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Mini-Review

Pharmacological effect of sodium-glucose co-transporter 2 inhibitors in reducing the incidence of nephrolithiasis

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Abstract

Nephrolithiasis is one of the common diseases without effective treatment, the incidence of which has increased in the world in recent decades. Sodium-glucose co-transporter 2 inhibitor can reduce the probability of nephrolithiasis in diabetic and non-diabetic people.

Keywords: Nephrolithiasis, Renal stone, SGLT2 inhibitors, Sodium-glucose co-transporter 2 inhibitors, Type 2 diabetes

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Introduction

Nephrolithiasis is one of the most common diseases all over the world, and its prevalence in men and women is 10% and 6%, respectively (1) and its risk is said to be 18.8% for men and 9.4% for women in Western countries (2).

Nephrolithiasis can relapse frequently and cause excessive morbidity and reduced quality of life (3), thus it is one of the costliest urological problems in the world (1). As the stone in the ureter moves from the kidney to the bladder, it causes intermittent pain in the abdomen and flank, which is usually followed by nausea, vomiting, and weakness (4).

For the formation of nephrolithiasis, the concentration of a mineral must be higher than its solubility, which is called supersaturation. Most kidney stones are composed of calcium oxalate (CaOx). Supersaturation phenomenon for stone formation can include brushite (calcium phosphate) and uric acid as well (2).

Sodium-glucose cotransporter 2 (SGLT2) is a high-capacity, low-affinity glucose transporter (5) in the border membrane of proximal convoluted tubule cells that reabsorbs 90% of the filtered glucose in the glomerulus (2), and it is encoded by SLC5A2(1).

Sodium-glucose co-transporter 2 inhibitor (SGLT2I) belongs to a new class of oral drugs which decrease the blood sugar (2), and by blocking glucose reabsorption in the S1 and S2 sections of the proximal convoluted tubule in the kidney, cause significant glycosuria along with a decrease in blood glucose levels (1,2). This drug is an insulin-independent method to increase urinary glucose excretion and better performance in blood control in patients with type 2 diabetes (5).

In addition to controlling blood sugar, the SGLT2 inhibitors have various functions such as weight loss and improving visceral fat, lowering blood pressure and improving cardiovascular outcomes, increasing urine volume, reducing serum uric acid levels, and anti-inflammatory effects. These effects reduce the possibility of nephrolithiasis (1,2).

Among the preventive measures for the relapse of nephrolithiasis, we can mention lifestyle modification (4) and thiazide diuretics (3). Lifestyle modification (increasing fluid intake, high fiber and vegetable diet, limiting sodium intake, calcium intake within the body's required range) is recommended for patients with a low risk of stone relapse, and thiazide diuretics are recommended for patients with relapsing stones. There is not enough evidence for the effectiveness of lifestyle modification in the prevention of kidney stone relapse, (4) in recent studies it has been stated that the data related to the effectiveness of thiazide diuretics compared to placebo is limited as well (3). As a result, until now, there have been no effective preventive or therapeutic drugs for nephrolithiasis (1).

Method of search

Articles with the following 3 keywords; nephrolithiasis, renal stone, SGLT2 inhibitors were searched in Google Scholar and PubMed databases, and finally 10 articles were confirmed and reviewed for this study.

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Implication for health policy/practice/research/ medical education

Recent studies show that sodium-glucose co-transporter 2 inhibitors significantly reduce the incidence of nephrolithiasis. In addition to reducing the occurrence of nephrolithiasis, these drugs have cardiovascular, renal and liver protective effects.

Results

In this study, we decided to review studies related to the effect of SGLT2 inhibitors drugs in reducing the probability of nephrolithiasis.

It has been pointed out in various studies that SGLT2 inhibitor drugs reduce the incidence of nephrolithiasis through 4 main mechanisms, which will be discussed here:

By reducing and inhibiting inflammation

In a study with a large statistical population in Japan, the therapeutic effect of SGLT2 inhibitors on the prevalence of nephrolithiasis was investigated. Additionally, in this study, treatment with SGLT2 inhibitors was investigated on rats with CaOx stones, and the result apart from water consumption, affected urine volume, and oxalate excretion. On the other hand, a clinical trial research showed that SGLT2 inhibitor drugs have nothing to do with nephrolithiasis. Probably the reason for this conclusion was the limited study population (1,6).

Crystal deposition causes inflammation, fibrosis, and loss of kidney cells; therefore, inhibiting inflammation can be effective in the treatment of nephrolithiasis. One of the inflammatory factors involved in the formation of kidney stones is osteopontin, which is one of the most important crystal core proteins in the kidney stone matrix. Osteopontin is a pro-inflammatory cytokine associated with macrophages, and its amount was increasing due to tubular injury before SGLT2 inhibition.

Moreover, macrophages cause fibrosis in CaOx nephrocalcinosis. SGLT2 inhibitors also inhibit cytokine expression and macrophages. Suppression of osteopontin production in proximal convoluted tubule which is done by SGLT2 inhibitors may prevent nephrolithiasis (1).

