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Analysis of patient-specific factors contributing to effectiveness of glucagon-like peptide-1 receptor agonists

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Abstract

Background: Glucagon-like peptide-1 receptor (GLP-1) agonists are antidiabetic medications used to improve hemoglobin A1c (HbA1c) and promote weight loss. Per the Veterans Affairs/Department of Defense guidelines for the management of type 2 diabetes, GLP-1 agonists are expected to lower HbA1c by 1%–1.5%. The clinical pharmacy specialist in the women's health primary care clinic at the Louis A. Johnson Veterans Affairs Medical Center noted cases of women started on GLP-1 agonists achieving greater than expected HbA1c reduction.

Objectives: The primary objective of this study was to determine if there are any patient-specific factors that may increase the effectiveness of GLP-1 agonists. Secondary objectives included an analysis of average weight and HbA1c, use of the Pearson rank correlation test to determine if there is a correlation between weight change and HbA1c reduction, and an analysis of HbA1c reduction associated with each GLP-1 agonist prescribed.

Methods: A retrospective chart review was conducted. Data collected from the charts included age, sex, height, GLP-1 agonist prescribed, and HbA1c and weight before and after GLP-1 agonist initiation. For primary outcomes, statistical analyses were run between 2 groups: patients who had an HbA1c reduction of greater than 1.5% and patients who had an HbA1c reduction less than or equal to 1.5%.

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Previous presentation: The findings of this analysis have previously been presented as a poster at the American Society of Health Systems Pharmacists in Las Vegas, NV in December 9, 2019.

Results: Women were more likely to have an HbA1c reduction of greater than 1.5% ($P = 0.001$). Patients with a lower baseline weight were more likely to attain an HbA1c reduction greater than 1.5% ($P = 0.045$). Higher baseline HbA1c was correlated with an increased likelihood of HbA1c reduction greater than 1.5% ($P = 0.001$).

Conclusion: GLP-1 agonists may be more effective at reducing HbA1c in female patients, those with a lower baseline weight, and those with a higher baseline HbA1c.

Background

Glucagon-like peptide-1 receptor (GLP-1) agonists are a class of medications commonly used in the treatment of type 2 diabetes. GLP-1 agonists work through stimulation of the GLP-1 receptor, which causes increased insulin secretion, decreased glucagon secretion, and slowed gastric emptying resulting in reduction in blood glucose and weight loss.¹ The American Diabetes Association guidelines cite GLP-1 agonists as one of the preferred agents in patients with type 2 diabetes and concomitant atherosclerotic cardiovascular disease, chronic kidney disease, or congestive heart failure.¹ Primary literature examining the effectiveness of GLP-1 agonists has reported a variable range of hemoglobin A1c (HbA1c) reduction depending on the specific GLP-1 agonist used, typically between 0.5% and 1.8%.^{2–7} Veterans Affairs (VA)/Department of Defense (DoD) guidelines suggest a typical HbA1c reduction in the range of 1%–1.5%.⁸

Despite an increase in GLP-1 agonist prescription in recent years, which patient populations may benefit the most from the initiation of a GLP-1 agonist in terms of HbA1c reduction and weight loss is largely unknown. Factors that may increase the response to GLP-1 agonists have been examined in various retrospective reviews and prospective studies; however, the available data are conflicting, making it difficult to discern which populations may benefit the most from a GLP-1 agonist, and as a result, tailor the prescribing of these agents in clinical practice (Table 1). Although there is a lack of conclusive evidence available to suggest a superior efficacy of GLP-1 agonists in certain populations, the clinical pharmacy specialist in the women's health clinic at the Louis A. Johnson VA Medical Center noted instances of female patients initiated on a GLP-1 agonist achieving greater than expected HbA1c reduction.

Objectives

The primary objective of this study was to determine if there were any patient-specific factors that might contribute to an increased response to GLP-1 agonists where response was classified on the basis of a change in HbA1c greater than 1.5% from baseline, the maximum expected change per the VA/DoD guidelines.⁸ Secondary objectives included an analysis of average weight and HbA1c reduction associated with GLP-1 agonist use, determining a correlation between weight change and HbA1c reduction through the Pearson's correlation test, and an analysis of HbA1c reduction associated with each GLP-1 agonist prescribed.

