

SGLT2 inhibitors: far too many cautions and alerts and limited efficacy

Abstract

SGLT2 inhibitors are very modest in their efficacy in terms of lowering glycemia while incurring undue cost burden to the patients, thus with very low cost efficacy. Moreover, the mechanism of action is extremely detrimental to quality of life attributed to polyuria, nocturia and consequential dehydration resulting in orthostatic hypotension as well as serious adverse outcomes secondary to increased serum viscosity. Alternatively, electrolyte imbalances including hypernatremia, hyperkalemia, hypercalcemia, hyper or hypophosphatemia, anion gap acidosis induced by ketonemia and/ketonuria with or without hyperglycemia as well as accumulation of other unmeasured anions, and the declining renal function as evident by rises in serum creatinine and urea nitrogen concentrations may contribute to increased morbidity requiring additional resources to cover escalating costs as well as a further decline in quality of life. Finally, the rise in LDL cholesterol may be a contributor to increased serum viscosity and both may have been responsible for increased incidence of strokes and lower limb amputations. Therefore, well established greater risks of occurrence of several serious adverse outcomes such as recurrent genitourinary infections including acute pyelonephritis and sepsis, ketoacidosis, strokes, lower limb amputations, osteoporosis and fractures, acute pancreatitis as well as other anticipated outcomes, e.g. renal calculi, nephrocalcinosis, uric acid nephropathy due to hypercalciuria and uricosuria are likely to further increase the costs and compromise the quality of life. Moreover, these findings may have prompted the FDA and European regulatory agency to issue far too many cautions and alerts. I believe that the regulatory agencies should rather terminate the approvals for these drugs instead, in the light of the serious nature of these outcomes, the hanging question of bladder cancer and the lack of knowledge of the effects of long term exposure of genitourinary tracts to hyperglycemic hyperosmolar urine with very limited cost efficacy and a marked decline in quality of life.

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Introduction

The major objective of management of any disorder must always be focused on improving the quality of life using cost effective therapy. The management of type 2 Diabetes deserves implementation of these same tenets as per the Hippocratic oath. This principle was evident all throughout my medical training, as a student, a resident in internal medicine and then as fellow in endocrinology as I was instructed and advised by my preceptors and my colleagues to induce remission of glycosuria to avoid loss of fluid and various electrolytes. This intervention distinctly relieved symptoms, e.g. polyuria, polydypsia, nocturia, and prevented onset of several clinical manifestations of consequential dehydration as well as electrolyte depletion, e.g. dizziness, fatigue, muscle cramps, lethargy as well as disturbances in cardiac conduction defects and arrhythmias, respiratory depression etc. Moreover, reversal of glycosuria induced remission of genitourinary infections and prevented recurrences. Therefore, the quality of life is promptly improved by providing the relief of the aforementioned clinical manifestations on reversal or prevention of glycosuria.

The proponents of using SGLT2 inhibitors promote the “beneficial” effects of weight loss, lowering of blood pressure and a decline in HbA1c. Firstly, these effects are exaggerated when compared to placebo rather than with the baseline values.¹⁻⁸ Moreover, both the weight loss and lowering of blood pressure are well established consequences of dehydration as documented by rises in both serum creatinine and urea nitrogen concentrations and therefore may not be necessarily healthy. Dehydration is certainly induced by polyuria

or “pollakiuria” caused by glycosuria and is further exacerbated by genitourinary tract infections. The clinical trials using these drugs report serum concentrations of electrolytes. However, none of these trials describe estimates of total body depletion of fluids and electrolytes despite documentation of rises in both serum creatinine and urea nitrogen concentrations, diagnostic of presence of dehydration. Nevertheless, hyperkalemia is documented to ensue in several subjects with renal dysfunction as well in subjects with normal renal function receiving concurrent therapy with drugs inhibiting renin-angiotensin-aldosterone system.¹⁻⁸ And al be it, these are the most frequently recommended drugs deemed to be most effective for treatment of hypertension and for preservation of renal function in subjects with type 2 diabetes. Moreover, “pollakiuria” or polyuria as well as urinary hesitancy and precipitancy are already frequently present in elderly men secondary to prostatism. Similarly, urinary incontinence is a frequent debilitating manifestation in several post menopausal women. Unfortunately, these are the populations most predisposed to occurrence of type 2 diabetes.⁹ Thus, administration of these drugs is likely to exacerbate these symptoms by induction of glycosuria and further compromise the quality of life in these subjects.

