Explore the Role and Influence of Bex gliflozin (A Type of SGLT-2 Inhibitors) in Type 2 Diabetes

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Abstract. There are many chronic metabolic diseases in the world, and diabetes is one of them. Blood sugar control and improvement of insulin resistance are the main means of clinical treatment of type 2 diabetes (T2D). A variety of hypoglycemic drugs are now used in the clinic, but due to the different physical conditions of patients, only 50% of the drugs that may play a certain curative effect. Traditional T2D drug treatment relies on the regulation of insulin and has a variety of side effects. Bex gliflozin, as a sodium-glucose co-transporter 2 inhibitor (SGLT2i), the tubules have a reabsorption effect on glucose in the original urine, and the mechanism of action of Bex gliflozin is to inhibit this function of the kidneys, which makes part of the glucose not reabsorbed by the renal tubules and excreted with urine, thereby achieving the purpose of hypoglycemia. As an approved SGLT2i, it has shown good hypoglycemic effect and safety in the treatment of diabetes, combined with others. In addition, Bex gliflozin has a certain protective effect on the heart and kidneys, and some studies have shown that it has no significant effect on blood pressure and weight. This article summarizes the therapeutic progress and mechanism of SGLT2i and Bex gliflozin in T2D, in order to expanse of the indications for Bex gliflozin.

Keywords: Type 2 diabetes, SGLT-2 Inhibitors, Bex gliflozin.

1. Introduction

Long-term chronic hyperglycemia caused by diabetes may cause organic damage, organ failure, and dysfunction of different organs, adverse effects on the kidneys, eyes, nerves, heart and blood vessels are particularly pronounced. According to the statistics of the International Diabetes Federation (IDF), in 2021, there will be about 540 million adult diabetic patients worldwide, accounting for 10.5% of the world population at this age, and it is expected that by 2045, diabetic patients will be up to 780 million.There are about 140 million adults with diabetes in China, with a prevalence of 11.6%, and continues to grow rapidly [1]. Diabetes is usually divided into two types.Type 1 diabetes(T1D), which is caused by the destruction of β cells, is a chronic autoimmune disease that usually begins at patients younger than 20 years of age, with obvious symptoms of "three more and one less", usually leads to absolute insulin deficiency. This form of diabetes accounts for only 5-10% of people with diabetes [2].Type 2 diabetes (T2D) is a lifelong disease, the insulin may not function normally, most patients will also have insulin resistance (IR), which accounts for 90-95% of diabetes patients, T2D is easy to occur in the elderly. Today, T2D has a high incidence and mortality rate worldwide [2].If diabetes is not intervened in time, it can lead to various complications as well as acute metabolic disorders like hyperosmolar coma and ketoacidosis, which in severe cases even leading to death.About 33% of the patients may eventually induce to chronic diabetic kidney disease (CKD). Patients need to take certain measures to block the development of complications, such as controlling blood sugar or using drugs that break the renin-angiotensin-aldosterone axis [3].

At present, the treatment of diabetes is still mainly based on diet control.Common drugs for the treatment of diabetes include biguanides, sulfonylureas, glinides, thiazolidinediones, DPP-4 inhibitors, α-glycosidase inhibitors, GLP-1 receptor agonists, insulin, and so on.However, they all have certain limitations and poor compliance. Options for oral antidiabetic therapy are becoming increasingly limited. Therefore, it is necessary to explore new oral therapies that may be effectively and also safely.

With the continuous progress of research,the application of SGLT-2 inhibitors in T2D has gradually attracted people's attention, especially for Bexagliflozin, which is approved by FDA,an oral medication taken once daily to treat adults with type 2 diabetes. However, at present, there is no comprehensive description of the application of Bexagliflozin in T2D and evidence. Therefore, this article focuses on the development status of Bexagliflozin in T2D, in order to provide more theoretical basis for the treatment of T2D.

2. Reasons for Using SGLT-2 Inhibitors in T2D

Glucose is the most important energy supply of living organisms, and is the energy source and metabolism of living cells products, and plays a vital role in cell signaling. Abnormal glucose metabolism is often associated with diabetes, retinopathy, Alzheimer's disease and cardiovascular disease.Sodium-glucose cotransporter 2 inhibitors (SGLT2i) can reduce the glucose reabsorption in the kidney and have a positive impact on blood glucose, blood pressure, body weight, etc.

