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Overview of Type 2 Diabetes Drugs on the Market

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a systemic metabolic disorder with complex pathogenesis. In recent years, a variety of new T2DM drugs have emerged, such as sodium-dependent glucose transporters 2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. As traditional medicines, insulin also has developed kinds of formulations such as quick-acting or premixed insulin. In addition, new treatment schedules combining multiple drugs are also fully explored. The efficacy, the administration, the mechanism, the safety and the price of these drugs are all different, providing patients with multiple options. This paper reviews the main types of type 2 diabetes drugs on the market and describes the mechanism of action. The representative type 2 diabetes treatment drugs are listed, and the advantages and disadvantages of these representative drugs are preliminarily evaluated. This information is reviewed to help doctors with clinical medication.

Keywords

Type 2 Diabetes Mellitus, Insulin, Sodium-Dependent Glucose Transporters 2, Glucagon-Like Peptide-1

1. Introduction

As the number of T2DM patients increases in recent years, more and more therapeutic drugs are emerging. The pathogenesis of T2DM is complex, and not only a single abnormal blood glucose metabolism disease, but also a metabolic disorder of the systemic system [1]. Therefore, relevant therapeutic drugs are also divided into multiple types with different mechanisms. It is important to understand the classification and mechanism of these drugs. In recent ten years, a

large number of hypoglycemic drugs have been approved for clinical application, including some new drugs, such as GLP-1 agonists [2], DPP-4 inhibitors [3] and SGLT-2 inhibitors [4]. At the same time, some long-established drugs, such as Caleviram and Bromocriptine, are also being used to treat diabetes indications. All of these drugs are effective in reducing two key indicators of diabetes, blood glucose and hemoglobin a1c (HbA1c) and the choice of drugs for patients depends on their individual conditions. Therefore, it is of great significance to comprehensively understand the advantages and disadvantages of various marketed type 2 diabetes treatment drugs.

In this paper, the main types of approved hypoglycemic drugs, representative drugs and their corresponding advantages and disadvantages are summarized.

2. Common Drugs for T2DM

2.1. Biguanides

Metformin is the only biguanide drugs that can be used clinically, and also the most widely used T2DM drug. Metformin has been proved to be effective, safe, inexpensive and with few side effects. For these reasons, metformin is recommended as first-line drug for T2DM by the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) [5]. Metformin has several mechanisms xu, including delaying the uptake of glucose in the gastrointestinal tract, intensifying insulin sensitivity to increase the use of peripheral glucose, and inhibiting excessive glycogenosis in the liver and kidney.

Reduceing blood glucose without causing hypoglycemia or weight gain (some patients may experience mild weight loss) is the major advantage of metformin. It does not stimulate insulin production, therefore the risk of hypoglycemia is low. Moreover, it can be used alone or in combination with almost any other diabetes drug. Another advantage of metformin is that it can reduce cardiovascular risk, significantly avoid myocardial infarction, and reduce diabete-related mortality and overall mortality [6] [7].

It is important to note that metformin is almost excreted through kidney and should be used mindfully in patients with renal dysfunction. Therefore, patients with high serum creatinine (male ≤ 1.5 mg·D^{-1}·L^{-1}, female ≤ 1.4 mg·D^{-1}·L^{-1}) or impaired kidney function are prohibited to used it. Metformin should also be avoided in patients who drink too much alcohol, since alcohol can increase lactic acid metabolism and may cause lactic poisoning. Patients may experience abdominal distension, diarrhea, nausea or anorexia with metformin at the beginning of treatment. Another important adverse effect of metformin is vitamin B12 deficiency in a small number of patients [6], which may lead to peripheral neuropathy and anemia.

