Evaluating the Effect on Total Daily Insulin Dose in Adult Patients with Type 1 Diabetes Managed with Metformin and/or GLP-1 or GLP-1/GIP Receptor Agonists

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Abstract
Purpose: There are few studies that have assessed the utility of metformin and glucagon-like peptide-1 receptor agonists (GLP-1 RA) in type 1 diabetes (T1D), specifically looking at glucose control indices. These studies have largely evaluated the impact of agents within the class that are not routinely used. Limited data exist on the use of the dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonist (GLP-1/GIP RA) in T1D. The objective of this study was to evaluate the effect of this growing practice in utilizing these common non-insulin therapies in T1D. *Methods*: This single-center, retrospective cohort study evaluated adult patients with T1D who received standard insulin therapy plus the following non-insulin therapies for at least 3 months: metformin; GLP-1 RA or GLP-1/GIP RA; or metformin and a GLP-1 RA or GLP-1/GIP RA (combination group). Data points were collected on starting dates of the first and second (if applicable) non-insulin agents, and the first office visit of at least 3 months on maximum tolerated doses. The primary endpoint was change in total daily insulin dose (TDD). Secondary and safety endpoints were evaluated in A1c, weight, and hypoglycemia. *Results*: A total of 110 of 366 patients met inclusion criteria. Changes in average insulin TDD were +4.06, -5.9 and -6.9 units for the metformin, GLP-1RA or GLP-1/GIP RA, and combination groups respectively (P =0.013). TDD after non-insulin therapy addition decreased in all patients on average 3.54 units (P =0.02). Non-insulin therapies showed a significant decrease in A1c by 0.62%, weight by 3.8kg, and hypoglycemia was seen in 76% of patients. *Conclusions*: Non-insulin therapies added to standard insulin therapy in T1D resulted in decreased insulin requirement, increased glycemic control, and decreased body weight. While statistically significant, it remains unclear if the decreased insulin requirement is clinically significant. Further prospective studies are warranted to validate these findings.

Keywords: type 1 diabetes, metformin, glucagon-like peptide-1 receptor agonists, GLP-1/GIP receptor agonists, glycemic control, non-insulin therapy

Background

Type 1 diabetes mellitus (T1D) is an autoimmune disease that causes destruction of insulin-producing pancreatic beta cells and over time, leads to absolute insulin deficiency.[1] Prior to the discovery of insulin, the prognosis for people with diabetes was poor.[2] Consequently, insulin has become the standard of care for patients with T1D. The 2024 American Diabetes Association Standards of Care in Diabetes recommends most patients with T1D should be treated with multiple daily injections of prandial and basal insulin, or with a continuous subcutaneous insulin infusion (Level of Evidence A).[3]

Insulin does not come without limitations and adverse effects. Administering exogenous insulin comes with a high risk of hypoglycemia. Insulin can also cause weight gain, which adversely affects a patient's cardiovascular risk profile, and may lead to treatment non-adherence. Non-insulin therapies have been developed, largely for use in the type 2 diabetes population, with a large focus on increasing insulin sensitivity.

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While most non-insulin therapies have traditionally been utilized in the type 2 diabetes population, there is a growing use of the glucagon-like peptide-1 receptor agonists (GLP-1 RA), and the novel dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonist (GLP-1/GIP RA) in T1D patients due to weight loss benefit and potential increase in insulin sensitivity due to loss of adipose tissue. Treatment with non-insulin therapies is becoming more prevalent despite mixed, limited data, as patients seek pharmacotherapy for obesity.

Most of the literature assessing the utility of GLP-1 RAs in T1D have looked at medications that are no longer the drug of choice due to dosing schedule and efficacy of newer GLP-1 RA options.[4-12] The ADJUNCT-1[9] and ADJUNCT-2[4] trials compared the once daily liraglutide to placebo in T1D patients and found that liraglutide added to insulin therapy reduced A1c levels, total daily insulin dose (TDD), and body weight. Increased rates of symptomatic hypoglycemia and hyperglycemia with ketosis were seen in both studies. A meta-analysis[10] of 24 randomized controlled trials showed liraglutide may provide therapeutic benefit for weight loss and appeared to decrease total daily insulin requirements dose-dependently but was associated with higher rates of nausea and ketosis events. There is but one case report evaluating the efficacy of the novel GLP-1/GIP RA in T1D.[13]

