Inhibitors of the sodium-glucose cotransporter type 2 in the diabetes melltius treatment

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Abstract

Sodium-glucose co-transporter inhibitors´ drugs (SGLT) work by selectively and reversibility inhibiting at the renal level. Through this mechanism, they reduce glucose reabsorption, which is excreted through urine and thus contribute to normalizing blood glucose. Administration of sodium-glucose co-transporter inhibitors induces favorable changes in glycosylated hemoglobin, body weight and blood pressure, as well as a low risk of hypoglycaemia. Although they are a pharmacological group that can be used as monotherapy, they are mostly used as adjuvants in the treatment of patients with diabetes mellitus who receive drug treatment with other normo or hypoglycemic medications and who have not met control goals. It is important to be alert to possible side effects or adverse reactions to discontinue treatment and take appropriate action. Given this problem, a detailed analysis will be highlighted.

Keywords: glyphozins; sodium-glucose cotransporter inhibitors; Mellitus diabetes; treatment; weightloss

INTRODUCTION

Noncommunicable diseases constitute a public health problem worldwide, and among them, diabetes mellitus (DM) has a high prevalence.(1) In people with this disease, the treatment priority is to achieve good metabolic control and thus avoiding the risk of extreme blood glucose values, thus avoiding future complications of this disease.(2) Avoiding hyperglycemia has a particular value, since it is known that it constitutes a marker of severity in critically ill patients, it is associated with worse outcomes and is an independent factor of mortality.(2)

The reasons for the increase in glycemia in these patients are related to non-compliance with the indicated treatment and, in general, to inadequate self-care behaviors for DM. Financial limitations to access the drugs used for the correct treatment of this disease can also contribute to metabolic uncontrol. Meanwhile, hypoglycemia in patients with DM generally occurs as a result of inadequate or erratic consumption of carbohydrates, after the administration of sulfonylureas or insulin. (2) For the proper treatment of DM, there are several groups of medications.

Among these, there are the so-called oral normoglycemic agents and hypoglycemic agents; the latter can be used orally or parenterally. Both groups of drugs reduce blood glucose, but the latter can -in addition- increase the risk of hypoglycemia if not used properly.(3) Hence, the importance of incorporating new hypoglycemic agents into the market that do not compromise the mechanisms of endogenous counterregulation, which would help reduce the frequency of this negative event.(3) Sodium-glucose cotransporter (iSGLT) inhibitor drugs meet this condition and currently iSGLT type 2 (iSGLT2, for its acronym in English) constitute an option for the treatment of type 2 DM (DM2).(4)

The iSGLT2, are also known by the pseudonym "glifozinas", although they can be used in monotherapy, they are considered as a coadjuvant pharmacological group in the control of patients with DM2, who receive treatment with other normal-type or hypoglycemic drugs, which control goals have not been achieved. Like any medication, it should be noted that despite its benefits, it is not free from some adverse effects and side reactions. (4)

However, due to its importance, SGLT2, as a new option, to obtain good glycemic control in patients with DM, it is necessary that our professionals are familiar with its use. Hence, the objective of this article was to describe the role of SGLT2-i in the treatment of DM.

Aim and objectives

This article aims to describe the role of sodium-glucose cotransporter type 2 inhibitors in the treatment of diabetes mellitus.

MATERIAL AND METHODS

The information necessary to write this article was carried out in the first semester of 2023. This was obtained from the evaluation of different review, research and Web pages, which in general were less than 10 years old, in Romanian or English. Specialized books were used as scientific information search engines and the study used 17 specialized books.

RESULTS

Mechanism of action of sodium glucose cotransporter inhibitors

Renal glucose reabsorption is the primary mechanism by which the kidneys influence glucose homeostasis. This function is fundamental and involves renal gluconeogenesis, which

is capable of producing 15 to 55 g of glucose per day, while the kidney can metabolize 25 to 35 g of it in the same period of time. Glucose uptake from the circulation and glomerular filtration constitute another of the mechanisms involved in blood glucose. (8)

Hypothetically, if it is considered that there is a glucose concentration of 100 mg/dl, with a normal glomerular filtration rate of approximately 180 L per day, healthy people should filter approximately 180 g per day of glucose. (8) This is reabsorbed -almost all- in the proximal convoluted tubule and returns to the circulation, in such a way that no glucose should be excreted in the urine of healthy subjects. The efficiency of this system is excellent and allows glucose to be conserved in the body, which constitutes a valuable source of energy. (9)