Methods

A retrospective chart review was completed at the Louis A. Johnson VA Medical Center in Clarksburg, WV. The research was approved by the institutional review board at our local university affiliate of West Virginia University as well as the Louis A. Johnson Research and Development Committee. All patients with an active prescription for a subcutaneous GLP-1 agonist between October 1, 2015 and September 30, 2019 were identified. Patients were excluded from the study if their GLP-1 agonist was initiated before October 1, 2015 or initiated at a non-VA facility or at another VA (excluding the VA Pittsburgh Healthcare System where patients may be referred for specialty care), their GLP-1 agonist was discontinued before HbA1c follow-up, their follow-up for HbA1c was less than or equal to 3 months after initiation of the GLP-1 agonist, or if there was documented nonadherence to GLP-1 agonists in the provider progress notes. Data were collected using the VA's Computerized Patient Record System (CPRS). Data collected from CPRS included patient age, sex, race, height, and HbA1c and weight before and after GLP-1 agonist initiation. The post-GLP-1 agonist initiation HbA1c and weight data collected were the first and second measurements (if a second measurement was available) after at least 3 months of GLP-1 agonist therapy. All post-GLP-1 agonist HbA1c and weight measurements collected were within 12 months of GLP-1 agonist initiation. It was also noted if there were any changes to the diabetes medication regimen during the follow-up period prior to subsequent HbA1c measurements.

For statistical analyses, the chi-squared tests or the Fisher exact test were used when appropriate for discrete data and independent sample *t* tests were used for continuous data. For the primary outcome, statistical analyses were conducted between baseline demographics in 2 groups: patients who achieved more than 1.5% HbA1c reduction and those who had less than or equal to 1.5% HbA1c reduction as defined by the expected HbA1c reduction when a GLP-1 agonist is initiated per the VA/DoD guidelines.⁸ The subsequent HbA1c measurement with the largest change from baseline was used to categorize the patients into the two groups. A multivariate model of HbA1c reduction was used to assess the effects of sex and weight reduction, adjusting for confounding variables including age, race, height, body mass index (BMI), concomitant diabetes medication changes, and initial HbA1c. The Pearson correlation analysis was used to assess the relationship between HbA1c and weight. A *P* value of 0.05 was used as the threshold for statistical significance. Statistical calculations were conducted by an independent statistician using SAS 9.2 (SAS Institute, Inc, Cary, NC) and R software, version R 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 227 patients were screened, with 136 meeting the inclusion criteria. All patients identified for inclusion were prescribed an injectable GLP-1 agonist for type 2 diabetes and were taking a therapeutic dose at the time of subsequent HbA1c measurements. A total of 3 patients (2.2%) were started on the GLP-1 agonist in 2016, 18 patients (13.2%) in 2017, 70 patients (51.5%) in 2018, and 45 patients (33.1%) in 2019. The demographic information can be found in Table 2. There were 122 men (89.7%), which is representative

of the veteran population in the geographic area in consideration. The mean ($\pm$ SD) age was 63.3 years $\pm$ 9.6 years, and the average baseline HbA1c was 9.1% $\pm$ 1.4%. Liraglutide and semaglutide accounted for 94.1% of all GLP-1 agonists prescribed, with liraglutide being the most frequently prescribed (52.9%). The average HbA1c reduction on a GLP-1 agonist was 1.6% $\pm$ 1.3%, and the average weight change was -5.5 kg $\pm$ 10.6. GLP-1 agonist use resulted in weight loss in 121 patients (89%).

In the study population, 88 patients (64.7%) were on metformin at baseline. The most common diabetes regimens before the initiation of a GLP-1 agonist were metformin plus insulin NPH/regular 70/30, metformin plus concentrated insulin U-500, and metformin plus glipizide with a total of 11 patients receiving each of these regimens at baseline.