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Metformin, long used for the treatment of type 2 diabetes, has become increasingly more common in the T1D population due to the effects of the drug being independent of beta cell function, in theory resulting in increased insulin sensitivity.[14] The largest trial evaluating the use of metformin in T1D, the REMOVAL[15] trial, found that metformin did not improve glycemic control but may have a larger role in cardiovascular risk management than current use. Other studies evaluating the use of metformin in T1D have shown reduced insulin requirements and body weight, but no significant changes in glycemic control.[14,16-20]

Though controversial, treatment with non-insulin therapies is becoming more widespread. This study, conducted in a single center, community hospital, sought to assess the impact of this practice on total daily insulin requirement and overall glucose control, as well as rates of adverse effects.

Methods

In this single-center, retrospective cohort study, we included all patients aged 18 years and older diagnosed with T1D who were treated with insulin therapy for at least 12 months prior to starting non-insulin therapy. Patients who had been on the following for 3 months or longer were included: monotherapy with metformin, or semaglutide, dulaglutide, or tirzepatide (henceforth termed "GLP-1 group"); a combination of metformin and semaglutide, dulaglutide, or tirzepatide (henceforth termed "combination group"). Patients taking semaglutide and dulaglutide were specifically targeted as these are the newest agents with a once weekly dosing schedule option and have not been as robustly investigated as other GLP-1 RA agents. At the time of the study, tirzepatide was the only FDA approved GLP-1/GIP RA.

All patients with diabetic diagnoses other than T1D, pregnant patients, patients who discontinued non-insulin therapies prior to the 3-month follow-up, patients on any other non-insulin therapy for diabetes, patients on the above medications solely for weight loss outside of a diagnosis of diabetes, and patients being managed outside of the health network were excluded.

The health network's institutional review board approved the study protocol. We used our electronic health record data exploration tool to generate a report of all patients treated in the outpatient setting with T1D who received the previously mentioned non-insulin therapies in addition to standard insulin therapy between April 1, 2021 and February 28, 2023. Data were collected and de-identified from the electronic medical records.

Data points for insulin TDD, A1c, and body weight were collected on the day of starting the first non-insulin medication, on the day of starting the second non-insulin medication (if applicable), and at the first follow up office visit on the maximum tolerated dose after at least 3 months of therapy (Figure 1). If A1c was not due at the first follow-up, the next available A1c was counted.

The primary endpoint was the change in insulin TDD. Insulin TDD was defined as the total amount of insulin per day including both short and long-acting insulins. The basal rate for patients utilizing insulin pumps was calculated, and the amount of bolus varied in calculation per patient. In instances where there was no record of pump statistics in the chart, the prescribed maximum amount of insulin per day was used as the TDD. Where pump statistics were available, those were utilized in lieu of using the prescription of record. The secondary endpoints were change in A1c and change in body weight. Safety endpoints included glucose-related emergency department (ED) visit or hospitalization due to diabetic ketoacidosis (DKA) or hypoglycemia, and patient-reported hypoglycemia. Patient-reported hypoglycemia was confirmed via glucometer data where available. Hypoglycemia was defined as a blood glucose of < 70mg/dL.

We estimated a sample size of 342 patients with 114 patients per treatment arm would provide 80% power to detect a 10% decrease in insulin TDD at a significance (alpha level) of 0.05. Statistical analyses were conducted using descriptive and inferential statistics in Microsoft Excel. Descriptive statistics were used to describe changes in TDD, A1c, and body weight. Paired t-tests were used to determine significant differences in outcomes with the addition of non-insulin therapy. One-way ANOVA was used to determine significant differences in outcomes between the 3 different non-insulin therapy options. Descriptive statistics were used to describe differences in safety outcomes and a Chi-square test of independence was used to determine significance. Baseline characteristics were described using descriptive statistics. A *P* value of < 0.05 was considered significant.

