ORIGINAL RESEARCH

Assessment of Glucagon-like Peptide-1 Receptor Agonists in Veterans Taking Basal/Bolus Insulin Regimens

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Background: Clinical use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) is well established as add-on therapy to oral medications and basal insulin. However, there is little published data regarding the use of GLP-1 RAs for longer than 12 months in patients taking basal/bolus insulin regimens. The primary goal of our study was to assess the long-term efficacy of GLP-1 RAs as add-on therapy to basal/bolus insulin regimens.

Methods: This study was a retrospective record review of all patients on basal/bolus insulin regimens who received additional therapy with a GLP-1 RA. The primary outcome was the change in glycosylated hemoglobin A_{1c} (HbA_{1c}) at 3, 6, 12, 18, and 24 months after initiation of the GLP-1 RA. Secondary outcomes included change in weight and total daily dose (TDD) of insulin and incidence of hypoglycemia and other adverse effects (AEs).

Results: Ninety-two patient records were reviewed. Mean glycemic control changed from baseline –1.1% (95% CI, –1.3 to –0.8; $P < .001$) at 3 months; –1.0% (95% CI, –1.3 to –0.7; $P < .001$) at 6 months; –0.9% (95% CI, 1.3 to –0.6; $P < .001$) at 12 months; –0.9% (95% CI, –1.4 to –0.3; $P = .002$) at 18 months; and –0.7 (95% CI, –1.4 to 0.1; $P = .07$) at 24 months. A significant decrease in weight was also observed from baseline through 18 months, and a significant decrease in TDD of insulin was identified from baseline through 12 months. Hypoglycemia was documented in 29.8% of patients at any point during GLP-1 RA therapy, and gastrointestinal AEs were documented in 18.3% of patients.

Conclusions: Adding GLP-1 RAs to complex insulin regimens may help achieve glycemic control while decreasing insulin requirements and mitigating undesirable AEs, such as weight gain.

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In 2019, diabetes mellitus (DM) was the seventh leading cause of death in the United States, and currently, about 11% of the American population has a DM diagnosis.[1] Most have a diagnosis of type 2 diabetes (T2DM), which has a strong genetic predisposition, and the risk of developing T2DM increases with age, obesity, and lack of physical activity.[1,2] Nearly one-quarter of veterans have a diagnosis of DM, and DM is the leading cause of comorbidities, such as blindness, end-stage renal disease, and amputation for patients receiving care from the Veterans Health Administration (VHA).[2] The elevated incidence of DM in the veteran population is attributed to a variety of factors, including exposure to herbicides, such as Agent Orange, advanced age, increased risk of obesity, and limited access to high-quality food.[3]

After diagnosis, both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) emphasize the appropriate use of lifestyle management and pharmacologic therapy for DM care. The use of pharmacologic agents (oral medications, insulin, or noninsulin injectables) is often determined by efficacy, cost, potential adverse effects (AEs), and patient factors and comorbidities.[4,5]

The initial recommendation for pharmacologic treatment for T2DM differs slightly between expert guidelines. The ADA and AACE/ACE recommend any of the following as initial monotherapy, listed in order to represent a hierarchy of usage: metformin, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter 2 (SGLT-2) inhibitors, or dipeptidyl peptidase-4 (DPP-4) inhibitors, with the first 3 agents carrying the strongest recommendations.[4,5] For patients with established atherosclerotic cardiovascular disease (CVD), chronic kidney disease, or heart failure, it is recommended to start a long-acting GLP-1 RA or SGLT-2 inhibitor. For patients with T2DM and hemoglobin A_{1c} (HbA_{1c}) between 7.5% and 9.0% at diagnosis, the AACE/ACE recommend initiation of dual therapy using metformin alongside another first-line agent and recommend the addition of another antidiabetic agent if glycemic goals are not met after regular follow-up. AACE/ACE recommend the consideration of insulin therapy in symptomatic patients with $HbA_{1c} > 9.0\%$.[5] In contrast, the ADA recommends metformin as first-line therapy for all patients with T2DM and recommends dual therapy using metformin and another preferred agent (selection based on comorbidities) when HbA_{1c} is 1.5% to 2% above

target. The ADA recommends the consideration of insulin with HbA_{1c} > 10% or with evidence of ongoing catabolism or symptoms of hyperglycemia.[4] There are several reasons why insulin may be initiated prior to GLP-1 RAs, including profound hyperglycemia at time of diagnosis or implementation of insulin agents prior to commercial availability of GLP-1 RA.

