Real-world evaluation of insulin requirements after GLP1 agonist or SGLT2 inhibitor initiation and titration

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Purpose. To describe insulin adjustments made following initiation of glucagon-like peptide 1 agonist (GLP1a) or sodium-glucose cotransporter-2 inhibitor (SGLT2i) therapy in patients within a primary care setting.

Methods. This was a multicenter, retrospective cohort study conducted at an academic health system. Adults with type 2 diabetes mellitus initiated on a GLP1a or SGLT2i while on insulin and managed by an ambulatory care pharmacist were included. The primary endpoint was the percent change in total daily insulin dose at specified time points (2 weeks, 4 weeks, 6 weeks, 3 months, and 6 months) after agent initiation. The secondary endpoints included a glycosylated hemoglobin (HbA_{1c}) value of less than 8%, change from baseline HbA_{1c}, and safety profiles of GLP1a therapy and SGLT2i therapy.

Results. Of the 150 patients included, 123 were initiated on a GLP1a and 27 on an SGLT2i. After 6 months, GLP1a initiation had resulted in a mean 23.5% decrease ($P < 0.001$) in insulin dosage and SGLT2i resulted in a mean 0.2% increase ($P = 0.20$). Insulin dosage reduction with GLP1a use was significantly different between baseline and each time point ($P < 0.001$). About 72% of patients initiated on a GLP1a and 59% of those initiated on an SGLT2i achieved an HbA_{1c} value of less than 8%. The mean absolute change from baseline in HbA_{1c} concentration was –1.7% with GLP1a use and –1.5% with SGLT2i use ($P < 0.001$ for both comparisons with baseline values). Hypoglycemia occurred in 21% of patients on a GLP1a and 11% of those on an SGLT2i.

Conclusion. After GLP1a initiation, the mean total daily insulin dose decreased by 23.5%; after SGLT2i initiation, insulin requirements increased by a mean of 0.2%. These results will help guide insulin adjustments after initiation of these medications.

Keywords: SGLT2 inhibitors, GLP1 agonists, diabetes, insulin, primary care

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Glucagon-like peptide 1 agonists (GLP1a) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) are 2 of the many pharmacological classes of medications used in the management of type 2 diabetes mellitus (T2DM). In addition to glycemic benefits, some agents within these classes have a demonstrated ability to reduce the incidence of negative cardiorenal outcomes.[1,2] Additionally, they provide the potential to reduce supplemental insulin requirements when utilized in patients requiring insulin therapy and may potentially help in reducing the risk of overbasalization.[3]

GLP1a and SGLT2i offer unique mechanisms in providing glycemic control. To reduce blood glucose, GLP1a augment insulin secretion and decrease glucagon secretion, therefore decreasing insulin resistance.[4] On the other hand, SGLT2i reduce blood glucose by inhibiting renal tubular glucose reabsorption and have been demonstrated to reduce insulin resistance.[5]

In clinical trials, GLP1a reduced glycosylated hemoglobin (HbA_{1c}) by 0.7% to 1.7%, while SGLT2i decreased HbA_{1c} by 0.3% to 1.2%.[6] Given these agents' mechanisms of action, HbA_{1c} reduction potential, and effect on insulin resistance, their initiation may warrant a reduction in insulin dosage requirements. This is particularly important to mitigate the risk of frequent hypoglycemic episodes and weight gain that can be associated with high doses of insulin.[7]

There are different recommendations by clinicians for insulin adjustment at the time of GLP1a initiation; some recommend a 30% to 50% preemptive reduction in the insulin dose when the agent is added.[2] Alternatively, in several studies of the various GLP1a medications (including liraglutide, dulaglutide, exenatide, and semaglutide), the insulin dose was typically reduced empirically by 20% in patients with an HbA_{1c} concentration less than 8% at the time of agent initiation.[8-11] On the other hand, with SGLT2i use, a reduction in the insulin dose is recommended by the American Diabetes Association (ADA), but specific guidance for empiric dose reduction is lacking.[12]

Real-world experience of insulin dose adjustments when initiating one of these agents may improve patient safety by reducing the adverse effects of insulin, such as hypoglycemic episodes. This can also alleviate patient concerns of initiating a new medication if their insulin therapy is appropriately adjusted. Therefore, the purpose of the study described here was to evaluate the impact of initiating GLP1a or SGLT2i therapy on insulin dose adjustments for pharmacist-managed patients with T2DM.