2.2. ATP-Sensitive K Channels (KATP) Blocker

KATP blockers are the first oral drug used in treating T2DM, and their mechanism is to inhibit KATP from binding to the pancreatic beta cell Sulfonylurea Re-

ceptor 1 (SUR1), thus increasing the secretion of insulin and reducing blood glucose. The first KATP blockers were introduced in 1950s and are now largely obsolete. Now the second generation mainly Glibenclamide [8], Glimepiride [9] and Glipizide [10] (**Figure 1**) are used clinically. These drugs all have sulfonylurea structural fragments, so they are also known as "sulfonylurea" diabetes drugs. Sulfonylureas are common second-line drugs for patients who cannot control target of HbA1c. For many patients newly diagnosed T2DM, sulfonylureas are widely used orally because of their low cost. However, sulfonylureas can increase insulin secretion in the short term, but cause rapid depletion of the already dysfunctional pancreas in the long run, thus resulting in the need for exogenous insulin therapy.

Sulfonylureas [11] reduce HbA1c by about 1.5% and cause a risk of severe hypoglycemia of about 1%, better than 10% with insulin but much higher than 0.05% with metformin. Patients should be fully aware of these risks before taking the drugs.

2.3. Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) Agonist

PPARγ agonists [12] [13] are considered to be the second or third-line choices after metformin for patients with blood glucose levels slightly above normal. This kind of drugs can activate PPARγ in fat and muscle nucleus, promote the expression of GLUT4 protein, and finally promote the uptake of glucose in peripheral tissues to reduce blood glucose with the assistance of insulin. PPARγ agonists increase the body's sensitivity to insulin, so they are also known as insulin sensitizers, representative by Rosiglitazone and Pioglitazone (**Figure 2**). The drugs increase glucose uptake by 30% to 50% in muscle and adipose tissue, reduce glucose production in the liver and reduce insulin resistance. In addition to

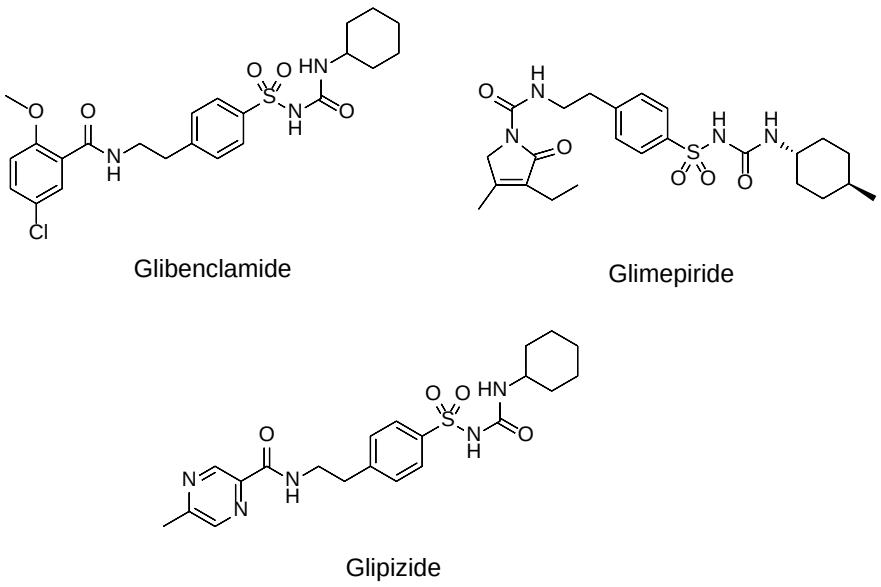


Figure 1. Representative sulfonylureas.

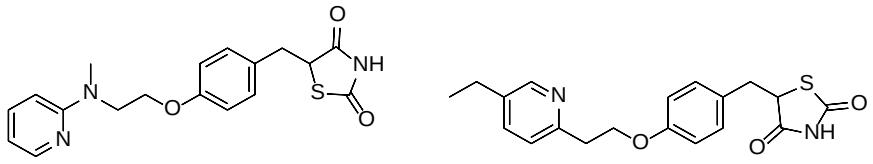


Figure 2. Representative PPARγ agonists.

regulating blood glucose, PPARγ agonists also lower triglycerides and regulate high density lipoprotein (HDL).