A total of 62 patients (45.6%) achieved an HbA1c reduction of more than 1.5%. Of these 62 patients, 2 (3.2%) were managed by an endocrinologist, 21 (33.9%) were managed by a clinical pharmacy specialist, and 39 (62.9%) were managed by a primary care provider. Of the 74 patients who did not achieve an HbA1c reduction of more than 1.5%, 20 (27%) were managed by a clinical pharmacy specialist, and 54 (73%) were managed by a primary care provider.

Results of the primary objective are displayed in Table 2. On the basis of the results of the primary analysis, women were more likely to attain more than 1.5% reduction in HbA1c ($P = 0.001$) compared with men. Baseline weight was lower in the group that achieved more than 1.5% HbA1c reduction ($P = 0.045$). Baseline HbA1c was higher in the group that achieved more than 1.5% HbA1c reduction ($P = 0.001$). Age, race, BMI, and the number of patients with concomitant diabetes medication changes did not differ between groups.

Of the 14 female patients included in this study, only 1 did not have an HbA1c reduction of more than 1.5%. Overall, female patients had a greater average weight loss and achieved a greater HbA1c reduction than male patients. Women lost an average of 8.4 kg compared with 4.4 kg in men ($P = 0.04$) and had an average HbA1c reduction of 3.23% versus 1.35% in men ($P = 0.001$). Semaglutide was the most commonly prescribed GLP-1 agonist for women, and liraglutide was the most commonly prescribed GLP-1 agonist for men. Figure 1 displays waterfall figures that graphically display male and female responses to GLP-1 agonists in terms of HbA1c reduction and weight.

Patients who achieved a HbA1c reduction of more than 1.5% compared with less than or equal to 1.5% were more likely to experience weight loss (-6.76 kg vs. -3.19 kg, $P = 0.004$). A Pearson rank correlation analysis (Figure 2) demonstrated a moderate correlation between change in weight and HbA1c ($r = -0.2$; $P = 0.02$).

A total of 51 (37.5%) of patients included had concomitant diabetes medication changes from the time of the initial GLP-1 agonist prescription to subsequent HbA1c measurements. The most common medication change was an adjustment in basal insulin, which occurred in 31 (62.7%) patients. In a comparison of patients who did not have any medication changes before subsequent HbA1c laboratory tests with those who did have concomitant diabetes medication changes, it was found that HbA1c change did not differ between the groups

(1.68% vs. 1.4%, $P = 0.24$); however, weight change between the 2 groups was different (-5.05 kg vs. -6.8 kg, $P = 0.001$).

To consider the impact of confounding variables on the reported outcomes, a multivariate analysis was conducted. In the multivariate analysis of HbA1c percentage reduction from baseline, age, race, height, BMI, sex, change in weight, and diabetes medication changes, sex ($P = 0.007$) and change in weight ($P = 0.013$) were predictors of HbA1c reduction.

With respect to GLP-1 agonist relative efficacy, semaglutide was associated with the largest average reduction in HbA1c (1.83%); however, this was not statistically significant when compared with other GLP-1 agonists. The average HbA1c reductions with the other GLP-1 agonists for the study period were as follows: liraglutide (1.47%), dulaglutide (0.85%), and exenatide (0.7%).

Discussion

Overall, the average HbA1c reduction found in this study was comparable with that reported in the literature.²⁻⁷ There were more men included for analysis than women owing to the demographics of the veteran population at our local facility. Despite a relatively low percentage of women included for analysis, the results obtained through the primary analysis and the multivariate analysis add validity to the reported results.

On the basis of the results of the primary objective, 92.3% of women included for analysis achieved an HbA1c reduction of more than 1.5% and were more likely to attain an HbA1c reduction of more than 1.5% as compared to men. The 1 female patient who had an HbA1c reduction of less than or equal to 1.5% had a baseline HbA1c of 6.6%. With a lower baseline HbA1c, the expected change in HbA1c for this patient was likely going to be minimal. This finding supports the hypothesis that GLP-1 agonists may be more efficacious when the baseline HbA1c is higher as reported in the literature.^{3,4}

In terms of the findings that GLP-1 agonists may be more effective in those with a lower weight, this result may be skewed owing to the lower total weight of women than that of men. We would expect that a higher baseline weight would increase the efficacy of GLP-1 agonists on the basis of the drug's mechanism of action at promoting satiety and weight loss; however, this predictor of GLP-1 agonist response is conflicting in the literature.^{3,4}

