2020

The Effects of a GLP-1 Receptor Agonist on HbA1c and Weight in Comparison to Standard Therapy in a Veteran Population

Isaac Warshawsky
Butler University

BUTLER UNIVERSITY HONORS PROGRAM

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Applicant: Isaac Wai Lun Warshawsky
(Name as it is to appear on diploma)

Thesis title: The Effects of a GLP-1 Receptor Agonist on HbA1c and Weight in Comparison to Standard Therapy in a Veteran Population

Intended date of commencement: May 9, 2020

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_____ Date

Reader(s) _____ Date

_____ Date

Certified by _____ Date
Director, Honors Program

The Effects of a GLP-1 Receptor Agonist on HbA1c and Weight in Comparison to Standard Therapy in a Veteran Population

A Thesis Presented to

The College of Pharmacy and Health Sciences

And

The Honors Program

of

Butler University

In Partial Fulfillment

of the Requirements for Graduation Honors

Isaac Wai Lun Warshawsky

May 9, 2020

Acknowledgements

The completion of this thesis would not have been possible without the help and support of Dr. Darin Ramsey, who served as the faculty advisor and guided the direction of the research as a whole. I would also like to extend a thank you to Dr. Shelby Beutel Darrow for collecting and analyzing the data for the comparator group in this study and for assisting in this completion of this research project. Special thanks to Dr. Chad Knoderer for serving as the second thesis reader and assisting with the statistical analysis, Dr. Chad Naville-Cook for his help with the data collection, and Dr. Jason Lantzer for his mentorship throughout my time in the Butler Honors Program.

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Abstract

Background: Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs) present a novel therapy for use in Type 2 Diabetes Mellitus (T2DM) patients to reduce Hemoglobin A1c (HbA1c) and weight. GLP-1 RAs are more expensive compared to other therapeutic options for diabetes and are not currently on the national formulary for Veterans Affairs medical centers. This study looks to explore the efficacy data in a veteran population.

Objectives: The specific aim of this study is to determine the change in HbA1c and weight in T2DM patients taking GLP-1 RAs compared to Standard Therapy with insulin and Oral Antidiabetic Drugs (OADs) at 26 weeks. Secondary objectives include comparing change in HbA1c, weight, and BMI at 52 weeks to validate the efficacy of GLP-1 RAs in the veteran population.

Methods: This research study is a retrospective cohort electronic medical record (EMR) review conducted at the Richard L. Roudebush Veterans Affairs Medical Center in Indianapolis, Indiana. The study compared data points from two cohorts of patients:

1. GLP-1 RA: patients treated with liraglutide or exenatide
2. Standard Therapy: patients treated with insulin detemir and/or insulin glargine

Results: In the first 26 weeks for the Standard Therapy group, HbA1c changed on average by -0.9%, weight by +2.41 kg, and BMI by +0.78 kg/m^2. In comparison, at 26 weeks for the GLP-1 RA group, HbA1c changed on average -1.34%, weight by -2.40 kg, and BMI by -0.7 kg/m^2. At 52 weeks for the Standard Therapy group, HbA1c changed on average by -0.74%, weight by +1.26 kg, and BMI by +0.46 kg/m^2 from baseline. At 52 weeks for the GLP-1 RA group, HbA1c changed on average by -1.31%, weight by -4.06 kg, and BMI by -1.36 kg/m^2 from baseline.

Introduction

Diabetes Mellitus Overview

Diabetes Mellitus results from an inability to metabolize sugars and starch, which results in abnormally high blood glucose levels known as hyperglycemia. Common forms of Diabetes Mellitus include Prediabetes, Gestational Diabetes, Type 1, and Type 2—this research is specifically focused on the Type 2 Diabetes Mellitus (T2DM) patient population. T2DM is the most common form of diabetes, affecting approximately 90% of diabetic patients.[1] The pathophysiology of T2DM involves the development of insulin resistance, which differs from Type 1 Diabetes Mellitus (T1DM) patients where the body becomes unable to produce insulin due to an autoimmune disorder.[2] Patients who are at increased risk for developing T2DM include those who are overweight or obese, 45 years of age or older, have high blood pressure, low level High-Density Lipoprotein (HDL) cholesterol, high level triglycerides, history of heart attack or stroke, or family history of diabetes.[3]

