

Efficacy of Subcutaneous Semaglutide Dose Escalation in Reducing Insulin in Patients With Type 2 Diabetes

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Background: Type 2 diabetes mellitus (T2DM) is a chronic disease that affects nearly 25% of patients in the US Department of Veterans Affairs (VA) health care system. Semaglutide 2 mg has been found to significantly improve hemoglobin A_{1c} (HbA_{1c}) when compared with semaglutide 1 mg in patients who are not taking insulin. The purpose of this study was to investigate the effect subcutaneous semaglutide dose escalation has on total daily insulin dose in patients with T2DM.

Methods: This retrospective, single-center chart review study was conducted at the VA Sioux Falls Health Care System. The primary endpoint was change in daily insulin dose from baseline to semaglutide dose increase after receiving semaglutide 2 mg for ≥ 3 months. Baseline was defined as initiation of semaglutide 0.5 mg. Secondary endpoints included changes in daily bolus or basal insulin doses, HbA_{1c}

level, and number of hypoglycemic events reported.

Results: Sixty-two patients were included. Daily insulin dose changed -5.6% (95% CI, 2.2-14.0; $P = .008$) from baseline to 1-mg dose initiation, -22.2% (95% CI, 22.0-35.1; $P < .001$) at 2-mg dose initiation, and -36.9% (95% CI, 37.4-56.5; $P < .001$) after ≥ 3 months at the 2-mg dose. Mean HbA_{1c} level decreased from 7.7% at baseline to 7.1% at 2-mg dose initiation (95% CI, 0.3-0.8; $P < .001$).

Conclusions: There were statistically significant reductions in total daily insulin dose when subcutaneous semaglutide was initiated and further reduction with each semaglutide dose increase. These results support the current practice of prescribing semaglutide to treat T2DM and suggest that when the dose is increased to 2 mg, patients may experience reductions in total daily insulin dose and HbA_{1c} levels.

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Type 2 diabetes mellitus (T2DM) is a chronic disease becoming more prevalent each year and is the seventh-leading cause of death in the United States.¹ The most common reason for hospitalization for patients with T2DM is uncontrolled glycemic levels.² Nearly 25% of the US Department of Veterans Affairs (VA) patient population has T2DM.³ T2DM is the leading cause of blindness, end-stage renal disease, and amputation for VA patients.⁴

According to the 2023 American Diabetes Association (ADA) guidelines, treatment goals of T2DM include eliminating symptoms, preventing or delaying complications, and attaining glycemic goals. A typical hemoglobin A_{1c} (HbA_{1c}) goal range is $< 7\%$, but individual goals can vary up to $< 9\%$ due to a multitude of factors, including patient comorbidities and clinical status.⁵

Initial treatment recommendations are non-pharmacologic and include comprehensive lifestyle interventions such as optimizing nutrition, physical activity, and behavioral therapy. When pharmacologic therapy is required, metformin is the preferred first-line treatment for the majority of newly diagnosed patients with T2DM and should be added to continued lifestyle management.⁵ If HbA_{1c} levels remains above goal, the 2023 ADA guidelines recommend adding a second medication, including but not limited to insulin, a glucagon-

like peptide-1 receptor agonist (GLP-1RA), or a sodium-glucose cotransporter 2 inhibitor. Medication choice is largely based on the patient's concomitant conditions (eg, atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease).

The 2023 ADA guidelines suggest initiating insulin therapy when a patient's blood glucose ≥ 300 mg/dL, HbA_{1c} $> 10\%$, or if the patient has symptoms of hyperglycemia, even at initial diagnosis. Initiating medications to minimize or avoid hypoglycemia is a priority, especially in high-risk individuals.⁵

Clinical evidence shows that GLP-1RAs may provide similar glycemic control to insulin with lower risk of hypoglycemia.⁶ Other reported benefits of GLP-1RAs include weight loss, blood pressure reduction, and improved lipid levels. The most common adverse events (AEs) with GLP-1RAs are gastrointestinal. Including GLP-1RAs in T2DM pharmacotherapy may lower the risk of hypoglycemia, especially in patients at high risk of hypoglycemia.

The 2023 ADA guidelines indicate that it is appropriate to initiate GLP-1RAs in patients on insulin.⁵ However, while GLP-1RAs do not increase the risk of hypoglycemia independently, combination treatment with GLP-1RAs and insulin can still result in hypoglycemia.⁶ Insulin is the key suspect of this hypoglycemic risk.⁷ Thus, if insulin dosage can be reduced

or discontinued, this might reduce the risk of hypoglycemia.

The literature is limited on how the addition of a GLP-1RA to insulin treatment will affect the patient's daily insulin doses, particularly for the veteran population. The goal of this study is to examine this gap in current research by examining semaglutide, which is the current formulary preferred GLP-1RA at the VA.