There are three families of glucose transports in the human genome, all belonging to the solute carrier (SLC)superfamily:SLC2, SLC5, and SLC50.Glucose transporters in the SLC2 family are key gateway proteins responsible for the flow of glucose into and out of cells in the body, and are crucial for energy supply and regulation of glucose homeostasis.The human SLC5 solute vector family consists of 12 members,which is widely expressed in the tissues that ranging from epithelial cells to the central nervous system [4, 5]. Among them, 10 members are plasma membrane Na+/ substrate cotransporters which is tightly coupled responsible for the transport of solute molecules such as glucose, inositol, vitamins, monocarboxylate and anions: one is Na+/Cl-/choline transporter;The other is that glucose activates ion channels that prompt Na+ to flood into the cell, but does not transport sugar [4]. SGLT1 and SGLT2 are key transport proteins in the SLC5 solute carrier family responsible for glucose reabsorption in the kidney and small intestine, an electrochemical gradient of sodium ions on the plasma membrane is used to power the glucose uptake. SGLT1 and SGLT2 bind glucose and Na+ at the ratio of 1: 2 and 1: 1, respectively, to form Na+-carrier-glucose complex, which enters the cell along the concentration gradient of Na+, and then SGLT1/2 returns to the initial state and continues to bind glucose and Na+ into the cell. Na+ is continuously pumped out by the Na+/K+-ATP to maintain the Na+ concentration difference inside and outside the cell and provide power for glucose to enter the cell against the concentration gradient(as shown in Figure1). SGLT1 is mainly located in brush border of the small intestine and meanwhile the third segment of the proximal convoluted tubules of the kidney is also its main location. It is encoded by the SLC5A1 gene, the mutation of which will lead to intestinal glucose/galactose malabsorption, clinically manifested as severe diarrhea and malnutrition, and even life-threatening in infants [6]. SGLT2 is encoded by the SLC5A2 gene, resides in the luminal surface of epithelial cells at both the initial and second segments of the proximal tubules and is mostly expressed in the kidney. It is in charge of reabsorbing the majority (about 90%) of the glucose in the filtrate of the glomerular system. SGLT2 is also expressed in the brain, liver, thyroid, and cardiovascular. However, its mRNA level is lower than that of kidney [7]. SGLT2 expression is also found in human prostate cancer and pancreatic cancer, and in highly differentiated lung adenocarcinoma samples, SGLT2 expression is higher [8, 9]. In 1993, researchers determined the location of SLC5A2 gene by hybridization of rodent and human somatic cells for the first time. SLC5A2 is located near the central point of p11.2 band of chromosome 16, with a total length of about 7.7kb, contains 14 exons, and the encoded product has 672 amino acids [10]. The relative molecular mass is about 73kD, which shares 60% of the sequence with SLC5A1 [11]. SGLT2 gene mutation can lead to the occurrence of familial renalglucosuria, also known as primaryrenalglucosuria, which is no different from normal people except for high urinary sugar [12]. This disease lays a foundation for SGLT2 as a new target for diabetes. Therefore, the dysfunction of SGLT2 is regarded as a novel avenue.

