

Chances and risks of SGLT2 inhibitors

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Type II diabetes mellitus (T2DM) is characterised by relative insulin deficiency caused by resistance of important target organs like liver and skeletal muscle towards insulin. During the course of the disease, pancreatic insulin production becomes decreased, and absolute insulin deficiency results (Kahn 2003). Based on these pathophysiological considerations, correcting the insulin resistance and substituting insulin is the current mainstay of diabetes therapy. To achieve the former goal, metformin (Bailey and Turner 1996) and pioglitazone (Nesto et al. 2003; Yki-Jarvinen 2004) are available. Insulin can be substituted either directly by (in most cases SC) injection or by indirect means to elicit liberation from stores in the pancreas. This is achieved for example by sulfonylureas (Groop 1992) or incretin mimetics (glucagon-like peptide (GLP)-1 analogues and DPP4 inhibitors, Amori et al. 2007; Drucker 2007). The aim of diabetes therapy is to maintain blood glucose level in a narrow range close to the physiological level. Indeed, the results of large clinical trials suggest that good glycemic control (often estimated by the fraction of pathologically glycosylated haemoglobin, HbA1c, in the blood) is the most important parameter in order to avoid the known long-term complications of diabetes (Diabetes Control Complications Research Group 1993; Holman et al. 2008). Thus, the increased blood glucose level itself appears to be responsible for the development of retino-, nephro- and neuropathy, to

name only a few. Other mechanisms such as increased insulin levels or insulin resistance may consequently play a minor role for the development of complications.

Based on these considerations, an unusual therapeutic approach appears logical: just removing glucose from blood by any means, regardless of T2DM aetiology and pathophysiology. Since pharmacologist and clinicians usually try to treat a disease by correcting the underlying defect as far as possible, such a merely “symptomatic” approach appears somewhat provocative. Nevertheless, exactly this direct way to simply remove glucose from the blood stream became now feasible and can be further investigated and exploited. With the development of a substance class called SGLT2 inhibitors, glucose levels can be lowered by just excreting this carbon hydrate molecule via the kidneys (for review, see Bailey 2011; Basile 2011; Chao and Henry 2010; Hardman et al. 2010; Ho et al. 2011; Pfister et al. 2011). SGLT stands for sodium–glucose co-transporter, and type 2 is virtually selectively expressed in the kidney. Its normal function is to reabsorb glucose from the glomerular ultrafiltrate to avoid loss of this—in former time valuable—energy carrier. Today, where obesity is increasingly widespread, the need to save energy carriers is no longer so urgent. Type 1 of the co-transporter, SGLT1, is expressed in many organs. It is for example responsible in the gut for glucose absorption from food.

Thus, the question remains whether this apparently straightforward way of diabetes therapy by directly lowering blood glucose without affecting insulin level or function will work. Many pharmacologists and clinicians may ask whether this concept may not be too simple. The work of Tahara et al. (2011) presents original data on the pharmacodynamic effects of a new representative of the SGLT2 inhibitor class, ipragliflozin, which highlights the perspectives and potentials but also potential drawbacks of SGLT2 inhibition. These pharmacodynamic data, along with

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theoretical considerations based on known physiological mechanisms, can help in identifying potential risks of this approach. The desired effects and expectations of SGLT2 inhibitors were already widely discussed in numerous reviews (see above) so that this editorial shall focus on potential and identified drawbacks. There are four phase III clinical trials on dapagliflozin (Bailey et al. 2010; Ferrannini et al. 2010; Nauck et al. 2011; Strojek et al. 2011), which allow an at least preliminary assessment of safety aspects of this first representative of therapeutically used SGLT2 inhibitors. In these trials efficacy and safety were tested of either dapagliflozin alone or as add-on to a baseline therapy with metformin or glimepiride. Either placebo or glipizide, a sulfonylurea, served as comparator. A systematic review and meta-analysis of all published clinical trials with SGLT2 inhibitors was performed by Musso et al. (2011). Information on adverse effects and other safety aspects of dapagliflozin was derived from these publications. This will be brought in line with physiological and pharmacodynamical considerations in the following to obtain a first impression what the risks and benefits of SGLT2 inhibitors for long-term therapy of T2DM could be.