Results

A total of 336 patients were identified as being prescribed insulin and one of the study drugs during April 2021 to February 2023. During the review, 25 patients were excluded due to concurrent use of other diabetic agents (largely sulfonylureas and sodium-glucose-co-transporter-2 inhibitors) and 121 patients were excluded as they were managed outside of the health system. Figure 2 summarizes the review process. The average duration of treatment was 69 weeks (time of first non-insulin therapy to time of last data collection point).

Baseline characteristics of the included patients are summarized in Table 1. Group distribution was not equal among included patients. The average baseline insulin TDD was 56.2 units in the metformin group, 62.6 units in the GLP-1 RA group, and 92.2 units in the combination group. The average baseline TDD among the three treatment groups was 70.7 units. The change in average TDD was +4.06 units, -5.9 units and -6.9 units, respectively (p=0.013). TDD after the addition of non-insulin

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therapies decreased by an average of 3.54 units (p=0.02) for all patients, a 5% decrease from baseline. These findings are summarized in Figure 3.

The average baseline A1c was 8.4% for the metformin group, 7.8% for the GLP-1 RA group, and 7.5% for the combination group. There was no statistically significant difference in change in A1c between the 3 treatment groups (-0.29%, -0.76% and -0.32%, respectively (p = 0.203). When comparing patients as a whole, addition of non-insulin therapies resulted in an overall decrease in average A1c by 0.62% (p < 0.05). These findings are summarized in Figure 4.

The average baseline body weight was 100.8kg for the metformin group, 98.4kg for the GLP-1 RA group, and 106kg for the combination group. Change in average weight was -0.53 kg, -5.15 kg, and -1.18 kg for the groups, respectively (p = 0.01). Addition of non-insulin therapies resulted in an overall decrease of 3.8 kg in average body weight (P < 0.05). These findings are summarized in Figure 5.

Three patients, all from the GLP-1 RA group, experienced DKA. None of the patients included in the study had an ED visit or hospitalization due to hypoglycemia. Patient-reported hypoglycemia was seen in 76% of patients after addition of non-insulin therapies (P = 0.009). Per study protocol, none of the study agents were discontinued due to adverse events.

Discussion and Conclusions

To our knowledge, this was the first study investigating the effect of the use of both metformin and GLP-1 RA or GLP-1/GIP RA in the same patient in addition to standard insulin therapy in adult patients with T1D. This is also the only retrospective cohort study investigating the effect of the dual GLP-1/GIP RA (tirzepatide) in addition to standard insulin therapy in this population at the time of the initiation of this project. The most robust data for GLP-1 RA use in T1D are from studies using liraglutide and exenatide. These agents have largely fallen out of favor due to daily dosing schedules.

Over an average duration of 16 months, we found the addition of non-insulin study agents to standard insulin therapy in the treatment of T1D resulted in a decrease in insulin requirement and lowered A1c. By the end of the study period, 53 patients (48%) achieved an A1c goal of <7%. A 10% decrease in insulin TDD is considered a clinically significant improvement within accepted literature. The 5% overall decrease in insulin TDD seen in this study, may have clinical significance depending on the patient's baseline insulin needs and their propensity for hypoglycemia.

Clinically more important than the decrease in TDD is the decrease in weight seen in all groups. The World Health Organization estimates that 1 in 8 adults are living with obesity (defined as a BMI of >30), and in the state of Ohio, where this study took place, 30% of adults are considered obese.[21,22] The health consequences of obesity are well known and can worsen the health impacts of long-standing diabetes of any type. While this study collected only body weight, it is clear that with an average population weight of 101.7kg that the population likely represents those above their ideal body weight. It is also worth noting that the diagnosis of type 1 diabetes was not confirmed by these investigators beyond the diagnosis listed within the electronic health record.

The 3 patients that experienced DKA were all in the GLP-1 RA group, having received either semaglutide or dulaglutide. Two of the three patients were on < 40 units of insulin per day. This study did not assess patients for adherence to their prescribed regimen outside of ensuring they were still prescribed the medication at the time of the last data collection point. This was largely due to limitations of the institution's electronic health record not linking adherence data from every insurance payor. Regimen non-adherence is a common cause of DKA in T1D. Although patient reported hypoglycemia occurred in the majority of patients, we did not see any occurrences of hypoglycemia warranting ED visits or hospitalizations.