Patients taking PPARγ agonists alone are not at risk for hypoglycemia, but gain 2 to 4 kg in weight in the first year and often suffer from peripheral edema. There was significant increase the risk of heart failure in patients taking insulin and PPARγ agonists simultaneously [14]. Therefore, PPARγ agonists should not be administered to patients with prior edema, heart failure, or liver function impairment. In addition, patients taking PPARγ agonists have an increased risk of fracture due to loss of minerals from their bones [15]. Because of the high number of side effects, the European Union (EU) has removed Rosiglitazone from its market.

2.4. α-Glucosidase Inhibitor

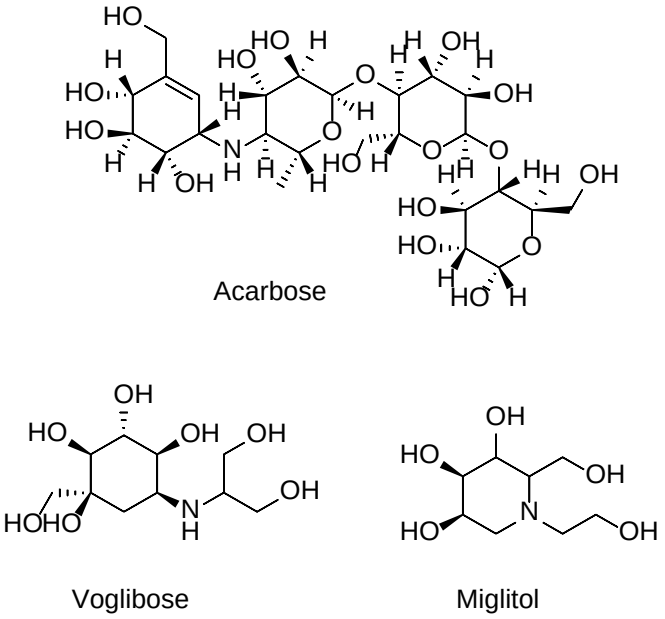
α-Glucosidase is located in the brush edge of villous mucosal cells in intestine. Its role in glucose metabolism is to decompose oligosaccharides into glucose and accelerate the absorption of carbohydrates in the small intestine. Alpha-glucosidase inhibitors competitively inhibit the hydrolysis of oligosaccharides by α-Glucosidase, thereby slowing down the decomposition of oligosaccharides into glucose monomers and reducing the absorption of glucose in intestine, thereby delaying postprandial blood glucose rise. Representative drugs (**Figure 3**) are Acarbose [16], Voglibose [17] [18] and Miglitol [19].

Acarbose was originally found in the metabolites of swimming actinomycetes SE50. It competitively inhibits glucose amylase, sucrase and so on to slow down the absorption rate of sucrose and starch. Using acarbose alone can reduce HbA1c by 0.5% - 0.9% and reduce postprandial blood glucose by 20% - 30%.

Voglibose is derived from the structural optimization of actinomycete metabolites, which mainly inhibits the disaccharide decomposition process by competitive inhibition of sucrase and maltase, but it does not inhibit the decomposition of sucrose. Miglitol was derived from the optimization of the structure of the metabolites of bacillus and inhibited most of the α-Glucosidase.

2.5. SGLT-2 Inhibitor

SGLT-2 is a transporter protein present in the proximal convoluted tubule of the kidney, which mediates the process of glucose reabsorption by the kidney. SGLT-2 inhibitors are a new class of diabetic drugs that inhibit the kidney's reabsorption of glucose, allowing excess glucose to be excreted from the urine



Voglibose

Miglitol

Figure 3. Representative *α*-glucosidase inhibitors.

and lowering blood glucose. Since the first SGLT-2 inhibitor was approved in 2012, these class of drugs maintained rapid growth with global sales reaching $2.6 billion in 2017 and accounting for 6.5% of the diabetes drugs market. EvaluatePharma predicts that the share of SGLT-2 inhibitors will surpass that of DPP-4 inhibitors as the leader in oral hypoglycemic drugs by 2022.