There are some hypotheses as to why GLP-1 agonists may be more effective in female patients and these are centered around biological differences between the sexes. It has been reported in the literature that there is a stronger obesity-diabetes risk association in women compared with men, as women with diabetes tend to have a higher BMI.⁹ Women also tend to have a greater increase in waist circumference as they age as compared to men.⁹ Taking this information into account, clinical pharmacy specialists involved in this research have theorized that GLP-1 agonists may be more effective at reducing weight in women because of the location of their weight.

Another theory may be related to the baseline levels of GLP-1, which are affected by the duration of diabetes, as the increased length of diagnosis leads to decreased beta cell

function and desensitization of the GLP-1 receptor on beta cells.^{2,10} It is possible that levels of GLP-1 may differ not only by duration of diagnosis but also by sex. Finally, it has been shown in animal models that the female may be more sensitive to the suppression of reward behaviors postinjection of the GLP-1 agonist than the male, possibly owing to central estrogen effects.¹¹ If this model holds true *in vivo*, women may be more susceptible to the satiety effects of the GLP-1 agonists, which would then promote an increased weight loss and decrease in HbA1c as compared with men.

Several limitations existed for this study. Only 14 women were included, representing 10.29% of the total study population. The low percentage of women aligns with the veteran population served at our facility. Another limitation is that the patients were not managed by the same provider or type of provider. Patients were followed up by primary care physicians, clinical pharmacy specialists, or endocrinologists, each with their own methods and preferences for managing type 2 diabetes, including the timing and selection of the GLP-1 agonist and concomitant diabetes medication changes. This could have also introduced selection bias as providers may have prescribed GLP-1 agonists to those patients who they felt would benefit most from a GLP-1 agonist on the basis of their previous experience with these medications. When comparing those who did not have diabetes medication changes before subsequent HbA1c measurements with those who did, a statistically significant difference was found in weight change but not HbA1c change. The weight change between the groups may have been because when GLP-1 agonists are initiated, insulin doses are typically reduced, which may promote weight loss in addition to the weight loss effects of the GLP-1 agonist. This was evident in our results as adjustment to the insulin dose was the most common medication change during the study period.

Although in clinical practice it is pertinent to determine whether the selected antihyperglycemic medications are able to assist patients in achieving their HbA1c goals, this study aimed to identify patient-specific factors that could lead to a greater than expected change in HbA1c when GLP-1 agonists were added to existing therapy regardless of baseline HbA1c. Because the magnitude of HbA1c change was the outcome of interest, data on the number of patients who reached their patient-specific HbA1c goals were not collected. Information regarding diabetes duration was not collected in this study, which may alter the response to GLP-1 agonist therapy. Other potential confounders that were not analyzed included concomitant disease states and medications aside from those for diabetes, changes in diet and physical activity, and information on patient motivation, which may have positively contributed to HbA1c reduction. Finally, a medication adherence threshold for medication refills was not used for inclusion, which may have affected the true impact of GLP-1 agonist therapy in some patients.

This research is the first to report primarily on patient-specific factors that may lead to an increased response to semaglutide. Semaglutide was not well represented in previous studies but was commonly prescribed in our study period owing to VA formulary preferences. This research also supports previous theories that there may be a difference in response to GLP-1 agonists on the basis of sex. In the future, a randomized controlled trial that would decrease the potential effects of confounders is required to confirm these and previously reported results in the literature.

Conclusion

GLP-1 agonists may be more effective at lowering HbA1c in female patients, those with a lower weight, and those with a higher baseline HbA1c. Additional research with a larger sample size and controlled for confounders is required to determine which populations are more likely to respond to GLP-1 agonists to allow for more targeted prescription of these agents.

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Key Points

Background:

- Glucagon-like peptide-1 receptor (GLP-1) agonists are expected to lower hemoglobin A1c by 1%–1.5%.
- Data regarding which populations may benefit the most from the addition of GLP-1 agonists are conflicting.

