

Clinical use of sgl-2 inhibitors for the management of type 2 diabetes in a patient centered medical home

Abstract

Purpose: To provide current data regarding the efficacy and tolerability of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in type 2 diabetes mellitus (T2DM) patients at a large patient-centered medical home (PCMH) Multi-Specialty Physicians' Group.

Methods: A retrospective observational study that took place at a PCMH located in Buffalo, NY. Eighty-one adults aged 18-95 years old with T2DM on a SGLT-2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin) for a minimum of 3 months. Change in hemoglobin A1c (HbA1c) in addition to the percentage of patients achieving a HbA1c level below 7%. Changes in weight, changes in systolic (SBP) and diastolic (DBP) blood pressures, percentage of patients reporting adverse effects of therapy, and percentage of patients with an estimated glomerular filtration rate (eGFR) <60mL/min/1.73%.

Results: 81 patients met inclusion criteria. Mean HbA1c was significantly reduced by 1.04% after 3 months of therapy with 25.9% more patients achieving target HbA1c below 7%. A significant reduction was also observed in weight by an average of 7.33 pounds and in both SBP by 10mmHg and DBP by 4mmHg. Adverse effects were reported in 14.8% of patients with only 3 out of the 10 patients discontinuing therapy due to intolerance to side effects. 18.5% of patients had a decline in eGFR less than 60mL/min/1.73%.

Conclusion: SGLT-2 inhibitors exhibited tolerability and efficacy in T2DM patients who need to treat multiple aspects of their disease. This class of diabetic agents has the capability of maintaining control of hyperglycemia as well as blood pressure and weight, with minimal incidence of side effects.

Keywords: sgl-2 inhibitors, PCMH, diabetes mellitus, efficacy, tolerability

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Abbreviations: PCMH, patient centered medical home; SGLT-2 Inhibitors, sodium glucose Cotransport-2 Inhibitors; T2DM, type 2 diabetes; A1c, hemoglobin a1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; Egfr, estimated glomerular filtration rate; CDC, centers for disease control; ADA, american diabetes association; AACE, american academy of clinical endocrinology; SU, sulfonylureas; TZD, thiazolidinediones; DPP-4 Inhibitor, dipeptidyl peptidase 4; EMR, electronic medical record; CAD, coronary artery disease; PAD, peripheral artery disease; T1DM, type 1 diabetes; ACE, angiotensin-converting-enzyme

Introduction

The National Diabetes Statistics Report, published by the Centers for Disease Control and Prevention (CDC), reports that 29.1 million Americans over 20 years old were estimated to have diabetes. This includes those that may be undiagnosed accounting for about 8.1 million adults.¹ Type 2 diabetes mellitus (T2DM) specifically affects 90% to 95% of diagnosed patients, characterized by insulin resistance due to pancreatic beta cell dysfunction. Diabetes becomes more complicated in its association with other serious health conditions such as cardiovascular disease, obesity, and kidney failure increasing the risk of death by 50% compared to people without diabetes.¹ Uncontrolled glycemic levels produce a vicious cycle of deteriorating beta cell function and further worsening of hyperglycemia.² The likelihood for treatment failure is heightened as beta cells become less responsive to changes in insulin sensitivity.

Majority of patients need combination therapy of metformin and one or more anti-hyperglycemic agents to maintain target HbA1c levels below 7%.^{1,3} Improved glycemic control has been shown to reduce the progression of microvascular complications as well as macrovascular complications.⁴ Guidelines for the American Diabetes Association (ADA) Standards of Care were recently updated to include sodium-glucose co-transporter 2 (SGLT-2) inhibitors as an appropriate adjunct therapy to Metformin.⁵ The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) consensus statement recommends using SGLT-2 inhibitors as first line therapy.⁶ Other agents include sulfonylureas (SU), thiazolidinediones (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and basal insulin. Though these treatment options have been available longer, they are restricted by side effects such as weight gain, hypoglycemia, and cardiovascular risk.⁷ Canagliflozin was the first SGLT-2 inhibitor approved in the United States, followed by dapagliflozin and most recently, empagliflozin. Their distinctive site of action in the kidneys and their insulin independent mechanism sets these drugs apart from previous pharmacologic targets in diabetic therapy allowing them to work well synergistically with other agents while avoiding common side effects.^{8,9} Renal filtration involves regulating plasma glucose concentration. In normal adults, 90% of glucose is filtered through the kidneys daily, then reabsorbed in the proximal tubule by the SGLT-2 transporters, thus resulting in a negligible amount of glucose excreted into the urine. By inhibiting SGLT-2 transporters, glucosuria occurs,