GLP-1 RAs are analogs of the hormone incretin, which increases glucose-dependent insulin secretion, decreases postprandial glucagon secretion, increases satiety, and slows gastric emptying.[6,7] When used in combination with noninsulin agents, GLP-1 RAs have demonstrated HbA_{1c} reductions of 0.5% to 1.5%.[8] The use of GLP-1 RAs with basal insulin also has been studied extensively.[6,8-10] When the combination of GLP-1 RAs and basal insulin was compared with basal/bolus insulin regimens, the use of the GLP-1 RAs resulted in lower HbA_{1c} levels and lower incidence of hypoglycemia.[6,9] Data have demonstrated the complementary mechanisms of using basal insulin and GLP 1 RAs in decreasing HbA_{1c} levels, insulin requirements, and weight compared with using basal insulin monotherapy and basal/bolus combinations.[6,9-13] Moreover, 3 GLP-1 RA medications currently on the market (liraglutide, dulaglutide, and semaglutide) have displayed cardiovascular and renal benefits, further supporting the use of these medications.[2,5]

Despite these benefits, GLP-1 RAs may have bothersome AEs and are associated with a high cost.[6] In addition, some studies have found that as the length of therapy increases, the positive effects of these agents may diminish.[9,11] In one study, which looked at the impact of the addition of exenatide to patients taking basal or basal/bolus insulin regimens, mean changes in weight were –2.4 kg at 0 to 6 months, –4.3 kg at 6 to 12 months, –6.2 kg at 12 to 18 months, and –5.5 kg at 18 to 27 months. After 18 months, an increase in weight was observed, but the increase remained lower than baseline.[11] Another study, conducted over 12 months, found no significant decrease in weight or total daily dose (TDD) of insulin when exenatide or liraglutide were added to various insulin regimens (basal or basal/bolus).[13] To date, minimal published data exist regarding the addition of newer GLP-1 RAs and the long-term use of these agents beyond 12 months in patients taking basal/bolus insulin regimens. The primary goal of this study was to evaluate the effect of adding GLP-1 RAs to basal/bolus insulin regimens over a 24-month period.

METHODS

This study was a retrospective, electronic health record review of all patients on basal and bolus insulin regimens who received additional therapy with a GLP-1 RA at Veteran Health Indiana in Indianapolis from September 1, 2015, to June 30, 2019. Patients meeting inclusion criteria served as their own control. The primary outcome was change in HbA_{1c} at 3, 6, 12, 18, and 24 months after initiation of the GLP-1 RA. Secondary outcomes included change in weight and TDD of insulin at 3, 6, 12, 18, and 24 months after the initiation of the GLP-1 RAs and incidence of patient-reported or laboratory-confirmed hypoglycemia and other AEs.

Patients were included if they were aged ≥ 18 years with a diagnosis of T2DM, had concomitant prescriptions for both a basal insulin (glargine, detemir, or NPH) and a bolus insulin (aspart, lispro, or regular) before receiving add-on therapy with a GLP-1 RA (exenatide, liraglutide, albiglutide, lixisenatide, dulaglutide, or semaglutide) from September 1, 2015, to June 30, 2019, and had baseline and subsequent HbA_{1c} measurements available in the electronic health record. Patients were excluded if they had a diagnosis of type 1 DM (T1DM), were followed by an outside clinician for DM care, or if the GLP-1 RA was discontinued before subsequent HbA_{1c} measurement. The study protocol was approved by the Research and Development Office of Veteran Health Indiana, and the project was deemed exempt from review by the Indiana University Institutional Review Board due to the retrospective nature of the study.

