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Editorial

SGLT2 INHIBITORS – IS THE PARADIGM IN TYPE 2 DIABETES MELLITUS MANAGEMENT CHANGING ?

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Background

It is already widely recognized that type 2 diabetes mellitus (T2DM) is a progressive chronic disease associated with a high risk of cardiovascular and renal morbidity and mortality. The global importance of the problem is multiplied by the enormous prevalence of T2DM (382 million people in 2013) and its rising incidence worldwide.

The existing oral anti-hyperglycemic therapies are generally limited due to the progressive nature of T2DM: they are losing efficacy over time as endogenous insulin secretion decreases. Another unsolved problem is the risk of adverse events associated with some oral therapies and insulin, mainly hypoglycemia and weight gain. Weight gain is a severe complication in T2DM patients (usually already obese), worsening insulin resistance and consequently increasing insulin dosage more and more.

Another unmet need in T2DM patients is the efficient control of hypertension, which is now considered the most important cardiovascular risk factor associated to hyperglycemia [1]. Under these circumstances, there is an increasing interest in new non-traditional therapies acting through insulin independent anti-hyperglycemic mechanisms with benefits beyond glycemic control (including weight control and anti-hypertensive effects).

Renal mechanisms in glucose metabolism

The kidneys have been thought for a long time to play only a minor role in glucose homeostasis. However, in the last years many papers brought convincing evidence regarding the key renal mechanisms involved in carbohydrates metabolism, both in healthy subjects and diabetics. Kidneys are responsible for about 25% of the total gluconeogenesis of the body in the post-absorptive state and also for the daily tubular reabsorption of approximate 180 g of glucose in normal healthy people (up to 250 g in T2DM patients). The reabsorption process, taking place in the proximal renal tubules is essential for the enhanced total glucose load of the body in T2DM (member in the famous pathogenic "ominous octet"). It became

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therefore a potential target for therapeutic intervention.

The tubular glucose reabsorption in healthy individuals is completely accomplished in the proximal tubules by the sodium/glucose co-transporters (SGLT) located in the brush border of the proximal tubular cells. Two different types of SGLTs have been described: type 1 (SGLT1) and type 2 (SGLT2). SGLT1, located in the third portion of the proximal tubule (S3), is a high affinity and low capacity transporter, responsible for about 10% of the total glucose reabsorption. SGLT1 is expressed in the kidneys as well as in the gastro-intestinal tract (where is reabsorbing glucose and galactose also), liver, lungs and Langerhans islets. SGLT2, located in the first convoluted part of the proximal tubule (S1), is a high capacity and low affinity transporter and achieves the reabsorption of the rest of 90% of filtered glucose.

The glomerular filtered glucose is completely reabsorbed until the maximum transport capacity (Tmax, the "renal threshold") is reached, corresponding to a blood glucose of about 180-200 mg/dl (11 mmol/L). Above this glycemic values, glucose appears in the urine (glycosuria). In T2DM, SGLT2 expression is up-regulated, so the renal threshold for glucose reabsorption becomes substantially higher and a greater amount of glucose is reabsorbed. Accordingly, hyperglycemia in diabetes mellitus (DM) is partially supported by the increased activity of renal SGLT2.

SGLT2 inhibition – an emerging new anti-hyperglycemic mechanism

The inhibition of SGLT2 leads to an increase of urinary glucose excretion (glycosuria), becoming a new mechanism to decrease elevated blood glucose levels in T2DM patients. Because SGLT2 are expressed only in the renal tubes, their selective inhibition is limited to glucose, sodium and water loss, without added digestive effects [1]. The lack of any other symptoms associated to long - term glycosuria was proven by a genetic disorder of SGLT2 named familial renal glycosuria. The members of affected families did not report an increased incidence of DM, kidney disease or urinary tract infections.

From the SGLT inhibitors class of drugs dapagliflozin and canagliflozin have been already approved for clinical use in the EU and USA. Recently, dapagliflozin has been also included in the list of DM therapeutics fully supported by the government in Romania.

SGLT2 inhibitors are lowering the total body glucose load and glycemia by inducing renal glycosuria. Their efficacy is dependent on the glomerular filtration rate and the glucose load filtered. In addition to reducing blood glucose levels, the SGLT2 inhibition is associated with a constant caloric elimination (as glucose *per se*), leading to weight loss. The consequent increased water and sodium excretion also results in a moderate blood pressure lowering effect which might be important in T2DM patients.