lowering plasma glucose levels. In addition to decreasing HbA1c, the renal mechanism has also promoted weight loss, improved systolic blood pressure, and minimized hypoglycemic events. Due to the fact that many T2DM patients are overweight or obese, weight loss mechanisms are highly desirable when choosing therapy. Patients with T2DM have a greater risk of developing cardiovascular and health complications.^{1,4} Although not proven to directly modify beta cell function, improvement in blood glucose with an SGLT-2 inhibitor has a favorable effect on beta cell function.^{9,10} SGLT-2 inhibitors offer a new role in T2DM therapy for patients who have not achieved HbA1c, blood pressure, and/or weight loss goals and have experienced negative side effects from other diabetes drug classes. The progressive nature of diabetes and its growing incidence necessitates effective treatment that will benefit multiple disease components.

Materials and methods

The objective of this study was to provide current data regarding the efficacy and tolerability of SGLT-2 inhibitors in T2DM patients at a large patient-centered medical home (PCMH) Multi-Specialty Physicians' Group. Patient data was collected from the electronic medical record (EMR) and analyzed separately to determine that all inclusion criteria were met. Findings were documented in a spreadsheet that organized patient demographics (age, gender, and race), pertinent co-morbidities (hypertension, obesity, coronary artery disease (CAD) or peripheral artery disease (PAD), and renal impairment), medication history (other diabetic agents and hypertension therapy), laboratory results (HbA1c, SCr, blood pressure, calculated BMI, and weight) and reported side effects associated specifically with SGLT-2 inhibitors (hypotension, decline in eGFR <45mL/min/1.73m², nasopharyngitis, urinary tract infections, and genital mycotic infections).

Candidates for the study were 18 to 95years old diagnosed with T2DM and had documentation of at least three months of SGLT-2 inhibitor use. Exclusion criteria included diagnosis of type 1 diabetes (T1DM) or gestational diabetes, pregnancy, declined renal function defined as an eGFR <45mL/min/1.73m², patients who changed diabetic (except insulin) and/or hypertension therapy during the study period, patients who underwent weight loss surgery or had a weight loss medication in their profile. The primary endpoint for evaluating the efficacy of SGLT-2 inhibitors was the change in HbA1c from baseline. This endpoint also assessed the difference in the percentage of patients who achieved optimal HbA1c goal <7% after the addition of SGLT-2 therapy. Secondary endpoints evaluating additional therapeutic effects and the safety profile of SGLT-2 inhibitors were changes in weight, changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), and percentage of patients who declined in renal function to an eGFR <60mL/min/1.73% compared to baseline. Descriptive statistics were used to summarize demographic and anthropometric characteristics of the study groups. Data normality was assessed using D'Agostino & Pearson normality test. Paired t-test was used to evaluate continuous variables. McNemar's test was used to evaluate nominal and dichotomous data. Statistical significance was determined by a P value <0.05. The University at Buffalo Institutional Review Board deemed this study to be exempt from IRB approval on May 14, 2015.

Results

An EMR search identified 137 candidates for the study. Using pre-specified exclusion criteria, a total of 56 patients were excluded with the majority being due to lack of sufficient data or follow-up (Figure

1). Eighty-one patients were eligible to participate in the study with demographics and baseline characteristics displayed in Table 1. The study population was predominantly Caucasian, middle aged to older adults with obesity. Additional diabetes and hypertension therapy is also shown in Table 1. The most common diabetic agents utilized at baseline were metformin, DPP-4 inhibitors, and sulfonylureas, which accounted for 72%, 43%, and 33% of the patient population respectively. Baseline co-morbidities (Table 1) included patients with history of hypertension (n=70), renal insufficiency (n=24), and obesity (n=60). Within our study population, 75% of patients were on either an angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

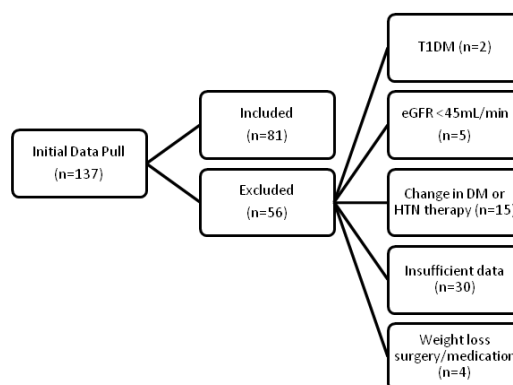


Figure 1 Pre-specified exclusion criteria.

T1DM=Type 1 Diabetes Mellitus; DM=Diabetes Mellitus; HTN=Hypertension.