Fortunately, a caution was issued recommending close monitoring for occurrence of hypotension and “orthostasis” in the elderly as a result of dehydration as well as increased prevalence of genitourinary infections in all comers.^{1-8,10-19} However, the data regarding negative impact of polyuria and/or “pollakiuria” on “quality of life”, e.g. recurrent visits to toilets with urgency and precipitancy during wakefulness and even incontinence during sleep resulting in

sleeplessness and its consequences although well known in clinical practice, are not well examined in the clinical trials using these drugs.^{1-8,10-19} Moreover, the long term consequences of persistent exposure of urinary tract including urinary bladder to hyperglycemic hypertonic urine are unknown although increased risk of bladder cancer has been reported.^{19,20} I believe that constant presence of sugar, the most efficient fuel for cell growth may have promoted growth of bladder cancer in situ and rendered it to be manifested rather than initiating the onset.

Several other undesirable adverse effects of SGLT2 inhibitors have prompted FDA and EMU to issue many further cautions and alerts. Alterations in several serum chemistry parameters are now reported in addition to elevations in serum urea nitrogen, creatinine and potassium documented in initial reports.^{1-8,11-14} These include severe hypercalcemia, hypophosphatemia with nonketotic anion gap acidosis (Fanconi Syndrome), hypernatremia, low serum uric acid concentration and Ketoacidosis.²⁰⁻²⁸ Severe hypercalcemia and hypernatremia may be attributed to dehydration and increase in uric acid excretion may be responsible for hypouricemia. Hypophosphatemia was secondary to phosphaturia and anion gap acidosis may be attributed to amino aciduria both being the characteristic manifestations of Fanconi Syndrome, a renal tubular defect which also caused proteinuria in this patient within a week of administration of Canagliflozin.²³ Finally, I recently encountered a subject with type 2 diabetes referred for 15kg weight loss, gradually progressive generalized muscle weakness and wasting over 3months following initiation and continuation of Empagliflozin (personal communication). This subject also manifested Hypophosphatemia, increased urinary excretion of phosphate, creatinine, urea nitrogen, calcium, protein and uric acid in addition to glycosuria. Fortunately, these alterations reversed within 2weeks on withdrawal of Empagliflozin. However, the subject has yet to regain the muscle strength and mass even after withdrawal of Empagliflozin 4months ago. The decline in muscle mass and strength may attributed to enhanced gluconeogenesis from muscle protein induced by hyperglucagonemia ensuing on administration of SGLT2 inhibitors and is consistent with similar manifestations in a subject with type 1 Diabetes at the onset of or with lapse of glycemic control.^{29,30}

Both the FDA and EMU recently reissued a major alert and a caution following several reports of ketoacidosis in subjects administered these drugs especially because the well documented serious and the lethal nature of ketoacidosis.^{27,28} The mechanism of predisposition, promotion and induction of ketoacidosis with administration of these drugs has been well discussed in several reports.³¹⁻³³ A close negative feedback regulation between plasma glucose and plasma glucagon present in normal subjects is well known to be almost abolished in subjects with uncontrolled diabetes.^{29,30,34,35} Thus, elevated circulating plasma glucagon level despite hyperglycemia is already present in subjects with uncontrolled diabetes.^{30,34,35} A further rise in plasma glucagon ensues on administration of these drugs.²⁹ The rise in plasma glucagon is apparently required to promote hepatic glucose production to compensate for glycosuria.²⁹ Hyperglucagonemia is also well documented to induce ketonemia and ketoacidosis by promoting ketogenesis via facilitation of lipolysis. Moreover, ketonemia and ketoacidosis may also be attributed to elevations in circulating plasma concentrations of other counter regulatory hormones including catecholamines, glucocorticoid and human growth hormone induced by stress secondary to dehydration as well as genitourinary sepsis, both well documented side effects of these drugs as well as the triggers in onset of diabetic ketoacidosis.³⁶⁻³⁸ FDA and EMU also noted that