Although several types of sodium-glucose cotransporters (SGLT) are known to exist, English), the present review focuses on the activity of two of its types, SGLT-1, distributed throughout almost the entire body -intestine, trachea, kidney, heart, brain, testis and prostate, and SGLT2, predominantly located at the renal level, theoretically allowing its local action. (9, 10) The latter are expressed in the proximal convoluted tubules of the kidney -in segment S1- and are responsible for most of the reabsorption of glucose filtered from the lumen of the tubules (approximately 90%). (10)

It has been shown that patients with DM2 have increased renal glucose reabsorption, which may contribute to persistently elevated blood glucose concentrations. (10) SGLT2-i act competitively, reversibly, and selectively at the level of SGLT2 receptors located in the proximal convoluted tubules and its action is independent of the secretion or action of insulin and the evolutionary stage of DM2. The inhibition lowers the saturation threshold for glycosuria in such a way that it starts with blood glucose levels between 60-80 mg/dL (<100 mg/dL). Likewise, it increases urinary glucose excretion by 60-80g/day (22) and decreases renal glucose reabsorption by 30-50%. (11, 12)

Some characteristics about sodium-glucose cotransporter inhibitors as part of the treatment of diabetes mellitus

Oral absorption of SGLT2-i is rapid (Cmax 1-2 h) and is not modified by food intake. At the same time, they present hepatic metabolism by glucuronidation, with little oxidation and participation of cytochromes, and it is confirmed that 60% of these drugs are eliminated through the feces, while 33% are eliminated through the urine.(12) Based on Given the efficacy and safety profile observed, iSGLT2 can be considered a treatment option in patients with a renal glomerular filtration rate > 60 ml/min, with special caution in elderly patients, who do not present acute or chronic diseases that may cause hypoxia. tissue. (13)

There are several drugs that have the ability to act through SGLT2 receptors and produce an osmotic diuresis; Among them, the following are described: dapagliflozin, canagliflozin and empagliflozin - although more recently rtugliflozin was incorporated into this group. These drugs act independently of insulin concentration or peripheral resistance to this hormone and dependent on plasma glucose concentrations, as well as the glomerular filtration rate of the subject. (13)

Initially, iSGLT2 have been authorized for the exclusive treatment of DM2.(14) However, due to the existing difficulties in the adequate therapeutic management of some patients with type 1 DM (DM1) and the need to search for drugs that can be used in combination with insulin to obtain optimal glycemic control, exploring the use of SGLT2-i in these patients is considered.(14) For this reason, the European Medicines Agency (EMA) has agreed to review submission of the registration dossier for sotagliflozin, which is a dual inhibitor of SGLT types 1 and 2. Oral treatment -if authorized- would be used as an adjunct to insulin treatment to improve glycemic control in adults with DM1. (15)

The FDA- and EMA-approved iSGLT2 agents for T2DM patients are in the commercial phase and are still undergoing long-term clinical safety trials. Their pharmacokinetic and pharmacodynamic properties are presented in Table 1. (15)