Patients who do not adequately treat or manage their T2DM are at risk for both macrovascular and microvascular complications, damage to the large blood vessels and small blood vessels respectively. Macrovascular complications include coronary artery disease, peripheral arterial disease, and stroke; whereas microvascular complications include diabetic nephropathy (kidneys), neuropathy (nerves), and retinopathy (eyes). Diabetic complications are not only debilitating for the patients, they also present a significant economic burden: $22.9 billion per year.[4] As a result, patients are typically instructed to closely monitor their blood glucose daily to improve glycemic control and therefore limit potential complications. The goal pre-prandial range for blood glucose in

diabetic patients is 80-130 mg/dL, and patients who stay within the target range reduce the risk for microvascular and macrovascular complications.[5] While patients often self-monitor their blood glucose, lab tests measuring Hemoglobin A1c (HbA1c) allow health practitioners to identify the average blood glucose for the patient within a 3-month time frame. The American Diabetes Association (ADA) guidelines recommend that patients aim for a target HbA1c < 7 percent, which correlates to an average blood glucose of approximately < 154 mg/dL. Measuring HbA1c has become a standard in assessing the diabetes management of patients because it provides data points that self-blood glucose monitoring may lack due to nonadherence to testing regimens. A decrease in HbA1c is representative of less microvascular and macrovascular damage due to tighter glucose control.[6]

Treatment Guidelines

Before patients are prescribed pharmacologic therapies to treat T2DM, nonpharmacologic treatment is encouraged. Obesity management has been shown to increase glycemic control, leading to lower HbA1c and improved health outcomes. Patients are encouraged to achieve a caloric deficit of 500-750kcal/day, utilize behavioral therapy, and exercise (200-300 minutes of physical activity per week) with the goal of achieving and maintaining a ≥5% weight loss.[6,8] The Indianapolis VA Medical Center implements a VA MOVE! Program that patients may sign up for to monitor their exercise goals and receive physical activity regimens.

For T2DM patients who struggle to maintain glycemic control, nonpharmacologic therapies often times are insufficient. Therefore, for those patients, pharmacologic treatments are utilized alongside diet, exercise, and behavioral therapy. Metformin has

been established as the 1st line pharmacologic treatment for T2DM patients; however, metformin is titrated up to a therapeutic dose due to dose-dependent gastrointestinal disturbances that may lead to discontinuation if intolerable. For patients unable to achieve diabetic control with metformin within 3 months, discontinue metformin, or are contraindicated to taking metformin, GLP-1 RAs are recommended as the 1st line therapy according to the American Diabetes Association (ADA) Guidelines. If heart failure or chronic kidney disease predominate health concerns, Sodium-Glucose Transport Protein 2 (SGLT2) inhibitors are preferred. GLP-1 RAs are also recommended for use in combination with metformin and an SGLT-2 inhibitor for patients with persistent hyperglycemia.[7]

GLP-1 Receptor Agonists

In response to oral dietary intake, the body produces incretin hormones to enhance insulin secretion to lower blood glucose levels. Incretins also reduce insulin release when glucose levels are within normal range, thereby reducing the risk of hypoglycemia, the common, life-threatening adverse effect of many diabetic medications. Glucagon-like peptide 1 is an incretin hormone that has been seen to decrease glucagon concentrations, improve insulin sensitivity, slow gastric emptying, increase satiety, and decrease body weight. GLP-1 receptor agonists act by stimulating the receptors and potentiating the incretin effects.[8]