Data analysis was performed using Excel. Change from baseline for each interval was computed, and 1 sample *t* tests (2-tailed) compared change from baseline to no change. Due to the disparity in the number of patients with data available at each of the time intervals, a mean plot was presented for each group of patients within each interval, allowing mean changes in individual groups to be observed over time.

RESULTS

One hundred twenty-three subjects met inclusion criteria; 16 patients were excluded due to GLP-1 RA discontinuation before

TABLE 1 Baseline Characteristics (N = 92)

Characteristics	Results
Age, mean (SD), y	64 (9.0)
Sex, No. (%)	
Male	87 (95)
Female	5 (5)
Race, No. (%)	
Black	6 (7)
White	82 (89)
Duration of diabetes mellitus, mean (SD), y	10 (6)
Body mass index, mean (SD)	38.9 (8.5)
Hemoglobin A_{1c}, mean (SD), %	9.2 (1.3)
Basal/bolus insulin regimen, No. (%)	
Insulin glargine/insulin aspart	84 (91)
Insulin detemir/insulin aspart	8 (9)
Total daily dose of insulin, mean (SD)	184 (90)
Duration of basal insulin regimen, mean (SD), y	7 (5)
Duration of basal/bolus insulin regimen, mean (SD), y	6 (5)
Additional oral antidiabetic medications, No. (%)	
None	17 (19)
Metformin	64 (70)
Dipeptidyl-peptidase 4 inhibitor	33 (35)
Sodium-glucose cotransporter-2 inhibitor	3 (3)
Sulfonylurea	1 (1)
Thiazolidinedione	1 (1)
α-glucosidase inhibitors	1 (1)
Oral antidiabetic medications used, No. (%)	
0	17 (19)
1	51 (55)
2	22 (24)
3	2 (2)
Glucagon-like peptide-1 receptor agonists, No. (%)	
Semaglutide	40 (44)
Liraglutide	36 (39)
Dulaglutide	12 (13)
Albiglutide	3 (3)
Exenatide	1 (1)

follow-up measurement of HbA_{1c}; 14 were excluded due to patients being managed by a clinician outside of the facility; 1 patient was excluded for lack of documentation regarding baseline and subsequent insulin doses. Ninety-two patient charts were reviewed. Participants had a mean age of 64 years, 95% were male, and 89% were White. Mean baseline HbA_{1c} was 9.2%, mean body mass index was 38.9, and the mean TDD of insulin was 184 units. Mean duration of DM was 10 years, and mean use of basal/bolus insulin regimen was 6.1 years. Most participants (91%) used an insulin regimen containing insulin glargine and insulin aspart; the remaining participants used insulin detemir and insulin aspart. Semaglutide and liraglutide were the most commonly used GLP-1 RAs (44% and 39%, respectively) (Table 1).

Since some patients switched between GLP-1 RAs throughout the study and there was variation in timing of laboratory and clinic follow-up, a different number of patient charts were available for review at each period (Table 2). Glycemic control was significantly improved at all time points when compared with baseline, but over time the benefit declined. The mean change in HbA_{1c} was −1.1% (95% CI, −1.3 to −0.8; $P < .001$) at 3 months; −1.0% (95% CI, −1.3 to −0.7; $P < .001$) at 6 months; −0.9% (95% CI, −1.3 to −0.6; $P < .001$) at 12 months; −0.9% (95% CI, −1.4 to −0.3; $P = .002$) at 18 months; and −0.7% (95% CI, −1.4 to 0.1; $P = .07$) at 24 months (Figure 1). Mean weight decreased from baseline −2.7 kg (95% CI, −3.7 to −1.6; $P < .001$); −4.4 kg (95% CI −5.7 to −3.2; $P < .001$) at 6 months; −3.9 kg (95% CI −6.0 to −1.9; $P < .001$) at 12 months; −4.7 kg (95% CI −6.7 to −2.6; $P < .001$) at 18 months; and −2.8 kg (95% CI, −5.9 to 0.3; $P = .07$) at 24 months (Figure 2). Mean TDD decreased at 3 months −12 units (95% CI, −19 to −5; $P < .001$); −18 units (95% CI, −27 to −9; $P < .001$) at 6 months; −14 units (95% CI, −24 to −5; $P = .004$) at 12 months; −9 units (95% CI, −21 to 3; $P = .15$) at 18 months; and −18 units (95% CI, −43 to 5 units; $P = .12$) at 24 months (Figure 3). The most common AEs were hypoglycemia (30%), diarrhea (11%), nausea (4%), and abdominal pain (3%).