few of these subjects manifested ketoacidosis without a significant hyperglycemia as documented in other recent reports.²⁵⁻²⁸ However, serum lipase and amylase concentrations were not reported probably because they were not determined in these subjects. In actuality, acute pancreatitis has been reported to occur following administration of Canagliflozin in several case studies.³⁹⁻⁴¹ Therefore, it is likely that Euglycemic Ketoacidosis described in these subjects²⁵⁻²⁸ may be 'Pancreatic Ketoacidosis' a serious complication of acute pancreatitis (Kabadi Syndrome) induced by markedly elevated circulating lipase concentration.⁴²⁻⁴⁶ I believe that the diagnosis of acute pancreatitis was probably missed in these subjects due to lack of a thorough evaluation by determination of appropriate laboratory testing.

Thus, despite a detailed description of the pathophysiologic mechanism and the reporting of several subjects in post marketing surveillance, manufacturers of these drugs continue to refute the significance of occurrence of Ketoacidosis based on the retrospective analysis of pre marketing clinical trials.^{47,48} The discrepancy between lack of significant occurrence of Ketoacidosis in these trials in contrast to the post marketing surveillance data may be explained by the fact that the participating subjects in the premarketing clinical trials are always relatively healthier because of their selection bias based on several inclusion and exclusion criteria when compared with the population of subjects with type 2 Diabetes in clinical practice. Moreover, it is likely that ketoacidosis did not occur in premarketing trials in these relatively healthier subjects because Genito urinary infections were probably mild in the early stage, diagnosed during recurrent study visits and hence were amenable to a prompt treatment. In contrast, Ketoacidosis occurred frequently in post marketing surveillance in presence of genitourinary infection because the greater severity with presentations including acute pyelonephritis probably due to immunosuppressor well documented to be present in subjects with persistent hyperglycemia. Alternatively, other triggers for promoting ketoacidosis did not ensue or were diagnosed in the early stage and managed promptly because of close monitoring routinely conducted as a part of the protocols in premarketing clinical trials.

Yet, another caution or alert was recently issued by both FDA and EMU regarding occurrence of osteoporosis and fractures with use of these drugs following their documentation in the postmarked ing surveillance data.⁴⁹ The authors attributed this finding to rise in PTH and FGF 23, both humoral factors known to cause bone resorption.⁵⁰ However, a simple pathophysiology for the onset of osteoporosis resulting in increased fractures is both the hyperphosphaturia and the hypercalciuria accompanying glycosuria induced by these drugs. Hypercalciuria of renal leak due to tubular mutation, a known familial disorder is well documented to induce osteoporosis and fractures.⁵¹ Moreover, osteoporosis may also be secondary to increased breakdown of matrix protein to sustain gluconeogenesis induced by hyperglucagonemia. This finding is similar to the increased prevalence of osteoporosis and fractures in subjects with both type 1 and type 2 diabetes.^{52,53} I believe that hypercalciuria with concurrent increase in renal excretion of uric acid as documented recently and dehydration is likely provide a suitable and fertile milieu for formation of renal calculi and consequential morbidity especially in tropical regions of the world with a frequent occurrence of dehydration particularly in the poor population and other subjects with extremes of age.

