehyde-3-phosphate (G3P) to dihydroxyacetone phosphate (DHAP), thereby inhibiting glycerol gluconeogenesis and increasing the cytoplasmic [NADH]:[NAD+] ratio. Lactate dehydrogenase (LDH) is inhibited by this increased [NADH]:[NAD+] ratio, thereby decreasing lactate gluconeogenesis. Metformin inhibition of GPD2 is the only mechanism independent of Complex I inhibition, resulting in substrate-selective inhibition of gluconeogenesis. Abbreviations: ACC,

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acetyl-CoA carboxylase; AMPK, adenylate-activated protein kinase; CBP, CREB-binding protein; CREB, cyclic AMP response element-binding protein 1; CRTC2, CREB-regulated transcriptional coactivator 2; DHAP, dihydroxyacetone phosphate; FBP, fructose 1.

2.2.2. Sulfonylureas

Sulfonylureas are insulin secretagogues that modulate the intracellular potential of pancreatic β cells, thereby stimulating calcium-mediated insulin release. Sulfonylureas are well absorbed orally, have high plasma protein binding, and many drugs have active metabolites [4]. The triggering mechanism of insulin secretion is that glucose diffuses into β cells and is metabolized to ATP (increased ATP:ADP ratio), which leads to the closure of ATP-sensitive potassium channels; membrane depolarization opens voltage-gated Ca^{2+} channels, causing calcium influx and increased intracellular Ca^{2+}, leading to the exocytosis of vesicles containing insulin. Sulfonylureas stimulate the closure of ATP-sensitive potassium channels, while diazoxide has the opposite effect. Octreotide can reduce cytoplasmic Ca^{2+}. Keywords: + stimulation; - inhibition; GCK glucokinase; GDH glutamate dehydrogenase; ATP adenosine triphosphate; KATP channels are composed of SUR1 (sulfonylurea receptor 1) and Kir6.2 (inwardly rectifier potassium channel 6.2).

3. Comparative analysis of drugs for treating different types of diabetes

3.1. Comparison of mechanisms of action

3.1.1. Biguanides

The hypoglycemic effect of biguanides is mainly due to their effect on the glucose processing capacity of hepatocytes, muscle cells, fat and pancreatic cells. Therefore, the drugs can inhibit the production of glucose in the liver, and increase the sensitivity of peripheral tissue to insulin and the utilization of glucose by adipose tissue and skeletal muscle [5]. At the same time, the drugs can also inhibit the secretion of glucagon by pancreatic cells. The above effects are all due to the regulation of cellular energy metabolism by activated protein kinase, because activated protein kinase will weaken the coordination of fatty acids, cholesterol and protein, and enhance the utilization of fatty acids.

3.1.2. Sulfonylureas

Sulfonylureas mainly act on the ATP-sensitive potassium channel (KATP) on the pancreatic B cell membrane. This channel is a heteromeric octamer (SUR/Kir6.x) composed of the regulatory subunit sulfonylurea receptor (SUR) and the channel-forming subunit inward rectifier potassium channel (Kir) in a 1:1 ratio. The main mechanism of action of sulfonylureas is to promote insulin release by closing this channel. Sulfonylureas and glucose (which produces ATP through transport, phosphorylation, and oxidative metabolism) can stimulate pancreatic B cells to release insulin through this mechanism [6].

3.1.3. Glinides

Glinides mainly react with pancreatic cells and adsorb sulfonylurea receptors in the cells, thereby blocking the ATP channel of pancreatic cells, causing cell membrane depolarization, causing calcium channels to open, and promoting insulin secretion [7].

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3.2. Comparison of hypoglycemic effects

3.2.1. Biguanides

The minimum effective dose of metformin is 500 mg/day, the optimal effective dose is 2,000 mg/day, and the maximum recommended dose for adults is 2550 mg/day [8]. The efficacy of metformin is dose-dependent. If the patient tolerates it, it is recommended to gradually increase the dose to the optimal effective dose. Metformin has a reliable blood glucose-lowering effect. Monotherapy can reduce HbA1c by 1.0% to 2.0% (after subtracting the placebo effect). Metformin can be used in combination with other non-insulin-based anti-glycemic agents. Patients whose blood glucose is poorly controlled after three months of treatment with the full dose of metformin may consider adding a second anti-glycemic agent to achieve further significant improvement in blood glucose levels. Combining metformin with insulin can further improve blood glucose control, reduce insulin dosage, and reduce insulin-induced weight gain and the risk of hypoglycemia. Patients with T1DM who need to control their blood glucose can take metformin in addition to insulin treatment.