The following GLP-1 RAs are currently FDA approved: exenatide (Byetta®, Bydureon®), liraglutide (Victoza®, Saxenda®), lixisenatide (Lyxumia®), albiglutide (Tanzeum®), dulaglutide (Trulicity®), and semaglutide (Ozempic®, Rybelsus®). With the exception of Rybelsus®, a once-daily tablet that was FDA approved in September 2019,

all GLP-1 RAs are administered subcutaneously with a dosing frequency ranging from twice daily to once weekly. Common side effects of GLP-1 RAs are nausea, vomiting, and diarrhea. GLP-1 RAs are also used concomitantly with other diabetic medications, which often include insulin and OADs. The two GLP-1 RAs included in this study were liraglutide and exenatide. Liraglutide is dosed as 0.6mg, 1.2mg, and 1.8mg once weekly injections; whereas, exenatide is dosed as 5μg or 10μg twice daily and 2μg extended release once weekly. Additionally, twice daily exenatide requires dosing within 1 hour before meals, while extended release exenatide and liraglutide may be administered without regard to mealtime.[9-16]

According to published literature, a 6-week study which compared an infusion of normal saline versus GLP-1 in patients with T2DM on no other diabetic medication resulted in an average reduction in HbA1c of 1.3% and an average weight loss of 1.9 kg.[17] In this study, a GLP-1 RA was not used, rather a subcutaneous injection of GLP-1 incretin hormone was administered via a continuous subcutaneous infusion. A review of head-to-head GLP-1 RA studies uncovered that the therapy results in an average HbA1c reduction of 0.78% to 1.9% at 26 weeks.[18] A meta-analysis of GLP-1 RAs in 2015 displayed an average reduction in weight of 1.01kg to 1.62kg over 26 weeks.[19] When comparing liraglutide and exenatide in combination with metformin or a sulfonylurea, a 26-week study showed a reduction in HbA1c of 1.12% for liraglutide and 0.79% for exenatide. The average reduction in weight was very similar between the two GLP-1 RAs groups: 3.24kg for liraglutide and 2.87kg for exenatide.[20] Another 26-week trial investigated the use of liraglutide 1.8mg alongside insulin and/or OADs compared to placebo and/or OADs. The trial displayed a decrease in HbA1c of 0.9% with liraglutide

compared to a decrease of 0.4% for the non-GLP-1 RA group, which represents a reduction in HbA1c of 0.5% with the addition of liraglutide.[15]

Veterans Affairs Formulary

Due to their high cost in comparison to other therapies on the market, GLP-1 RAs were traditionally reserved once insulin, along with other oral therapies, had failed to reduce HbA1c. However, recent guidelines from the ADA now recommend treatment with GLP-1 RAs after standard metformin therapy for most patients. Despite the recommendation for GLP-1 RA use, at the time of this study, they were excluded on the VA national formulary and therefore are less accessible for patient use.[21] Formulary-excluded medications have higher costs for patients due to lower reimbursement rates and are less likely to be stocked in the pharmacy and available for patients. The prevalence of T2DM has been noted to be higher in the veteran population than the general US population: 25% compared to 20.5% respectively. Possibly due to multiple factors, the high rate of obesity amongst the veteran population is suspected to be a key contributor to the increased incidence of diabetes.[22] Data demonstrating the value of GLP-1 RAs in improving diabetes health outcomes in the veteran population may encourage the decision to include these therapies on the national formulary.

Objectives

The specific aim of this study is to determine the change in HbA1c and weight in T2DM patients taking GLP-1 RAs compared to Standard Therapy with insulin and OADs at 26 weeks. Secondary objectives include comparing change in HbA1c, weight, and BMI at 52 weeks to validate the efficacy of GLP-1 RAs in the veteran population.

Methods

Data Collection

This research study was a retrospective cohort electronic medical record (EMR) review conducted at the Richard L. Roudebush Veterans Affairs Medical Center in Indianapolis, Indiana. The Decentralized Hospital Computer Program (DHCP) was used to generate a list of patients within the inclusion parameters of the study and data was obtained from the Computerized Patient Record System (CPRS). The study compared data points from two cohorts of patients:

1. GLP-1 RA: patients treated with liraglutide or exenatide[23]
2. Standard Therapy: patients treated with insulin detemir and/or insulin glargine, excluding those treated with a GLP-1 RA

The data points were arranged in categories of 0, 1, 2, 3, 6, 9, 12, 16, 20, 24, 30, 36, 42, and 48 months. Data collected at 6 months and 12 months were assumed to be equivalent to 26 weeks and 52 weeks respectively. For each group, the following data points were collected for each of the above months that the data was available: specific drug used in diabetes management (insulin or GLP-1 receptor agonist) and dose, patient weight, BMI, HbA1c, other oral diabetes medications, enrollment in the VA MOVE! Program, and total daily units used of both long-acting and short-acting insulin requirements.