KEY POINTS

- Glucagon-like peptide 1 agonists (GLP1a) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) are commonly used in the treatment of type 2 diabetes mellitus; however, literature regarding insulin dose adjustments upon initiation and titration is lacking.
- In a multicenter, retrospective cohort study (n = 150), the mean total insulin dose decreased by 23.5% from baseline 6 months after GLP1a initiation and slightly increased (by 0.2%) after SGLT2i initiation.
- Most patients achieved a glycosylated hemoglobin (HbA_{1c}) concentration of less than 8% after GLP1a or SGLT2i initiation, and the average absolute decrease in HbA_{1c} values was more than 1.5% after initiation of either medication class.

Methods

This multicenter, retrospective cohort analysis included adults with T2DM initiated on a GLP1a or SGLT2i from January 2016 to December 2019 while on concomitant insulin therapy (basal with or without bolus). Patients with at least 1 visit (face-to-face or telemedicine) with an ambulatory care pharmacist at Henry Ford Health System (HFHS) were included. Patients who were pregnant, greater than 80 years of age, or actively managed by endocrinology (defined by at least 2 visits in the past 6 months) were excluded. HFHS is an urban, academic health system in the metropolitan area of Detroit, MI; at the time of the study, there were 5 ambulatory care pharmacists at 6 primary care sites. The study was intended to focus on medication adjustments performed by the ambulatory care pharmacist. This study was reviewed and approved by the HFHS institutional review board prior to data collection.

Each ambulatory care pharmacist has a collaborative practice agreement within their clinic that includes management of T2DM, hypertension, and dyslipidemia. The collaborative practice agreement allows pharmacists to adjust medications based on current guidelines rather than a protocol. Given the benefits of GLP1a and SGLT2i use, pharmacists attempted to start either of these agents when indicated based on comorbidities, patient willingness, cost, insurance authorization, and other patient-specific factors. Follow-up intervals were based upon the pharmacists' discretion and could range from within 3 days to within 1 to 2 months after the initial visit. Patients received follow-up care either by telephone or face-to-face encounters. For any concerns that arose after hours, patients were provided the contact information for the 24/7 medical advice line in order to speak with a team member for urgent issues. The clinic workflow is displayed in Figure 1.

The primary endpoint was the percent change in total insulin dose from baseline to different time intervals (2 weeks, 4 weeks, 6 weeks, 3 months, and 6 months) following initiation of a GLP1a or SGLT2i. The secondary endpoints included the proportion of patients achieving an HbA_{1c} value less than 8%, change from baseline HbA_{1c}, discontinuation of sulfonylurea therapy at 6 months, change from baseline weight, and adverse effect profile of the agents. Though the HbA_{1c} target is typically individualized based on several factors, attainment of an HbA_{1c} value of less than 8% was defined as a secondary endpoint to align with quality standards (ie, Healthcare Effectiveness Data and Information Set [HEDIS] measures).[13]

Data collection. Patients meeting inclusion and exclusion criteria were identified via the electronic health record. The following data was manually collected via chart review: baseline demographics, insulin doses (basal and bolus), concomitant antihyperglycemic agent use (including metformin, sulfonylurea, dipeptidyl peptidase 4 inhibitors, and thiazolidinedione), HbA_{1c} and weight at predefined time points (at baseline, 3 months, and 6 months), patient loss to pharmacist follow-up, frequency of attainment of the maximum

Figure 1. Visit flowchart. GLP1a indicates glucagon-like peptide 1 agonist; SGLT2i, sodium-glucose cotransporter 2 agonist.