Ertugliflozin (2017) [20], Canagliflozin, Empagliflozin, Dapagliflozin, and Empagliflozin are all SGLT-2 inhibitors approved by FDA. Iglinnet and Togllinnet are marketed in Japan [21] (**Figure 4**). SGLT-2 inhibitors are well tolerated, have a low risk of hypoglycemia, do not interact with metformin, and have osmotic diuresis (moderate blood pressure reduction) [22]. In view of SGLT-2 inhibitors have some cardiovascular benefits, the ADA guidelines for Diabetes Prevention and Control, published in 2019, indicated that SGLT2 inhibitors are preferred for patients with T2DM who have been diagnosed with atherosclerosis.

The most common adverse events of using SGLT-2 inhibitors are genital fungal infection, uncomplicated urinary tract infection, and hypotension, so these drugs are recommended to be avoided in patients with a history of frequent urogenital tract infections. Even though the efficacy is moderate and the cost is high, SGLT-2 inhibitors provide low risk of hypoglycemia and additional blood pressure lowering for T2DM patients with hypertension, thus ADA and AACE identified SGLT-2 inhibitors as second-line drugs and used them as adjuvant to metformin in the treatment of T2DM [15] [23]. Among the three approved SGLT-2 inhibitors, Empagliflozin has the best therapeutic efficacy and safety data [22], and is recommended for priority use.

2.6. GLP-1 Agonist

GLP-1 is endogenous intestinal hypoglycemic hormone acting on islet cells in

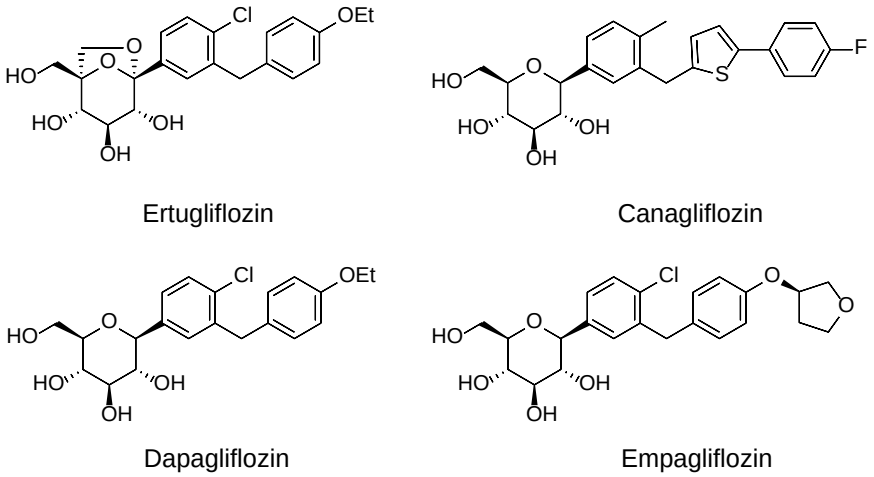


Figure 4. Representative SGLT-2 inhibitor drugs.

the case of high glucose levels, which can, promote insulin gene transcription, insulin synthesis and secretion, delay gastric empty-out, enhance satiety, and lead to weight loss. Now, GLP-1 analogues are the main drugs targeting GLP-1 receptors, which can simulate the mechanism of GLP-1, increase glucose-mediated insulin secretion, reduce glucagon secretion, delay gastric empty-out and improve the symptoms of early satiety.

As ADA and AACE suggested, GLP-1 agonists are suitable to use along or as an adjunct medicine for metformin when patients are intolerant to metformin [15] [23]. So far, eight GLP-1 receptor agonists have been approved for marketing by FDA, including: Exenatide, Long-acting Exenatide, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide and Semaglutide [24].

The enterohypoglycemic analogues above can improve the HbA1c level by reducing HbA1c 0.5% - 1.9%, reduce fasting and postprandial blood glucose, and reduce body weight (1.4 - 3.7 kg). Semaglutide is a GLP-1 receptor agonist approved by THE FDA in 2019, which is also the third hypoglycemic drug with cardiovascular benefits, after Engelazine and Liraglutide. Compared with placebo, Semaglutide reduced the risk of primary end points (such as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) by 26%. After 2 years of treatment, Semaglutide significantly reduced the risk of non-fatal stroke by 39%, the risk of non-fatal myocardial infarction by 26%, and the risk of cardiovascular death by 2% [7] [25] [26].