These findings do highlight the need to evaluate insulin dose adjustment practices when adding non-insulin therapies in T1D. This study strengthens current literature by addressing a gap regarding the addition of non-insulin therapies to standard insulin therapy in T1D and addressing the use of the dual GLP-1/GIP RA (tirzepatide) in T1D where previously a single case report exists. This study also adds more validity to the growing evidence that non-insulin therapies, specifically GLP-1 Ras, may offer benefits in T1D. As patients continue to seek pharmacotherapy options for weight loss, literature such as this provides valuable data on safety and efficacy in an understudied population.

The scope of the study is limited due to being a retrospective chart review with a small sample size. Our study was underpowered because we experienced a higher-than-expected rate of exclusions. There were disruptions in therapy due to GLP-1 RA and GLP-1/GIP RA shortages and denials of insurance coverage since these medications are only FDA approved for use in T2D and are being used off-label for T1D. Even when covered by insurance, the high copay for the GLP-1 RAs and GLP-1/GIP RA can be a burden for patients. We were not able to assess the adherence of patients due to the retrospective nature of this study and the lack of reliable adherence data that could be obtained from the electronic health record.

Overall, our study results support continued use of metformin and GLP-1 RAs and GLP-1/GIP RAs in adult patients with T1D for improved glycemic control and weight loss. Further prospective studies are needed to validate these findings.

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References

1. Lucier J, Weinstock RS. Type 1 Diabetes (updated 2023). www.ncbi.nlm.nih.gov/books/NBK507713/ (accessed 2023 September 1).
2. American Diabetes Association. The History of A Wonderful Thing We Call Insulin (2019) www.diabetes.org/blog/history-wonderful-thing-we-call-insulin (accessed 2023 September 1).
3. American Diabetes Association. Diabetes Care. Standards of Care in Diabetes (2024). www.diabetesjournals.org/care/issue/47/Supplement_1 (accessed 2024 April 20).
4. Ahrén B, Hirsch IB, Pieber TR, et al.; ADJUNCT TWO Investigators. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. Diabetes Care 2016; 39:1693–1701.
5. Dejgaard TF, Frandsen CS, Hansen TS, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2016; 4:221–232.
6. Frandsen CS, Dejgaard TF, Holst JJ, et al. Twelve-week treatment with liraglutide as add-on to insulin in normal-weight patients with poorly controlled type 1 diabetes: a randomized, placebo-controlled, double-blind parallel study. Diabetes Care. 2015; 38:2250–2257.
7. Herold KC, Reynolds J, Dziura J, et al. Exenatide extended release in patients with type 1 diabetes with and without residual insulin production. Diabetes Obes Metab. 2020; 22:2045-2054.
8. Hari Kumar KVS, Shaikh A, Prusty P. Addition of exenatide or sitagliptin to insulin in new onset type 1 diabetes: a randomized, open label study. Diabetes Res Clin Pract. 2013; 100:e55-e58.
9. Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. Diabetes Care 2016; 39:1702 –1710.
10. Park J, Ntelis S, Yunasan E, et al. Glucagon-like peptide 1 analogues as adjunctive therapy for patients with type 1 diabetes: an updated systematic review and meta-analysis. J Clin Endocrinol Metab 2023; 109:279-292.
11. Rother KI, Spain LM, Wesley RA, et al. Effects of exenatide alone and in combination with daclizumab on ?-cell function in long-standing type 1 diabetes. Diabetes Care. 2009; 32:2251-2257.
12. Traina AN, Lull ME, Hui AC, et al. Once-weekly exenatide as adjunct treatment of type 1 diabetes mellitus in patients receiving continuous subcutaneous insulin infusion therapy. Can J Diabetes. 2014; 38:269–272.
13. Mendoza F, Parsiani R. Impact of tirzepatide in a patient with type 1 diabetes and obesity: a case report. J Am Pharm Assoc (2003). 2023; 63:1821-1825.
14. Jacobsen IB, Henriksen JE, Beck-Nielsen H. The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control. Basic Clin Pharmacol Toxicol. 2009; 105:145–9.
15. Petrie JR, Chaturvedi N, Ford I, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017; 5:597–609.
16. Hamilton J, Cummings E, Zdravkovic V, et al. Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. Diabetes Care. 2003; 26:138–43.
17. Khan AS, McLoughney CR, Ahmed AB. The effect of metformin on blood glucose control in overweight patients with type 1 diabetes. Diabet Med J Br Diabet Assoc. 2006; 23:1079–84.
18. Lund SS, Tarnow L, Astrup AS, et al. Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control: a randomized study. PLoS One. 2008; 3:e3363.
19. Meng H, Zhang A, Liang Y, et al. Effect of metformin on glycaemic control in patients with type 1 diabetes: a meta-analysis of randomized controlled trials. Diabetes Metab Res Rev 2018; 34: e2983.
20. Meyer L, Bohme P, Delbachian I, et al. The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients. Diabetes Care. 2002; 25:2153–8.
21. Obesity and overweight. World Health Organization. Updated March 1, 2024. Accessed October 18, 2024. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
22. Obesity-Associated Cancers in Ohio 2023. Ohio Cancer Incidence Surveillance System, Ohio Department of Health. Updated January 2023.