3.2.2. Sulfonylureas

Sulfonylurea monotherapy can reduce HbA1c by 1% to 2%. The hypoglycemic effect is dose-dependent within the conventional dose range, and the higher the patient's baseline HbA1c, the greater the reduction in HbA1c [9]. Sulfonylureas can be used in combination with a variety of other hypoglycemic drugs and can be used long-term as one of the basic drugs in the treatment plan. Patients who use sulfonylureas for a long time should be closely monitored for hypoglycemia and weight gain. Patients who use sulfonylureas need to have a certain level of pancreatic function. Patients with a short course of diabetes who can adhere to diet and exercise interventions may have better efficacy with sulfonylureas.

3.2.3. Glinides

Repaglinide monotherapy has a significant and stable hypoglycemic effect. For patients with newly diagnosed type 2 diabetes, repaglinide has a hypoglycemic effect similar to metformin and sulfonylureas, reducing HbA1c by about 1%, and the incidence of hypoglycemia is lower than that of sulfonylureas [10].

3.3. Side effect comparison

3.3.1. Biguanides

The most common adverse reaction to metformin is gastrointestinal discomfort, which is dose-dependent. Enteric-coated capsules and tablets can greatly reduce irritation to the stomach and intestines without affecting the hypoglycemic effect. However, common dosage forms have many defects: (1) There is an "absorption window phenomenon", that is, the water-soluble strong absorption site is concentrated in the stomach and the upper half of the small intestine. In a short period of time, the "burst release" of the disintegration-dissolution-release process of the drug preparation can form a local supersaturated concentration: first, it is easy to cause gastrointestinal irritation, and second, local absorption saturation; at the same time, the high concentration in the gastrointestinal wall is 10 to 100 times the plasma concentration, and the concentration in the

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kidneys, liver and salivary glands is 2 times higher than the plasma, which cannot effectively retain it at the absorption site. The above reasons make its absorption and plasma concentration curves unstable; (2) The structure is stable. The binding rate with plasma protein is less than 5%. More than 90% is eliminated by urine within 12 hours. Therefore, the entire pharmacokinetics process is determined by the absorption process alone; (3) The plasma peak time is fast, but the duration of action is not long. The plasma half-life is 0.9 hours to 2.6 hours, and the duration of action is 4 hours to 8 hours. It needs to be taken 2 to 3 times a day, which greatly reduces the patient's medication compliance; (4) The oral dose is large, and the daily dose can reach 2250 mg [11].

3.3.2. Sulfonylureas

The mechanism of action and dosage form of different sulfonylurea drugs are different, and the incidence of hypoglycemia is also different. Among them, glibenclamide has a higher risk of hypoglycemia.

The effects of different sulfonylurea monotherapies on body weight are different, and the modified dosage form has a smaller effect on body weight. This adverse reaction may be completely or partially offset when sulfonylureas are used in combination with drugs that have weight-loss effects. However, their combination with GLP-1 receptor agonists or DPP-4 inhibitors significantly increases the risk of hypoglycemia. The cardiovascular safety of sulfonylureas still needs to be confirmed by well-designed prospective randomized controlled studies.

3.3.3. Meglitinide side effects

The most common side effect of repaglinide monotherapy is hypoglycemia, followed by weight gain (1.8 kg/16 weeks). The Whipple triad of hypoglycemia is defined as the presence of symptoms of hypoglycemia, true hypoglycemia (<50 mg/dL), and resolution of symptoms after glucose administration.

The use of repaglinide has been reported with sulfonylureas.

Other notable adverse effects compared with placebo include upper respiratory tract infections and sinusitis. Weight gain, diarrhea, and arthralgia have also been reported.