Finally, elevation in serum LDL cholesterol and non HDL cholesterol levels well documented in clinical trials following administration of these drugs are well established to promote atherosclerosis. Moreover, dehydration noted in clinical trials is

the most common cause of increased serum viscosity which is well known to induce and promote hypercoagulable milieu responsible for ensuing adverse thrombotic cardiovascular outcomes, e.g. deep vein thrombosis, macro vascular events including myocardial ischemia and stroke as well as microvascular complications in the long term.^{1-8,10-19,54} Therefore, the presence of both these aberrations may have contributed to a significantly higher occurrence of non fatal strokes documented in subjects receiving canagliflozin as well as Empagliflozin when compared with subjects administered placebo.⁵⁴⁻⁵⁶ Increased serum viscosity may also be responsible for the increase in occurrence of lower limb amputations mainly affecting toes documented in a post marketing cardiovascular trial known as CANVAS (Cardiovascular Assessment Study) with Canagliflozin. Based on this interim data, EMU and FDA issued another alert for Canagliflozin.^{57,58} Many of these concerns raised by FDA and EMU were described in an earlier report in 2013.⁵⁹ Finally, another warning was issued recently by FDA regarding onset of renal dysfunction on use of these drugs.⁶⁰

Therefore, in the light of the data regarding increased strokes and lower limb amputations probably caused by increased serum viscosity, it was interesting to read the recent article regarding a efficacy of Empagliflozin in reducing all cause and especially cardiovascular mortality.⁵⁶ However, on further examination, the methodology appears to be flawed and hence the results and conclusions deserve a stringent scrutiny, validation and confirmation. An important comparative data between monotherapy with Empagliflozin and placebo or a comparator is not included. Subjects who received even a single dose of Empagliflozin, subjects who received for a short duration as well as the drop outs are included in the final analysis. These subjects must be excluded from the analysis since they are not exposed to Empagliflozin at all or exposed for a short duration. Moreover, the statistically significant difference for cardiovascular outcomes between subjects administered placebo and the overall population of subjects treated with Empagliflozin is beyond reconciliation especially because no significant differences were documented between placebo group on one hand and the two individual groups of subjects treated with two different daily doses of empagliflozin, 10mg and 30mg on the other.

It is apparent that the differences regarding mortality became visible in the early duration, within 6 weeks after randomization. It is unlikely that regression of atherosclerosis could occur in such a short time especially with rising LDL cholesterol levels. This finding is in stark contrast to UKPDS and other studies in which the improvement in microvascular outcomes was evident after a much prolonged duration of intensive treatment.⁶¹⁻⁶⁴ The differences in outcomes may be secondary to the differences in demographics among the subjects between these groups, e.g. age, duration of diabetes, presence or absence of obesity, comorbidities including micro and macro vascular complications, hypoglycemic events, glycemic control, blood pressure control, interactions between medications etc. Other concerns include a multinational design of the study thus including subjects with varying ethnicities, genetic traits, dietary patterns, insulin resistance as opposed to decline in insulin secretion as a major pathophysiologic factor and the different philosophies on the part of individual investigators regarding desirable goals of control and use of drugs as available in the locale in management of glycemia, hypertension and Dyslipidemia as well as preventive use of aspirin. Moreover, inclusion of deaths with unknown cause as cardiovascular deaths may not be appropriate and therefore unacceptable. Similar issues are raised recently in other publications as well.^{64,65} Therefore, the results and conclusions in this Empagliflozin study appear less than reliable and ‘too good to be true’.⁶⁵

In the final analysis, far too many side effects including detrimental changes in serum chemistries, interactions with other frequently used drugs leading to serious adverse outcomes have led the regulatory agencies to issue concerns, cautions and alerts at frequent intervals since approval. In fact, all the advertisements in and even ‘prescribing information (PI) has far more words for description of serious side effects, drug interactions and cautions regarding onset of detrimental adverse outcomes when compared to limited efficacy. Therefore, I believe that the regulatory agencies have overlooked ‘Hippocratic Oath’ at the expense of continuing approval of this drugs.⁶⁶

Conclusion

Both the short term and the long term efficacies and safety of SGLT2 inhibitors remain to be established. In fact, these drugs possess much lesser efficacy with far greater costs and undesirable adverse effects with onset of serious adverse outcomes worsening quality of life.

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Conflict of interest

Author declares that there is no conflict of interest.

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