The most common side effects to GLP-1 agonists are nausea, vomiting, diarrhea, and constipation. Nausea and vomiting are dose-dependent and will alleviate over time. Using GLP-1 agonists alone or in combination with metformin are rarely associated with hypoglycemia, but GLP-1 agonists combined with hypoglycemic agents such as insulin or sulfonylureas may increase the risk of hypoglycemia. It is worth noting that multiple cases of pancreatitis and pancreatic cancer in patients using enterohypoglycemic agents (GLP-1 agonists and DPP-4 inhibitors) have been reported in the post-marketing clinical data [27]. There-

fore, warnings about pancreatitis and pancreatic cancer will appear in the product labels of these drugs.

Taking into account the differences in safety, tolerability, efficacy, price, and simplicity, the GLP-1 agonists are best used in either daily or weekly.

2.7. DPP-4 Inhibitor

DPP-4 is an enzyme in human body, whose main function is to break down proteins in the body. GLP-1 is one of the proteins that can be broken down by DPP-4. Therefore, DPP-4 is the upstream regulator of GLP-1, and DPP-4 inhibitors can achieve similar therapeutic effects as GLP-1 agonists. DPP-4 inhibitors can affect both fasting and postprandial blood glucose levels, and drug action ceases when glucose returns to the normal range. Since DPP-4 inhibitors are effective and can be taken orally, they have become one of the main developing directions of diabetes drugs in recent years. In 2019, the global market of DPP-4 inhibitors and their formulations exceeded US$12 billion, among which Siglitine taken up the highest sales volume, with a market size of US$6.4 billion [28].

Five DPP-4 inhibitors, including Sitagliptin [28], Vildagliptin, Saxagliptin, Alogliptin [29] and Linagliptin (**Figure 5**) have been approved by FDA, while Teneligliptin, Gemigliptin, Anagliptin, Trelagliptin and Evogliptin are available in Japan and Korea. DPP-4 inhibitors are suggested to be used combining with metformin as second-line drugs by ADA, the European Association for the Study of Diabetes and THE AACE Guidelines. In addition to metformin, DPP-4 inhibitors can be used in combination with SGLT-2 inhibitors or PPAR agonists. Although more expensive than Metformin and Sulfonylureas, DPP-4 inhibitors may be preferred for T2DM in the future because they are well tolerated, administered orally, have a low risk of hypoglycemia, and do not cause weight gain.

Multiple studies [30] [31] [32] have shown that DPP-4 inhibitors are well tolerated, and their side effects are few and slight. Using DPP-4 inhibitor alone has

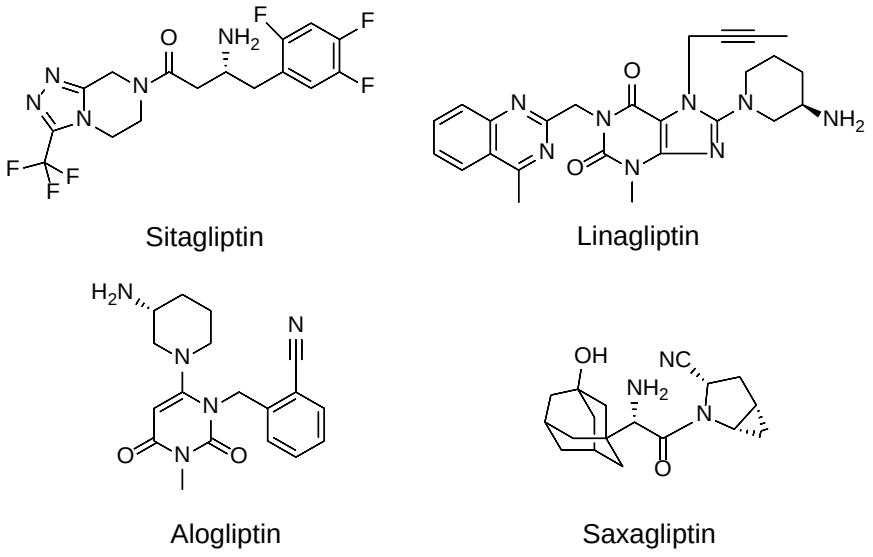


Figure 5. Representative DPP-4 inhibitor drugs.

