Effects of Combination of SGLT-2 Inhibitor and GLP-1 Receptor Agonist on Renal Outcome in T2D with GFR below 30 and Macroalbuminuria : A Case Series

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Precis: Renal Outcomes of Combination of SGLT-2 Inhibitor and GLP-1RA in T2D Patients with GFR below 30 and macroalbuminuria

Key words: SGLT-2 inhibitor, Renal Protection, Type 2 Diabetes, Macroalbuminuria, GFR below

Key Clinical Message: Renal protection is likely to be a class effect of SGLT-2 inhibitors and GLP-1RA. When used simultaneously there may be a synergistic effect. Both agents are also safe to use in high renal risk patients(eGFR between 21 to 30 ml/minute/1.73m2)

Abstract

We hypothesized that the combination therapy of SGLT-2(Sodium-glucose co-transporter-**2**)inhibitor and Glucagon-like peptide-1 receptor agonist(GLP-1RA) provide renal protection in adults with type 2 diabetes (T2D) even if estimated GFR (eGFR) is below 30ml/minute/1.73 m^2. We hereby describe four consecutively treated high renal risk patients with T2D with eGFR between 21 to 30ml/minute/1.73 m^2 with KDIGO Stage G4A3 and NIH Stage 4 CKD with concomitant SGLT-2 inhibitor and GLP-1RA . Case 1 and 4 received daily Empagliflozin (10 mg) while case 2 and 3 received daily Dapagliflozin (5 mg) and Ertugliflozin (15 mg) respectively. All four cases received Dulaglutide 1.5 mg weekly concomitantly with above described SGLT-2 inhibitor. The mean Urinary Albumin Creatinine Ratio (UACR) at baseline was 1211±304 mg/g. Cases 1, 2 and 3 had nephrotic range proteinuria while case 4 had UACR of 527 mg/g. There was a regression of mean UACR of all four cases by 16%, 65% and 77% at 3 months, 6 months and 9 months of treatment respectively compared to baseline. None of the four cases reported end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml/min/1.73m^2, a doubling of the serum creatinine level, or death from renal or cardiovascular causes during a follow up period ranging from 6 to 30 months.

Introduction:

The arrival of SGLT-2 inhibitors has spelt a revolution in the way we manage our adults with type 2 diabetes (T2D) today (Lo et al., 2020; Perkovic et al., 2019). Its powerful glycemic control, weight loss and anti-hypertensive effects are lucrative (Lo et al., 2020). In addition, these agents also have shown benefits in reducing cardiovascular and renal risk (Lo et al., 2020). Diabetes is the leading cause of kidney disease and kidney failure in the United States (Lo et al., 2020). Chronic Kidney Disease (CKD) or Diabetic Kidney Disease (DKD) is progressive, irreversible and often goes undetectable (Lo et al., 2020). CREDENCE trial showed that Canagliflozin (100 mg per day dose) when used in adults with Diabetic Kidney Disease (DKD) with GFR of > 30 ml/min/1.73m^2 and median Urinary Albumin Creatinine Ratio (UACR) of 927 mg/day lead to reduction in primary composite endpoint of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml/min/1.73m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes(Perkovic et al., 2019).Recently, DAPA-CKD showed similar benefits with Dapagliflozin in patients with and without T2D with GFR as low as 25 ml/min/1.73m^2 (Heerspink et al., 2020) A study comparing Dulaglutide with insulin Glargine (AWARD-7) in which 29% of the participants had a GFR of <30 ml/minute/ 1.73 m^2 showed reduced decline in GFR and increased reduction in albuminuria comparing to the insulin group in post hoc analysis(Tuttle et al., 2018). However, the effects of concomitant SGL-2 inhibitor with the GLP1 RA on renal outcomes has not been reported to the best of our knowledge in patients with DKD

with GFR below 30 (between 21 to 30 ml/minute/ 1.73 m^2). We hereby describe four such case reports.

Methods: We hypothesized that concomitant use of SGLT-2 inhibitors and GLP-1 RA provide renal protection in patients with GFR below 30 ml/minute/ 1.73 m^2. We implemented this strategy at our clinic and retrospectively collected the required follow up data of 4 consecutively treated patients who had at least one baseline HbA1c, UACR, Basic Metabolic panel (BMP) and at least a total of two follow up HbA1c, UACR and Basic Metabolic Panel(BMP) at approximately 3 months interval. The main methods used include measuring Urinary Albumin Creatinine Ratio (UACR), HbA1c and Basic Metabolic Panel at approximately every 3 months follow up period. We hereby describe these four individual case reports.