Glycemic efficacy of SGLT2 inhibitors

SGLT2 inhibitors (dapagliglozin and canagliflozin) demonstrated their efficacy across a wide range of T2DM patient populations: newly diagnosed, patients within the first five years of DM evolution or patients with poor glycemic control on different oral therapies or insulin regimens. In a recent study, a head-to-head comparison of dapagliflozin and glipizide was made in T2DM patients inadequately controlled on metformin [2]. HbA1c reduction was similar at 52 weeks in both groups (0.52 versus 0.52 %). This reduction was sustained for up to 4 years [3], suggesting that dapagliflozin might be used for the long term therapy of T2DM.

Another head-to-head comparison study has been made between canagliflozin and glimepiride in T2DM patients on metformin [4]. This study showed the non-inferiority of the two canagliflozin doses (100 mg and 300 mg) to glimepiride at 52 weeks (HbA1c decrease of 0.82 and 0.93 for the two canagliflozin doses versus 0.81 % for glimepiride). These results were also maintained for two years during the follow up period.

SGLT2 inhibitors and weight loss

In the Nauck et al. study [2], dapagliflozin led to an average weight loss of 3.2 kg at 52 weeks versus a weight gain of 1.4 kg in patients on glipizide ($p < 0.001$). Moreover, dapagliflozin therapy maintained the weight loss for at least 4 years [3]. Another study [5] compared weight changes in dapagliflozin treated patients versus placebo, both added in T2DM patients inadequately controlled on glimepiride. The results have shown a weight loss of 2.9 kg for dapagliflozin versus a weight gain of 0.4 kg for placebo at 24 weeks ($p<0.001$).

Significant reductions in body weight have been also noted in canagliflozin studies. Thus, in the CANTATA-SU Study [6] both canagliflozin doses of 100 mg/day and 300 mg/day produced clinically significant weight losses at 52 weeks (3.7 and 4.0 kg, respectively) when added in T2DM patients inadequately controlled on metformin, compared with an average weight gain of 0.7 kg in patients with glimepiride addition ($p<0.001$). These reductions were also sustained for 104 weeks [4].

SGLT2 inhibitors and blood pressure control

A clinically significant reduction in systolic blood pressure was observed in T2DM patients treated with both dapagliflozin and canagliflozin. These reductions ranged between 3.5 and 6.9 mm Hg [2,4] and were maintained at 52 weeks. They were rarely associated with orthostatic hypotension.

The blood pressure reductions are probably related to water and sodium loss through osmotic diuresis. The risk of hypotension episodes is real, mainly in patients at risk: elderly or treated with loop diuretics. However, the orthostatic hypotension frequency was similar in SGLT2 versus placebo (or other comparators) treated patients.

Adverse effects of SGLT2 inhibitors

Hypoglycemic episodes were rare and usually classified as minor in the dapagliflozin studies in which dapagliflozin was added to metformin [2], glimepiride [5] or even to insulin [7]. In the head-to-head comparison study versus glipizide [2], the dapagliflozin treated patients reported about 10 fold fewer hypoglycemic episodes compared to glipizide treated patients (5.4 % versus 51.5 %) during the 4 years follow up period [3].

The number of patients reporting severe hypoglycemic episodes was also low in studies with canagliflozin added to sulphonylureas or insulin therapy and no hypoglycemia was detected when canagliflozin was added in patients inadequately controlled on metformin monotherapy. The head-to-head comparison of canagliflozin and glimepiride [4,6] has shown a significantly lower incidence of hypoglycemic episodes in patients on canagliflozin (4.9 % on 100mg/day and 5.6 % on 300 mg/day) versus 34.2 % in patients on glimepiride.

Infections affect mainly the genital tract, are generally mild to moderate, mostly with different types of *Candida*, and observed more frequently in women than men. In patients on dapagliflozin 10mg/day, events suggesting genital infections occurred with a significantly higher incidence (6.6 – 12.9 %), compared to placebo (7.0-7.5 %) at 24 and 48 weeks [2,3].

The infections were reported in the first 24 weeks (88 %) of treatment and only few recurrences appeared. Standard antimicrobial and antifungal therapies were efficient and rarely lead to discontinuation of dapagliflozin. In the head-to-head comparison study with dapagliflozin or glipizide added to metformin, genital infections frequency was 12.3 % with dapagliflozin versus 2.7 % with glipizide after one year and 16.3 % versus 4.2 % at the end of the fourth year [2,3].

Urinary tract infections (UTIs) prevalence was also higher in dapagliflozin treated patients (5.3 – 10.8 %) versus placebo (4.0 – 8.0 %) at 52 weeks in most studies [2,8,9]. However, the reported UTIs were responsive to standard antimicrobial therapies and no discontinuations have been noted.

