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Sodium glucose cotransporter 2 inhibitors (SGLT2i) in the treatment of type 2 diabetes mellitus: Literature review

Inhibidores del cotransportador de sodio y glucosa tipo 2 (SGLT2i) en el tratamiento de la diabetes mellitus tipo 2: revisión de la literatura

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Summary

Diabetes mellitus is a chronic disease that affects the world's population. In Latin America, the prevalence rates are high and mortality is increasing. In Ecuador, in 2017, 4,895 deaths were reported due to this disease. Sodium-glucose cotransporter inhibitors (SGLT2 inhibitors) have been shown to be suitable for the treatment of diabetes mellitus. They help reduce body weight and glycosylated hemoglobin, especially in patients with good kidney function. SGLT2 inhibitors, approved in recent years, block the renal reabsorption of glucose, promoting its excretion through urine. This reduces blood glucose and offers additional benefits such as kidney protection and decreased cardiovascular risks. **Methodology:** non-experimental, bibliographic review. **Objective:** To analyze the overall benefits of SGLT2 transporter inhibitors in the treatment of type 2 diabetes mellitus. **Results :** The main SGLT2 inhibitors each with specific pharmacokinetic characteristics and therapeutic applications that can be taken advantage of when treating patients with diabetes mellitus. **Conclusions :** Type 2 diabetes mellitus is a chronic pathology that merits timely and adequate treatment with drugs that have clinical benefits for the patient. Taking into account SGLT2 inhibitors, diabetic patients can be provided with a novel treatment that is generally well tolerated according to the patient's conditions.
Keywords : Diabetes mellitus, diabetes complications, ISGLT2.

Resumen

La diabetes mellitus es una enfermedad crónica que afecta a la población mundial. En América Latina, las tasas de prevalencia son altas y la mortalidad va en aumento. En Ecuador, en 2017, se reportaron 4.895 muertes por esta enfermedad. Los inhibidores del cotransportador de sodio-glucosa (inhibidores de SGLT2) han demostrado ser adecuados para el tratamiento de la diabetes mellitus. Ayudan a reducir el peso corporal y la hemoglobina glicosilada, especialmente en pacientes con buena función renal. Los inhibidores de SGLT2, aprobados en los últimos años, bloquean la reabsorción renal de glucosa, promoviendo su excreción a través de la orina. Esto reduce la glucosa en sangre y ofrece beneficios adicionales como protección renal y disminución de riesgos cardiovasculares. **Metodología:** revisión de literatura no experimental. **Objetivo:** Analizar los beneficios globales de los inhibidores del transportador SGLT2 en el tratamiento de la diabetes mellitus tipo 2. **Resultados**: Los principales inhibidores de SGLT2 tienen cada uno características farmacocinéticas específicas y aplicaciones terapéuticas que pueden aprovecharse al tratar a pacientes con diabetes mellitus. **Conclusiones:** La diabetes mellitus tipo 2 es una patología crónica que amerita un tratamiento oportuno y adecuado con fármacos que aporten beneficios clínicos al paciente. Teniendo en cuenta los inhibidores de SGLT2, se puede brindar a los pacientes diabéticos un tratamiento novedoso que en general es bien tolerado de acuerdo a la condición del paciente.
Palabras clave: Diabetes mellitus, complicaciones de la diabetes, ISGLT2.

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1. Introduction

Diabetes mellitus is a serious public health problem that brings with it multiple complications that can even be fatal. Currently, approximately 463,000,000 people between 20 and 79 years of age suffer from this pathology, which represents 9.3% of the population around the world. It is expected that by 2030 this number will increase to 578,000,000 (10.2%) and in 2045 to 700,000,000 (10.9%). The importance of prevalence lies in identifying the population that has the highest risk of developing the disease, greater impact on their quality of life and premature mortality (1).

It is a pathology of great significance, since in Latin America and the Caribbean the prevalence is high, for example, Mexico has a prevalence of 10.7%, Bogotá 10%, Guatemala 8%. In Ecuador the mortality rate has increased in recent years due to this pathology, in 2017 a total of 4895 deaths were reported (2).