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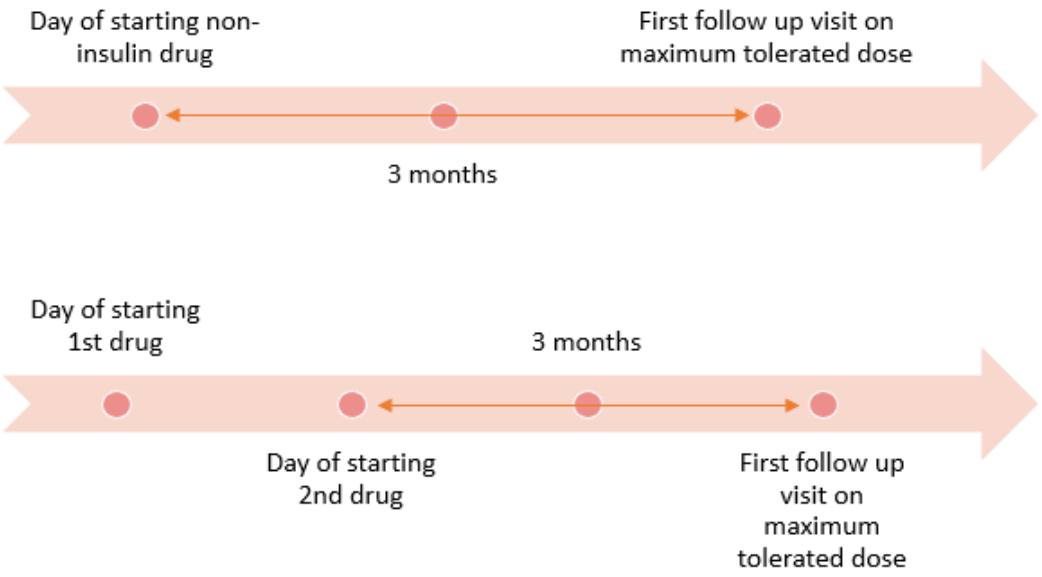