By reducing blood uric acid

The effect of SGLT2 inhibitor drugs causes the reduction of serum uric acid through a mechanism that is not yet fully understood (5).

This drug may decrease the blood uric acid level and increase the urine uric acid level through the slc2a9 (glut9) transporter, which transports glucose and uric acid (due to the increase in urine glucose, since the exchange of these channels increases too). This condition may be the cause of uric acid stones, but it has not been proven yet; however, the reduction of serum uric acid due to the reduction of the formation of uric acid crystals can have a protective role on the kidney. Likewise, reducing uric acid in diabetic patients can be very useful because it has protective effects on the heart (5).

The phenomenon of supersaturation is necessary for the formation of kidney stones. A 24-hour urine is used to measure urine supersaturation. If the supersaturation is more than one, the crystal will form, and if it is less than one, the crystal will dissolve. In a study that examined the effects of treatment on kidney stones, it was found that the reduction of urine supersaturation is closely related to the reduction of kidney stone formation (2).

By reducing urine supersaturation

In a clinical trial study called SWEETSTONE, the effect of SGLT2 inhibitor drugs on kidney stone formation was investigated. The purpose of this study is to investigate the effect of empagliflozin on the prevention of nephrolithiasis in non-diabetic people, the largest group of society in terms of having nephrolithiasis. People were divided into three categories based on the type of stone:

1) Supersaturation of CaOx
2) Supersaturation of calcium phosphate (brachyte)
3) Supersaturation of uric acid

The results of this study have not yet been published (2).

Furthermore, SGLT2 inhibitor drugs increase urinary pH, and this increase in the urinary pH reduces the adhesion of CaOx crystals to the tubular surface (1).

In another study, healthy individuals without nephrolithiasis were examined after 4 weeks of treatment with empagliflozin by 24-hour urine collection. In these people, CaOx supersaturation did not change, nevertheless the proportion of mineral supersaturation decreased. This mechanism may reduce the formation of kidney stones due to the increase in urine citrate and decrease in urine pH. The investigations about the reducing effect of SGLT2 inhibitor drugs and the type of reduced stones are not enough. For example, it has been mentioned in this study that the increase in urine uric acid supersaturation after treatment with empagliflozin may cause the formation of uric acid stones (7).

By a diuretic effect

One of the effects of SGLT2 inhibitor drugs that prevents nephrolithiasis is the diuretic properties and the increase in the urine volume, which leads to the dilution of lithogenic substances in the urine, which has been stated in several studies (7).

SGLT2I drugs also have protective effects, and the use of these drugs goes beyond the control of type 2 diabetes and includes the treatment of heart failure, chronic kidney disease in diabetic and non-diabetic people (8), non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (9).

Hyperuricemia is known as the cause of metabolic syndrome, diabetes and high blood pressure; patients with type 2 diabetes and hyperuricemia are at high risk of cardiovascular incidents and mortality (10). By improving myocardial energy and decreasing aortic stiffness (1),

SGLT2 inhibitor reduces cardiovascular complications or mortality in high-risk patients (6).

Finally, we discuss the most important side effects of SGLT2 inhibitor drugs.

The following points are the known side effects of SGLT2 inhibitors:

1) Increased incidence of genital infections: the most common side effect of this drug is fungal infections of the genital tract (although rare) (2). Women with a risk of 10-15%, those with a history of genital fungal infection, and uncircumcised men are at the highest risk (8).
2) Euglycemic ketoacidosis: it is more common in people with type 1 diabetes than in patients with type 2 diabetes; however, it has not been seen in people without diabetes who are treated with SGLT2 inhibitors (2). Diabetic patients under SGLT2 inhibitor treatment who experience ketoacidosis (incidence 0.1%) refer with normal or relatively high blood glucose levels (8).
3) Lower extremity amputation at metatarsal toe level: this adverse effect has only been reported with canagliflozin (2). However, there is currently no evidence that treatment with SGLT2 inhibitors increases the risk of amputation (8).
4) Increased risk of bone fractures: this is present in patients treated with canagliflozin and dapagliflozin compared to placebo. In contrast, another study did not show an increase in the risk of bone fractures in type 2 diabetes patients with empagliflozin treatment (2).

Conclusion

Finally, studies show that SGLT2 inhibitors significantly reduce the incidence of nephrolithiasis. In addition to reducing the occurrence of nephrolithiasis, these drugs have cardiovascular, renal and liver protective effects. On the other hand, their side effects are fewer than other kidney stone prevention drugs such as thiazide diuretics (high doses of these drugs are recommended for kidney stone prevention, as the increased risk of side effects at this dose level is known). Therefore, SGLT2 inhibitor drugs are a turning point in the treatment and reduction of nephrolithiasis.

Authors' contribution

Conceptualization: AN, SE.
Validation: AN, SE.
Investigation: AN, SE.
Resources: AN, SE.
Data curation: AN, SE.
Writing–original draft preparation: AN, SE.
Writing–review and editing: AN, SE.
Visualization: AN, SE.
Supervision: AN, SE.
Project administration: AN.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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