Due to the retrospective nature of this study, no direct patient enrollment was needed for study participation. For the GLP-1 RA group, a confidential list of 90 patients was generated by the DHCP record system in the outpatient pharmacy. For the Standard Therapy group, the list generated by DHCP included approximately 7000 patients based

on the inclusion criteria. From the list, patients were randomly selected by every 100 patients, resulting in approximately 70 subjects for data analysis.

Outcomes

Primary Outcomes

The change in HbA1c and weight at 26 weeks in patients on insulin and/or OADs compared to patients with the addition of GLP-1 RAs.

Secondary Outcomes

The change in HbA1c, weight, and BMI at 52 weeks in patients on insulin and/or OADs compared to patients with the addition of GLP-1 RAs.

Inclusion and Exclusion Criteria

Inclusion criteria

GLP-1 RA group: Patients at the Indianapolis VAMC with a diagnosis of T2DM and use of a GLP-1-RA, ages 18-80 from the date range: 1/1/2010 – 9/1/17. Those on two separate GLP-1 agonists for two distinct time periods were included.

Standard Therapy group: Patients at the Indianapolis VAMC with a diagnosis of T2DM and use of insulin detemir and/or insulin glargine, ages 18-80 from the date range: 1/1/2010 – 9/1/2017 were compared.

Exclusion criteria

Patients with type 1 diabetes mellitus, patients who discontinued a GLP-1 RA within the first month, lack of baseline and/or follow up data points for HbA1c and/or weight.

Standard Therapy Group: Patients using a GLP-1 RA were excluded.

Statistical Analysis

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 26 software. Nominal data (MOVE! Program enrollment and specific use of other diabetes medications) were evaluated with Chi square to identify potential confounding factors or abnormal distribution. Descriptive statistics were used to describe group characteristics. Continuous interval data (HbA1c comparison, weight, BMI) were evaluated using independent sample t-test, with p-values <0.05 considered statistically significant, and Mann-Whitney U for non-normally distributed data.

Results

The GLP-1 RA group included 80 patients during the study period, 19 of which were excluded due to insufficient A1c and weight data. 10 of the 19 excluded patients discontinued use of a GLP-1 RA within one month of initiation. The GLP-1 RA group included 4 patients (6.6%) on exenatide and 57 patients (93.4%) on liraglutide. Of the 4 patients on exenatide, one used the once-weekly formulation (Bydureon®), whereas the other 3 patients used the twice-daily formulation (Byetta®).[23] When collecting data for the Standard Therapy group, due to the 7000 patients eligible within the inclusion parameters, patients were randomized and then excluded as needed until 61 patients were obtained to meet the number set by the GLP-1 RA group.

The baseline demographics (Table 1) of the Standard Therapy group and the GLP-1 RA group were comparable in terms of distribution of sex, enrollment in the VA MOVE! Program, and age. The average baseline HbA1c was also similar between the two groups: 9.25% for the Standard Therapy group and 9.07% for the GLP-1 RA group. In contrast, the weight and BMI were higher in the GLP-1 RA group: 126.6 kg and 40.5 kg/m^2 compared to 104.5 kg and 33.3 kg/m^2 in the Standard Therapy group. Additionally, more patients in the GLP-1 RA group were taking Metformin within their regimen (93.4% versus 54.1% in the Standard Therapy group). Patients in the GLP-1 RA group were also taking, on average, 1 – 2 more OADs at baseline than patients in the Standard Therapy group.