DISCUSSION

Adding a GLP-1 RA to basal/bolus insulin regimens was associated with a statistically significant decrease in HbA_{1c} at each time point through 18 months. The greatest improvement in glycemic control from baseline was seen at 3 months, with improvements in HbA_{1c} diminishing at each subsequent period. The study also demonstrated a significant decrease in weight at each time point through 18 months. The greatest decrease in weight was observed at both 6 and 12 months. Statistically significant decreases in TDD were observed at 3, 6, and 12 months. Insulin changes after 12 months were not found to be statistically significant.

Few studies have previously evaluated the

TABLE 2 Data Available at Each Time Period

Time period	Baseline	3 mo	6 mo	12 mo	18 mo	24 mo
Patients reviewed, No.	92	70	83	69	42	27

FIGURE 1 Change in Glycemic Control Over Time

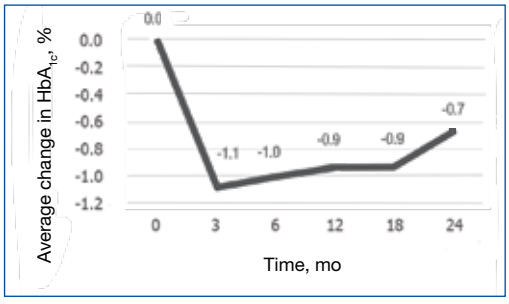


FIGURE 2 Change in Body Weight Over Time

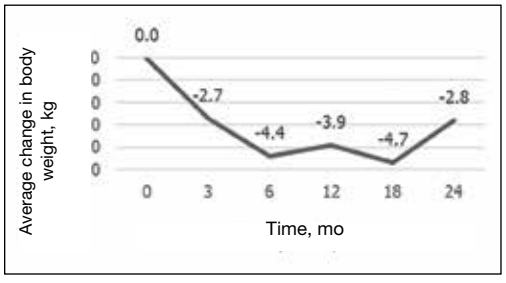
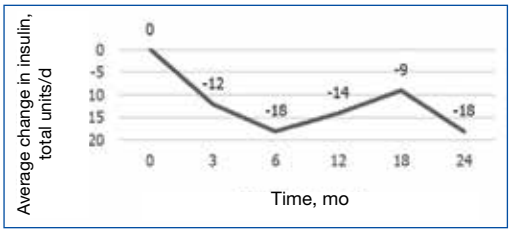


FIGURE 3 Change in Insulin Dose Over Time



use of GLP-1 RAs in patients with T2DM who are already taking basal/bolus insulin regimens. Gyorffy and colleagues reported significant improvements in glycemic control at 3 and 6 months in a sample of 54 patients taking basal/bolus insulin when liraglutide or exenatide was added, although statistical significance was not found at the final 12-month time point.[13] That study also found a significant decrease in weight at 6 months; however there was not a significant reduction in weight at both 3 and 12 months of GLP-1 RA therapy. There was not a significant decrease in TDD at any of the collected time points. Nonetheless, Gyorffy and colleagues concluded that reduction in TDD leveled off after 12 months, which is consistent with this study's findings. The small size of the study may have limited the ability to detect statistical significance; however, this study was conducted in a population that was racially diverse and included a higher proportion of women, though average age was similar.[13]

Yoon and colleagues reported weight loss through 18 months, then saw weight increase, though weights did remain lower than baseline. The study also showed no significant change in TDD of insulin after 12 months of concomitant exenatide and insulin therapy.[11] Although these results mirror the outcomes observed in this study, Yoon and colleagues did not differentiate results between basal and basal/bolus insulin groups.[11] Seino and colleagues observed no significant change in weight after 36 weeks of GLP-1 RA therapy in Japanese patients when used with basal and basal/bolus insulin regimens. Despite the consideration that the population in the study was not overweight (mean body mass index was 25.6), the results of these studies support the idea that effects of GLP-1 RAs on weight and TDD may diminish over time.[14]