Likewise, according to data from the WHO (World Health Organization), 66% of diabetics suffer from some type of disability compared to 29% who do not suffer from this pathology, demonstrating its importance in the quality of life of the population that suffers from it. Gomezcoello et al (3) showed that the prevalence of diabetes mellitus in the Enrique Garcés General Hospital in older adults was 14%, it is worth mentioning that the majority presented chronic complications that were related to longer duration of the disease along with higher values of H b A1C (glycosylated hemoglobin).

Sodium-glucose cotransporter inhibitors, also known by their acronyms as iSGLT, are drugs that have a series of benefits for the body of a diabetic patient. Lytvyn et al. (4) indicate that iSGLT help to reduce 2-3kg of body weight by blocking glucose reabsorption, and also reduce glycosylated hemoglobin values by an average of 0.7%. It should be noted that this reduction is more evident in patients who have proper kidney function.

In the search for drugs that provide protection in renal function, trials have been carried out with inhibitors of the renin-angiotensin-aldosterone system and endothelin receptor antagonists, the results of which were not favorable, which is why the use of iSGLT is motivated since these do provide renal protection. High levels of glycemia or insulinemia can cause kidney

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damage due to hyperfiltration of the nephron or intraglomerular hypertension, iSGLT2 by reducing glucose can prevent these entities that are common in diabetic patients, taking into account that 40% of this group develops end-stage renal disease (4).

The importance of knowing the therapeutic options for diabetes lies in the high global prevalence and the public health problem that it entails.

The fact that doctors have the ability to make the diagnosis and provide correct management is essential since it would be reflected in a controlled chronic disease and possible complications are minimized (5).

In patients suffering from diabetes, the incidence of myocardial infarction and cerebrovascular events has decreased in the last 30 years; on the contrary, terminal renal disease remains and its most frequent cause is diabetic nephropathy (4).

2. Methodology

A literature research study was conducted using a bibliographic review method with a qualitative approach of descriptive linking and with a non-experimental design in which bibliographic sources such as PubMed, ScienceDirect and Google Scholar were used. The information search was carried out using keywords, which were taken from MES and DeCS. The terms that were selected in DeCS were "Diabetes mellitus" AND "Diabetes complications" AND "ISGLT", then the MESH terms "Diabetes mellitus" AND "Diabetes complications" AND "ISGLT" were selected. After this, the review of the scientific articles according to the research was carried out, the most relevant for the present study was chosen and its results were evidenced to capture the present research. It is worth mentioning that observational, descriptive, retrospective, prospective studies, systematic reviews, bibliographic reviews and meta-analysis were used.

3. Development

Diabetes is a chronic metabolic disease associated with an unsatisfactory prognosis and a high cost in controlling the disease. This disease is classified into type 1 and type 2. Type 2 diabetes is a nutritional disorder generated by the lack of response to the action of insulin resulting in high serum glucose levels,

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which could have complications such as kidney failure, diabetic retinopathy or a high cardiovascular risk (6).

In 2017, its annual prevalence was 425 million worldwide and type 2 diabetes corresponds to more than 85% of the total cases. It is expected that by 2045 it will affect approximately 629 million people (6,7). It is widely distributed throughout the world, however, there are certain patterns that determine a greater or lesser prevalence, among these stand out age, sex, genes, ethnicity, residence; these also influence the type of diabetes to be presented, whether 1 or 2 (7).

In relation to the above mentioned, Forouhi & Wareham (7) establish that diabetes is a public health problem that increases over time, and they also indicate that this increase is due to the concomitance of a growing prevalence of obesity, also associated with bad eating habits and low physical activity. For this reason, numerous drugs have been developed in order to treat this disease, however, it must be kept in mind that every treatment has its pros and cons, which is why through the following research work, the characteristics, pharmacokinetics, pharmacodynamics, mechanism of action, indications, contraindications and adverse reactions that it produces will be analyzed (8).

The industrial revolution is advancing and the new thing on the market is the sodium-glucose cotransporter 2 inhibitors, this type of drugs will reduce the levels of glucose in the blood by blocking the renal reabsorption of glucose, and its protective effect at the renal and cardiac level has also been recognized (9).