Table 1. SGLT2 inhibitor drugs commercially approved in the USA and Europe

Drug	**Dapagliflozina**	**Canagliflozina**	**Empagliflozina**	**Ertugliflozina**
Tradename	Farxiga	Invokana	Jardiance	Steglatro
Selectivity	1200 times more selective to SGLT-2	250 times more selective to SGLT-2. SGLT-1 low potency inhibition	2500 times more selective to SGLT-2	2000 times more selective to SGLT-2
Half life	12,2 h	11-13 h	22,4 h	16,6 h
Bioavailability	78%	65%	>60%	100%
Metabolism	Hepatic due to glucuronidation	Hepatic due to glucuronidation	Hepatic due to glucuronidation	Hepatic due to glucuronidation
Excretion	Urinary with inactive metabolites	Fecal and urinary as drug	Fecal (41%) and urinary (54%)	Renal and fecal excretion (1.5% renal route and 33.8% fecal route as drug)
Drug interaction	No clinical relevance	No clinical relevance	No clinical relevance	No clinical relevance
Renal adjustment	Not recommended in patients GFR <60ml/min/1.73mp	Not recommended in patients GFR<45ml/min/1.73mp. Limit dose to 100mg in patients with GFR between 45-60ml/min/1.73mp	Not reommended in patients GFR <45ml/min/1.73mp	Not recommended in patients GFR<30ml/min/1.73mp. Not recommended in patients with GFR between 30-60ml/min/1.73mp
Hepatic adjustment	No hepatic adjustment required Child Pugh missing data	Child Pugh A and B do not require adjustment. Child Pugh missing data	Missing data. could be used	Child Pugh A and B do not require adjustment. Child Pugh missing data
Pharmacodynamics	Urinary glucose excretion of approximately 70 g per day	Decreases the renal threshold to 70-90mg/dl. It causes a mean urinary glucose excretion of 100 g per day.	Between 64-78 g daily of glucose excreted via the urine	Between 45-68 g of glucose excreted via the kidneys
Presentation	5mg and 10mg tablets	100mg and 300mg	10mg and 2mg	5mg and 15mg

These drugs are available both as single-ingredient products and in formulations combined with other drugs for the treatment of DM, to make their use more feasible (15) (Table 2).

Table 2. Combination formulations of SGLT2 inhibitor drugs with other drugs for the treatment of diabetes mellitus

Name	Administration	Presentation	Suggested maximum dose
Xigduo XR	Oral 1 tab/day	2.5 mg Dapagliflozin / 1000 mg Metformin XR 5mg Dapagliflozin / 500mg Metformin 10 mg Dapagliflozin / 500 mg Metformin 5 mg Dapagliflozin / 1000 mg Metformin XR 10 mg Dapagliflozin / 1000 mg Metformin XR	10 mg Dapagliflozin / 2000 mg Metformin
Invokament	Oral 2 tab/day	50 mg canagliflozin/500 mg metformin XR 50 mg canagliflozin/1000 mg metformin XR 150 mg canagliflozin/1000 mg metformin XR	150 mg canagliflozin/1000 mg metformin XR
Glyxambi	Oral 1 tab/day	10 mg empaglifozina/5 mg linagliptina 25 mg empaglifozina/5 mg linagliptina	25 mg empaglifozina/5 mg linagliptina
Segluromet	Oral 2 times/day	2,5 mg ertugliflozina/1000 mg metformina 2,5 mg de ertugliflozina/850 mg metformina 7,5 mg ertugliflozina/850 mg metformina 7,5 mg ertugliflozina/1000 mg metformina	2,5 mg ertugliflozina/1000 mg metformina
Steglujan	Oral 1 tab/day	5 mg ertugliflozin and 100 mg sitaglipti15 mg ertugliflozin and 100 mg sitagliptin	15 mg ertugliflozin and 100 mg sitagliptin

iSGLT2 may play an important role as an oral "antidiabetic" (ADO), this is because they have a similar effectiveness to sulfonylureas and achieve a decrease in HbA1c equivalent to metformin (0.8% to 1.0%), if we start from a value of 8% during two years of treatment.(14) Glycosuria caused by the administration of iSGLT2 induces a decrease in basal glycemia,

glycemia and HbA1c, and is shown to be at the same level as other OADs in the reduction of HbA1c, being higher -in some cases- in weight loss or blood pressure, with an incidence of hypoglycemia similar to that observed with placebo.(14)

All of which provides an element of tranquility for the patient and the doctor. iSGLT2 induce a decrease in albuminuria in patients with DM2 and -as already mentioned- weight loss secondary to the excretion of glucose (calories) in the urine, which is accompanied by a reduction in waist circumference and waist circumference, fat mass, especially visceral adipose tissue. (15) However, the pharmacodynamic response to SGLT2-i decreases in chronic kidney disease, which is related to the severity of renal failure. Hence, the recommendation to consult the prescribing information related to dose adjustments or restrictions in moderate to severe renal dysfunction, where its use is not recommended. (15)

Some results of interest related to the use of sodium-glucose cotransporter inhibitors in people with diabetes mellitus

The use of dapagliflozin has been studied in the specialized literature-the first of these drugs to be approved and marketed in 2012- in patients with DM. The results suggest that it is promising to add this medication to insulin treatment in order to improve glycemic control in these patients. (16) In a study with patients that had DM2 and treatment with dapagliflozin found that the use of this drug did not result in a higher or lower rate of cardiovascular death, myocardial infarction, or ischemic stroke than placebo. However, they did find a lower rate of cardiovascular death or hospitalization for heart failure.

