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Use of SGLT-2 Inhibitors in Patients With Type 1 Diabetes Mellitus

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Abstract

Introduction: Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are the newest class of oral antihyperglycemic medications approved for the treatment of type 2 diabetes mellitus (DM2). Although they are not approved for use in type 1 diabetes mellitus (DM1), SGLT2 inhibitors may help DM1 patients achieve their HbA1c goals by decreasing their insulin requirements, without inducing hypoglycemic episodes and weight gain. **Methods:** We conducted a retrospective chart review of 26 patients with DM1 treated with off-label SGLT-2 inhibitors. The primary objective was change in HbA1c and weight. The secondary objective was assessing the effect on insulin requirements, blood pressure, and lipid profile. **Results:** Improvement in HbA1c level was seen in 20 of the 26 patients (77%) after initiation of SGLT-2 inhibitors. The average decrease in HbA1c was 0.32% ($P = .032$), with changes seen as early as 1 month posttherapy and maintained with continued SGLT-2 inhibitor use. There was a trend toward weight loss that was not significant. No significant changes in blood pressure or lipid profiles were seen except for a slight increase in low-density lipoprotein ($P = .049$). No patient developed euglycemic diabetic ketoacidosis. Three patients discontinued therapy due to uncontrolled genital yeast infections. **Conclusion:** SGLT-2 inhibitors can be a useful adjunctive therapy in patients with DM1 to improve glycemic control and weight. Although our study did not show any significant changes in the metabolic profile and insulin requirements in these patients, a larger sample size may yield different results.

Keywords

managed care, medications, disease management, practice management, long-term care

Introduction

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are the newest class of oral antihyperglycemic medications approved for the treatment of type 2 diabetes mellitus (DM2). They block SGLT-2 transporters in the kidney and inhibit glucose reabsorption from the renal tubules. Current studies have shown significant improvement in glycemic control, cardiovascular outcomes, and metabolic parameters in patients with type 2 diabetes.[1-6] Although they are not approved for use in type 1 diabetes mellitus (DM1), SGLT-2 inhibitors may improve glycemic control, decrease insulin requirements and help with weight loss. We aimed to evaluate the change in glycemic control and metabolic profile seen in DM1 patients treated with combination SGLT-2 therapy and insulin at the Cleveland Clinic.

Methods

We conducted a retrospective chart review of 50 patients with DM1 at the Cleveland Clinic who had at least 1 follow-up visit after initiation of off label SGLT-2 therapy (canagliflozin, empagliflozin, or dapaliflozin). Those treated with only insulin prior to initiation of therapy with off label SGLT-2 inhibitors were included. This study was approved by the institution review board at the Cleveland Clinic. All authors had access to the data. The following ICD-9 (250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31. 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 150.73, 250.81, 250.83, 250.91, 250.93) and ICD-10 (E10.00-E10.99) codes were used. There is no conflict of interest to report.

Objectives

The primary objective was evaluation of change in HbA1c and weight. The secondary objective was assessing the effect on insulin requirements, blood pressure (BP), and lipid profile.

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Table 1. Baseline Characteristic of the Patients With DM1.

Baseline Characteristics	Mean	Range
HbA1c (%)	8.27	6.4-10.7
Age (years)	47	23-67
Weight (kg)	88.4	63-117
BMI (kg/m^2)	29.81	22-47
Systolic BP (mm Hg)	122	90-173
Diastolic BP (mm Hg)	73	53-104
TG (mg/dL)	83	35-228
Cholesterol (mg/dL)	169	120-249
HDL (mg/dL)	60	37-112
LDL (mg/dL)	92	60-143

Abbreviations: DM1, diabetes mellitus type 1; HbA1c, glycated hemoglobin; BMI, body mass index; BP, blood pressure; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Statistical Analysis

Nonparametric data were analyzed using Wilcoxon signed rank test. Spearman correlation (rho) was used to assess the relationship between change in HbA1c and duration of therapy.

Baseline Characteristics

A total of 26 patients were included, 17 of whom were female, and 9 were male. Fourteen patients were on insulin pump therapy while the rest were on insulin injections. The average baseline characteristics were as follows: age 45 years, body mass index (BMI) 29.4 kg/m^2, HbA1c 8.26%, weight 88.4 kg, duration of DM1 28 years (n = 15 due to incomplete data). The average duration of SGLT-2 therapy was 10 months (range 1-42 months; see Table 1).