Semaglutide is subcutaneously initiated at a dose of 0.25 mg once weekly for 4 weeks to reduce gastrointestinal symptoms, then increased to 0.5 mg weekly. Additional increases to a maintenance dose of 1 mg or 2 mg weekly can occur to achieve glycemic goals. The SUSTAIN-FORTE randomized controlled trial sought to determine whether there was a difference in HbA_{1c} level reduction and significant weight loss with the 2-mg vs 1-mg dose.⁸ Patients in the trial were taking metformin but needed additional medication to control their HbA_{1c}. They were not using insulin and may or may not have been taking sulfonylureas prior to semaglutide initiation. Semaglutide 2 mg was found to significantly improve HbA_{1c} control and promote weight loss compared with semaglutide 1 mg, while maintaining a similar safety profile.

Because this study involved patients who required additional HbA_{1c} control, although semaglutide reduced HbA_{1c}, not all patients were able to reduce their other diabetes medications, which depended on the baseline HbA_{1c} level and the level upon completion of semaglutide titration. Dose reductions for the patients' other T2DM medications were not reported at trial end. SUSTAIN-FORTE established titration up to semaglutide 2 mg as effective for HbA_{1c} reduction, although it did not study patients also on insulin.⁸

Insulin is associated with hypoglycemic risk, weight gain, and other AEs.^{7,8} This study analyzed whether increasing semaglutide could reduce insulin doses and therefore reduce risk of AEs in patients with T2DM.

METHODS

A retrospective, single-center, chart review was conducted at VA Sioux Falls Health Care System (VASFHCS). Data were collected through manual review of VASFHCS electronic medical records. Patients aged ≥ 18 years with active prescriptions for at least once-daily insulin who were initiated on 2-mg weekly dose of semaglutide at the VASFHCS clinical pharmacy practitioner medication management clinic between January 1, 2021, and September 1, 2023, were included. VASFHCS

TABLE 1. Baseline Characteristics (N = 62)

Criteria	Result
Age, mean (SD), y	66 (9.5)
White race, No. (%)	62 (100.0)
Weight, mean (SD), lb	246 (49.5)
Body mass index, mean (SD)	35.5 (7.5)
Hemoglobin A _{1c} , mean (SD), %	7.7 (0.9)

clinical pharmacy practitioners have a scope of practice that allows them to initiate, modify, or discontinue medication therapy within medication management clinics.

The most frequently used prandial insulin at VASFHCS is insulin aspart, and the most frequently used basal insulin is insulin glargine. Patients were retrospectively monitored as they progressed from baseline (the point in time where semaglutide 0.5 mg was initiated) to ≥ 3 months on semaglutide 2-mg therapy. Patients were excluded if they previously used a GLP-1RA or if they were on sliding scale insulin without an exact daily dosage.

The primary endpoint was the percent change in total daily insulin dose from baseline to each dose increase after receiving semaglutide 2 mg for ≥ 3 months. Secondary endpoints included changes in daily prandial insulin dose, daily basal insulin dose, HbA_{1c}, and number of hypoglycemic events reported. Data collected included age, race, weight, body mass index, total daily prandial insulin dose, total daily basal insulin dose, HbA_{1c}, and hypoglycemic events reported at the visit when semaglutide was initiated.

Statistical Analysis

The sample size was calculated prior to data collection, and it was determined that for α = .05, 47 patients were needed to achieve 95% power. The primary endpoint was assessed using a paired *t* test, as were each secondary endpoint. Results with *P* < .05 were considered statistically significant.

RESULTS

Sixty-two patients were included. The mean HbA_{1c} level at baseline was 7.7%, the baseline mean prandial and insulin daily doses were 41.5 units and 85.1 units, respectively (Table 1) From baseline to initiation of a semaglutide 1-mg dose, the daily insulin dose changed −5.6% (95% CI, 2.2-14.0; *P* = .008).

TABLE 2. Impact of Semaglutide 0.5-mg Weekly Dose Change (N = 62)

	Baseline	After ≥ 3 mo	P value (95% CI)
Daily dose of insulin, mean, units			
Prandial	41.5	24.6	< .001 (12.6 to 21.2)
Basal	85.1	52.1	< .001 (23.9 to 42.0)
Hemoglobin A _{1c} , mean, %	7.7	7.1	< .001 (0.3 to 0.8)
Hypoglycemic events reported, mean	3.6	3.2	.21 (−0.6 to 0.1)

From baseline to 2-mg dose initiation daily insulin changed −22.2% (95% CI, 22.0-35.1; $P < .001$) and for patients receiving semaglutide 2 mg for ≥ 3 months it changed −36.9% (95% CI, 37.4-56.5; $P < .001$) (Figure).

After receiving the 2-mg dose for ≥ 3 months, the mean daily dose of prandial insulin decreased from 41.5 units to 24.6 units (95% CI, 12.6-21.2; $P < .001$); mean daily dose of basal insulin decreased from 85.1 units to 52.1 units (95% CI, 23.9-42.0; $P < .001$); and mean HbA_{1c} level decreased from 7.7% to 7.1% (95% CI, 0.3-0.8; $P < .001$). Mean number of hypoglycemic events reported was not statistically significant, changing from 3.6 to 3.2 (95% CI, −0.6 to 0.1; $P = .21$) (Table 2).

