

Looking into the future of diabetes care with the sodium glucose co-transporter-2 inhibitors

Editorial

The most exciting development in diabetes care in the last few years (My Opinion) has been the addition of the sodium glucose co-transport-2 inhibitors (SGLT-2) to the diabetes treatment regimen. I have just returned from the American Association of Clinical Endocrinologists (AACE) Annual Meeting where the SGLT-2 inhibitors were creating quite a buzz. Briefly, in the United States there are three available for use alone or in combination with metformin or linagliptin: canagliflozin, dapagliflozin or empagliflozin. All are indicated as an adjunct to the treatment of Type 2 diabetes when life style modification is not effective. All possess good glucose lowering capacity and may be associated with slight blood pressure reduction, weight reduction, and a decrease in GFR. They are not recommended for use with renal impairment, gfr's less than 45-60 (depending on the agent).¹

The initial fear was that worsening of renal function would occur. Current findings suggest that fear is not true and perhaps these agents may be protective of renal function. Recent evidence suggests that the SGLT-2 inhibitors may reduce microalbuminuria.² There can be correction of diabetes induced renal hyperperfusion and hyperfiltration.³ There is reduced proximal sodium absorption leading to an increase in distal delivery of sodium to the macula densa with a subsequent reduction in intra glomerular pressure with decreased RAAS activation.^{3,4}

Lowering of plasma uric acid levels is also seen.⁵ This is felt to also be involved in a potential renal protective effect.⁶ I heard several people mentioning that they felt this may ultimately provide a cardio protective effect since uric acid elevation is thought to be a cardiovascular risk factor. It may also be helpful in preventing the occurrence of renal stones, since elevated uric acid may play a role there.⁷ Tubular hypertrophy with resultant renal hypertrophy may be inhibited by SGLT-2's.^{2,8}

The weight loss seen with the SGLT-2 inhibitors has been associated with a loss in visceral adiposity. Visceral adiposity has emerged as a major risk factor for the development of cardiovascular disease.⁹ No study to date has indicated that the SGLT-2 inhibitors provide a direct reduction in cardiovascular risk, and several studies are underway looking to see if there is any increase in cardiovascular risk with these agents. It has been proposed that beneficial effects of SGLT-2 inhibitors can occur through improving arterial stiffness and oxidative stress. With the LDL increase seen being offset by HDL increase and other factors.¹⁰ In animal studies SGLT-2 Inhibitors have been shown to improve hyperlipidemia, hepatic steatosis, reducing plasma and hepatic levels of oxidative stress biomarkers and inflammatory markers(interleukin 6, tumor necrosis factor alpha, monocyte chemoattractant protein-1, and C-reactive protein) With the improvement in glucose control, improvement in beta-cell function and insulin resistance has been noted.¹¹

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Clinical labeling has indicating that Mild reductions in blood pressure and weight may occur with a hemoglobin A1C lowering around 1 %¹ In the "real world" reductions in blood pressure seen may require reduction in antihypertensive medication dosage and reduction in insulin doses or with insulin secretagogues.¹² Weight reduction and the improvement in hyperglycemia may also play a role here.

Several safety concerns are also present. The product labelling warns of the possibility of increased urinary infections and genital mycotic infections. In my clinical trial experience with these agents, no patients withdrew from the trials due to these problems.¹³ Although a few mycotic infections occurred, they were typically self-treated by the patients. A more serious concern is the recent warning by the United States Food and Drug Administration of the occurrence of 20 cases of diabetic ketoacidosis reported in patients treated with the SGLT-2 Inhibitors. All the drugs seem to be involved along with patients with both Type 1 and 2 diabetes.¹⁴ The cause of this has not been identified yet. It has been shown that SGLT-2 use is associated with an increase in glucagon levels and whether this may be the mechanism or part of the mechanism is unknown at this time.¹⁵ Another concern is whether there is an increase in fractures with SGLT-2 inhibitor use. A recent report suggests an increased frequency of fractures with the risk increasing over time.¹⁶

Thus it will be quite interesting to see how treatment with the group progresses over time and whether this is the diabetes treatment that provides the elusive cardiovascular protection.

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Conflicts of interest

The author declares there is no conflict of interest.

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