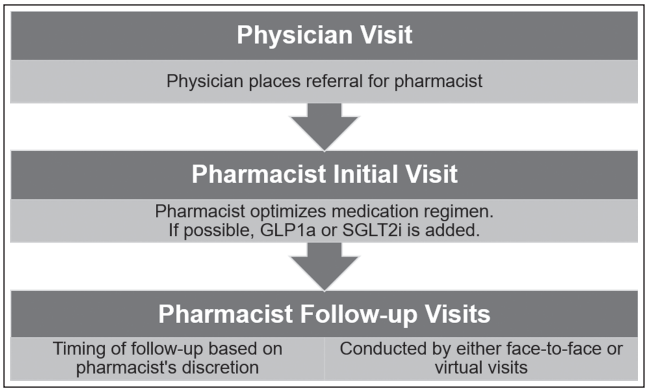
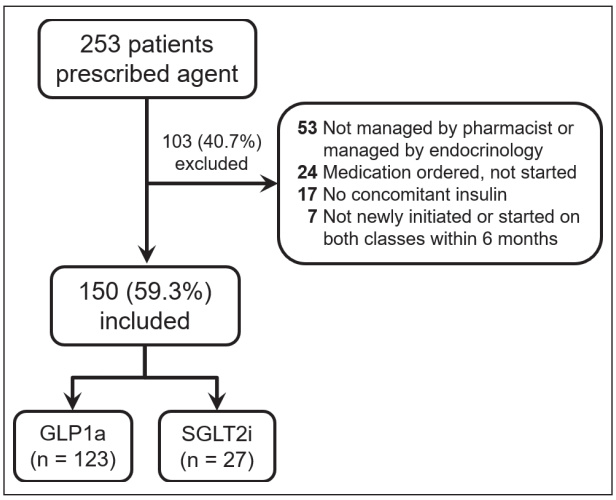


Figure 2. Patient enrollment flowchart. GLP1a indicates glucagon-like peptide 1 agonist; SGLT2i, sodium-glucose cotransporter 2 agonist.



GLP1a or SGLT2i dosage, frequency of bolus insulin discontinuation, and adverse effects (including hypoglycemia, nausea or vomiting, diarrhea, pancreatitis, tachycardia, urinary symptoms, and genital infection). Hypoglycemia was defined as a patient-reported blood glucose concentration of less than 70 mg/dL. Patients who were deemed lost to follow-up had 3 unsuccessful outreaches to reschedule the visit. The maximum dosage for each medication considered at the time of the study can be found in the eAppendix.

Statistical analysis. Descriptive statistics were used to characterize demographic and baseline factors. Categorical variables were described using frequencies and proportions, and continuous variables were expressed as mean and standard deviation (SD) since the data was normally distributed. The primary endpoint was analyzed by repeated-measures analysis of variance (ANOVA) to compare the total insulin dosage from baseline to each consecutive time point; the Greenhouse-Geisser correction was used to correct for lack of sphericity. If a statistically significant difference was found with ANOVA, a Bonferroni post hoc test was conducted to identify at which time interval the difference occurred. The secondary endpoint of HbA_{1c} less than 8% was analyzed with the chi-square test. Change from baseline HbA_{1c} was compared with a paired *t* test, and discontinuation of sulfonylurea therapy at 6 months was evaluated with McNemar's test. All other categorical variables were analyzed with the chi-square test and continuous variables with Student's *t* test. Logistic regression was also conducted to analyze which predictive factors were more likely to result in achievement of HbA_{1c} less than 8% or discontinuation of bolus insulin. All data was analyzed using SPSS, version 26.0 (IBM Corporation, Armonk, NY), and statistical significance was indicated by a *P* value of ≤0.05.

Results

A total of 253 patients were screened and, of these, 150 met criteria for inclusion in the analysis (Figure 2); 123 patients were initiated on a GLP1a and 27 were started on an SGLT2i. Baseline characteristics are displayed in Table 1. In the GLP1a group, 37 patients (30.1%) were on liraglutide, 68 (55.3%) were on dulaglutide, and the remaining 2 patients (1.6%) were on exenatide. The majority of patients in the SGLT2i group were started on empagliflozin (24 patients, 88.9%), and 3 patients (11.1%) were initiated on canagliflozin. The average baseline metformin daily dose was approximately 1,720 mg in both groups, which did not necessitate much titration by the pharmacist. However, in patients who were initiated on a GLP1a, the metformin dose was increased in 4 patients; it was decreased in 1 patient due to progressing chronic kidney disease. Since use of a dipeptidyl peptidase 4 inhibitor was discontinued in the 4 patients who were initiated on a GLP1a, only 2 patients continued to receive either a dipeptidyl peptidase 4 inhibitor or a thiazolidinedione. No other antihyperglycemic agents were identified at baseline.

