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Case Report
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Effect of Sodium-Glucose Co-Transporter 2 Inhibitor on an Obese Patient with Long-Standing Type 2 Diabetes and Solitary Kidney

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Abstract

An obese 62-year-old woman, with a prior history of left nephrectomy due to hydro nephrosis, had been on insulin therapy for the past ten years. Living with a solitary kidney (with presumptive hyper-filtration), her renal function remained preserved for decades. However, since 2015, her albuminuria deteriorated despite the addition of renin-angiotensin-aldosterone system blockade medications. She was then treated with a sodium-glucose-co-transporter-2 (SGLT2) inhibitor. This resulted in improvement of her glycemic control, body mass index, blood pressure and near normalization of albuminuria. There is a need to further evaluate the reno-protective role of SGLT2 inhibitors in individuals with glomerular-hyperfiltration, which is related to obesity and usually occur during early phase of diabetic kidney disease.

Keywords: Type 2 Diabetes; Nephrectomy; Sodium-Glucose-Co-Transporter-2 inhibitor

Introduction

Diabetic kidney disease (DKD) is a major complication of Type 2 Diabetes (T2D). It was reported that kidney complications occur in about 25% to 40% of individuals with T2D [1]. One of the early manifestations of DKD is glomerular hyper-filtration. This could be attributed to a myriad of factors including hemodynamic factor, vasoactive mediators, tubular-glomerular feedback, and systemic factors in diabetes [2]. In a unique situation of unilateral nephrectomy, glomerular hyper-filtration occurs secondary to elevated renal plasma flow in the nephrons of the remaining kidney [2]. Hence a case of co-existing T2D and unilateral nephrectomy holds intrigue to clinicians as it requires special attention on kidney function. Of emerging interest in treatment is the potential reno-protective role of sodium-glucose co-transporter (SGLT2) inhibitors in slowing renal progression by presumably ameliorating hyperfiltration and albuminuria through reduction in proximal tubular sodium and glucose transport [3].

Here, we report an uncommon case of long-standing progressive DKD and solitary kidney which responded to SGLT2 inhibitor as an add-on therapy to existing Renin-Angiotensin-Aldosterone System (RAAS) blockade.

Case Report

A 62-year-old obese (with Body Mass Index (BMI) 32 kg/m^2) Chinese woman had left total nephrectomy performed due to hydronephrosis at age 29. Four years later at the age of 33, she developed type 2 diabetes (T2D) which progressed to requiring insulin therapy 14 years after onset of diabetes. Over the past 10 years, she had fairly stable glycemic control, achieving Hemoglobin A1c (HbA1c) (done 2-3 times annually) between 7% to 8%. Her co-morbidities include stable hypertension and hyperlipidemia.

Her estimated glomerular filtration rate (eGFR) as calculated by Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation has been largely stable over the past 10 years, hovering at 60 to 70 mls/min/1.73 m^2. However, urinary albumin/creatinine ratio (uACR) worsened to reach a peak of 906 µg/mg in 2007. Therefore, she was treated with a combination of enalapril 10mg BD and losartan 100mg once daily with progressive reduction of uACR to 167 µg/mg in year 2010. Her other regular medications include: Mixtard (30/70) 24 units every morning and 22 units every evening, metformin 850 mg twice daily, hydrochlorothiazide 25 mg once daily and aspirin 100 mg once daily.

However, albuminuria gradually deteriorated again from 2011, reaching a height of 1125 µg/mg in mid-2015. Therefore, incremental anti-proteinuric therapy (i.e. spironolactone, a mineralocorticoid receptor antagonist) [4,5] was added in tandem (Figure 1). However, further intensification of rennin-angiotensin system blockade was constrained by tendency for hyperkalemia. Ultrasound kidney dated Jul 2013 confirmed absent left kidney. Right kidney measured 12.2 cm with good parenchymal thickness. To simultaneously address the suboptimal glycemic control over and above renal-retardation, Canaglifozin, a sodium-glucose-co-transporter-2 (SGLT2) inhibitor, was introduced at sub-maximal dose of 150 mg/day (interestingly, observations from recent landmark clinical trial suggested that SGLT2 inhibition at sub-maximum dose yielded similar renal-protection as maximum dose) [6]. This resulted in a reduction in HbA1c (8.6% to 6.7%), BMI (33.4 kg/m^2 to 31.4 kg/m^2), blood pressure (133 mmHg to113 mmHg) and interestingly near normalization of albuminuria (55 µg/mg). However, eGFR transiently decreased (over two months) from 56 ml/min/1.73 m^2 (CKD stage 2) to 45 ml/min/1.73 m^2 (CKD stage 3a), followed by a recovery to 57 mls/min/1.73 m^2 two months later. Alternative therapeutic that was considered to retard the renal progression included Pentoxifylline (a non-specific phosphodiesterase inhibitor). However, experience on the use of Pentoxifylline was largely derived from small-scale clinical study with relatively short duration of follow-up i.e. not as robust as SGLT2 inhibition [7]. Additionally, Pentoxiflylline has limited impact on glycemic control when compared to SGLT2 inhibitors.