Results:

Please also refer to Table 1, Figure 1-4 for more details.

Case 1:

68 year old Caucasian gentleman with six years history of T2D presented to our clinic with HbA1C of 11.4%, UACR of 2000 mg/g, a GFR of 21 ml/ min/1.73m^2, BUN of 43 mg/dl, creatinine of 2.67 mg/dL, NIH Stage 4 CKD and KDIGO Stage G4A3. His vitals were: BP 126/80 mm Hg, Pulse 78 bpm, Wt 102.5 kg (226 lb) and BMI 33.37 kg/ m^2. His electrolytes levels were all within normal limits. At the time of his first visit with us, his T2DM was managed with glimepiride 4mg two times daily, 30mg of Pioglitazone daily, 98 units of insulin Glargine 300 units/ml at bedtime and 30 units of insulin Aspart (100 units/ml) before breakfast, lunch and dinner. He was on rosuvastatin 40 mg and valsartan 80mg daily to treat his dyslipidemia and HTN respectively. Empagliflozin 10 mg daily was initiated along with Exenatide ER SC once weekly. He was on Exenatide ER once weekly for two weeks then it was changed to Dulaglutide 1.5 mg weekly based on insurance

formulary. We changed his basal insulin from 98 units to 160 units at bedtime. His Glimepiride was discontinued and we continued the Pioglitazone 30 mg daily. His bolus insulin dose was kept at 30 units before meals three times a day and if not eating, the patient was instructed to not inject the 30 units and only use a correction factor of 1 unit for every 50mg/dL of BG above 150 mg/dL. At baseline his fasting blood sugar (FBG) and other random times of the day was averaging 300-400mg/d/L, at baseline. Approximately at 50 days after his initial visit with us his BG started averaging 60-100mg/dL which led to us decreasing his insulin Aspart (100u/ml) dose to 20 units before breakfast, lunch and dinner and decreasing his insulin glargine (300u/ml) to 100 units at bedtime. After approximately 3 months of follow up, the patient reported a home BG log averaging 100-130 throughout the day. Toward the end of a 12 months period, the patient was requiring less insulin and had two hypoglycemic events; so his insulin glargine (300U/ml) was decreased to 68 units at bedtime and his insulin Aspart 100 units/ml was decreased to 15 units before meals. The patient's UACR dropped from 2000 mg/g to 887mg/g, 382mg/g, 410mg/g and 221mg/g at approximately 3, 6, 9 and 12 months of follow up respectively. It fell from the baseline level of 2000 mg/g to around 82 mg/g at approximately 30 months follow up (figure 1). The GFR was maintained around the baseline value throughout the follow up period (Figure 2). The patient's A1C dropped from the baseline value of 11.4 to 7.4, 8.3 and 8.1 at approximately 3, 6 and 12 months respectively and his fructosamine was 219 mmol/L (which correlates to an A1C of 5-5.5%) toward the end of the 30 months follow up periods. There was no significant change in the patient's electrolyte levels from baseline with all basic metabolic panel values continued to be within normal limits throughout the 30 months. Left upper extremity radiocephalic AV fistula was placed in anticipation of possible progression to ESRD requiring hemodialysis (HD). Eight months later he had a left upper extremity AV brachial cephalic fistula replacing the first left upper extremity brachial basilic. None of the AV fistulas were utilized as he never required HD. There was one instance when patient developed severe diarrhea and vomiting with dehydration due to a viral infection and his GFR had

dropped to 9 ml/ min/m^2 but reverted back to 26 ml/ min/m2 within 5 days with adequate hydration. He did discontinue empagliflozin during these 5 days.

Case 2

71 years old Caucasian gentleman with history of T2DM for 7 years presented to endocrinology clinic with baseline A1C of 6.1%, Serum BUN: 28 mg/dL; Serum Creatinine: 2.96 mg/dL GFR: 21 mL/min/1.73 m^2, UACR: 1253 mg/g, NIH Stage 4 CKD and KDIGO Stage G4A3. Vital signs: BP 104/64 mm Hg, pulse 60 bpm, Wt 90 kg (198 lb) and BMI 26.9 kg/m². All electrolyte were within normal limit. This patient was being managed with Nateglinide120 mg three times daily. The patient was checking his BG randomly and he was averaging in the 120-130 mg/dl range. Dapagliflozin 5 mg daily was initiated. Dulaglutide 0.75 mg weekly was also started for the first 4 weeks and then increased to1.5 mg weekly thereafter, Nateglinide was stopped after one week. At 8 weeks follow up, the patient's A1C dropped from 6.1 to 5.3%. UACR dropped from 1253 to 159 mg/g (figure 1). Patient's GFR, BUN and serum creatinine were unchanged over the 8 weeks period compared to baseline (figure 2-4). At approximately 3 months follow up, his fasting BG and prandial BG were averaging between 100-130 mg/dL.