The average insulin dose adjustments following initiation of GLP1a or SGLT2i are displayed in Table 2. The mean total insulin dose was 72.2 units prior to initiation of GLP1a and 73.3 units prior to SGLT2i initiation. Repeated-measures ANOVA showed a significant change in total insulin

Table 1. Baseline Characteristics by Study Group

Variable	GLP1a (*n* = 123)	SGLT2i (*n* = 27)
Age, mean (SD), y	59.9 (11.2)	60.4 (10.0)
Female, No. (%)	80 (65.0)	11 (40.7)
African American, No. (%)	97 (78.9)	23 (85.2)
Concomitant metformin use, No. (%)	82 (66.7)	22 (81.5)
Average daily dose, mean (SD), mg	1,729.4 (415.5)	1,727.3 (493.8)
Concomitant sulfonylurea use, No. (%)	17 (13.8)	5 (18.5)
Dipeptidyl peptidase 4 inhibitor use, No. (%)	4 (3.3)[a]	1 (3.7)
Thiazolidinedione use, No. (%)	0 (0)	1 (3.7)
HbA_{1c} mean (SD), %	9.3 (1.6)	9.5 (1.6)
HbA_{1c} <8%, No. (%)	13 (10.6)	3 (11.1)
Weight, mean (SD), kg	107.6 (26.1)	104.4 (26.1)
Body mass index (kg/m^2), mean (SD)	37.3 (7.6)	37.5 (8.9)
GFR (mL/min/1.73 m^2), mean (SD)	84.5 (25.5)	86.0 (21.5)
<60 mL/min/1.73 m^2, No. (%)	24 (19.5)	6 (22.2)
Insulin dosage prior to initiation, mean (SD)		
Total insulin units	72.2 (47.9)	73.3 (48.4)
Basal insulin units	54.7 (28.9)	56.9 (33.3)
Bolus insulin units	17.5 (28.5)	16.4 (25.4)

Abbreviations: GFR, glomerular filtration rate; GLP1a, glucagon-like peptide 1 agonist; HbA_{1c}, glycosylated hemoglobin; SD, standard deviation; SGLT2i, sodium-glucose cotransporter 2 inhibitor.
[a]Dipeptidyl peptidase 4 inhibitor use discontinued at GLP1a initiation.

Table 2. Mean Absolute Percent Change in Insulin Dose After GLP1a or SGLT2i Initiation

Study Group	Empiric[a]	2 wk	4 wk	6 wk	3 mo	6 mo	*P* Value[b]
GLP1a (*n* = 123)	–7.5	–10.3	–10.6	–13.0	–21.4	–23.5	<0.001
SGLT2i (*n* = 27)	–3.6	–4.1	–3.7	–3.5	–1.7	+0.2	0.20