Table 1 Demographical Data

Demographic data(n=81)	
Mean age (years)	61
Gender, n(%)	
Male	57(70.4)
SGLT-2, n(%)	
Canagliflozin	69(85.2)
Dapagliflozin	10(12.3)
Empagliflozin	2 (2.5)
Mean duration of SGLT-2 use (months)	5
Race, n(%)	
Caucasian	64 (79)
African American	9 (11.1)
Asian	3 (3.7)
Hispanic	1 (1.2)
Native American/Alaskan	3 (3.7)
Unknown	1 (1.2)
Comorbidities, n(%)	
Obesity	60 (74.1)
Hypertension	70 (86.4)
CAD	21 (25.9)

Table continued...

Demographic data(n=81)	
PAD	4 (4.9)
Renal insufficiency	24 (29.6)
Concurrent diabetes medications, n(%)	
Metformin	58 (71.6)
Sulfonylurea	27 (33.3)
Alpha-glucosidase inhibitor	1 (1.2)
Thiazolidinedione	7 (8.6)
Dipeptidyl Peptidase-4 (DPP-4) Inhibitor	35 (43.2)
Glucagon-like Peptide-1 (GLP-1) Agonist	18 (22.2)
Insulin	25 (30.9)
Concurrent blood pressure medications, n(%)	
Angiotensin-Converting Enzyme (ACE)/ Angiotensin Receptor Blocker (ARB)	61 (75.3)
Beta Blocker (BB)	31 (38.3)
Calcium Channel Blocker (CCB)	22 (27.2)
Diuretic	28 (34.6)
Other	2 (2.5)

Table 2 Primary and secondary endpoints

Characteristic(n=81)	Baseline	3months	P-value
HbA1c (%), mean±SD	8.67±1.49	7.63±1.31	< 0.0001
HbA1c <7%, n(%)	7 (8.6)	28 (34.6)	< 0.0001
Weight (lb), mean±SD	233±48	226±50	< 0.0001
SBP (mmHg), mean±SD	134±15	124±11	< 0.0001
DBP (mmHg), mean±SD	77±8	73±8	0.0021
eGFR <60mL/min/1.73%, n(%)	5(6.2)	15(18.5)	0.0063

SBP=systolic blood pressure; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate

Table 3 Side effects reported

Side effect reported (n=81)	n(%)
eGFR decline (<45 mL/min/1.73%)	5 (6.2%)
Nasopharyngitis	3 (3.7%)
Genital Mycotic Infection	2 (2.5%)
Hypotension	1 (1.2%)
Urinary Tract Infection	1 (1.2%)

eGFR=estimated glomerular filtration rate

Of the SGLT-2 inhibitors, canagliflozin was used by 85% with only 10% accounting for dapagliflozin users and 2% accounting for empagliflozin users. Canagliflozin was often initiated at 100 mg daily and titrated to a daily dose of 300mg if the patient sufficiently tolerated use. Mean duration of SGLT-2 inhibitor therapy was 5months. Summary of results from study primary and secondary endpoints can be viewed in Table 2. In at least 3months of use, mean HbA1c was significantly reduced by 1.04%(<0.0001) with 28 patients (P<0.0001) reaching an HbA1c goal of <7%, which was 21 more patients than

at baseline. All secondary endpoints reached statistical significance. Participants lost an average of 7.33 pounds (P<0.0001). Blood pressure reduction was seen in both SBP (-10mmHg; P<0.0001) and DBP (-4mmHg; P=0.0021). SGLT-2 inhibitor effects on renal function was found in 10 more patients compared to baseline showing decline in eGFR <60mL/min/1.73% (P=0.0063). Side effects (Table 3) were reported in 14.8% of patients, with the most common being decline in eGFR to <45mL/min/1.73% (n=5) and nasopharyngitis (n=3). There were no documented events of hypoglycemia. Ten patients (12.3%) discontinued therapy with the most common reason being that they switched therapy to another SGLT-2 or other diabetes agent (n=6) and only two (20%) reported stopping due to genital mycotic infections and one (10%) reported stopping due to nasopharyngitis.

Table 4 Reason for discontinuation of SGLT-2 inhibitor

Discontinuation reason(n=10)	n(%)
Cost/Insurance	2(20%)
Genital Mycotic Infection	2(20%)
Nasopharyngitis	1(10%)
Switched therapy	6(60%)

Discussion

Only 3 out of the 10 patients that discontinued therapy did so due to intolerance to side effects, specifically development of genital mycotic infection (n=2) and nasopharyngitis (n=1). While genital mycotic infections are a documented side effect and cause for discontinuation, nasopharyngitis is much less common and surprising to see in these results.¹⁰⁻¹³ Previously published data reports higher incidence of genital mycotic infections and much lower incidence of nasopharyngitis compared to our data.^{10,13} This could be due to the geographical location of the PCMH in the northeast where nasopharyngitis is common during certain times of the year and symptoms of nasopharyngitis can be easily mistaken for an allergy to pollen, another a common ailment in the northeast.