Case 3

A 64 years old pacific islander gentleman with 4 years history of T2D presented to our clinic with A1C of 13.0%, GFR: 27 mL/min/1.73m^2, Serum BUN: 17mg/dL, Serum Creatinine: 2.96 mg/d and UACR of 1065.0 mg/g, NIH Stage 4 CKD and KDIGO Stage G4A3 Vital Signs: BP: 148/78 mm Hg, Pulse: 86 bpm, Weight: 87.1 kg (192 lb); BMI: was 28.34 kg/m². The patient's electrolytes levels were all within normal

limits. His BG ranged from 200-220 mg/dL at different times of the day. The patient was being managed with insulin Glargine (100 units/ml) 45 units at bedtime and 4-8 units of insulin Lispro (U-100) with each meal. The patient was also on atorvastatin 20mg daily and losartan 100mg daily for the management of dyslipidemia and hypertension respectively.

This patient was started on Ertuglflozin 15 mg daily, Dulaglutide 0.75 mg weekly and his insulin glargine was increased to 60 units at bedtime. Dulaglutide dose was then increased to 1.5 mg weekly after 8 weeks. After 3 months of being on the previously mentioned regimen, the patient's A1C decreased from 13% to 6.5% and BP dropped from 148/78mmHg to less than 130/80 mmHg . At 6 months follow up; UACR fell from 1065 to 474 mg/g (figure 1) GFR went up from from 27 to 52 mL/min/1.73m^2 (figure 2),. Patient was then started on Metformin 500 mg twice daily. Over the proceeding 8 weeks, the dose of insulin Glargine (100 u/ml) was gradually decreased to 20 units at bed time to target a fasting blood glucose of 80-120 mg/dL.

Case 4

74 years old Spanish female with history of T2DM for 8 years. At presentation, the patient's A1C was 7.8%, Serum BUN: 37 mg/dL; Serum creatinine: 1.87 mg/dL; GFR: 26 mL/min/1.73m^2 UACR: 527 mg/g, NIH Stage 4 CKD and KDIGO Stage G4A3. Vitals: BP 98/60 mm Hg, Pulse 82 bpm, Wt 71.6 Kg and BMI 27.95 kg/m^2. Electrolyte levels at baseline were all within normal limit. T2DM in this case was being managed with 40 units of insulin Glargine (100U/ml) at bedtime, Dulaglutide 1.5 mg weekly and insulin Lispro (100U/ml) as per sliding scale (1 unit for 50 points above 150 mg/dL of blood glucose around meal times). This patient was also on Losartan 100mg daily and Rosuvastatin 40mg for the management of hypertension and dyslipidemia respectively. Blood glucose readings were around 200 mg/dL throughout the day. This patient was started on Empagliflozin 10 mg daily, the insulin Lispro (U-100) was changed to 15 units prior to each meal and her insulin glargine(100 units/ml) was increased to 45 units at

bedtime. At the 3 months follow up her blood glucose readings were averaging between 130-150 mg/dL and her A1C decreased to 6.6. Her GFR was maintained at 23 mL/min/1.73m^2 and stayed around that level for the entire 15 months of patient follow up course (figure 2). The patient's UACR decreased from 527 at baseline to 92 mg/g at 6 months and continued to drop until the 15 months mark when it was 66mg/g (figure 1).

All the above described four cases maintained their bicarbonate levels similar to their baseline levels(Table 1) at periodic follow up intervals ranging from 3 to 30 months.

Discussion:

To the best of our knowledge, positive renal outcomes with safety of concomitant SGLT-2 inhibitor and GLP1 RA in GFR below 30 ml/min/m2 with macroalbuminuria has not been previously described. Three out of four patients had nephrotic range proteinuria at baseline. None of these patients had end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 mL/min/1.73m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes while on these combination therapy. These benefits were seen in patients stratified to have KDIGO Stage G4A3 and therefore very high risk renal patients.