In the 19th century, researchers discovered a substance extracted from the apple tree that produces glucosuria, this is phlorizin. Interest in this compound began around the 1950s, since it was shown that it blocks the transport of glucose to some tissues, in which the kidney was found, which is why it was later used to study the function of SGLT transporters. Phlorizin began to be evaluated for therapeutic purposes when it was shown that there is excessive reabsorption of glucose by the kidney, and this plays a role in the pathology of type 2 diabetes mellitus, thus giving rise to selective SGLT2 inhibitor drugs (10).

Sodium-glucose cotransporter 2 inhibitors play important roles in the aforementioned pathology such as glomerular hyperfiltration, renal hypoxia,

its effect of reversibly reducing the glomerular filtration rate, in addition to preserving the glomerular filtration rate in the future (9).

We must not forget that SGLT2 and SGLT1 are secondary active cotransporters. SGLT2 perform reabsorption in the S1 and S2 segments of the proximal tubule, unlike SGLT1, which do so in the S3 segment (9,11).

SGLT2 transporter inhibitors

They are drugs capable of selectively and reversibly inhibiting the sodium-glucose cotransporter (SGLT2), thus decreasing post-prandial hyperglycemia (12). It is known that the kidney helps control plasma concentration levels, physiologically the glomerular tuft filters 180 g/day/1.7m2 (healthy patient) and represents 30% of the daily energy demand, which is absorbed in the proximal tubules and returns to the blood mainly thanks to the type two glucose-sodium cotransporters known as SGLT2 (8,9).

In patients suffering from diabetes, the glomerulus filters a greater amount of glucose due to existing hyperglycemia. In this situation, the activity of SGLT2 increases with the purpose of reabsorbing and returning to the blood this amount of glucose present in the tubule, maintaining high blood glucose levels (8,9).

As its name indicates, this type of medication fulfills its role in inhibiting the passage through these glucose-sodium cotransporters, ultimately leading to the excretion of glucose through urine (8,9).

Thanks to the contribution of SGLT2, patients with type 2 Diabetes Mellitus can excrete around 80% of glucose per day. Two things must be clear: first, that glucose reabsorption is carried out by SGLT2 in the proximal convoluted tubule around 80-90%, second, that only the remaining 10% is done by SGLT1, which has a lower affinity and concentration capacity, which is why there is a 100% glucose recovery (9,11).

The use of SGLT2 is indicated exclusively for the management of type 2 diabetes mellitus, especially in the early stages of the disease. Nespoux (9) mentions the use of empagliflozin in diabetic patients with high cardiovascular risks and in patients with an estimated glomerular filtration rate >30m L / min /1.73m2. Finally, the role of SGLT2 is recognized, first as a kidney protection

agent and second, to prevent cardiovascular problems in patients with type 2 diabetes mellitus with a high risk. It can be used as dual therapies or triple therapies together with insulin to treat patients with type 2 diabetes mellitus.

The use of SGLT2 inhibitors is contraindicated in the treatment of type 1 mellitus, and is not recommended for use in patients with severe renal failure, or in patients with a glomerular filtration rate of less than 60 mL/min. (8). It is important not to administer this type of medication in pregnant women, which is why the FDA classifies it within category C (medications that can be used during pregnancy), leading to the development of kidney damage in the fetus (8). Patients who use ASA or Pioglitazone diuretics are associated with developing marked dehydration and even hypotension (9). It has been shown that Dapagliflozin should be contraindicated during breastfeeding (8).

Empagliflozina

It is a drug that has a high selectivity in relation to SGTL2, an approximate half-life of 23 hours, oral bioavailability greater than 60%, metabolism occurs thanks to the glucuronidation process and around 75 grams of glucose are excreted daily through urine (8,9).

Romera et al (13) analyzed the safety and efficacy of empagliflozin plus other oral hypoglycemic agents in an analysis of 3 trials that are in phase III in patients with type 2 diabetes mellitus, they received placebo, empagliflozin 10 or 25 mg every day for 24 hours in combination with metformin, metformin ± pioglitazone or metformin + sulfonylurea. It was shown that Empagliflozin in combination with other oral antidiabetics vs placebo helped to significantly reduce HbA1c, blood pressure, body weight with adequate tolerance and good safety profile.