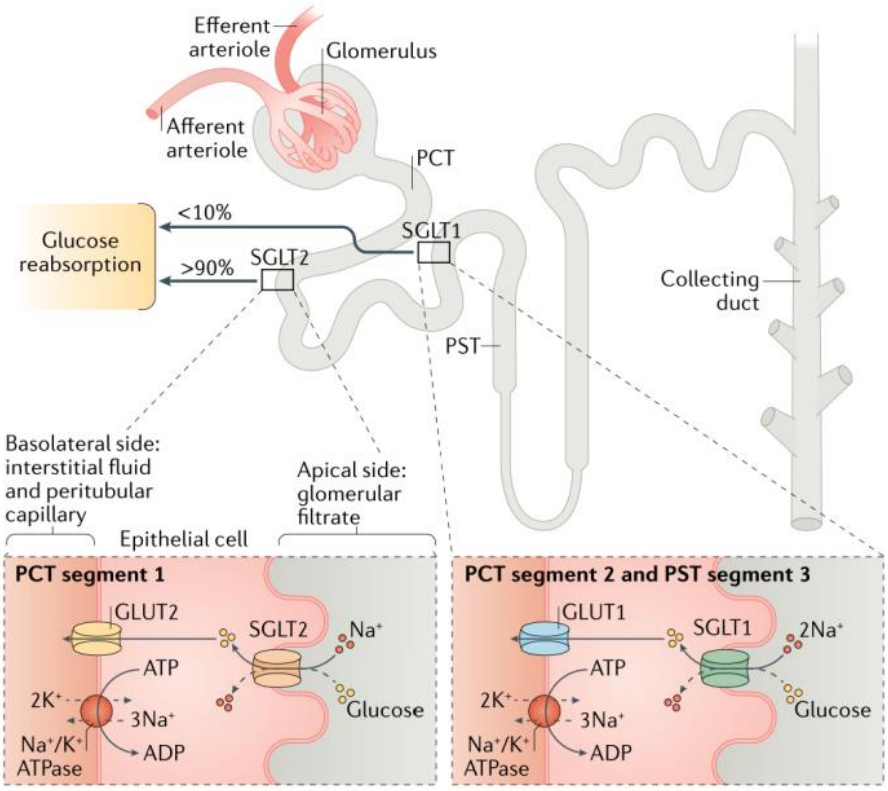


Figure 1. Glucose reabsorption in the kidney(non-original originated from[13])

The long-term high blood sugar in diabetic patients leads to various tissues chronic damage and functional disorders, which seriously affects people's production and life. As a new type of hypoglycemic drug, SGLT2i is not insulin-dependent and is not affected by insulin resistance. Therefore, patients with IR can also benefit from SGLT2i, and it does not effect other tissues and organs, providing a reasonable treatment for controlling the blood sugar level of diabetic patients [14]. SGLT-2 inhibitors regulates glucose metabolism in three main ways: First, through the process of gluconeogenesis, non-sugar substances are converted into glucose or glycogen, so that it enters the blood circulation; Second, the kidney absorbs glucose in the blood circulation as a metabolic substrate to meet its own energy needs; The third occurs when SGLT1 and SGLT2 in the proximal curved renal tubules reabsorb glucose in the ultrafiltrate. The high threshold for glucose to enter the urine and the kidney's capacity to reabsorb glucose both contribute to high blood sugar levels in diabetics. Because SGLT2i may considerably lower the threshold of renal glucose excretion, which promotes excessive glucose excretion in urine and lowers blood glucose levels, SGLT2 has recently been chosen as a therapeutic target for T2D. Hhypoglycemic effect of SGLT2i is blood glucose level dependent, and SGLT2i alone will not cause hypoglycemia. This ensures the hypoglycemic safety of this class of drugs. At the same time, it is speculated that there are two mechanisms for the removal of SGLT2i. One is that SGLT2i is dissociated after its effect; the other is that new SGLT2 is constantly transported to the cell membrane, so SGLT2i will not always play a role [5].

In addition, SGLT2i may improve blood pressure level and reduce body weight, and also shows good renal and cardiovascular protective effects, and plays a role through various mechanisms [14].

3. Molecular Structure and Pharmacological Characteristics of Bexagliflozin(A Type of SGLT-2 inhibitors)

TheracosBio is developing Bexagliflozin,an SGLT-2 inhibitor that is used orally,to treat essential hypertension and T2D.

It was initially authorized in the US on January 20, 2023, for use in individuals with T2D as a supplement to a glycaemic diet and exercise [15, 17]. Patients with T1D should not use Bexagliflozin;

it is also absolutely forbidden for those receiving dialysis or for individuals with a glomerular filtration rate (eGFR) of less than 30 milliliters per minute/1.73 m2 [15]. Before the treatment,renal function should be assessed and also the volume status,which are with volume depletion corrected, t hereafter, periodic assessment of renal function may be required based on clinical circumstances [15].

The synthesis route of Bexagliflozin: intermediate 2 from 2**-** (2**-** bromoethyl) **-** 1,3-dioxane via Barbarities intramolecular cycleation and nucleophilic substitution reaction;Using 4-Bromine-1-chlorine-2-(4-ethoxy-benzyl) benzene as the starting material, intermediates 4, 4 and 5 were obtained by deethylation through nucleophilic substitution, Grindberg reaction and desilicether protection group, and the last 6 was obtained by reduction.The resultant route is shown in Figure 2 [16].