Different results were found in literature, by specialists who observed that dapagliflozin was associated with lower risks of cardiovascular events and all-cause mortality, when compared with dipeptidyl peptidase-4 inhibitors, in a real-world clinical setting and a large population of DM2.

In a systematic review that included twelve randomized clinical trials, with a total of 3986 patients, groups of patients treated with dapagliflozin plus metformin were compared against placebo plus metformin, or dapagliflozin plus insulin versus placebo plus insulin, with follow-up ranging from 12 to 104 weeks. It was observed that the addition of dapagliflozin to conventional DM treatment optimized the control of HbA1c levels and glycemic levels compared to the control group; Furthermore, it was found that the group of patients with DM treated with dapagliflozin reduced body weight, a favorable condition for the metabolic control of these patients. (16)

A retrospective observational study, describe the results of treatment with different iSGLT2 in 2113 patients with DM2 (0.74% of all those treated with OAD); of which 53.10% were men. The average age was 64.54 years and the treatment for a period of more than six months, between 2022-2023. Their results suggest that an adequate prescription of iSGLT2 in patients with DM2 offers a short-term benefit in reducing the figures of Body Mass Index (BMI), HbA1c and cholesterol, without repercussions on blood pressure and renal function.

The CANVAS program integrated data from two trials with a total of 10,142 participants with DM2 and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a median of 188.2 weeks. It was shown that patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo, which supports its cardioprotective effect, but unfortunately a higher risk of amputation was found, mainly at the level of the toes or metatarsals. (15, 16)

It should be noted that the results of the CANVAS program are similar to those obtained in the EMPA-REG OUTCOME trial, (16) where empagliflozin reduced the risk of major cardiovascular events in patients with DM2 with this condition. Likewise, it is known that SGLT2-i also have a nephroprotective effect, (54,55) a criterion supported by other authors.

In another investigation (17) on the action of canagliflozin on the kidney in 1450 patients with DM2 on treatment with metformin who were randomized to receive daily canagliflozin 100 mg (483), canagliflozin 300 mg (485) or glimepiride (482) in increasing doses between 6-8 mg/day, it was observed how canagliflozin, compared to glimepiride, decreased the progression of kidney disease in patients with DM2 treated with metformin in the two years that the study lasted, and independently of the glycemic decrease, which would suggest a reindeer protective effect.

These effects are probably based on the favorable effects of SGLT2-i on glomerular hemodynamics, decreasing hyperfiltration, reducing glucose tubular toxicity, as well as its beneficial effects on blood glucose, blood pressure blood pressure, weight, and uricemia. As can be seen, one of the merits currently attributed to the use of SGLT2-i is cardiovascular and renal protection. (17) Some researchers (13,14) have proposed hypotheses that try to explain this behavior, based on the metabolic and hemodynamic effects caused by these medications and which are described below:

- Metabolic effects: includes the reduction of glucotoxicity induced by glycosuria, the reduction of fat mass (especially perivisceral), the hypouricemia effect due to uricosuria and the preferential use of fats instead of carbohydrates, which leads to to the increased production of ketoacids, which are a more efficient fuel for the ischemic heart and kidney.

- Hemodynamic effects: osmotic diuresis induced by glycosuria and natriuresis reduces preload (volemia) and afterload (blood pressure) and improves tubuloglomerular feedback and intraglomerular pressure, all without increasing sympathetic tone.

In addition, hemoconcentration increases hematocrit (although there also appears to be an increase in erythropoietin), which may facilitate oxygen delivery to ischemic tissues. Some researchers conducted a phase III, double-blind trial at 133 centers worldwide, randomly assigning 1402 patients with DM1 receiving treatment with any insulin therapy (pump or injections) to receive sotagliflozin (400 mg daily) or placebo for 24 weeks. It was observed that 28% of patients receiving the drug achieved the primary endpoint of maintaining HbA1c below 7%, without severe hypoglycemia or ketoacidosis compared to 15% of patients in the placebo group. In the sotagliflozin-treated group, HbA1c decreased by 0.46%, weight loss was 2.98 kg, blood pressure decreased among those with hypertension by 3.5 mm Hg, and the dose of daily insulin was significantly lowered.