Findings:

- Analysis of baseline demographics to determine hemoglobin A1c reduction in response to GLP-1 agonists identified that women were more likely to respond to these agents.
- Semaglutide and patient-specific factors related to its efficacy, which have not been previously reported, were examined.

Figure 1.

Waterfall figures depicting male (left column) versus female (right column) responses to glucagon-like peptide-1 agonists in terms of HbA1c change (top row) and weight change (bottom row). Abbreviation used: HbA1c, hemoglobin A1c.

Figure 2.

Correlation between change in weight and change in HbA1c in men and women.

Abbreviations used: HbA1c, hemoglobin A1c; GLP-1, glucagon-like peptide-1.

Table 1
Previously published literature on patient-specific factors that may increase GLP-1 agonist effectiveness

Author, y	Methodology	Primary objective	GLP-1 agonist studied	Outcome
Hemmer et al. 2019 ²	Observational, retrospective study	Evaluate long-term evolution of HbA1c after initiation of GLP-1 agonist for up to 4 y	All included, exenatide IR and liraglutide compared head-to-head	Men and patients with baseline HbA1c >9% had a 2.55–2.09 higher risk for treatment “failure”-defined as worsening glycemic control during treatment (HbA1c > 7.5% or a decrease of < 1% after 1 y of treatment)
Anichini et al. 2013 ⁵	Observational, retrospective review	Determine if sex affects therapeutic response	Exenatide IR	Women were more likely to achieve target weight loss at mo 8 and 12, but males were more likely to achieve target HbA1c after 4 and 12 mo of therapy Each increase in 1-y diabetes duration reduced likelihood of achieving HbA1c goal by ~6% Each 1% increase in HbA1c decreased probability of achieving HbA1c goal at 12 mo by ~35%
Babenko et al. 2019 ³	Prospective observational study	Identify predictors of effectiveness of GLP-1 agonists on HbA1c reduction, weight reduction, and lipid panel	Exenatide BID Liraglutide	No association of sex, age, diabetes duration, and initial BMI on weight loss HbA1c reduction was associated with baseline HbA1c and GLP-1 levels Most weight loss was observed in obese patients and increased duration of diabetes
Franch-Nadal et al. 2019 ⁴	Retrospective review	HbA1c and weight control after 6 and 12 mo of therapy	Liraglutide, lixisenatide, exenatide IR	Patients with baseline HbA1c > 10%, BMI > 35 kg/m ² had the largest decrease in HbA1c

Abbreviations used: HbA1c, hemoglobin A1c; GLP-1, glucagon-like peptide-1; IR, immediate release; BID, twice daily; BMI, body mass index.

Table 2

Primary outcomes and baseline demographics

Characteristic	Total n = 136	> 1.5% HbA1c reduction n = 62	1.5% HbA1c reduction n = 74	P value
Male, n (%)	122 (89.7)	49 (79)	73 (98.7)	0.001
White, n (%)	132 (97.1)	59 (95.2)	73 (98.7)	0.33
Average age, y (SD)	63.3 (9.6)	61.9 (9.47)	64.4 (9.8)	0.10
Baseline weight, kg (SD)	115.6 (9.6)	111 (18.6)	119.5 (24.4)	0.045
Body mass index, kg/m ² (SD)	37 (6.7)	36.4 (6.3)	37.5 (7.1)	0.54
Baseline HbA1c, % (SD)	9.1 (1.4)	9.8 (1.3)	8.44 (1.1)	0.001
GLP-1 agonist prescribed, n (%)				
Exenatide	2 (1.5)	—	2 (2.7)	0.30
Dulaglutide	6 (4.4)	2 (3.2)	4 (5.4)	—
Liraglutide	72 (52.9)	30 (48.4)	26 (35.1)	—
Semaglutide	56 (41.2)	30 (48.4)	42 (56.8)	—
No. patients who had concomitant diabetes medication changes before subsequent HbA1c measurements, n (%)	51 (37.5)	21 (33.9)	30 (40.5)	0.48

Abbreviations used: HbA1c, hemoglobin A1c; GLP-1, glucagon-like peptide-1.