García et al (14) conducted a longitudinal, prospective study with 25 patients to whom empagliflozin was administered gradually starting with a dose of 10 mg orally every day for 4 weeks. Weight loss, elevated blood glucose and decreased glycosylated hemoglobin were observed.

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Dapagliflozin

It is the greatest exponent of the ISLGT2, it has been shown to be useful in reducing HbAc1 and fasting glycemia in the long term having beneficial results for the patient, it has also been shown to reduce weight by causing glucosuria, in addition to reducing systolic blood pressure by 5 mmHg. At doses of 2.5 - 50 mg every day for 12 weeks in patients with Diabetes Mellitus 2, it excretes glucose in 52 - 85 mg. Caution should be taken when administering to patients with cardiovascular diseases, moderate renal failure, shock or hypotension, moderate dehydration (15).

The pharmacokinetic and pharmacodynamic characteristics are: maximum plasma concentration at two hours, oral bioavailability at doses of 10 mg is 80% , the interaction of dapagliflozin with high-fat foods reduces the plasma concentration by half, and also prolongs the effect, it has the ability to bind 85% with plasma proteins, it is metabolized thanks to the enzyme UDP-glucuronosyltransferase 1-9, we must keep in mind that this unit will be found at the renal and hepatic level (8,9).

Hidalgo et al (16) conducted a prospective observational study with 32 patients with type 2 diabetes mellitus before starting dapagliflozin and the patients were analyzed in follow-up at 6 and 12 months for biochemical parameters in urine and blood and the carotid-femoral pulse velocity was determined, demonstrating that there is a decrease in it, showing that it produces a medium and long-term decrease in arterial stiffness.

On the other hand, Escudero et al (17) analyzed the results of seven randomized clinical trials, two of which were used as monotherapy with 840 patients and five as combined therapy with other oral antidiabetics (3184 patients). In all seven trials, dapagliflozin helped reduce HbA1c levels compared to placebo, except for one study in which the comparison was made against glipizide. However, it should be noted that the present study concludes that dapagliflozin does not provide advantages with respect to pharmacotherapy for type 2 diabetes mellitus due to the absence of important clinical benefits and the high cost.

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Canagliflozina

It is a drug administered as monotherapy, which is indicated in adults suffering from type 2 diabetes mellitus when exercise and diet do not achieve the objectives and the use of metformin is contraindicated. It can also be indicated as a complementary treatment when administered with other medications such as insulin or antihyperglycemic agents. The mechanism of action is the reversible inhibition of the sodium-glucose cotransporter 2, thus decreasing the reabsorption of glucose in the kidney, increasing urine, and thus decreasing blood glucose (18).

It is rapidly absorbed, reaching its maximum concentration at 1-2 hours. Absorption is not affected when administered with food, it is distributed mainly with albumin (98%), and it is eliminated in feces and urine. It interacts with rifampicin, digoxin and diuretics (18).

Ertugliflozina

This drug has a half-life of 16 hours, has a bioavailability of 100%, has renal (2%) and fecal (34%) excretion and has a hepatic metabolism (8,9).

Ipragliflozina

Drug being developed in Japan. Doses between 50-300 mg as monotherapy every 24 hours were evaluated in patients with type 2 diabetes mellitus, and who have not taken or are on previous treatment. Ipragliflozime plus metformin was also evaluated. As a result of these treatments, there was a quite significant decrease in blood glucose and glycosylated hemoglobin compared to placebo at 12-24 weeks. This drug as monotherapy decreased the weight of patients by 1.47 kg at 16 weeks, as well as systolic blood pressure decreased by 3.2 to 4.3 mmHg at 12-16 weeks. However, urinary tract infections occurred more frequently compared to placebo (19).

Metha et al (20) conducted a study with a group of volunteers where the following results were obtained: the maximum absorption of this drug was 1.5 to 2.1 hours, and the concentrations will decrease in a biphasic pattern. The half-life is 13.1 hours. With a dose of 10 mg it will inhibit the reabsorption of glucose by 40% of the filtered glucose and when high doses are given it can

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inhibit up to 60%. Studies show that there is no need to adjust the dose when kidney function is impaired, and it has also been shown that it does not produce significant interactions with other medications.