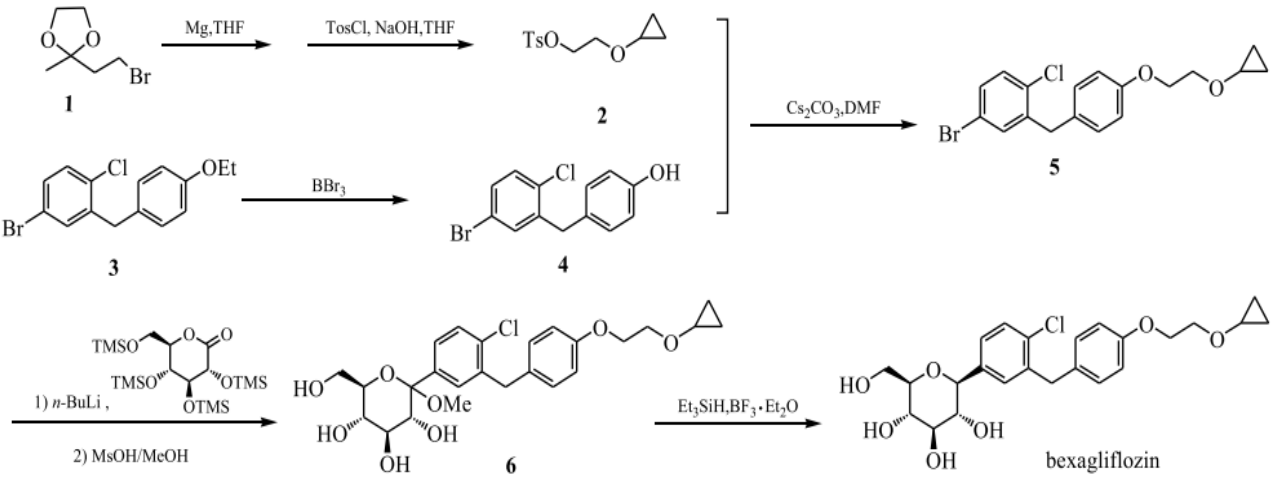


Figure 2. The resultant route of Bexagliflozin (non-original originated from [16])

4. Application of Bexagliflozin in T2D

4.1. Monotherapy Therapy

Adult T2D patients (mean age 55 years, not treated for at least 6 weeks) and poorly controlled HbA1c were randomized to a placebo (n = 69) or Bexagliflozin (n = 138, 20 mg/d) group in a 24-week placebo-controlled, double-blind, randomized III trial (NCT02715258) in order to monitor their blood glucose control. The results showed that after 24 weeks of treatment, Bexagliflozin significantly reduced HbA1c by 5%, significantly better than placebo group by 1% ($p< 0.025$, adjusted mean difference from placebo-0.4%. The proportion of bexagliflozi reducing HbA1c by more than 7% was significantly better than that of the placebo group (31% vs. 20%), and fasting plasma glucose (FPG) levels were also found to be significantly lower in the Bexagliflozin group [15].

A randomized, placebo-controlled trial,including 288 adults with T2D, randomly divided into Bexagliflozin and placebo group for a total of 96 weeks to observe the safety and long-term efficacy of Bexagliflozin. The results showed that Bexagliflozin 20mg/d was well tolerated, safe and effective for long-term use, effectively controlled HbA1c, reduced body weight and the blood pressure, and did not increase the occurrence of adverse event(Bexagliflozin 2.8% vs. placebo 8.5%). A international, randomized, double-blind, parallel-group clinical study lasting 96 weeks assessed the efficacy and safety of Bexagliflozin as a stand-alone treatment for individuals with T2D [17].