We believe these renal benefits to be a class effect of SGLT-2 inhibitors and GLP1 RA. We report the above stated benefits with Empagliflozin 10 mg in case 1 and 4 and with Dapagliflozin 5 mg and ertugliflozin 15 mg in case 2 and 3 respectively. All four cases were concomitantly treated with Dulaglutide 1.5mg. The choice of agents was based on insurance coverage/formulary. Possible underlying renoprotective mechanisms are still under investigation. Several considerations on the

mechanism in which SGLT-2 inhibitors exert its effect include thrifty substrate hypothesis (ketosis theory), reduction in GFR triggered by vasoconstriction of afferent renal arteriole from macula densa sensing high distal tubal sodium overload and approximately 3% rise in erythropoiesis thereby reducing the work load of an overloaded/hypoxic kidney. Furthermore, reduction in oxidative stress, serum uric acid and renal angiotensinogen may also contribute(Ferrannini, Mark, & Mayoux, 2016; Mudaliar, Alloju, & Henry, 2016). Renoprotective effects of GLP-1RA could be due to it's anti-inflammatory effects, vascular endothelium protection(Dandona et al., 2018) and amelioration of oxidative stress through the GLP-1 receptors found on the glomerular, tubular and the vascular cells of the kidney(Dandona et al., 2018; Mudaliar et al., 2016) .

In CREDENCE trial the regression of UACR was approximately 35% (from app.927 mg/g to app. 600 mg/g) at 6 months follow up and maintained for a total duration of 2.62 years(Perkovic et al., 2019). AWARD-7 trial reported app.23% reduction in UACR with dulaglutide at 6 months in post hoc analysis of patients with GFR below 30 mL/min/ 1.73m^2(Tuttle et al., 2018). Here we report regression of mean UACR of all four cases by 16%, 65% and 77% at 3 months, 6 months and 9 months respectively comparing to baseline. Such impressive and continued reduction in UACR over time could be due to higher baseline UACR and also due to possible synergistic renoprotective effects of two different class of medication used together. The mean estimated GFR in CREDENCE trial (Perkovic et al., 2019) and DAPA-CKD trial(Heerspink et al., 2020) was 56.2±18.2 and app. 43 ml/min/1.73 m^2 respectively vs 23.75± 1.6 ml /minute /1.73 m^2in our case series. While these trials reported positive renal outcomes along with it's safety with SGLT-2 inhibitor ,we report the same with concomitant GLP-1RA and SGLT-2 inhibitor.

Case 1 underwent three different AV shunt placement procedures on three different occasions over a period of 2.5 years in anticipation for possible HD; however he continues to do well and has not required HD still. The timing of these procedures will have to be modified if such patients are doing well with this strategy. Near doubling of eGFR in case 3 over a period of 6 months is not fully understood; however we attribute this to impressive A1c and BP reduction along with renoprotective effects of GLP-1RA and SGLT-2 inhibitor.

Limitations of our study include retrospective study design and small sample size, but it is an important proof of concept study that will facilitate the design and conduct of large randomized clinical trials to confirm these benefits. Since the initial success of these four patients described here; it has become a standard practice for our clinic to be using SGLT-2 inhibitors concomitantly with GLP-1RA in DKD with GFR below 30 ml /minute /1.73 m^2. Therefore; we shall be able to report longer durability of renal outcomes in larger group of patients in the future.

We conclude that addition of SGLT-2 inhibitor and GLP-1RA in patients with DKD and GFR below 30 ml /minute /1.73 m^2 with microalbuminuria leads to positive composite endpoint of slowing the progression to end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. We recommend careful use of this approach only by an experienced endocrinologist to obtain the benefits and minimize the adverse events profile especially volume depletion related events in patients with KDIGO stage G4A3 kidney disease. Further randomized clinical studies will be required to confirm the benefits, durability and possible underlying mechanisms.

Author contributions: NDK: concept and design, execution of the study, wrote first draft of the manuscript and made subsequent revisions.IM: execution of the study and edits.

Data Availability Statement: Data available on request due to privacy/ ethical restrictions.

Conflict of interest: NDK serves as faculty member for speaker bureau for BI & Lily, Novo Nordisk & Astra Zeneca

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Figure Legends:

Figure 1: Graph Showing Trends of UACR of Cases 1-4

Figure 2: Graph showing Trend of eGFR in Cases 1-4 Over Time

Figure 3: Graph showing Trend of Serum BUN in Cases 1-4 Over Time

Figure 4: Graph showing trend of Serum Creatinine in Cases 1-4 Over Time