Hypoglycemia is more frequently reported when repaglinide is used in combination with metformin, and studies have shown an increased risk of peripheral edema with concomitant use of thiazolidinediones.

4. Choice of diabetes treatment medications in special circumstances

4.1. Diabetes with coexisting cardiovascular disease

4.1.1. GLP-1 receptor agonists

The current ADA/EASD consensus algorithm recommends that GLP-1 RAs be used as first-line therapy for patients with established atherosclerotic cardiovascular disease, as well as for patients without established cardiovascular disease but with high-risk indicators [12], such as age ≥55 years, carotid, lower limb, or coronary artery stenosis >50%, left ventricular hypertrophy, eGFR < 60 ml/min, or albuminuria, after failure of metformin therapy.

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4.1.2. SGLT-2 inhibitors

SGLT-2 receptors are found only on the proximal convoluted tubules of the kidney and are responsible for reabsorbing virtually all of the body's glucose and the majority of sodium filtered in the glomerulus. Inhibition of these receptors induces a diuretic effect, leading to sodium and glucose excretion, offering an insulin-independent method for lowering serum glucose levels without increasing the risk of hypoglycemia.

In addition to its role in treating heart failure, results from the SGLT-2 CREDENCE study demonstrated that canagliflozin significantly reduced adverse events in chronic kidney disease (DAPA-CKD)27 (EMPA-KIDNEY)28). SGLT-2s significantly impact numerous organ systems, including the kidneys, heart, and endocrine system, and are innovative metabolic medicines. When used to treat type 2 diabetes, SGLT-2 inhibitors only modestly reduce glycated hemoglobin A1c; however, they significantly reduce cardiovascular events in these patients, suggesting that adverse cardiovascular events in patients with type 2 diabetes may not be solely related to glycemic disturbances.

4.2. Diabetes combined with obesity

The main mechanism of action of metformin is to improve peripheral insulin sensitivity and reduce hepatic glucose output. The 2012 IDF Global Guidelines for the Prevention and Treatment of Type 2 Diabetes pointed out that metformin is more effective than other hypoglycemic drugs in weight loss and can also reduce the all-cause mortality and cardiovascular event rates in obese type 2 diabetic patients. In addition, it is inexpensive, has a low risk of hypoglycemia, has no contraindications and is well tolerated. Therefore, current domestic and international guidelines recommend metformin as the first choice for the treatment of obese type 2 diabetic patients or as the basic drug for combination therapy.

SGLT-2 inhibitors can selectively inhibit SGLT-2 on the lumen side of the epithelial cell membrane of the proximal convoluted tubules of the kidney, increase urinary glucose excretion, and prevent glucose reabsorption. This process does not depend on the action of insulin, so it is also applicable to the late stage of type 2 diabetes with low insulin levels [13]. SGLT-2 inhibitors can reduce blood sugar and weight while also reducing blood uric acid and systolic blood pressure levels. However, in clinical application, attention should be paid to the adverse reactions that may be caused, namely increased urinary calcium excretion, hypovolemia, urinary tract infection, and genital fungal infection. Therefore, the glucose-lowering effect of SGLT-2 inhibitors may be compromised in elderly patients, those with volume depletion, and those taking diuretics.

GLP-1 receptor agonists mimic the physiological effects of endogenous GLP-1, promoting insulin secretion in a glucose-dependent manner and inhibiting glucagon secretion. Furthermore, they can suppress food intake and appetite through central effects, effectively delaying gastric emptying, resulting in a lower incidence of hypoglycemia and sustained weight loss. However, they are associated with a higher incidence of gastrointestinal adverse reactions such as vomiting and nausea, which typically occur in the initial stages of treatment and gradually decrease with prolonged treatment. Regarding safety, although extensive research evidence suggests that GLP-1 receptor agonists do not increase the risk of pancreatic cancer or acute pancreatitis, caution is advised in patients with a history of pancreatitis. If acute pancreatitis develops during treatment, the drug should be discontinued immediately.