a very low risk of hypoglycemia, however, combining with sulfonylureas or insulin may increase the risk of hypoglycemia. Post-marketing surveillance reported that DPP-4 inhibitors may cause anaphylaxis, such as angioedema and Stevens Johnson syndrome. In 2015, an FDA advisory panel issued a safety warning [33] that DPP-4 inhibitors may increase the incidence of severe joint pain.

2.8. Insulin

Insulin is a natural hormone in human body, which can effectively reduce blood glucose level [34]. In T2DM patient, approximately 50% islet cells fail to produce insulin, and the number of effective islet cells continues to decrease over time. Eventually, all patients may need insulin injections. Insulin can generally be injected using syringes, insulin pen devices, injectors, subcutaneous injection ports, and insulin pumps. Hypoglycemia and weight gain are possible risks for all patients who use insulin.

According to the onset and duration of insulin, they are generally classified into long-acting, short-acting, quick-acting, premixed insulin and a few of new types insulin (Table 1).

Table 1. List of insulin types and representative drugs.

Insulin name (Brand)	Onset (hours)	Peak (hours)	Duration (hours)
Rapid acting			
Lispro (Humalog)	~0.25	0.5 - 2.5	≤5
Aspart (Novolog)	~0.25	1 - 3	3 - 5
Glulisine (Apidra)	~0.25	1.6 - 2.8	3 - 4
Human insulin inhalation powder (Afrezza)	~0.25	~1	2.5 - 3
Short acting			
Regular (Novolin R or Humulin R)	0.5 - 1	2.5 - 5	4 - 12
Intermediate acting			
NPH (Novolin N or Humulin N)	1 - 2	4 - 12	14 - 24
Long acting			
Glargine(Lantus)100 units/mL	3 - 4	None	>24
Glargine(Toujeo) 300 units/mL	6	None	24 - 36
Detemir (Levemir)	3 - 4	3 - 9	Dose dependent 6 - 23
Degludec(Tresiba)100 units/ml; 200 units/ml	3 - 4	None	>42
Combination products			
70/30 NPH/regular (Humulin or Novolin)	0.5 - 1	2 - 12	18 - 24
70/30 NPH/aspart (Novolog Mix)	~0.25	~1 - 4	18-24
75/25 NPH/lispro or 50/50 NPH/lispro (Humalog Mix)	~0.25	~1 - 5	14 - 24
70/30Degludec/aspart (Ryzodeg)	~0.25	~1 - 4	>42
Concentrated insulin			
U-500 regular (Humulin R U-500)	0.5 - 1	2.5 - 5	Up to 24

2.8.1. Long Acting Insulin

Long acting insulin can provide a stable and continuous supply for up to 24 hours. For most patients with T2DM, long acting insulin is the first choice for improving blood glucose control. Two insulin analogs: Detemir (Levemir) and Glargine (Lantus) [35] are the most commonly used long-acting insulin today. For most patients, a daily dose of long acting insulin meets insulin requirements for up to 24 hours. Attention should be paid to the administration of long-acting insulin at the same time of day, which is essential to maintain stable insulin concentrations in patients [36].

Degludec (Tresiba) [37] is the long-acting insulin with the longest duration of action, which was approved by FDA in 2015 for patients with T1DM or T2DM. Degludec was also approved to be used in combination with Aspart [38] as premixed insulin, whose formulation composed of Insulin Degludec and Aspart in 70/30. It is an ultra-long-acting insulin that can works for up to 42 hours.