Results

Therapy with SGLT-2 inhibitors ranged from 1 month to 14 months (average 7.5 months). Twenty out of the 26 patients showed improvement in their HbA1c, 1 patient did not show any change, while 5 had worsening of their glycemic control. Of those that had worsening in their glycemic control, 2 were treated with empagliflozin and the rest with canagliflozin. The characteristics of these patients is shown in Table 2. HbA1c improved to 7.9% (SD 1.2) with a decrease of 0.32% ($P = .032$) with therapy. Improvement in glycemic control was seen as early as 1 month posttherapy and was maintained with continued SGLT-2 inhibitor use. There was a slight increase in LDL level with therapy, from mean of 93 mg/dL (SD 29) to 98 mg/dL (SD 32); $P = .049$. No significant changes were seen with regard to weight ($P = .518$), systolic BP ($P = .95$), diastolic BP ($P = .273$), triglycerides ($P = .84$), high-density lipoprotein (HDL; $P = .094$), or cholesterol ($P = .60$). Changes in the metabolic profile are shown table 3. There was a non-significant weak negative correlation between HbA1c change and duration of SGLT-2 inhibitor therapy (rho -0.2, p=0.35) indicating that the change in HbA1c may not be solely associated with the latter; limitation may be due to low power to detect differences.

Adverse Events

No patients developed euglycemic diabetic ketoacidosis. The medication was discontinued in 3 patients due to uncontrolled genital yeast infections. Cost was a limiting factor in most patients as the cost can range up to several hundred dollars for a month supply if not covered by the insurance

Discussion

DM1 is a lifelong disease requiring continuous insulin therapy. Glycemic control is essential in these patients to help decrease the development of microvascular and macrovascular complications. Intensification of therapy is usually limited out of concern for hypoglycemic episodes. Insulin is also associated with weight gain and worsening of blood pressure due to its anabolic effects, which in turn may exacerbate cardiovascular complications. The role of oral medications to target the metabolic profile of these patients is currently being investigated. To date, pramlintide is the only oral medication approved for use in patients with DM1. Its use may be limited by multiple daily dosing and gastrointestinal side effects. Metformin has not been shown to improve HbA1c levels in patients with DM1 despite the significant improvement in weight and insulin requirements seen. Similarly, dipeptidyl peptidase-4 inhibitors have been shown to reduce insulin requirements without a significant change in the HbA1c level. Data regarding improvement in glycemic control with glucagon-like peptide-1 receptor agonists have been inconsistent.

In 2013, canagliflozin was the first SGLT-2 inhibitor therapy to be approved for use in the United States after early results from the CANVAS trial showed significant improvement in cardiovascular outcome in patients with DM2. Studies have since shown significant cardiovascular and renal benefit in patients with DM2 on the various SGLT-2 inhibitor therapy. The significant improvement in weight, insulin requirements, and BP control seen has made this class of antidiabetic medication among the preferred choice of therapy in patients with DM2.

Although not approved for use in patients with DM1, SGLT-2 inhibitors may improve glycemic control, decrease insulin requirements, and help with weight loss. Hypoglycemic episodes can also be potentially avoided since they do not involve endogenous insulin production. Early studies evaluating the role of SGLT-2 inhibitors in

Table 2. Characteristics of the Patients Who Either Had No Improvement or Worsening of Glycemic Control With SGLT-2 Inhibitor Therapy.

HbA1c Change (%)	Insulin Regimen	SGLT-2 Inhibitor Prescribed	Duration of SGLT-2 Inhibitor Therapy (Months)	Reason for SGLT-2 Inhibitor Discontinuation	Age (Years)	BMI (kg/m^2)	Gender	Duration of DM1 Prior to Initiation of SGLT-2 Inhibitor Therapy (Months)
No change	Insulin pump	Canagliflozin 300 mg daily	14	—	68	30	Male	New diagnosis
Increase by 0.4	Insulin pump	Empagliflozin 25 mg daily	12	—	24	22	Male	12
Increase by 1	Insulin pump	Empagliflozin 10 mg daily	11	—	73	27	Female	5
Increase by 1.3	Basal/Bolus	Canagliflozin 100 mg daily	1	—	24	22	Male	24
Increase by 0.2	Basal/Bolus	Canagliflozin 100 mg daily	4	Fatigue	54	25	Male	3
Increase by 0.7	Basal/Bolus	Canagliflozin 300 mg daily	3	Cost	48	29	Female	1

Abbreviations: SGLT-2 inhibitor, sodium-glucose cotransporter 2 inhibitor; DM1, diabetes mellitus type 1.