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5. Conclusion

This article primarily examines the hypoglycemic efficacy, mechanism of action, side effects, and precautions of the three main diabetes medications: biguanides, sulfonylureas, and glinides. It also addresses the selection of diabetes medications for specific circumstances. Biguanides and sulfonylureas have roughly equivalent hypoglycemic effects, and both can be used in combination with other medications. However, biguanides are more susceptible to gastrointestinal side effects, while sulfonylureas are more likely to cause hypoglycemia. While glinides are less effective than the biguanides, they also reduce the risk of hypoglycemia. This article also addresses the use of diabetes medications in specific circumstances, including those with coexisting cardiovascular disease, those with coexisting obesity, and elderly patients with diabetes. GLP-1 receptor agonists and SGLT-2 inhibitors are primarily used to treat coexisting cardiovascular disease in diabetic patients, but these two medications can also be used as treatments for those with coexisting obesity.

Overall, this review and comparison of diabetes medications still has some limitations. On the one hand, the role of novel medications such as SGLT2 inhibitors and GLP-1 receptor agonists in cardiorenal protection and weight management is insufficiently explored, and systematic comparisons with traditional medications are lacking. On the other hand, existing evidence largely derives from international clinical trials, and the utilization of local real-world data is insufficient, limiting the generalizability of research conclusions. Furthermore, research data still have room for methodological improvement, such as the lack of direct comparative trials and limited follow-up. Future diabetes research will require not only more comprehensive evaluations of glucose-lowering efficacy but also the inclusion of broader outcome measures such as long-term complication prevention, improved quality of life, and cost-effectiveness analyses. Furthermore, with the continued development of multi-targeted new drugs, personalized treatment strategies, and digital management tools, the focus of diabetes drug treatment research is expected to shift from single glucose-lowering approaches to comprehensive health benefits. Through continuous optimization of methods and content, relevant research will provide a more scientific and comprehensive basis for clinical decision-making.

References

[1] World Health Organization. (2024) Urgent action needed as global diabetes cases increase four-fold over past decades.
[2] Zhao H., Swanson K.D., Zheng B. (2021) Therapeutic Repurposing of Biguanides in Cancer. Trends Cancer. Aug; 7(8): 714-730.
[3] LaMoia T.E., Shulman G.I. Cellular and Molecular Mechanisms of Metformin Action. Endocr Rev. 2021 Jan 28; 42(1): 77-96.
[4] Klein-Schwartz W., Stassinos G.L., Isbister G.K. (2016) Treatment of sulfonylurea and insulin overdose. Br J Clin Pharmacol. Mar; 81(3): 496-504. doi: 10.1111/bcp.12822.
[5] Ting Miao, Ziyan Liu, Yuyuan Liu, et al. (2019) Study on the pharmacological effects and mechanisms of metformin [J]. Medical Information, 32(14): 53-56.
[6] Tong Wang, Kaisi Zhu. (2012) Mechanism of action of sulfonylureas [J]. Drug Evaluation, 9(4): 10-12.
[7] Junying Hao. (2016) Current status and progress of application of glinides [J]. Chinese Journal of Metallurgical Industry Medicine, 33(3): 350-351.
[8] (N.A.) (2019) Expert consensus on the clinical application of metformin (2018 edition) [J]. Chinese Journal of Diabetes, 27(3): 161-173.
[9] Yiming Mu, Wenying Yang, Dalong Zhu, et al. (2017) Expert consensus on the clinical application of sulfonylureas (2016 edition) [J]. Drug Evaluation, 14(1): 5-12+54.
[10] Xiaodan Liu, Yan Li. (2015) Comprehensive evaluation of the efficacy and safety of glinides [J]. Drug Evaluation, 12(13): 16-18+20.

DOI: 10.54254/2753-8818/2025.LD27310

[11] Shige Zhang. (2006) Advantages and evaluation of biguanide hypoglycemic drugs [J]. Chinese Hospital Drug Evaluation and Analysis, (5): 268-271.
[12] Nauck M.A., Quast D.R., Wefers J., Meier J.J. (2021) GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. Apr., 46: 101102.
[13] Xuefen Zhao. (2023) Research progress in the treatment of obese type 2 diabetes [J]. China Urban and Rural Enterprise Health, 38(5): 58-60.