The incidence of severe hypoglycemic episodes was significantly lower compared to the placebo group; instead, the cases of diabetic ketoacidosis were higher. Situation reported previously by the FDA and the EMA, with the use of other iSGLT2. (30, 58, 59) This situation agrees with a 17-year-old patient without ketosis for 9 years with DM1, who started treatment with dapagliflozin 10 mg/day and who unexpectedly had an event of this nature. Logically, the authors believe that this result is of particular concern, due to the use of SGLT2-i in people with DM1, and they support the criteria of Crasto, W. (13) who suggest that health professionals should carefully seek and evaluate the presence of ketoacidosis in these patients. Given this situation, iSGLT2 should be discontinued and appropriate measures taken to correct this health problem as soon as possible.

One of the elements of great interest pointed out by several publications is the beneficial effect exerted by iSGLT2 on weight loss, which had been outlined previously. Its use is postulated to be associated with a dose/response weight loss, mean loss of 2.1 kg compared to placebo after 12 weeks of use, and mean loss of 2.9 kg after two years, compared to other drugs. (17)

The ertugliflozin efficacy evaluation and cardiovascular safety outcomes trial (VERTIS-CV trial; NCT01986881) addressing cardiovascular health in people using this product could not be compared with the results of the research discussed above, as such investigation was ongoing at the time of writing this article.

The aforementioned means that SGLT2-i, at least in theory, can be considered candidates of interest, at least as an adjuvant, associated with metformin, for the treatment of insulin resistance syndrome by contributing to the improvement of its components, despite not to act directly on insulin resistance.

The most common side effects and adverse reactions observed during the use of sodium-glucose cotransporter inhibitors

SGLT2-i inhibitors represent a novel approach in the treatment of DM2. They can be used in combination therapy with other oral normal or hypoglycemic drugs or even with insulin and have potential application in patients who are intolerant to metformin due to gastrointestinal side effects. (17)

SGLT1 inhibition is associated with potentially serious adverse reactions. Although SGLT1 plays an insignificant role at the renal level, this transporter, located mainly in the small intestine, facilitates the absorption of glucose from food and its inhibition can lead to an increase in glucose in the intestinal lumen, with risk of appearance of osmotic diarrhea. (16,17)

The recently introduced iSGLT2 drugs in DM therapy are sufficiently selective over SGLT2 so that no effects are produced on intestinal SGLT1. The ability to inhibit renal SGLT2 without modifying intestinal SGLT1 is important for the practical use of these drugs. Likewise, an increase in glucose in the distal intestine could increase the secretion of glucagon-like peptide 1 (GLP1), (68) which is useful in subjects with DM2.

The most common side effects and adverse reactions observed in people using iSGLT are related to their mechanism of action (17) (Fig. 1).