4.2. Combination Therapy

A 24-week randomized, double-blind, placebo-controlled III trial (NCT03259789) of adult T2D patients (mean age 56 years, 4% of whom were > 75 years) treated with metformin but poorly controlled HbA1c were randomized to metformin plus Bexagliflozin (Bexagliflozin 20 mg/day, n=158) and metformin plus placebo (n=159), with an average HbA1c of 8.5% before treatment and 8.5%, the effect is almost the same, with no difference. To study the improvement effect of the drugs

on HbA1c. Data showed that metformin plus Bexagliflozin improved HbA1c after treatment compared with metformin plus placebo (-1.05% vs. -0,56%, p<0.0001). A sensitivity analysis showed that this therapy had an overwhelming impact. The proportion of Bexagliflozin reducing HbA1c by more than 7% was significantly better than that of placebo (26% vs. 10%) the mean change that adjusted in the FPG level from baseline was – 42 and – 20mg/dL (adjusted mean difference with placebo plus metformin – 22 mg/dL) [15,18].

5. Adverse Events

Treatment with SGLT2i or Bexagliflozin is accompanied by certain adverse effects. Urinary tract infections and genital infections caused by excessive glucose excretion in the urine have been the most interesting adverse effects of these drugs. Mesh meta-analysis (n=46697), including 100 articles, examined the possibility of vaginal or urinary tract infections in individuals with T2D caused on by SGLT2i. (including Canagliflozin, Dapagliflozin, Bexagliflozin,Remogliflozin, Ertugliflozin and Henagliflozin, etc.). Ninety-seven reported data on urinary tract infections and 28 reported data on genital infections. The control interventions involved included other hypoglycemic drugs and placebo (n=33284), and other hypoglycemic drugs specifically included dipeptidyl peptidase IV inhibitors (DPP4i), insulin, sulfonylureas, etc. Studies have shown that when the possibility of urinary tract infection caused by various SGLT2i drugs was compared, it was found that the risk of Bexagliflozin (OR=0.43, 95% CI 0.19-0.98) was lower, but when compared to Henagliflozin and insulin, Bexagliflozin increased the risk, 3.15 times (95% CI: 1.08-15.95) and 11.16 times (95% CI: 1.27-116.55). However, more prospective research are required to confirm this finding, or post-marketing safety evaluation of drugs in the future [19].

6. Conclusion

Varied SGLT2i have been authorized for the treatment of T2D. SGLT2 inhibitors have hypoglycemic effects while lowering the risk of hypoglycemia in comparison to the insulin and also the sulfonylureas. They may be used for a long period by T2D patients because of their method of action, which has no impact on cell activity or insulin secretion.SGLT-2i have a more pronounced protective effect on the heart and kidneys than conventional hypoglycemic medications, and they may further lower blood sugar levels when used with these medications.

Bexagliflozin works by inhibiting the kidney's ability to reabsorb glucose, causing more glucose to exclude the body through the urine and achieving hypolycemic effects. Some clinical trials have verified its effectiveness to a certain extent. It can effectively regulate kidney function and glucose metabolism, and is safe. It is a relatively effective treatment method.But for now, adverse effects of Bexagliflozin still occur in the clinical treatment of patients. The most common adverse effects were fungal infections of female genitalia, urinary tract infections, and increased urination.Due to the Bexagliflozin has not been on the market for a long time, there is not enough clinical data to support absolute efficacy and safety. In the future, if the drug is applied to a wide range of people, its efficacy and adverse effects will need to be monitored. To generate additional high-quality evidence-based date for clinical application,the sample size must be further increased,and the research methodology must be strengthened.Bexagliflozin’s early and extensive clinical use is anticipated,giving more people with T2D a new treatment alternative.

References

[1] Ding J C. Effects of Daglipzin, an SGLT-2 inhibitor, on cognitive function and related factors in middle-aged and elderly patients with type 2 diabetes mellitus [D]. Anhui Medical University, 2023.

[2] American Diabetes Association (2011). Diagnosis and classification of diabetes mellitus. Diabetes care, 34 Suppl 1(Suppl 1), S62 – S69.

[3] Allegretti, A. S., Zhang, W., Zhou, W., Thurber, T. K., Rigby, S. P., Bowman-Stroud, C., Trescoli, C., Serusclat, P., Freeman, M. W., & Halvorsen, Y. C. (2019). Safety and Effectiveness of Bex gliflozin in Patients with Type 2 Diabetes Mellitus and Stage 3a/3b CKD. American journal of kidney diseases: the official journal of the National Kidney Foundation, 74 (3), 328 – 337.