Table 1. Baseline Characteristics of the Patients

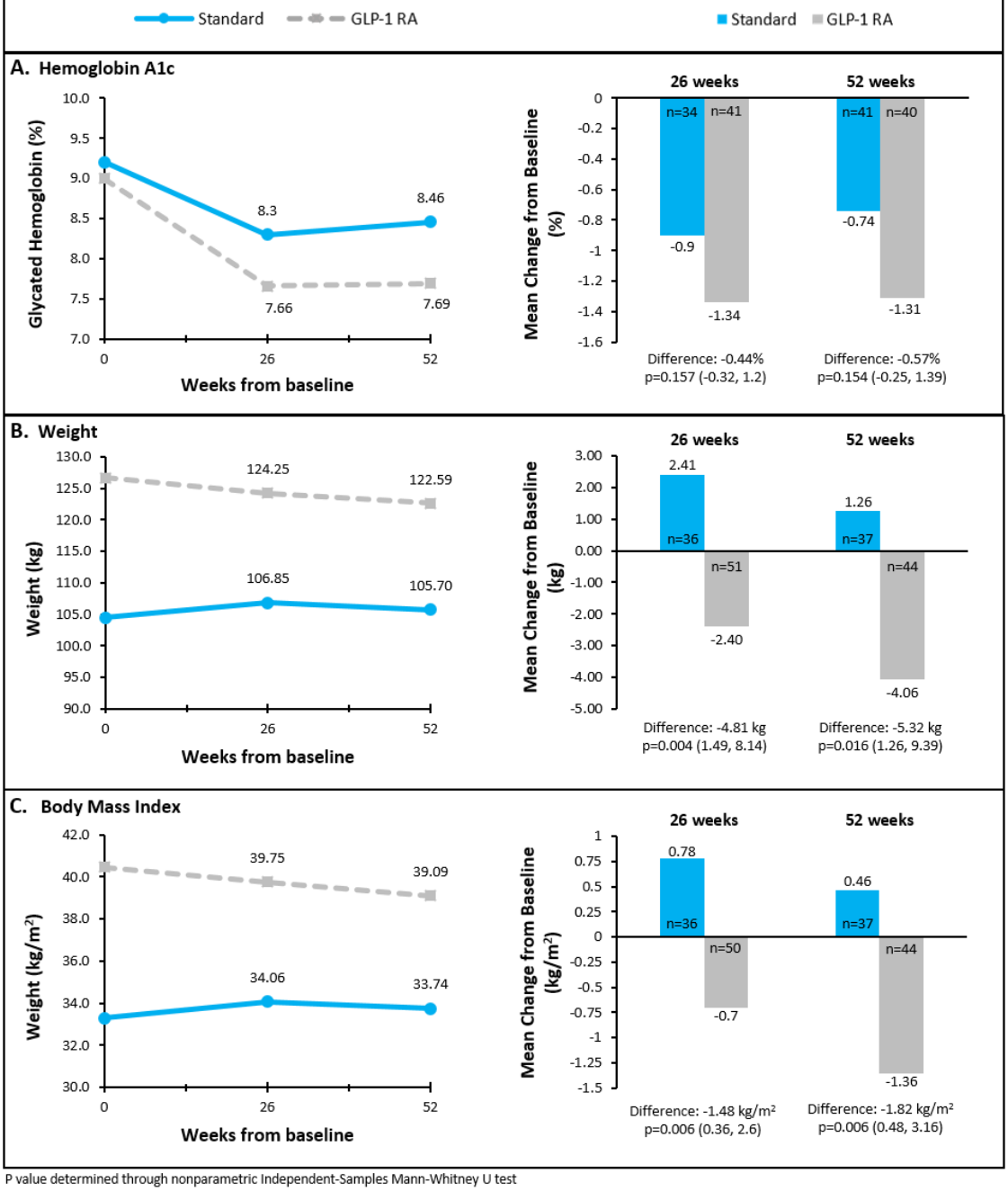
Characteristic	Standard Therapy (n = 61)	GLP-1 RA (n = 61)
Female sex – no. (%)	3 (4.9%)	6 (9.8%)
VA Move! Program	2 (3.3%)	2 (3.3%)
Age – yr	61 ± 11.9	62 ± 8.4
Total daily insulin dose – units	56 ± 46.5	133 ± 124.1
HbA1c – %	9.25 ± 2.2	9.07 ± 1.5
Weight – kg	104.5 ± 17.5	126.6 ± 23.3
BMI – kg/m^2	33.3 ± 5.3	40.5 ± 7.7
Diabetes Treatment – no. (%)		
GLP-1 Receptor Agonist	0	61 (100%)
Long Acting Insulin	61 (100%)	48 (78.7%)
Biguanide*	33 (54.1%)	57 (93.4%)
Sulfonylurea	16 (26.2%)	13 (21.3%)
DPP-4 Inhibitor	1 (1.6%)	16 (26.2%)
SGLT-2 Inhibitor	0	0
Thiazolidinedione	1 (1.6%)	5 (8.2%)
α-glucosidase inhibitor	0	1 (1.6%)
# of Oral Antidiabetic Drugs – no. (%)		
Average # of OADs	0.84	1.58
0 medications	23 (37.7%)	0
1 medication	26 (42.6)	2 (3.3%)
2 medications	11 (18%)	33 (54.1%)
3 medications	1 (1.6%)	20 (32.8%)
4 medications	0	5 (8.2%)
5 medications	0	1 (1.6%)

