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Exploring the Safety of Sodium Glucose Co-Transporter-2 Inhibitors at the Imperial College London Diabetes Centre, UAE

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***Abstract*—**Introduction: Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a new class of oral anti-diabetic drugs with a unique mechanism of action. They are used to improve glycaemic control in adults with type 2 diabetes by enhancing urinary glucose excretion. In the UAE, there has been certainly an increased use of these medications. As with any new medication, there are safety considerations related to their use in patients with type two diabetes. A retrospective study was conducted at the three main centres of the Imperial College London Diabetes Centre. Methodology: All patients in electronic database (Diamond) from October 2014 to October 2017 were included with a minimum of six months usage of sodium glucose co-transporter inhibitors that comprise canagliflozin, dapagliflozin and empagliflozin. There were 15 paired sample biochemical and clinical correlations. The analysis was done at the start of the study, three months and six months apart. SPSS version 24 was used for this study. Conclusion: This study of sodium glucose co-transporter-2 inhibitors used showed significant reductions in weight, glycated haemoglobin A1C, systolic and diastolic blood pressures. As the case with systematic reviews, there were similar changes in liver enzymes, raised total cholesterol, low density lipopoptein and high density lipoprotein. There was slight improvement in estimated glomerular filtration rate too. Our analysis also showed that they increased in the incidence of urinary tract symptoms and incidence of urinary tract infections.

***Keywords*—**SGLT2 inhibitors dapagliflozin empagliflozin canagliflozin, adverse effects, amputation diabetic ketoacidosis DKA, urinary tract infection.

I. Background

A retrospective observational study was conducted at the Imperial London College Diabetes Centres (ICLDC) in Abu Dhabi, Alain and Zayed Sports City (ZSC).

Imperial College London Diabetes Centre is one of the most advanced diabetes centres in UAE. There are three main centres; the first in Abu Dhabi, the second in Zayed Sport city in Abu Dhabi, and the third in Alain which is the Eastern city of Abu Dhabi.

The centres have a specialist outpatient facility with no inpatient beds. Unstable patients are usually referred to local hospitals for admission and further assessments.

There is no single patient record at the time being in UAE, and so, it is very difficult to track patient records who are being treated in other centres.

There were 15 paired sample correlations including the following variables of interest related to the use of SGLT2 inhibitors; weight, eGFR, ALT, AST, GGT, ALP, blood pressure, standing blood pressure, LDL, HDL, total cholesterol, triglycerides, and HBA1C.

The results were recorded at the start of the study, three months and six months intervals.

The analysis was done using SPSS version 24 (release 24.0.0.1).

Student T test methodology was applied to the paired samples, and comparative analysis was made at the intervals stated earlier.

The study comprised patients with age groups of mean of 53 years (16-103 years), mean weight 87.5, eGFR 114.7, mean ALT 29.5, AST 22.11, GGT 40.6, ALP 78, sitting BP 129, standing BP 132.5, sitting diastolic blood pressure 72.7, standing diastolic blood pressure 74, LDL 2.58, HDL 1.17, total cholesterol 4.16.

The males to females ratio was 5908 males over 5208 females. There was no difference in SGLT2I choice by gender with similar number of males and females. There were 1796 females and 1589 males in the canagliflzoin 100 mg strength group, 166 females and 156 males in the canagliflzon 300 mg strength group, 2654 females and 2239 males in the dapagliflzoin 10 mg strength group, 137 females and 105 males in the dapagliflzoin 10 mg combined with metformin group, 132 females and 135 males in the dapagliflzon 5 mg combined with metformin group, and finally there were 1023 females and 984 males in the empagliflozin group.

The individual SGLT2 inhibitors contributions were canagliflozin 100 mg, canagliflozin 300 mg, dapagliflozin 10 mg, dapagliflozin 10 mg/ metformin, dapagliflozin 5 mg/metformin and empagliflozin.

The variables measured units were as follows; mmol/l for lipids, U/L for liver enzymes, % for HBA1C, mmol/l for glucose, and ml/min for eGFR.

The total number of patients studied was 11116 patients. There were about 3385 patients (30.5%) on canagliflozin strength 100 mg, 322 patients (2.9%) on canagliflozin strength 300 mg, 4893 patients (44% on dapagliflozin 10 mg, 242 patients (2.2%) on dapagliflozin 10 mg combined with 1000 mg of metformin, 267 patients (2.4%0 on dapagliflozin 5 mg and metformin 1000 mg and 2007 patients (18.1%) on empagliflozin therapy.

The total mean duration of therapy with SGLT2I was

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17.312 months (minimum 6.016 months, maximum 43.693 months) with a median value of 15.699 months with first quartile 10.225 and third quartile of 23.211; however, the analysis did not look at the results beyond the initial six months period from commencement.