[4] Wright E. M. (2013). Glucose transport families SLC5 and SLC50. Molecular aspects of medicine, 34 (2-3), 183 – 196.

[5] Ding B.X. Sodium-glucose cotransporter 2 and its inhibitors and related diseases [J/OL]. Chin J Biochem Mol Biol: 1 - 16.

[6] Pode-Shakked, B., Reish, O., Aktuglu-Zeybek, C., Kesselman, D., Dekel, B., Bujanover, Y., & Anikster, Y. (2014). Bitterness of glucose/galactose: novel mutations in the SLC5A1 gene. Journal of pediatric gastroenterology and nutrition, 58 (1), 57 – 60.

[7] Wright, E. M., Loo, D. D., & Hirayama, B. A. (2011). Biology of human sodium glucose transporters. Physiological reviews, 91 (2), 733 – 794.

[8] Scafoglio, C., Hirayama, B. A., Kepe, V., Liu, J., Ghezzi, C., Satyamurthy, N., Moatamed, N. A., Huang, J., Koepsell, H., Barrio, J. R., & Wright, E. M. (2015). Functional expression of sodium-glucose transporters in cancer. Proceedings of the National Academy of Sciences of the United States of America, 112 (30), E4111 – E4119.

[9] Scafoglio, C. R., Villegas, B., Abdelhady, G., Bailey, S. T., Liu, J., Shirali, A. S., Wallace, W. D., Magyar, C. E., Grogan, T. R., Elashoff, D., Walser, T., Yanagawa, J., Aberle, D. R., Barrio, J. R., Dubinett, S. M., & Shackelford, D. B. (2018). Sodium-glucose transporter 2 is a diagnostic and therapeutic target for early-stage lung adenocarcinoma. Science translational medicine, 10 (467), eaat5933.

[10] Wells, R. G., Mohandas, T. K., & Hediger, M. A. (1993). Localization of the Na+/glucose cotransporter gene SGLT2 to human chromosome 16 close to the centromere. Genomics, 17 (3), 787 – 789.

[11] Hatano, M., Udagawa, T., Kanamori, T., Sutani, A., Mori, T., Sohara, E., Uchida, S., Morio, T., & Nishioka, M. (2022). A novel SLC5A2 heterozygous variant in a family with familial renal glucosuria. Human genome variation, 9 (1), 42.

[12] Yu, L., Wu, M., Hou, P., & Zhang, H. (2020). SLC5A2 mutations, including two novel mutations, responsible for renal glucosuria in Chinese families. BMC nephrology, 21 (1), 69.

[13] Cowie, M. R., & Fisher, M. (2020). SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nature reviews. Cardiology, 17 (12), 761 – 772.

[14] Margonato, D., Galati, G., Mazzetti, S., Cannistraci, R., Perseghin, G., Margonato, A., & Mortara, A. (2021). Renal protection: a leading mechanism for cardiovascular benefit in patients treated with SGLT2 inhibitors. Heart failure reviews, 26 (2), 337 – 345.

[15] TheracosBio LLC. BRENZAVVY (bexagliflozin) tablets, for oral use: US prescribing information; 2023. https:// www. fda. gov/. Accessed 26 Jan 2023.

[16] Liu Chongyu, Guo Chun. Bex gliflozin, Brenzavvy [J/OL]. Chinese Journal of Medicinal Chemistry: 1.

[17] Halvorsen, Y. C., Walford, G. A., Massaro, J., Aftring, R. P., & Freeman, M. W. (2019). A 96-week, multinational, randomized, double-blind, parallel-group, clinical trial evaluating the safety and effectiveness of Bex gliflozin as a monotherapy for adults with type 2 diabetes. Diabetes, obesity & metabolism, 21 (11), 2496 – 2504.

[18] Halvorsen, Y. D., Conery, A. L., Lock, J. P., Zhou, W., & Freeman, M. W. (2023). Bex gliflozin as an adjunct to metformin for the treatment of type 2 diabetes in adults: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes, obesity & metabolism, 25 (10), 2954 – 2962.

[19] Liu F Q, et al. Network meta-analysis of the risk of urinary tract or genital infection caused by sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus [J]. Chinese Journal of Diabetes Mellitus, 2019, 14 (8): 799 - 808.