Table 3. Changes in the Metabolic Profile Seen With SGLT-2 Inhibitor Therapy in Patients With DM1.

Characteristics	Pretherapy Mean	Posttherapy Mean	SD	*P*
HbA1c (%)	8.27	7.9	1.2	.032
Weight (kg)	88.4	88	10.1	.518
Systolic BP (mm Hg)	121.5	121.8	13.9	.951
Diastolic BP (mm Hg)	73	71	9.9	.273
TG (mg/dL)	83	95	55	.841
Cholesterol (mg/dL)	169	165	46	.603
HDL (mg/dL)	60	61	19	.094
LDL (mg/dL)	92	98	32	.034

Abbreviations: SGLT-2 inhibitor, sodium-glucose cotransporter 2 inhibitor; DM1, diabetes mellitus type 1; BP, blood pressure; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SD, standard deviation.

DM1 patients were soon abandoned after an increased incidence of euglycemic diabetic ketoacidosis was seen, leading to the US Food and Drug Administration warning in 2015.[7] Recent results from the DEPICT-1 trial have shown otherwise, where patients with DM1 treated with dapagliflozin displayed a significant improvement in their HbA1c level with no increased risk of diabetic ketoacidosis compared with the control group. More studies are needed to evaluate the role this medication class in patients with DM1.

Our study showed a significant improvement in HbA1c level in patients with DM1 treated with SGLT-2 inhibitors. The improvement seen was less than that reported in literature for DM2 patients where rates ranged between 0.5% and 1.05%. Reduction in weight reported in literature has ranged between 1.2 and 2.37 kg, again based on the dose and type of SGLT-2 inhibitor medication used.[8] The mechanism for weight loss appears to be secondary to glycosuria and alteration in fat metabolism.[9] There continues to be ongoing studies looking at the mechanism of weight loss induction by these medications, including the use of combined GLP-1 (glucagon-like peptide 1) agonist therapy to help maximize weight loss by suppressing the increased appetite seen with SGLT-2 inhibitor therapy. Although our study showed a downward trend in weight in our patients (mean decrease of 0.5 kg), it was not statistically significant.

A mild increase in LDL-cholesterol levels was seen consistent with previous studies. LDL-cholesterol is composed of small density LDL (sd LDL) and large buoyant LDL (lb-LDL). Lb-LDL has been shown to be less atherogenic than sd-LDL with higher sd-LDL levels being associated with an increased risk of coronary artery disease.[10] The rise in LDL-C with SGLT-2 therapy is reflective of an increase in lb-LDL, while sd-LDL levels are decreased.[11,12] While other studies have shown an increase in HDL levels with SGLT-2 inhibitor therapy, we did not find any significant change in the remaining lipid panel in our study.

Reduction in blood pressure and improvement in cardiovascular profile such as reduced arterial stiffness has also been shown with SGLT-2 inhibitors in patients with type 2 diabetes.[13-17] No significant changes in systolic or diastolic BP were seen in our study, partly due to insufficient data and small sample size. Recent studies evaluating dual SGLT-1 and SGLT-2 inhibitor therapy (sotagliflozin) to inhibit glucose reabsorption in both the intestine and kidney have been promising, including in patients with DM1.[8,18,19]

Limitations

Our study is a retrospective study and is limited by our small sample size. No comparison was done between medications within the SGLT-2 inhibitor class. In addition, there was no standardization of therapy amongst the patients included and information on adherence with medical therapy was limited.

Conclusion

Our study shows that SGLT-2 inhibitors can potentially be used as adjunctive therapy in patients with DM1 to improve glycemic control with sustainable results. Larger prospective trials are needed to shed more light in this regard. No incidence of euglycemic diabetic ketoacidosis was seen, however the duration of therapy was limited to 42 months. Studies have shown improvement in the metabolic profile of patients with DM2 treated with SGLT-2 inhibitors and this benefit may also be seen in patients with DM1. Although our study did not show any significant changes in weight or metabolic profile in these patients, our sample size was small.

Declaration of Conflicting Interests

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