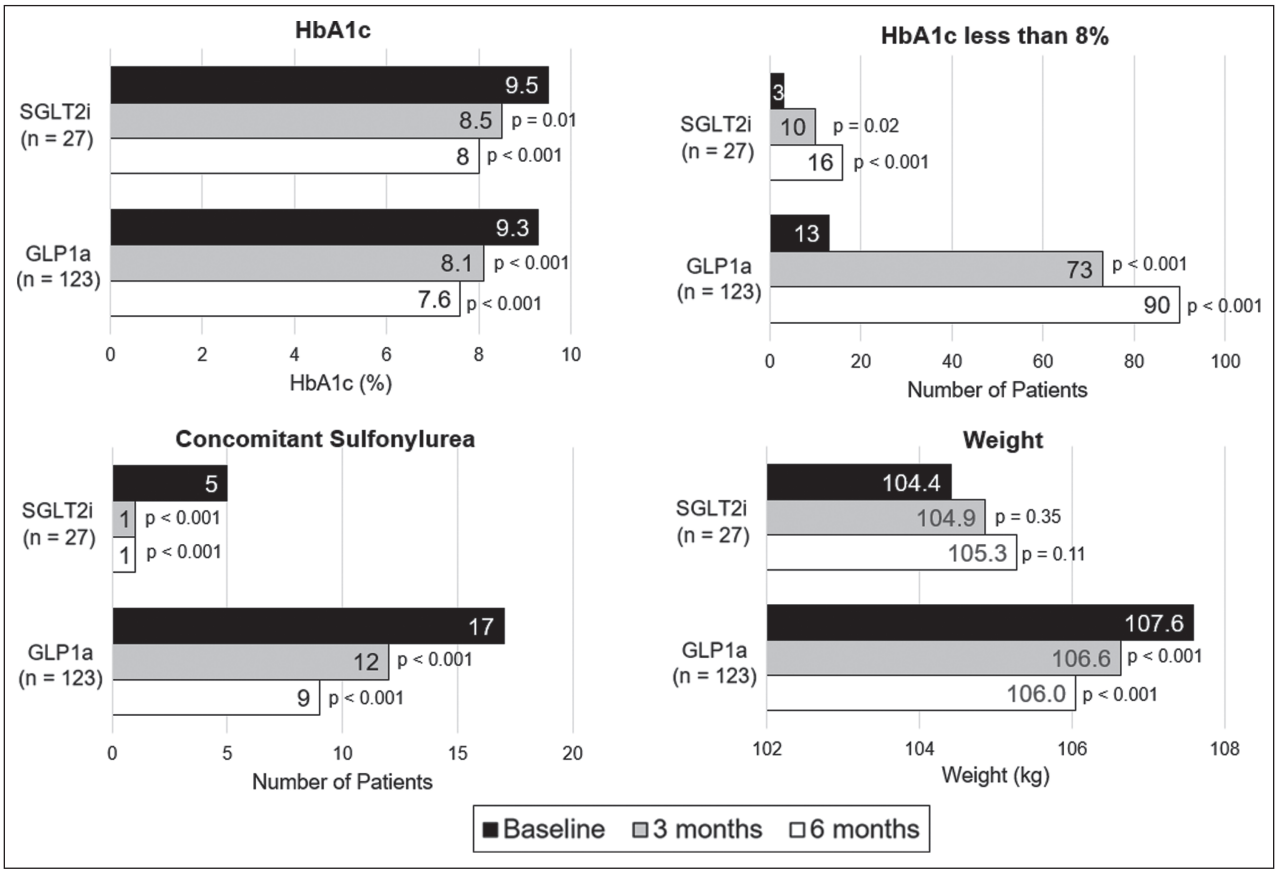
Abbreviations: GLP1a, glucagon-like peptide 1 agonist; SGLT2i, sodium-glucose cotransporter 2 agonist.
[a]Insulin dose reduction upon initiation of adjunctive GLP1a or SGLT2i therapy.
[b]*P* values are for between-group significance after analysis of variance.

dose after GLP1a initiation (F = 25.7, P < 0.001) between the time points. Post hoc comparisons revealed a significant difference between baseline total insulin and each individual time point (P < 0.001 for all between-group comparisons), and there was a 23.5% decrease in insulin requirements after 6 months. After SGLT2i initiation, there was no significant change in total insulin dose (F = 1.61, P = 0.20) between the time points. Though the mean insulin dose was initially decreased, it gradually rose, and requirements ultimately increased by 0.2% by 6 months. This change equated to an absolute mean (SD) decrease in total insulin use of 14.2 (23.5) units in the GLP1a group and an increase of 0.1 (13.1) units in the SGLT2i group.

Figure 3 displays comparative data on secondary outcomes at baseline, 3 months, and 6 months, including mean HbA_{1c}, HbA_{1c} less than 8%, concomitant sulfonylurea use, and weight. Prior to GLP1a initiation, 10.6% of patients had an HbA_{1c} value less than 8%, and this proportion increased to 72.4% after 6 months (P < 0.001); after SGLT2i initiation, this percentage increased from 11.1% to 59.3% (P < 0.001). Furthermore, bolus insulin was discontinued in 24 out of 56 patients (42.9%) on a GLP1a and in 2 out of 12 patients (16.7%) who were on an SGLT2i.