DISCUSSION

This study investigated the effect of subcutaneous semaglutide dose escalation on total daily insulin dose for patients with T2DM. There was a statistically significant decrease in total daily insulin dose from baseline to 1 mg initiation; this decrease continued with further insulin dose reduction seen at the 2-mg dose initiation and additional insulin dose reduction at ≥ 3 months at this dose. It was hypothesized there would be a significant total daily insulin dose reduction at some point, especially when transitioning from the semaglutide 1-mg to the 2-mg dose, based on previous research.^{9,10} The additional reduction in daily insulin dose when continuing on semaglutide 2 mg for ≥ 3 months was an unanticipated but added benefit, showing that if tolerated, maintaining the 2-mg dose will help patients reduce their insulin doses.

In terms of secondary endpoints, there was a statistically significant decrease in mean total daily dose individually for prandial and basal insulin from baseline to ≥ 3 months after semaglutide 2 mg initiation. The change in HbA_{1c} level was also statistically significant and decreased from baseline, even as

insulin doses were reduced. This change in HbA_{1c} level was expected; previous literature has shown a significant link between improving HbA_{1c} control when semaglutide doses are increased to 2 mg weekly.¹⁰ Due to having been shown in previous trials, it was expected that HbA_{1c} levels would decrease even when the insulin doses were being reduced.¹⁰ Insulin dose reduction can potentially be added to the growing evidence of semaglutide benefits. The change in the number of hypoglycemic events was not statistically significant, which was unexpected since previous research show a trend in patients taking GLP-1RAs having fewer hypoglycemic events than those taking insulin.⁶ Further investigation with a larger sample size and prospective trial could determine whether this result is an outlier. In this study, there was no increase in HbA_{1c} or hypoglycemic events reported with increasing semaglutide doses, which provides further evidence of the safety of semaglutide even at higher doses.

These data suggest that for a patient with T2DM who is already taking insulin, the recommended titration of semaglutide is to start with 0.5 mg and titrate up to a 2-mg subcutaneous weekly dose and to then continue at that dose. As long as the 2-mg dose is tolerated, it will provide patients with the most HbA_{1c} control and lead to a reduction of their total daily insulin doses according to these results.

Strengths and Limitations

This study compared patient data at different points. This method did not require a second distinct control group, which would potentially introduce confounding factors, such as different baseline characteristics. Another strength is that documentation was available for all patients throughout the study so no one was lost to follow-up. This allowed comprehensive data collection and provided a stronger conclusion given the completeness of the data from baseline to follow-up.

Limitations include the retrospective design and small sample size. In addition, the study design did not allow for randomization. There is no documentation of adherence to medication regimen, which was difficult to determine due to the retrospective nature. Other changes to the patients' medication regimen were not collected in aggregate and thus, it is possible the total daily insulin dose was impacted by other medication changes. There is also potential for inconsistent documentation of the patients' true total daily insulin dose in the medical record, thus leading to inaccuracy of recorded data.

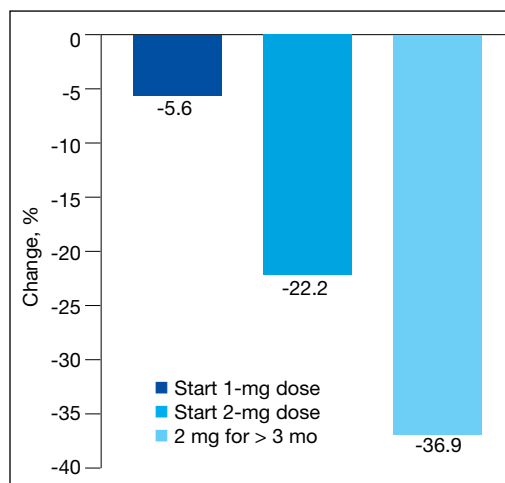


FIGURE. Change in daily insulin dose at time of semaglutide dose changes.

CONCLUSIONS

A small sample of veterans with T2DM had statistically significant reductions in total daily insulin dose when subcutaneous semaglutide was initiated, as well as after each dose increase. There was also a statistically significant reduction in HbA_{1c} levels from baseline even as patient insulin doses were reduced. These results support the current practice of using semaglutide to treat T2DM, suggesting it may be safe and effective at reducing HbA_{1c} levels as the dose is titrated up to 2 mg. There was no statistically significant change in the number of hypoglycemic events reported as semaglutide was titrated up. Thus, when semaglutide is increased to the maximum recommended dose of 2 mg for T2DM, patients may experience a reduction of their total daily dose of insulin and HbA_{1c} levels. These benefits may reduce the risk of insulin-related AEs while maintaining appropriate glycemic control.

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Ethics and consent

This study was approved by The University of South Dakota Health Care System Institutional Review Board as well as the Veterans Affairs Sioux Falls Research and Development Committee.

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