Figure 1. Data collection time points

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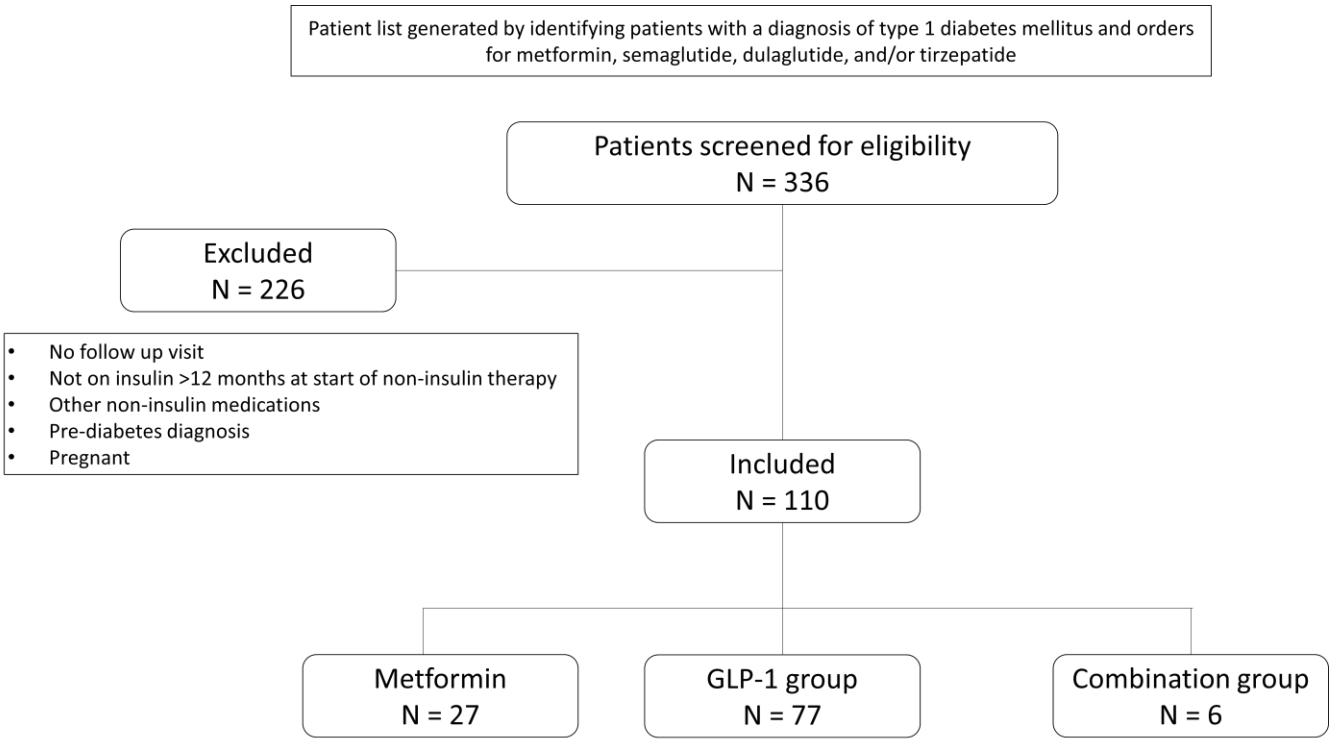

Figure 2. Flowchart of the patient screening and inclusion process

*GLP-1 group: semaglutide, dulaglutide, or tirzepatide; Combination group: metformin and semaglutide, dulaglutide, or tirzepatide

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		Metformin (N = 27)	GLP-1 Group (N = 77)	Combination Group (N = 6)
Age, years (± SD)		39.4 (12.9)	43.1 (12.7)	41.3 (15.2)
Male sex		11 (40.7)	18 (23.4)	3 (50)
Race	White	24 (88.9)	73 (94.8)	5 (83.3)
	Black/African American	2 (7.4)	1 (1.3)	0
	Unable to determine	1 (3.7)	2 (2.6)	0
	Mixed	0	1 (1.3)	1 (16.7)
Ethnicity	Not Hispanic/Latino	26 (96.3)	74 (96.1)	6 (100)
	Hispanic/Latino	0	2 (2.6)	0
	Unable to determine	1 (3.7)	1 (1.3)	0
Average insulin TDD, units (± SD)		56.2 (26.9)	63.6 (30)	92.2 (55)
Average A_{1c} % (± SD)		8.4 (1.9)	7.8 (1.3)	7.5 (1.1)
Average weight, kg (± SD)		100.8 (23.9)	98.4 (20.4)	106 (25.4)

Table 1. Baseline Characteristics
*Data presented as n (%) unless otherwise noted