Patient-reported and pharmacist- or provider-documented adverse effects occurred in 41% of patients on a GLP1a, including 21% of patients

Figure 3. Comparison of secondary outcomes at baseline, 3 months, and 6 months. *P* values shown at each time point are for comparison with baseline values. For the outcomes of glycosylated hemoglobin (HbA_{1c}) concentration and weight, the averages at each time point are shown; the outcomes of HbA_{1c} less than 8% and concomitant sulfonylurea use are represented as number of patients. GLP1a indicates glucagon-like peptide 1 agonist; SGLT2i, sodium-glucose cotransporter 2 agonist.



who experienced hypoglycemia. With SGLT2i use, adverse effects occurred in 26% of patients and 11% of patients experienced hypoglycemia. Other reactions that occurred with GLP1a use included nausea or vomiting (11.4%), diarrhea (4.9%), pancreatitis (0.8%), and tachycardia (0.8%); 7 patients (5.7%) experienced 1 or more adverse reactions. After SGLT2i initiation, 7.4% experienced urinary symptoms or genital infection and 3.7% had diarrhea. One patient in each group had an unspecified reaction.

After 6 months, 41.5% of patients reached the maximum GLP1a dose and 40.7% reached the maximum SGLT2i dose available at the time of the study. When considering consistent follow-up with the ambulatory care pharmacist, 37.4% of patients on a GLP1a and 40.7% on an SGLT2i were lost to pharmacist follow-up; however, they maintained provider follow-up and were therefore included in the analysis.

To understand which factors might predict the achievement of an HbA_{1c} concentration of less than 8%, sulfonylurea use at baseline and HbA_{1c} value at baseline were included in the regression model given their known association with that outcome. As shown in Table 3, HbA_{1c} at baseline was a significant variable ($\beta = 0.23$, $P = 0.04$). Total insulin and basal insulin at baseline were variables that were associated with the outcome of bolus insulin discontinuation and were included in the regression model. Of these, total insulin dose at baseline was significant ($\beta = 0.039$, $P = 0.03$).

Discussion

Within 6 months, there was an associated decrease in mean total insulin dose of 23.5% after GLP1a initiation and slight increase of 0.2% after SGLT2i initiation. The majority of patients achieved an HbA_{1c} value of less than 8% after agent initiation, and absolute HbA_{1c} decreases were 1.7% and 1.5% with GLP1a and SGLT2i therapy, respectively. Sulfonylurea therapy and bolus insulin discontinuation was also achieved in a portion of patients after GLP1a or SGLT2i initiation. Hypoglycemia was the most common adverse effect among both GLP1a- and SGLT2i-treated patients.

Various literature suggests preemptive insulin dose decreases

Table 3. Results of Logistic Regression for Association of Baseline Factors With Selected Outcomes

Outcome and Factors	Unstandardized Coefficient (β)	95% CI for β		Odds Ratio	*P* Value
		Lower Bound	Upper Bound		
HbA_{1c} <8% within 6 mo					
HbA_{1c} at baseline	0.23	1.01	1.56	1.25	0.04
Sulfonylurea use at baseline	–0.41	0.25	1.72	0.66	0.40
Discontinuation of bolus insulin within 6 mo					
Total insulin dose at baseline	0.04	1.01	1.08	1.04	0.03
Bolus insulin dose at baseline	–0.03	0.93	1.02	0.97	0.27

Abbreviations: CI, confidence interval; HbA_{1c}, glycosylated hemoglobin.

ranging from 20% to 50% after GLP1a initiation.[2,3] In clinical trials of GLP1a agents—including dulaglutide, liraglutide, semaglutide, and exenatide—insulin doses were typically reduced by 20% if patients had a baseline HbA_{1c} of 8% or less; however, patients' baseline insulin dose was continued if their HbA_{1c} was above 8%.[8-11] In the study described here, the average preemptive insulin dose decrease of 7.5% was more conservative than is typically recommended upon GLP1a initiation. However, there was a large range for baseline HbA_{1c} level (7.1%-12.9%, with an average of 9.3%) in the GLP1a group, which could mean that these patients did not require substantial insulin dosage adjustments, unlike those with a lower baseline HbA_{1c} level; given the relatively high incidence of hypoglycemia in the GLP1a group, this may highlight the need for more aggressive insulin dose reduction.