The mean time on an SGLT-2 inhibitor during our study period was 5months and it is known that the maximum effect can take up to 6months to be realized.¹² Our study showed that these agents show efficacy, with an average HbA1c lowering of -1.04%, when used in a clinical environment in a PCMH. This is unique in that our mean change in HbA1c after 3months was better than previously published data. Monami et al published a met-analysis that showed a mean change in HbA1c of -0.695%,¹² Rosentock et al.¹⁰ showed a similar lowering of HbA1c from baseline of -0.76%, and Berhan & Barker¹¹ reported a mean change in HbA1c of -0.78%. Similarly, our results showed an average change in weight of -7 pounds (-3.17kg) while other studies have shown weight changes of -5.7 pounds (-2.6kg) and -1.3 pounds (-0.59kg). In addition, our results showed a more pronounced lowering of SBP and DBP (-10mmHg and -4mmHg respectively) as compared to other published data.^{10,13}

Hypoglycemia was not reported as a side effect or reason for discontinuation in our study population which is supported by their mechanism of action and overall incidence of hypoglycemia.⁸ Data was collected and reported on how many patients had a decline in renal function as measured by eGFR, since SGLT-2 inhibitors act on the kidneys and have to be renally dosed.^{8,14} In addition, there were no documented cases of diabetic ketoacidosis (DKA) in this study

population. Data related to the incidence of eGFR decline has not been previously published in a way that is meaningful to a PCMH clinician. Having a sense of how many of your patients will have declining renal function on an SGLT-2 inhibitor is invaluable to clinicians because they are better able to weigh the risks and benefits with patients before making a drug therapy decision.

Limitations

Our study has several limitations, including utilization of observational techniques. Although SGLT-2 inhibitors demonstrated favorable results, there is no establishment of cause and effect due to the retrospective nature of this study. Outcomes were demonstrated in a small patient population limited to one PCMH. A larger sample size in a variety of settings and locations may elicit different results. The study population was also predominantly Caucasian (79%), middle aged to older adults (61 years) with obesity (74.1%). Additionally, the majority of participants were male (70.4%). Lack of diversity shown in this population may hinder the applicability of these results to groups that do not fit this patient profile. The larger male representation could have also affected the incidence of certain adverse events such as genitourinary infections, which had a lower occurrence than expected.

A major limitation to our study was reliance on EMR for data collection. Only documented labs and reported side effects could be included, thus additional adverse events may have occurred that were not reported by patients or documented by clinicians. Some patient data was incomplete with all the required information for appropriate assessment of clinical efficacy of SGLT-2 inhibitors (e.g. HbA1c labs in the period of SGLT-2 use). Absence of necessary labs caused many patients to be excluded from the study to expand the analyzed population. Another drawback from EMR, was that eGFR values were not uniformly reported in patient records. For example, instead of indicating a specific eGFR value, eGFR >60mL/min/1.73% would be reported instead. This prevented more accurate statistical analysis of changes in eGFR to display the effects of SGLT-2 inhibitors on renal function.

Adherence was not evaluated, but it can be inferred that oral once daily dosing would cause less missed doses and better compliance compared to multiple daily doses and injectable therapy. Another uncontrollable factor was the development of infections and illnesses during the study period. These occurrences can exacerbate patients' glycemic control through stress, interruption in chronic therapy, hospitalizations, and steroid use. And given that this study took place in the northeastern region of the United States, allergies and the common cold are quite prevalent. Lastly, as the first SGLT-2 inhibitor approved, most patients observed were using canagliflozin as expected. Study outcomes can be possibly viewed as a more accurate representation of canagliflozin rather than a class effect.

Conclusion

This retrospective observational study in T2DM patients in a single PCMH demonstrated SGLT-2 inhibitor efficacy and safety showing significant improvements in HbA1c, the number of patients to reach HbA1c goal <7%, weight loss, and blood pressure with minimal incidences of discontinuation and adverse events. SGLT-2 inhibitors exhibited a variety of favorable effects that would be beneficial in uncontrolled T2DM patients who have been unsuccessful with other diabetes drug classes. They are a safe and effective option for targeting

multiple aspects of diabetes and the co-morbidities that accompany its progression.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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