HbA1c, Hemoglobin A1c; BMI, Body Mass Index; GLP-1, Glucagon-Like Peptide 1; DPP-4, Dipeptidyl Peptidase 4; SGLT-2, Sodium-Glucose Transport Protein 2; OAD, Oral Antidiabetic Drug
*Metformin in all cases

In the first 26 weeks for the Standard Therapy group, HbA1c changed on average by -0.9% [95% Confidence Interval: -1.54, -0.27], weight by +2.41 kg [-1.04, 5.86], and BMI by +0.78 kg/m^2 [-0.38, 1.94]. In comparison, at 26 weeks for the GLP-1 RA group,

HbA1c changed on average -1.34% [-1.78, -0.91], weight by -2.40 kg [-3.88, -0.92], and BMI by -0.7 kg/m^2 [-1.19, -0.21]. At 52 weeks for the Standard Therapy group, HbA1c changed on average by -0.74% [-1.40, -0.08], weight by +1.26 kg [-2.13, 4.65], and BMI by +0.46 kg/m^2 [-0.66, 1.58] from baseline. At 52 weeks for the GLP-1 RA group, HbA1c changed on average by -1.31% [-1.81, -0.81], weight by -4.06 kg [-6.55, -1.58], and BMI by -1.36 kg/m^2 [-2.19, -0.54] from baseline.

Table 2. Results



P value determined through nonparametric Independent-Samples Mann-Whitney U test

Statistical analysis showed that the change in HbA1c for both 26 weeks and 52 weeks were not statistically significant ($p = 0.157$ and $p = 0.154$ respectively). However, both change in weight and BMI from baseline at weeks 26 and 52 were statistically significant, with p values < 0.05.

Discontinuation of GLP-1-RAs were most often due to GI intolerance (7%), combined prescriber and patient decisions (4%), and miscellaneous factors (4%). All five of the patients who discontinued GLP-1-RAs due to GI intolerance stopped within the first month of use. The majority (72%) of patients continued GLP-1-RA use through the study. Miscellaneous factors for discontinuation included pancreatitis, concern for cancer, dislike of needles, provider change, bariatric surgery, relocation, and death. There were no patients in this study who discontinued GLP-1-RAs due to cost.[23]