There is minimal current literature that supports empiric reduction of the insulin dose after SGLT2i initiation, and this study demonstrated that even though the mean insulin dose was preemptively decreased by 3.6%, insulin requirements increased within 6 months. This finding was unanticipated since the ADA guidelines suggest that adjunctive use of an SGLT2i may allow reduction in the amount of insulin needed in patients with suboptimal glycemic control.[12] In addition, a meta-analysis of 7 randomized controlled trials with a mean trial duration of 48 weeks showed that the insulin dose after SGLT2i initiation decreased by an average of 8%.[14] However, the mean baseline HbA_{1c} value in that study was 8.4%, with a range of 8.2% to 8.9%, which was less than the mean baseline value in our study's SGLT2i group (an average of 9.5%, with a range of 6.6%-13.5%). Similar to findings in our study's GLP1a group, this higher range of HbA_{1c} may have contributed to a need for less insulin adjustments than expected—or potentially increased insulin requirements based on uncontrolled hyperglycemia even after medication optimization—compared to other studies.

In our study, the significant mean HbA_{1c} decreases of 1.7% with GLP1a therapy and 1.5% with SGLT2i therapy after 6 months were at the high end or slightly greater than anticipated decreases, given published evidence suggesting HbA_{1c} decreases of 0.7% to 1.7% after GLP1a initiation and 0.3% to 1.2% after SGLT2i initiation.[6] This finding may have been due to closer follow-up with a pharmacist as opposed to standard care. Though hypoglycemia occurred in many patients on a GLP1a and also a few on an SGLT2i, this may point towards the need for more significant decreases in insulin doses to prevent these episodes, since neither class causes hypoglycemia given the mechanism of action. The hypoglycemia was likely due to patients' concomitant use of insulin and/or sulfonylurea. Furthermore, though a higher baseline total insulin dose and higher baseline HbA_{1c} value were found to predict discontinuation of bolus insulin and achievement of an HbA_{1c} concentration of less than 8%, respectively, this may have been due to closer follow-up with a pharmacist if either of these factors was present. Similar to findings in our study, another study of SGLT2i therapy showed larger reductions in HbA_{1c} among those who had higher baseline HbA_{1c} values.[15]

One of the strengths of this study was that patients with a higher HbA_{1c} concentration at baseline were not excluded, which increases the external validity. Also, insulin dosage was measured at multiple time points, which provides further guidance on insulin titration. Certain limitations should be considered when interpreting this data. Since the study was retrospective in nature and the sample size was small, this study provided only a brief snapshot of real-world insulin changes; a larger sample would allow for more robust guidance in insulin adjustments. A randomized controlled trial would be necessary to truly evaluate the impact of GLP1a or SGLT2i initiation on insulin doses and degree of change in insulin doses. It is also important to avoid making direct comparisons between the study groups since they were not matched, there was a significant difference in sample size between the groups, and given the retrospective nature of the study. An additional limitation of this study was the inclusion of only patients managed by a clinical

pharmacist as opposed to all patients within the system. Pharmacists have demonstrated the ability to provider closer follow-up than is typical with standard care and, consequently, superior HbA_{1c} control.[16,17] Given that potentially closer pharmacist follow-up allows for more frequent insulin adjustments, these results may have limited generalizability to patients outside of pharmacist-supported management. There may have also been changes to the group between each time point, such as discontinuation of sulfonylurea, which may have influenced the percent change in insulin dose. Additionally, at the time of the study, the higher recommended doses of dulaglutide (3 mg and 4.5 mg) were not yet approved. Also, some agents within each class of medication were not prescribed to patients in the study population, including semaglutide or dapagliflozin, which may have been due to use of preferred agents on insurance formularies or the timing of Food and Drug Administration approval relative to approval of other agents within a class.

Future directions may include the evaluation of differences in insulin dosage adjustment based on baseline HbA_{1c}, especially since in most pertinent studies of GLP1a initiation insulin doses were decreased empirically by 20% only for those with a baseline HbA_{1c} less than 8%.[8-11] The results of our study provide a foundation for clinics to develop a policy or educate on proactively adjusting insulin doses prior to initiating a GLP1a or an SGLT2i. Another potential area to assess would be evaluating insulin dose adjustments for patients on both GLP1a and SGLT2i therapy.

Conclusion

Initiation of a GLP1a resulted in an associated decrease in the mean total insulin dose of 23.5%; use of an SGLT2i initially corresponded to an insulin dose reduction but gradually led to a slight increase in total insulin use (0.2% after 6 months). Application of these results will help guide insulin dose adjustments after GLP1a or SGLT2i initiation.

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Disclosures

The authors have declared no potential conflicts of interest.

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