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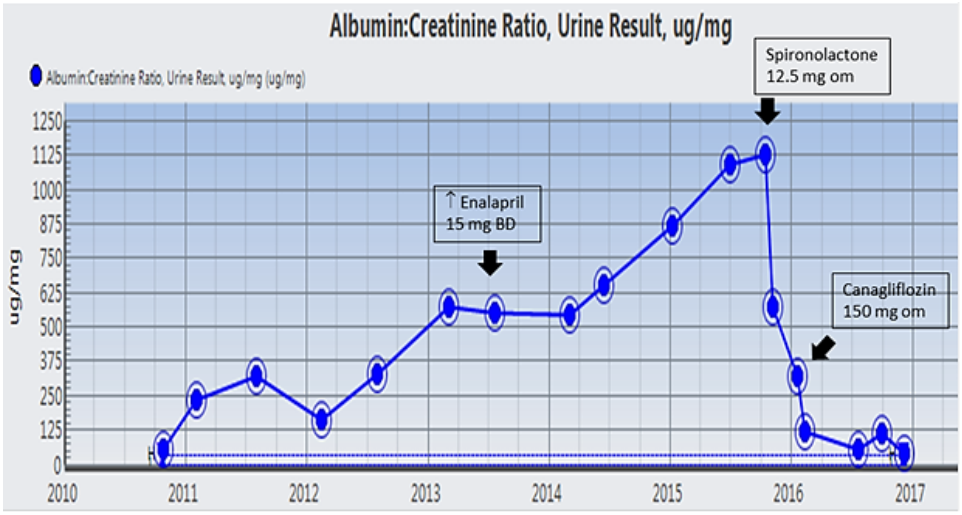

Figure 1: Albumin: Creatinine ratio of the subject.

Discussion

After unilateral nephrectomy, maladaptive hemodynamic changes typically occur in nephrons of the remaining kidney. This includes increased renal plasma flow, interglomerular pressure, glomerular-hyperfiltration and hypertrophy [8]. The phenomenon of glomerular hyper-filtration in such a situation is more marked in individuals with obesity. Furthermore, insulin resistance and hyperinsulinemia may contribute to the pathogenesis of obesity leading to proteinuria [9].

RAAS blockade induces vasodilation of renal-glomerular efferent arterioles, thereby reducing intra-glomerular pressure leading to anti-proteinuria. Inhibition of SGLT2 in proximal renal tubules purportedly increases delivery of sodium distally to macula dense, leading to adenosine release and afferent arteriolar vasoconstriction. This leads to reduced renal plasma flow and hence, reduction in intra-glomerular pressure and GFR [3]. The phenomenon is elegantly demonstrated in this unique individual with diabetic kidney disease (DKD) and solitary kidney.

Besides brisk short-term reduction of albuminuria, other potential longer-term renal-benefits of SGLT2 inhibition includes reduction of blood pressure and arterial stiffness, and decreased effective circulating fluid volume [10]. Consistent with this paradigm, recent clinical trial suggested a short-term eGFR reduction of ~5% among individuals with grade 2 chronic kidney disease with initiation of SGLT2 inhibitors [6]. However, this is usually followed by a plateauing of eGFR sustained over 3-4 years, suggesting stabilization of renal filtration function [6].

Recent evolving insights suggested the potential profound impact (e.g. on epi-genome) of regulating SGLT2. For instance, study has shown that diabetes can induce aberrant DNA methylation occurred at the genes involved in glucose metabolism, including Sglt2 [11]. This observation indicates that abnormal expression of Sglt2 might plays a role in the initiation and development of diabetes and the expression of Sglt2 might be controlled by the DNA methylation deposited at its promoter. Since DNA methyltransferases (DNMTs) are the main enzymes that are required for the establishment and maintenance of DNA methylation [12], moving forward, it is essential to investigate whether the aberrant DNA methylation patterns at Sglt2 is associated with affected function of DNMTs in diabetes patients. Interestingly, as lymphocytes derived from patients with diabetes display a distinct profile of H3K9me2 [13] and recently histone methyltransferases G9a is also found to protect DNA methylation [14], study the expression level and catalytic activity of the above epigenetic modifiers, such as DNMTs and G9a, might create a novel direction for further understanding the diabetes associated diseases in humans.

In summary, in this unique obese individual with long-standing progressive DKD and solitary kidney, we demonstrated that SGLT2 inhibitors (add-on to existing RAAS blockade) swiftly and substantially lowered albuminuria (even in macroalbuminuric range) presumably via amelioration of glomerular hyper-filtration. This suggests the need to further evaluate the reno-protective role of SGLT2 inhibitors in individuals with glomerular-hyperfiltration which usually occurs during early phase of DKD and in the presence of prevalent susceptibility factor such as obesity.

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