Within the VHA, GLP-1 RAs are nonformulary medications. Patients must meet certain criteria in order to be approved for these agents, which may include diagnosis of CVD, renal disease, or failure to reach glycemic control with the use of oral agents or insulin. Therefore, participants of this study represent a particular subset of VHA patients, many of whom may have been selected for consideration due to long-standing or uncontrolled T2DM and failure of previous therapies. The baseline demographics support this idea, given poor glycemic control at baseline and high insulin requirements. Once approved for GLP-1 RA therapy, semaglutide is currently the preferred agent within the VHA, with other agents available for select considerations. It should be noted that albiglutide, which was the primary agent selected for some of the patients included in this study, was removed from the

market in 2017 for economic considerations.[15] In the case for these patients, a conversion to a formulary-preferred GLP-1 RA was made.

Most of the patients included in this study (70%) were maintained on metformin from baseline throughout the study period. Fifty-seven percent of patients were taking TDD of insulin > 150 units. Considering the significant cost of concentrated insulins, the addition of GLP-1 RAs to standard insulin may prove to be beneficial from a cost standpoint. Additional research in this area may be warranted to establish more data regarding this potential benefit of GLP-1 RAs as add-on therapy.

Many adverse drug reactions were reported at different periods; however, most of these were associated with the gastrointestinal system, which is consistent with current literature, drug labeling, and the mechanism of action.[16] Hypoglycemia occurred in about one-third of the participants; however, it should be noted that alone, GLP-1 RAs are not associated with a high risk of hypoglycemia. Previous studies have found that GLP-1 RA monotherapy is associated with hypoglycemia in 1.6% to 12.6% of patients.[17,18] More likely, the combination of basal/bolus insulin and the GLP-1 RA's effect on increasing insulin sensitivity through weight loss, improving glucose-dependent insulin secretion, or by decreasing appetite and therefore decreasing carbohydrate intake contributed to the hypoglycemia prevalence.

Limitations and Strengths

Limitations of this study include a small patient population and a gradual reduction in available data as time periods progressed, making even smaller sample sizes for subsequent time periods. A majority of participants were older, males and White race. This could have limited the determination of statistical significance and applicability of the results to other patient populations. Another potential limitation was the retrospective nature of the study design, which may have limited reporting of hypoglycemia and other AEs based on the documentation of the clinician.

Strengths included the study duration and the diversity of GLP-1 RAs used by participants, as the impact of many of these agents has not yet been assessed in the literature. In addition, the retrospective nature of the study allows for a more realistic representation of patient adherence, education, and motivation, which are likely different from those of patients included in prospective clinical trials.

There are no clear guidelines dictating the optimal duration of concomitant GLP-1 RA and insulin therapy; however, our study suggests that there may be continued benefits past short-term use. Also our study suggests that patients with T2DM treated with basal/bolus insulin regimens may glean additional benefit from adding GLP-1 RAs; however, further randomized, controlled studies are warranted, particularly in poorly controlled patients requiring even more aggressive treatment regimens, such as concentrated insulins.

CONCLUSIONS

In our study, adding GLP-1 RA to basal/bolus insulin was associated with a significant decrease in HbA_{1c} from baseline through 18 months. An overall decrease in weight and TDD of insulin was observed through 24 months, but the change in weight was not significant past 18 months, and the change in insulin requirement was not significant past 12 months. Hypoglycemia was observed in almost one-third of patients, and gastrointestinal symptoms were the most common AE observed as a result of adding GLP-1 RAs. More studies are needed to better evaluate the durability and cost benefit of GLP-1 RAs, especially in patients with high insulin requirements.

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Ethics and consent

This project was reviewed and determined to be exempt by the Veteran Health Indiana Institutional Review Board.

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