There were negative correlations between age and change in weight at six months (Pearson correlation = -0.037; p= 0.001; n = 7894) and essentially very weak correlations between change in HbA1c and change in weight with the other variables age, gender and type of SGLT2I used.

A Pearson product-moment correlation coefficient was computed to assess the relationship between gender and change in weight after six months. There was a weak positive correlation between the two variables (r = 0.29, p=0.001, n = 7894).

For descriptive purposes, we recorded mainly the changes that occurred between baseline figures at the start of the study and six months later using T test measures.

The mean changes for the whole group of SGLT2I showed the following statistically significant results with P value <0.05%.

1. There was a mean weight loss of 2.11 kg (SD 3.5; CI 2.03-2.19).
2. Mean reduction of eGFR by 1.95 ml/min (CI 1.26-2.64)
3. Mean reductions in liver enzymes were 3.7, 1.61, 5.9 and 2.7 mmols/l for ALT, AT, GGT and ALP, respectively.
4. Mean reduction of sitting systolic and diastolic BP by 3.9 and 2.4 mm/Hg, respectively.
5. Mean reduction of standing systolic and diastolic BP by 4.3 and 1.24 mm/Hg, respectively.
6. Mean reduction of total cholesterol by 0.07 mmol/l, LDL by 0.06 mmols/l, increased HDL by 0.02 mmol/l and triglyceride by 0.6 mmol/l.
7. Mean reduction of HBA1C by 0.71% (SD 1.29; CI 0.68-0.74).

During the period of six months therapy for 11116 patients with SGLT2I, there were about 248 mid steam urine specimens sent for culture and 132 samples had positive urinary cultures.

Of the 3385 patients who received canagliflozon, 71 patients had urine cultures being requested of which 9% were positive (30 cases) and all of them were prescribed antibiotics.

In 2007, 20 patients who were on empagliflozin had positive urine cultures (1%) and 15 patients had negative cultures (0.7%).

In the dapagliflozin group, there were 63 patients (1.3%) out of 4893 patients having positive cultures and 51 (1%) had negative cultures.

There were no reports of amputations or bone fractures in our institution, but probably more time needed to pick any new pathology. Also, the facility is outpatient based and treatment may have been offered in other medical centres or may not have been recorded by the physician.

One case report of eugkycemic diabetic ketoacidosis was reported; she was 46 year old lady T2DM for 17 years with chronic poor diabetic control on oral therapy and basal insulin. She also had Retinopathy, Sensory neuropathy but no micro albuminuria. She was morbidly obesity with BMI 46.2,

Following gastric sleeve surgery in October 2016, she had lost 18 kg (BMI 38.58%). She was off insulin since surgery and been on dapagliflozin, linagliptin, metformin, atorvastatin, aspirin and esomeprazole.

She presented with abdominal, tiredness and nausea. Further investigations confirmed the diagnosis of eugkycaemic DKA and were admitted 3 days in the high dependency unit after which she made a complete recovery.

The limitations of the study are that it was a retrospective cohort and not randomised trial; some of the physicians may not have entered any other adverse events and the weight of some patients has not been recorded in subsequent visits.

There were also some missing data like standing blood pressure at all time points.

However, there was large sample size been included. The study was well matched for gender. There were large numbers of patients taking different types of SGLT2I except smaller numbers were note in the dapagliflozin 5 mg group.

II. Previous Local Study from UAE 2017 and Asia 2012

Total number of Emirati patients studied was 307 with baseline HBA1C 8.9 +- 1.7% who were treated with SGLT2I. 21.8% were >65 years and 78.2% were below 65 years. Females were 63.2%. Changes were recorded at 6 months and one year.

There was significant change in SBP in the Emirati patients (137 +-15.9 mm Hg at baseline vs. 134 +- 15.7 mmHg at 6 months with P value of 0.002) but no significant change in diastolic BP.

The changes in TG and HDL were not significant but here was a significant reduction in total cholesterol and LDL levels. There were only eight reported drug related effects. There were also three cases of genital infection and five cases of UTIs. The overall percentage of reported side effects was 1.9%. There were no reports of severe hypoglycaemia [1].

In a study of the Emirati population, combination treatment with sodium glucose co- transporter 2 inhibitors and glucagon like peptide 1 (GLP1) agonists achieved a significant improvement in HbA1c of 0.6% within 3 months, with no further reduction at the subsequent time points studied. Weight loss of up to 2.3 kg continued to a nadir at 6 months [2].

III. Discussion

SGLT2I are potent highly selective sodium glucose transporter inhibitors that lower blood glucose in an insulin dependent manner.

Most of the trials that studied SGLT2I were randomised controlled double blind trials that compared the efficacy and potency of these medications as either monotherapy or as combination therapy with an oral ant diabetic medications as well as insulin therapy.