Canagliflozin treated patients registered also a significantly higher prevalence of genital and urinary tract infections for both doses (10.8 % and 11.1 % respectively, versus 3.2% in the placebo group) at 52 weeks [4,6]. As in dapagliflozin treated patients, the infectious episodes related to canagliflozin were generally mild to moderate in severity, treated with standard therapies and only rarely lead to discontinuation of canagliflozin therapy.

SGLT2 inhibitors in special populations

Impaired renal function. Dapagliflozin is not recommended in patients with eGFR persistently reduced below 60 ml/min, because of lack of efficiency, but no dosage adjustment is necessary above this limit. Renal safety data on dapagliflozin therapy in patients with mild to moderate renal impairment [10] have shown no significantly different number of kidney related adverse events compared to placebo at 102 weeks (1.9 % versus 1.7 %) as well as volume depletion episodes (1.5 % versus 0.9 %).

In the only study with dapagliflozin versus placebo performed in T2DM patients with stage 3 chronic kidney disease [11], significant weight loss and blood pressure reductions have been noted in the dapagliflozin group, but no improvement in the glycemic control was observed. The eGFR and serum creatinine remained stable for 102 weeks of the follow up period.

Canagliflozin use is not recommended in T2DM patients at eGFR lower than 45 ml/min. The maximum recommended dose for patients with eGFR between 45 and 60 ml/min is 100 mg/day and no dose adjustment is needed for eGFR values above 60 ml/min. Low incidence of kidney-related adverse events (less than 1.7 % in the canagliflozin group versus 0.7 % in the placebo group) was noticed in the pooled safety data at 26 weeks. These led to a low rate of discontinuation, higher in the canagliflozin group compared to the placebo group (0.8% versus 0.2%).

Elderly people. In a pooled analysis of data regarding dapagliflozin safety, the global incidence of adverse effects in patients aged over 65 years was similar to that in the general population [12]. However, because elderly people are more prone to have baseline low eGFR, the most prominent reported adverse effect was volume depletion and some increase in the serum creatinine, transient and reversible. Hence, it is recommended to take into account the risk of volume depletion and acute kidney injury when prescribing dapagliflozin in elderly patients and initiation of such therapy is not recommended after the age of 75 years.

The same precautions are also valid for canagliflozin therapy. Thus, 100 mg/day is the maximum recommended dosage in elderly and assessement of kidney function is an important criterion before starting treatment in these patients.

REFERENCES

1. **Moses RG, Colagiuri S, Pollock C.** SGLT2 inhibitors: New medicines for addressing unmet needs in type 2 diabetes. *Australas Med J* 7: 405-415, 2014.

2. **Nauck MA, Del Prato S, Meier JJ et al.** Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized 52 weeks, double-blind active-controlled non-inferiority trial. *Diabetes Care* 34: 2015-2022, 2011.

3. **Del Prato S, Nauck MA, Duran-Garcia S et al**. Durability of dapagliflozin vs glipizide as add-on therapy in T2DM inadequately controlled on metformin: 4 year data. *Diabetes* 62[Suppl. 1] - 73rd ADA Scientific Sessions 2013, Chicago, poster #62-LB, 2013

4. **Cefalu WT, Leiter LA, Yoon KH et al.** Canagliflozin demonstrates durable glycemic improvements over 104 weeks versus glimepiride in subjects with type 2 diabetes mellitus on metformin. *Diabetes* 62[Suppl. 1] - 73rd ADA Scientific Sessions 2013, Chicago, poster #65-LB, 2013

5. **Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S.** Effect of dapagliflozin in patients with type 2 diabetes mellitus who have inadequate glycemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diab Obes Metab* 13: 928-938, 2011.

6. **Cefalu WT, Leiter LA, Yoon KH et al.** Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomized double-blind, phase 3 non-inferiority trial. *Lancet* 382: 941-950, 2013.

7. **Wilding JP, Woo V, Rohwedder K et al.** Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. *Diab Obes Metab*, 16: 124-136, 2014.

8. **Wilding JP, Woo V, Soler NG et al.** Long term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med* 156: 405-415, 2012.

9. **Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF.** Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled, 102-week trial. *BMC Med* 11: 43, 2013.

10. **Ptaszynska A, Chalamandris AG, Sugg J et al.** Effect of dapagliflozin on renal function. *Diabetes* 61[Suppl. 1] - 72nd ADA Scientific Sessions, Philadelphia, 2012, Oral presentation

11. **Kohan DE, Fioretto P, Tang W, List JF.** Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int* 85: 962-971, 2014.

12. **Ptaszynska A, Johnsson K, Parikh S, de Bruin TW, Apanovitch AM, List JF.** Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. *Drug Saf* 37: 815-829, 2014.