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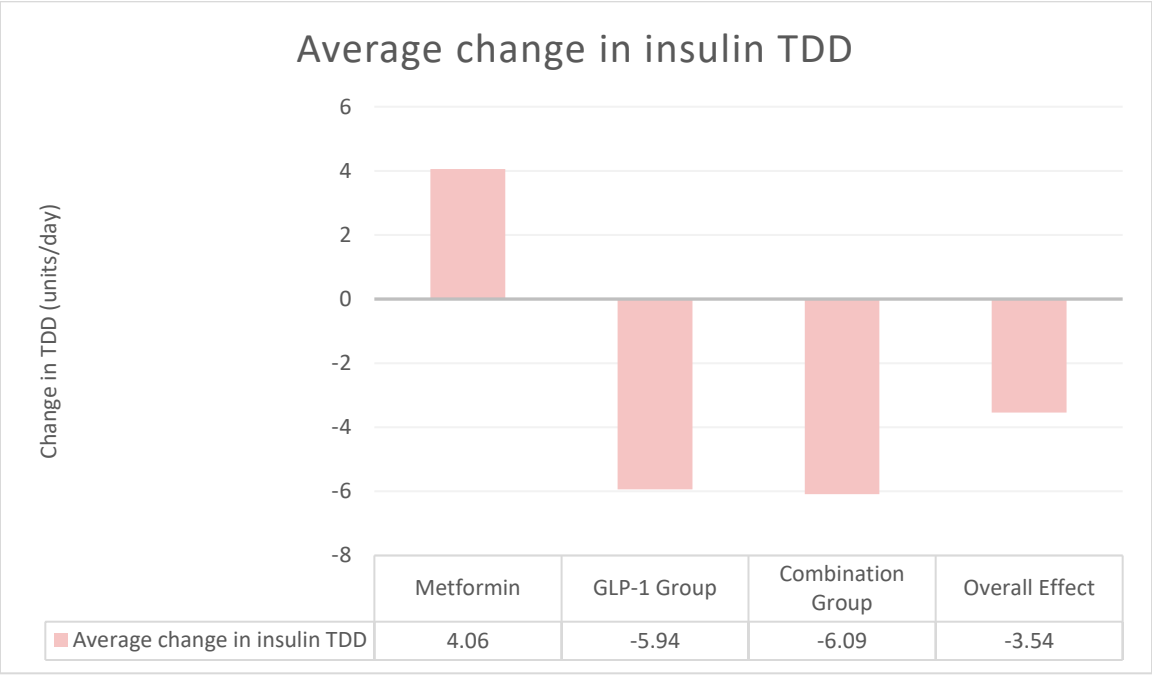

Figure 3. Effect of non-insulin therapies on average insulin TDD

*P = 0.013, average change in insulin TDD compared between the non-insulin therapies

**P = 0.02, overall change in insulin TDD with addition of non-insulin therapies to standard insulin therapy vs. standard insulin therapy only