Treatment with empagliflozin vs sitangliptin monotherapy in patients with type 2 diabetes mellitus who are not receiving treatment and with a baseline HbA1c between 7-10% showed that the two drugs reduced glycosylated hemoglobin equally. Empagliflozin reduced weight, blood pressure and abdominal circumference of patients more than sitangliptin. The rate of urinary tract infections was similar with both drugs (20).

Tofogliflozina

It is a selective SGLT2 inhibitor, which was approved in Japan as a treatment for type 2 diabetes mellitus. A good efficacy and safety profile was demonstrated in Japanese patients with diabetes mellitus (21).

In the study by Masayaku and Hisatako (21), s6897 patients were included who took Apleway 20 mg tablet and Deberza 20 mg tablet (tofogliflozin 20 mg is usually given once a day orally before or after breakfast). The study lasted 12 weeks. Good results were shown, as it decreased the patients' HbA1c as well as body weight. It was concluded that this drug is well tolerated, and significantly improved glycemic control (21).

Luseogliflozina

It is a highly selective inhibitor of SGLT2, it was developed in Japan by "Taisho Pharmaceutical" and approved for the treatment of type 2 diabetes mellitus in 2013. It is administered at a dose of 2.5 mg every day. In the study carried out by Soichi Sakai and collaborators (22), which included 1031 patients with type 2 diabetes mellitus, and was stratified by the BMI they had, 2.5 mg daily was administered (even up to 5 mg) in which the efficacy of the drug was attempted to be verified by glycosylated hemoglobin , fasting plasma and body weight. It was shown that HbA1c and body weight decrease in patients, as well as the decrease in glycemia tends to be lower in patients with a BMI of 22.5 kg/m ^{2}.

Table 1. Characteristics of the main SGLT2 transporter inhibitors in the treatment of type 2 diabetes mellitus (23,24).

	Dapagliflozin	Canagliflozina	Empagliflozina	Ertugliflozina
Dose	Initial dose 10 mg orally every 24 hours.	Initial dose 100 mg every 24 hours.	Dosis inicial 10 mg cada 24 horas. Dosis máxima 25 mg cada 24 horas.	Dosis inicial 5 mg cada 24 horas. Dosis máxima 15 mg cada 24 horas.
Side effects	Genital infections, urinary tract infections, increased creatinine, hypoglycemia, nausea, vomiting, constipation, low back pain.	Genital fungal infections, hypercholesterolemia, urinary tract infections, hypertriglyceridemia, increased creatinine, hypoglycemia, orthostatic hypotension, nausea, vomiting, bone fractures, asthenia, pancreatitis.	Urinary tract infections, genital infections, hypovolemia, hypoglycemia, pruritus.	Urinary tract infections, polyuria, genital infections, hypoglycemia, pruritus, angioedema.
Maximum dose 25 mg every 24 hours.	Initial dose 5 mg every 24 hours.	Ertugliflozin	Insuficiencia renal grave (filtrado glomerular <30 mL/ min/1,73 m^2), pacientes en diálisis o con que padezcan enfermedad renal en etapa terminal	Insuficiencia renal grave (filtrado glomerular <30 mL/min/1,73 m^2), pacientes en diálisis o con que padezcan enfermedad renal en etapa terminal
Contraindications	Contraindicated in glomerular filtration rate <30 mL/min/1.73 m 2 .	severe renal impairment (glomerular filtration rate <30 mL/min/1.73 m2) , patients on dialysis or with end-stage renal disease	Severe renal insufficiency (glomerular filtration rate <30 mL/ min/1.73 m2) , patients on dialysis or with end-stage renal disease	Severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73 m2) , patients on dialysis or with end-stage renal disease

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4. Discussion

SGLT2 inhibitors have revolutionized the treatment of type 2 diabetes mellitus by providing not only effective glycemic control but also cardiovascular and renal benefits. SGLT2i, such as empagliflozin and canagliflozin, have been shown to be effective in reducing glycated hemoglobin (HbA1c) levels (25,26). In clinical trials, these drugs have been reported to reduce HbA1c by 0.5% to 1.5% depending on the dose and patient. This is in contrast to other treatments, such as dipeptidyl peptidase-4 inhibitors (DPP-4i), which generally achieve smaller reductions, typically in the range of 0.5% to 0.8% (26).