The most prominent and most obvious consequence of SGLT2 inhibition is glucosuria. This may favour urinary tract infections (UTIs) since the urinary glucose may serve as a nutrient for microorganism and hence favour their proliferation. In fact, an increased incidence of signs of cystitis was observed in some of the clinical trials cited above in the patient group receiving dapagliflozin. Due to the probable physiological link one can assume that increased incidence of cystitis is a class effect of SGLT2 inhibitors. More severe UTIs like pyelonephritis were not reported to date to occur more frequent with dapagliflozin therapy. Notably, a more pronounced difference between SGLT2 and comparator treatment than in the incidence of UTIs was observed in the incidence of genital infections. It is likely that this effect is also related to glucosuria. Alternatively one could assume that the genital infection might be a sign of immunosuppression by SGLT2 inhibitors, but to date there are no hints in this direction. The events of UTIs and genital infection appear manageable, but it appears advisable to keep these adverse effects in mind to allow early intervention.

Beyond local infection glucosuria has further, in part, more indirect effects. Excreted glucose acts as an osmotic diuretic in the kidney. Hence, the urine volume is increased, and there is water loss. In consequence, the patient's fluid intake has to increase. Therefore, inadequate fluid intake, in particular by elderly patients, could cause problems of dehydration. Notably, increase in serum sodium (hypernatremia) as a sequel of dehydration was not observed, at least in animal models as reported by Tahara et al. (2011). This could be due to the fact that SGLT2 is a co-transporter

for sodium and glucose so that sodium is also excreted, along with water, upon blockade of this carrier. Since it is known that hypernatremia is an important factor for stimulating thirst (Adeleye et al. 2002), it is conceivable that water loss induced by SGLT2 inhibitors is less well corrected than if caused, e.g. by diuretics. Hence the risk of dehydration may be higher.

The signs and symptoms of dehydration are well established. Most important are mental disturbance and arterial hypotension with the risk of syncope. Small increases in hematocrit were observed in clinical trials which most likely reflect a slight hemoconcentration. The question remains whether relevant hemoconcentration may occur in the long term which in turn could increase the risk of venous or arterial thrombosis. Cardiovascular (CV) events are difficult to assess in (healthy) experimental animals. Accordingly, common clinical trials are usually also too small and of too short duration to yield reliable information on the risk of CV events. Nevertheless, prolonged CV outcome studies in a population at increased risk are nowadays increasingly performed with new antidiabetics. Therefore, such studies may help to decide whether or not SGLT2 inhibitors might contribute to the risk of thrombosis.

Loss of water also leads to loss of body weight. Body weight reductions were indeed observed in clinical trials with dapagliflozin, the first representative of the SGLT2 inhibitor family. Usually weight reduction is desirable in T2DM patients since fat mass contributes to insulin resistance. This however implies that the body weight reduction must be due to fat loss and not due to water loss to be advantageous for the patient. Unfortunately no discrimination was made between body fat and water content in the published clinical trials. Therefore it is not known whether SGLT2 inhibitors lead to a net loss of water (i.e. the increased water excretion exceeds the increased water intake by drinking) or whether the water balance is maintained and the weight loss is due to fat loss. The fat loss could result from the caloric loss which results from the excretion of glucose. Thus, if this caloric loss is incompletely compensated by increased food intake, body fat loss could result. If there were indeed fat loss, this would be a relevant benefit for diabetes therapy.