There are still on-going trials for certain groups of this class of medications in which the results will be released by next year and hopefully that can tell us more about further uses or new emergent hazards and adverse effects.

There is keen interest in assessing the risk benefit profile of SGLT2I because they are a relatively new class of ant hyperglycaemic agents.

Add to this there seems to be a great enthusiasm from the different pharmaceutical industries to have the funding for more trials to show the superiority of their own products compared to others especially following the recent reports or some adverse effects on bones and reports of amputations.

The regulatory authorities issued drug safety communications in 2016 regarding the risk of atypical DKA, fractures, lower limb amputations, serious UTIs, pyelonephritis and urosepsis with the use of SGLT2I.

The limitations of use of SGLT2I can be due to;

1) Propensity to cause DKA
2) Limited use with low GFR
3) Sick day management
4) Mode of action defying normal physiology
5) Possibility of amputation- CANVAS
6) Fractures- CANVAS
7) Genital yeast infection
8) Possible need to adjust blood pressure medications
9) Possible need to adjust lipids medications (Increase LDL by around 6%)
10) Relatively weak anti hyperglycaemic agents.
11) They are not safe to be used in T1DM or ketosis prone T2DM

Since they cause mild dehydration, they should be used in caution with the following group of drugs; NSAIDS, ACE inhibitors, ARBs, diuretics, hypovolaemia, heart failure, liver injury, risk for UTI, low bone mineral density and high risk of falls.

From the clinical trials highlighted earlier there is about 2-4 fold increase in mycotic genital infections and increase colonisation of the urinary tract [3].

There was also fatal urosepsis and pyelonephritis requiring hospitalisation [4].

In post marketing surveillance studies, there were about 10 cases of bladder cancer in subjects using dapagliflozin; five of these occurred in the first six months of treatment.

Safety signals related to breast and bladder cancer have arisen with dapagliflozin though these are unsubstantiated and likely ascribed to the presence of pre-existing cancer [5].

There seems to be no long-term data on the safety of the long-term effects of glucosuria on the urinary tract and more time needed to assess this.

Given the modest improvement in glycaemia and absence of long-term safety data on the effect of prolonged glucosuria and absence of cardiovascular data in diabetic individuals without overt cardiovascular disease, we will not routinely use SGLT2I as combination therapy in T2DM.

SGLT2I should be stopped in cases of pancreatic insulin deficiency, reduced insulin dose or discontinuation, calorie restriction, alcohol abuse, extensive exercise, myocardial infarction, stroke, severe infection, surgery and extreme stress [6].

Based on the putative mechanism, we highlighted earlier with regards to canagliflozin effects on bone mass, it is likely that other SGLT2I may reduce bone mass too.

Canagliflozin should therefore not be given to patient at risk of foot amputation including neuropathy, foot deformity, vascular disease and history of previous foot ulcerations.

Patients taking canagliflozin should be monitored for signs and symptoms of foot ulceration.

The Declare Timi 58 trial population is broad and includes large groups of patients with established CVD or multiple risk factors for CVD. The extended follow up of the Declare Timi 58 trial will help to determine the impact of prolonged treatment with dapagliflozin. The study is also expected to provide more conclusive data on the effect of treatment with dapagliflozin versus placebo ("Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events - Full Text View [7].

During the dapagliflozin clinical trial programme, the overall proportion of patients with malignant tumours was similar between those treated with dapagliflzoin 1.47% and those treated with placebo or comparator [8].

On-going clinical trials and post marketing surveillance data will be key for determining if there are and additional safety concerns [9].

While these medications have favourable effects on reducing both systolic and diastolic BP, exercise must be cautioned especially in the elderly patients who are already on antihypertensive and loop diuretics.

SGLT2 inhibitors endorse the renal excretion of glucose and thereby modestly lower elevated blood glucose levels in patients with type 2 diabetes. They do not frequently cause hypoglycemia in the presence of therapies that else cause hypoglycemia. SGLT2 inhibitors decrease blood pressure and weight and can cause adverse effects in the elderly and those who are volume depleted from diuretics.

SGLT2 inhibitors are not regarded as primary therapy for the majority of patients with type 2 diabetes.

The management of patients with type 2 diabetes mellitus includes education, with stress on lifestyle changes including diet, exercise, and weight reduction when appropriate. In the absence of contraindications, metformin is usually the initial pharmacologic therapy for most patients with type 2 diabetes.

The therapeutic options for patients who fail initial therapy with lifestyle intervention and metformin are to add a second oral or injectable agent, including insulin, or to switch to insulin. The choice of therapy should be individualized based upon patient characteristics, preferences, and costs. Options include thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, SGLT2 inhibitors, alpha-glucosidase inhibitors, and insulin. All of these medications have advantages and disadvantages.