Considering that metformin is the first-line treatment for type 2 diabetes and can reduce HbA1c by 1% to 2%. However, its use may be limited in patients with impaired renal function; ISGLT2s can be used as an adjunctive therapy, providing additional benefits in terms of weight loss and blood pressure reduction (25,26).

DPP-4i, like sitagliptin, provide similar reductions in HbA1c (approximately 0.5% to 0.8%), but do not provide the significant cardiovascular benefits seen with SGLT2i. A comparative study showed that patients treated with SGLT2i had a 15% lower risk of adverse cardiovascular events compared with those treated with DPP-4i (27).

SGLT2i are not only effective for glycemic control, but have also been shown to reduce the risk of hospitalization for heart failure and improve renal outcomes. Studies such as EMPA-REG OUTCOME have shown a 38% reduction in the risk of hospitalization for heart failure and a significant reduction in the progression of diabetic nephropathy. These benefits are particularly important for patients with T2DM who have cardiovascular comorbidity (28).

Various studies are being carried out with ISGLT2 in which an attempt is being made to find the benefit that exists in the reduction of cardiovascular events in patients who have heart failure, regardless of whether they suffer from type 2 diabetes mellitus. Currently, the only studies that are in phase 3 are the combination of dapagliflozin plus pioglitazone in patients who have heart failure with a preserved ejection fraction (29).

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) play a dual role in type 2 diabetes mellitus, as they can contribute to both renal damage and renal

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protection. SGLT2i can cause a modest and rapid decrease in GFR (between 3% and 10%) at the start of treatment. This reduction is usually temporary and stabilizes thereafter. However, SGLT2i have been shown to reduce albuminuria levels, suggesting a benefit in preserving renal function in the long term. This is critical to delay the progression of diabetic nephropathy (23,25).

Table 2. General comparison of antidiabetics mainly used in type 2 diabetes mellitus (24,27,31,32)

Treatment	Average reduction in HbA1c	Cardiovascular benefits	Common side effects
iSGLT2	0.5% - 1.5%	Reduction of major cardiovascular events	Genital infections, polyuria, dizziness, diabetic ketoacidosis, acute renal failure.
Metformin	1% - 2%	Moderate	Gastrointestinal discomfort, lactic acidosis, hypoglycemia, taste disturbance, weight loss.
iDPP-4	0.5% - 0.8%	Limited	Pancreatitis, respiratory infections, nausea , diarrhea, vitamin B12 deficiency anemia.
Sulfonylureas/Insulin	Up to 2%	Increased cardiovascular risk	Hypoglycemia, nausea, skin rashes, allergic reactions, weight gain

Prepared by: authors of the work.

5. Conclusions

Diabetes mellitus is a chronic, non-communicable disease with increasing prevalence and incidence worldwide, which poses serious public health problems due to its high associated morbidity and mortality. The complications of this disease not only affect the quality of life of patients, but also create a significant burden on health care systems. Therefore, it is essential to deepen our knowledge of this pathology, as well as the therapeutic options available for its effective management.

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In this context, sodium cotransporter inhibitors (ISGLT2) have gained importance in the treatment of diabetes mellitus 2. These drugs are distinguished by their ability to reduce HbA1c levels by 0.5% to 1.5%, which translates into more effective blood glucose control. However, their positive impact goes beyond glycemic control, as ISGLT2 has also been shown to provide significant renal and cardiovascular benefits.

Recent studies have shown that these drugs not only reduce the risk of adverse cardiovascular events, but also protect kidney function, which is essential for the long-term well-being of patients with diabetes.

A comprehensive approach to diabetes mellitus management, including the use of ISGLT2, represents an important advance in the effort to improve the quality of life of patients and reduce the burden of this disease in the population. It is essential that healthcare professionals and patients are informed about these innovative treatments, as well as the importance of rigorous diabetes control to minimize its complications and improve long-term health outcomes.

6. Contribución de los autores

BAOT: Analysis of results, review of the article.
AFGM: Analysis of results, review of the article
EGCO: Analysis of results, review of the article
PJFB: Analysis of results, review of the article

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