The kidney is the main target organ for SGLT2 inhibitors and is primarily affected by this substance class. On the other hand, the disease to be treated by SGLT2 inhibitors, T2DM, may itself damage the kidney (Salvatore et al. 2011). This becomes obvious by a decreasing glomerular filtration rate (GFR) over time if diabetes is badly controlled. Thus, is there any hint that SGLT2 inhibitors could worsen diabetic nephropathy? No reports were published that would give a hint for adverse effects of SGLT2 inhibitors on the kidney. But what is more important is the fact that the efficacy of SGLT2 inhibitors depends on GFR.

Glucose in the blood is filtered through the glomeruli, reaches the renal tubules and is reabsorbed from there by SGLT2. Thus, SGLT2 inhibitors cannot increase glucose excretion unless glucose has previously passed the glomerulus. In consequence, a low GFR diminishes the rate of glucose excretion and hence the blood glucose-lowering effects of SGLT2 inhibitors. Therefore, SGLT2 inhibitors are most likely not suited for patients with higher degrees of renal damage.

Of course, SGLT2 inhibitors not only have drawbacks but also clear benefits. Probably the most important advantage of this new substance class is the fact that the blood glucose level hardly decreases below the physiological range. This is very favourable because it allows a tight control of the blood glucose level and thereby helps to prevent late complications of diabetes. Classical antidiabetic agents like insulin and sulfonylureas dose dependently lower the blood glucose level to any value; their action does not cease when the physiological level is reached. Hence, these agents cause severe and life-threatening hypoglycemia if not dosed very carefully. By the way round, to prevent hypoglycemia as far as possible, the target blood glucose level of the therapy with these agents is often chosen considerably above the physiological range so that fluctuations in the blood glucose level do not reach hypoglycemic values (Cryer 2008). This in turn however favours late complications. Thus, agents that do not lower blood glucose beyond physiological levels are highly desired. There are already substance classes available with this property (e.g. biguanides and thiazolidinediones; for review of their desired and undesired effects, see for example Bailey and Turner 1996; Nesto et al. 2003; Yki-Jarvinen 2004). But the glucose-lowering effect of each individual compound is usually rather small so that antidiabetics of different classes are often combined. Each class of antidiabetics has its own side effects and drawbacks; some classes, e.g. the GLP-1 analogues or the DPP4 inhibitors (DPP4—dipeptidylpeptidase 4) are rather new (for review, see for example Amori et al. 2007; Drucker 2007) so that their place in diabetes therapy cannot yet be fully determined. SGLT2 inhibitors provide a new option and may help to increasingly improve blood glucose control together with existing antidiabetics. Thus SGLT2 inhibitors appear useful unless severe side effects become obvious during ongoing trials.

One potential side effect of SGLT2 inhibitors which could prevent their use is currently discussed. It was observed that in clinical trials with dapagliflozin, the incidence of bladder cancers was higher in the pooled dapagliflozin arms than in the pooled placebo arms of all larger trials (Jones 2011). There was an incidence of 0.16% in the dapagliflozin-treated patients versus an incidence of 0.03% with placebo. The total study population encompassed around 8,600. No such large data set is yet available for

other SGLT2 inhibitors. Nevertheless, the difference in bladder cancer incidence was not statistically significant because of the low absolute tumour count. So the question is whether the effect is true or just a chance finding. A reasonable explanation could be a detection bias. As mentioned above, SGLT2 inhibition appears to cause an increased incidence of cystitis. Hence, patients receiving an SGLT2 inhibitor are expected to consult a urologist more often than patients receiving placebo. This could result in a more frequent diagnosis of asymptomatic, pre-existing bladder tumours. It was also stated that the tumours were so large at the time of diagnosis so that it is unlikely that these tumours arose during the trial. This again argues for the assumption that the tumours were pre-existing and not caused by dapagliflozin.

Nevertheless, should SGLT2 inhibition indeed indirectly be linked to the induction of bladder tumours or cause accelerated proliferation of pre-existing cancer, then results from ongoing clinical trials on various SGLT2 inhibitors under development may settle the case. Currently at least ten different SGLT2 inhibitors are being developed so that the expected amount of data will allow firmer conclusions (Chao and Henry 2010; Jones 2011).

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