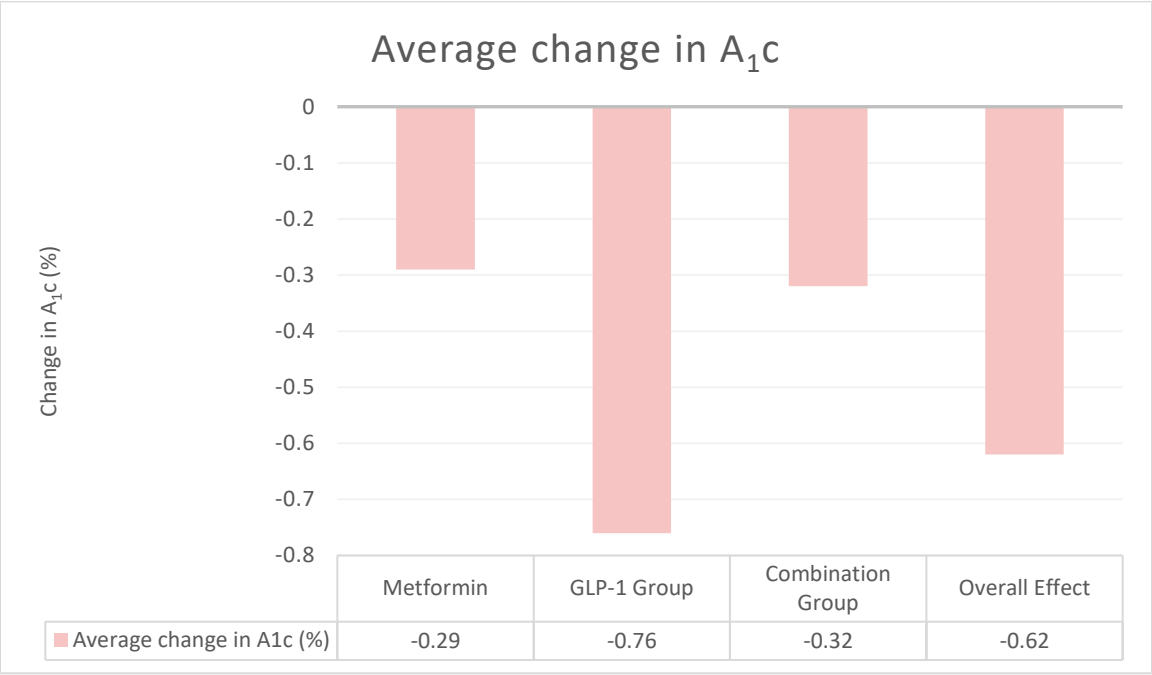

Figure 4. Effect of non-insulin therapies on A_1c

*P=0.203, average change in A_1c compared between the non-insulin therapies

**P < 0.005, overall change in A_1c with addition of non-insulin therapies to standard insulin therapy vs standard insulin therapy only

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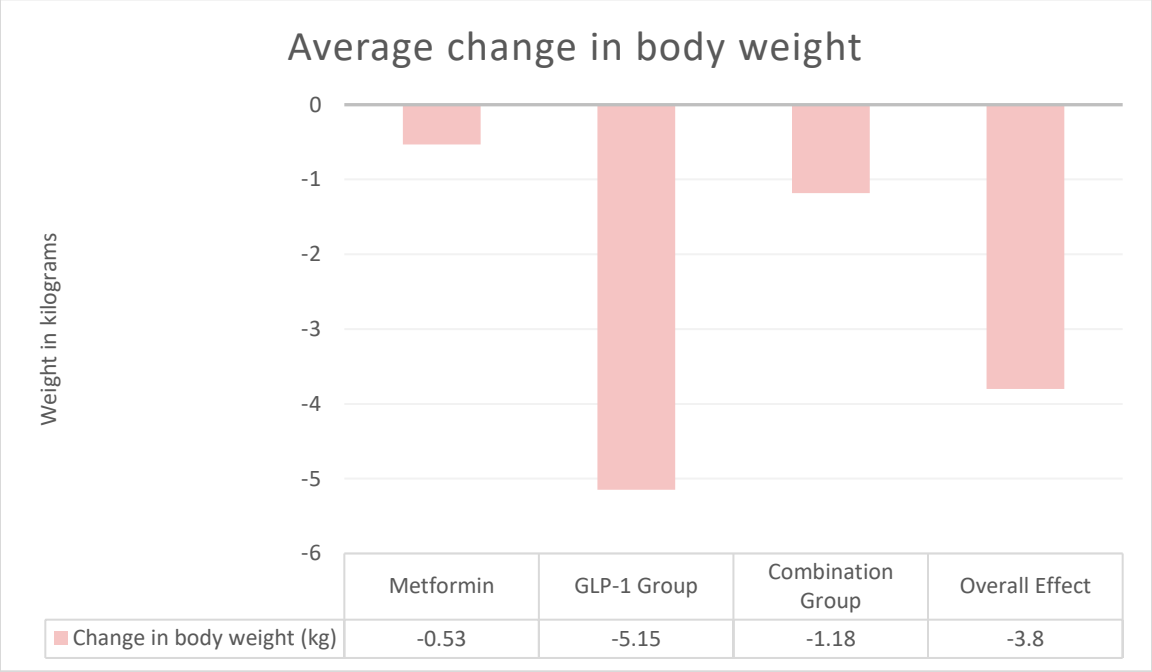

Figure 5. Effect of non-insulin therapies on body weight

*P = 0.01, average change in body weight compared between the non-insulin therapies

**P = < 0.005, overall change in body weight with addition of non-insulin therapies to standard insulin therapy vs. standard insulin therapy only

Figure 6. Safety Outcomes

*P = 0.516, incidence of DKA

**P = 0.009, incidence of patient-reported hypoglycemia, after initiating non-insulin therapy vs standard insulin therapy only

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