Given the modest improvement in glycaemia, cost, absence of long-term safety data on the effects of prolonged glucosuria, and absence of cardiovascular data in diabetic individuals without overt cardiovascular disease (CVD), it is best not to routinely use SGLT2 inhibitors as combination therapy in patients with type 2 diabetes.

Empagliflozin may play a role in patients with overt CVD not reaching glycemic goals with metformin and lifestyle

modifications.

SGLT2 inhibitors in general may have a role as a third agent in those who cannot or will not take insulin, when full doses of metformin and a sulfonylurea have not produced satisfactory metabolic control, or in patients in whom risk of hypoglycemia is high (frail, older adults) or in whom avoidance of weight gain is a priority. However, long-term safety has not been established.

When a decision has been made to use an SGLT2 inhibitor in a patient with type 2 diabetes and CVD, it seems reasonable to start empagliflozin, rather than another SGLT2 inhibitor. This is based on the results of the empagliflozin and cardiovascular outcomes study. In patients without CVD, choice of SGLT2 inhibitor is often dictated by cost and insurer formulary preference.

Volume status and renal function (serum creatinine with estimation of glomerular filtration rate [eGFR]) should be assessed prior to starting an SGLT2 inhibitor and periodically thereafter.

The most common side effects of SGLT2 inhibitors are vulvovaginal candidal infections and hypotension. Acute kidney injury, urinary tract infections, euglycemic diabetic ketoacidosis, increased risk of lower extremity amputation, and bone fractures have also been reported.

The retrospective data analysis from our institution (Imperial College London Diabetes Centre) in UAE had nearly mirrored those results from the systematic reviews stated earlier.

There were increased rates of urinary tract infections, modest weight loss, reduction in both systolic and diastolic blood pressures, improvement in eGFR.

The liver tests were not changed in our study and there were no reports of bone fractures or amputations. One case of euglycaemic diabetic ketoacidosis was reported following reduced carbohydrate intake from bariatric sleeve gastrectomy and reduction of insulin dose.

IV. Conclusion

Current estimates show a continuing increase in the number of people diagnosed with T2DM worldwide. A large percentage of patients with T2DM fail to reach glycaemic goals with lifestyle changes and pharmacotherapy.

The SGLT2I are a new class of anti-diabetic medications with unique insulin dependent mechanism that rely only on plasma glucose and renal function. These drugs are orally available with lower risk of hypoglycaemia when compared to insulin and sulfonylurea.

Today, only C-glucoside SGLT-2 inhibitors are in clinical progress for the treatment of type 2 diabetes, including dapagliflozin, canagliflozin, empagliflozin, ipragliflozin and tofogliflozin.

The projected case study described herein demonstrates that not one remedy fits every patient; it also emphasises the need to customize ant diabetes therapy based on the specific features of the patient, as suggested by recent ADA/EASD and AACE guidelines.

The appraisal of the important randomised double blind controlled trials showed that patients taking SGLT2I are more prone to urinary tract infections, genital infections, hypovolaemia and orthostatic hypotension.

Euglycaemic diabetic ketoacidosis was also observed. This observation is very important because the side effects of diabetic ketoacidosis can occur irrespective of the patient's blood sugar.

SGLT2I are not indicated in the treatment of type 1 diabetes as these patients will have increased risk of developing diabetic ketoaciodosis.

Symptoms of ketoacidosis are variable and may include nausea, vomiting, abdominal pain and shortness of breath. Patients should then stop SGLT2 inhibitors immediately and seek medical review [10].

Further studies should concentrate to identify pleiotropic effects of SGLT2 inhibitors, particularly with other oral antihyperglycemic drugs or insulin.

The analysis of the literature proposes that patients who are diabetics and have low C peptideare at increasing risk of developing ketoacidosis especially if these patients were put on diuretics or statins.

More studies are needed for further understanding of the mechanisms of ketoacidosis [11].

Additional long-term studies examining the cardiovascular effects of canagliflozin and dapagliflozin are on-going and will deliver additional evidence regarding the cardiovascular safety of SGLT2 inhibitors. Studies are also currently happening to assess the effectiveness and safety of SGLT2 inhibitors in patients with type 1 diabetes. The existing data on SGLT2 inhibitors support their use as a treatment choice in patients with T2DM.

The data analysed in our Imperial College London Diabetes Centre showed similar adverse effects profile compared to other worldwide trials. Having said this, we are finding increasing use of SGLT2I when compared to DPP4I and/or GLP1RA; the main reason is weight loss in a very obese cohorts of diabetic patients.

Conclusion of the study of canagliflozin, dapagliflozin and empagliflozin showed significant reductions in weight, HBA1C, systolic and diastolic blood pressure.

The lipids profile showed raised total cholesterol, LDL and HDL.

There was also an increase in the incidence of urinary tract infections.

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