Discussion

Findings from the GLP-1 RA cohort suggest a decrease in HbA1c of 1.34% at 26 weeks, which is comparable to published literature showing a reduction in HbA1c of 0.78% to 1.9% at 26 weeks.[18] There was a -0.44% difference in HbA1c between the GLP-1 RA group versus standard therapy at 26 weeks in this study, which is fairly similar to the HbA1c reduction in a clinical trial studying the addition of liraglutide to standard therapy: -0.5%.[15] However, the difference in HbA1c in this study between the GLP-1 RA group and the Standard Therapy group lacked statistical significance, which inhibits its generalizability. A meta-analysis of GLP-1 RAs in 2015 showed an average change in weight of -1.01kg to -1.62kg over 26 weeks.[20] In comparison, this study produced greater weight loss results as the GLP-1 RA group had a change in weight of -2.40 kg at 26 weeks. Overall, the findings of this study shows a similar HbA1c reduction and a larger weight reduction in the veteran population compared to published data.

Although VA Medical Centers currently exclude GLP-1 RAs from formulary, the results of this study present statistically significant reduction in weight and BMI over a 26 week and 52 week period in the veteran population. If the reduction in HbA1c were statistically significant, the data would further establish a reason to increase accessibility of GLP-1 RAs for veterans. With the current ADA guidelines promoting GLP-1 RAs as preferred therapies after metformin, an increasing number of diabetic patients have begun using GLP-1 RAs. With an increase in patient use comes an increase in real-world evidence, which may clarify the benefits of using a GLP-1 RA on HbA1c, weight, and BMI.

However, lack of formulary access may, in turn, hinder the amount of real-world evidence available due to the limited use of GLP-1 RAs.

From a formulary management perspective, a reduction in weight is beneficial for a T2DM patient, but HbA1c reduction is deemed more important. Despite the cardiovascular benefits that come along with weight loss, HbA1c reduction results in less macrovascular and microvascular complications. These complications can result in hospitalizations which can, in turn, lead to morbidity and mortality for the patient and are also costly to the payer.

Strengths

This study is very applicable to veterans because the patients included were patients treated within the VA Medical Center in Indianapolis. Due to the random selection of enrollment, specifically for the standard therapy group, the data is representative of the veteran population. The statistical significance of both the difference in weight and BMI at 26 and 52 weeks serves as a strength of this study.

Limitations

Although the Standard Therapy and GLP-1 RA groups were comparable for certain demographics, they varied in baseline data for average total daily dose of insulin, weight, BMI, Metformin use, and number of OADs. Additionally, only two GLP-1 RAs were tested in this study, which may limit the generalizability to the therapeutic class outside of liraglutide and exenatide. Additionally, there were few patients on exenatide compared to liraglutide, which lessens the applicability of the study results to patients using exenatide. Although SGLT-2 inhibitors are used often in current practice due to

their 1st line place in therapy after Metformin use, there were no patients in either group who were using an SGLT-2 inhibitor at baseline. SGLT-2 inhibitors are commonly used in combination with GLP-1 RAs to achieve greater glycemic control, and it would be interesting to further explore a cohort on SGLT-2 inhibitor therapy. Cardiovascular benefit is becoming increasingly important for diabetic treatments, so cardiovascular outcomes would have been a valuable secondary endpoint to have studied.

A potential confounding variable involved a change in diabetic regimen leading to a further decrease in HbA1c, weight, and/or BMI. For the Standard Therapy group, the average OADs increased from 0.84 at baseline to 0.92 at 26 weeks and decreased to 0.75 at 52 weeks. In comparison, for the GLP-1 RA group, the average OADs decreased from 1.58 at baseline to 1.25 at 26 weeks and further decreased to 1.23 at 52 weeks. Although there was a larger average of OADs in the GLP-1 RA group, the key takeaway revolves around the difference in OADs throughout the study period. A decrease in the amount of OADs within a patient's regimen would reduce the overall HbA1c reduction potential and could also influence weight/BMI depending on the OAD.

Conclusion

GLP-1 RAs are effective in reducing weight and BMI in the veteran population when added in combination to standard therapy. Veterans experience a similar reduction in HbA1c when using GLP-1 RAs compared to published data although the difference as compared to standard therapy was not statistically significant. Our findings highlight the need to further evaluate the benefit of GLP-1 RAs in reducing HbA1c in the veteran population.

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