2.8.2. Short-Acting Insulin

Short acting insulin, commonly referred to as normal insulin, mimics the insulin produced by the normal pancreas. This kind of insulin is generally used as mealtime insulin, that is, administered 30 to 45 minutes before a meal, the onset time is 30 to 45 minutes, and the peak efficacy reaches within 4 to 6 hours [39]. Different from quick-acting insulin, normal insulin needs a 30-minute waiting time for taking effect, so close attention should be paid to match the expected meal time. If the meal is delayed or omitted due to unforeseen circumstances, hypoglycemia may occur. For this reason, fast-acting insulin is easier and more reliable to use, but normal insulin costs less than quick acting insulin analogues, so there is still a market for it. Novolin and Humulin are the normal insulin most commonly used on the market today.

2.8.3. Quick-Acting Insulin

As diabetes progresses, many patients need mealtime insulin in their basic treatment to adequately control their postprandial blood glucose. Aspart (Novolog), Glulisine (Apidra) [40], or Lispro (Humalog) [41] are the three most commonly drugs used as quick acting insulin analogues. These drug molecules have been structurally optimized and can be absorbed quickly taking effect within 15 minutes after injection reaching their peak potency in 1 - 2 hours and lasting about 2 to 4 hours. These quick acting insulin preparations can be injected during meals, and the dosage should match with the time of meal, the amount of diet, and the carbohydrate content. The insulin pen, an administration device developed for these drugs, facilitates injection and allows flexible dose control [36]. Another advantage of quick acting insulin is that it can be taken with every meal without worrying about overlapping with the long acting insulin dose.

2.8.4. Premixed Insulin

In order to combine the advantages of short-acting insulin with than of long acting insulin, researchers developed a premixed combination of quick acting

insulin and long acting insulin, typically consisting of Humulin, Novolog Mix and Humalog Mix and Ryzodeg (Table 1). Premixed insulin can meet the insulin demand both for foundation and meal. For example, Ryzodeg containing 30% of Aspart, for the needs to meal insulin, and the other 70% is Degludec for basic insulin, so patients carrying only one insulin preparations can take full control of fasting and postprandial blood glucose.

2.8.5. New Insulin

In 2014, a non-injectable form of insulin called Afrezza [42] was approved by the FDA. Afrezza is inhaled and administered by a portable dosing device, which is suitable for blood glucose control in adult patients with T1DM or T2DM. The drug is prohibited during episodes of hypoglycemia, and the most common adverse reactions (about 2% incidence) are hypoglycemia, cough, and sore throat. It is banned in patients with chronic obstructive pulmonary disease and chronic respiratory diseases such as asthma. As Afrezza is an ultra-short-acting insulin, its target audience is mainly diabetics who resist injection and emergency use, so its market is small.

Concentrated U-500 [43] conventional recombinant human insulin may be a preferred alternative to normal insulin in patients requiring high doses of insulin (e.g., 200 - 300 units per day^{-1}). U-500 insulin is 500 units/ml, so its concentration is five times than that of most normal insulin (100 times milliliter^{-1}). For patients with requirement of a general insulin more than 300 units/day, two injections of U-500 insulin per day are enough, which not only reduces the injection frequency but also reduces the dose per injection. In 2016, FDA approved an improved Humulin Insulin pen, a kind of U-500 insulin, which improves on the traditional U-500 insulin and makes it more convenient to use.

3. Summary and Prospect

Diabetes is a disease with complex causes and symptoms. In order to cope with the symptoms of the patients, the type and the number of diabetic drugs are expanding. In terms of drug research, as diabetes is a chronic disease requiring long-term medication, strict requirements on drug toxicity have brought challenges to the development of related drugs. On the other hand, although insulin drugs have the advantages of high efficiency and low toxicity, they are not easy to carry and use, which is the biggest bottleneck in the study of insulin drugs. Though Metformin is a commonly recommended first-line treatment drug, T2DM patients need more personalized treatment, and the corresponding drug treatment needs to be combined with cardiovascular or HbAlc condition. As the treatment concept proposed by the ADA and the European institute of diabetes research, we should take the patient in center with the treatment plan consisting of effectiveness, cost, potential side effects, patients' weight, the ability of the kidney heart liver, low glycemic risk and patient preferences. At the same time, we should provide patients with knowledge about the disease and drug, which can also improve the therapeutic effect and reduce adverse reactions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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