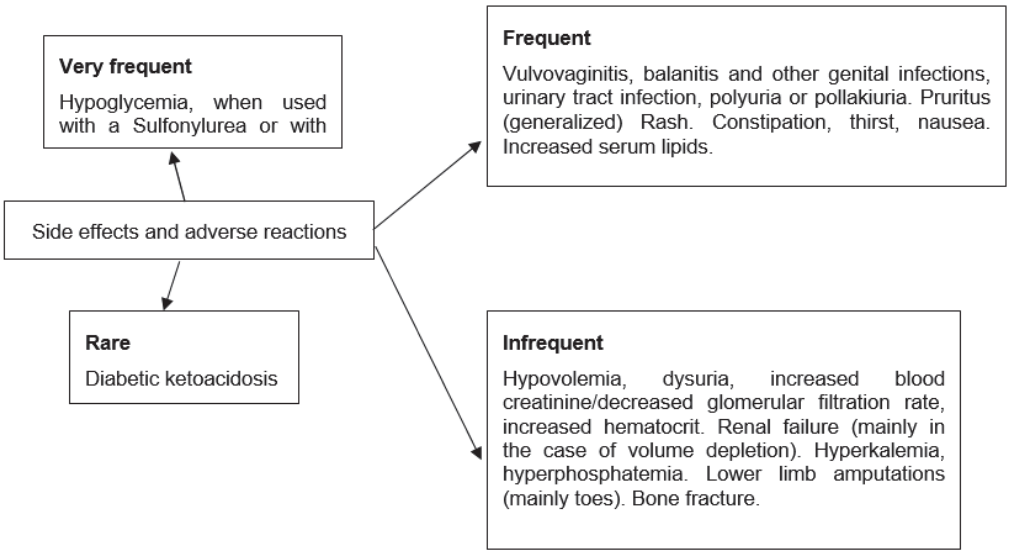

Figure 1. Side effects and adverse reactions that can occur during the use of iSGLT

In fact, Van Bommel (17) indicate that the most common side effects and adverse reactions observed at the population population using SGLT-2-i since their commercialization have been urogenital tract infections, ketoacidosis, and kidney damage. Urinary sepsis was mostly not serious, although ketoacidosis and kidney damage were, generating income and sometimes endangering the lives of patients. Bailey, C.J. (11) in an investigation carried out for this reason, describe adverse effects and secondary reactions to treatment with iSGLT2, although these were low in frequency (urinary tract infections (UTI): 5.31%; vaginal mycosis: 2.65%; hypoglycemia: 0.88%; diabetic ketoacidosis: 0.00%; intolerance to dapagliflozin: 4.42%).

Which, in part, coincides with the majority of adverse effects and side reactions reported by other authors. (12, 14)

Despite the benefits of iSGLT, reality requires careful prescription, consulting the warnings published by the health authorities and notifying any adverse reaction when suspected. In this way, Van Bommel it contributes to their better and more complete knowledge. (17)

DISCUSSIONS

The use of iSGLT-2 not only reduces the reinjection of glucose already filtered from urine into the blood, improving the metabolic control of DM, but also restores tubuloglomerular feedback by increasing glycosuria and distal urinary flow. But the most notable effect is due to the inhibition of glucose entry into the proximal tubular cell, since glycosuria is toxic to the kidney, particularly to cells capable of transporting glucose, that is, proximal cells endowed with SGLT2.

These effects of iSGLT2 in the human clinic have shown their ability to reduce kidney damage and cardiovascular risk in patients with DM2, (12) when they are indicated, taking into account the recommendations for their use. Inhibition of the SGLT2 cotransporter leads to a caloric deficit and a set of metabolic and endocrine adaptations such as: use of lipids as an energy substrate, increased ketogenesis, increased gluconeogenesis, and increased insulin sensitivity. iSGLT2 have been shown to reverse endothelial dysfunction, inflammation, oxidative stress, and interstitial fibrosis, which delays the progression of chronic DM complications and improves the cardiometabolic profile. (10) Likewise, the reduction in effective circulating volume and increase in the activity of circulating renin-angiotensin-aldosterone system blockers, thus creating a nephroprotective effect. (8)

Something especially useful about the use of SGLT-2-i and which has been indicated by several researchers (17) is that the weight loss achieved with its use is predominantly from adipose tissue and particularly from visceral adipose tissue, which represents an important aspect in the improvement of the cardio-metabolic profile of these patients.

Weight loss is mainly due to glycosuria, with an estimated caloric deficit of 50 kcal/day, despite the possible contribution of other mechanisms, such as brown adipose tissue activation and insulin reduction. In patients with DM1 and DM2 treated with insulin and iSGLT2, it is observed that the daily needs of insulin doses decrease and hypoglycemia is less frequent. However, these drugs must be prescribed cautiously, especially in young patients with DM1, due to the greater possibility of ketoacidosis and with a low body mass index, due to the weight loss that it can induce. (17)

CONCLUSIONS

In conclusion, note that the administration of iSGLT2 induces favorable changes in HbA1c, body weight and blood pressure; exhibiting a low risk of hypoglycemia. Although they constitute a pharmacological group that can be used as monotherapy, SGLT2-i are generally used as adjuvants in the treatment of patients with DM2 who receive pharmacological treatment with other normal or hypoglycemic drugs, in case they have not achieved control goals. You must be alert for the appearance of possible side effects and adverse reactions, in this case, discontinue the treatment and take the necessary measures to resolve this situation.

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