Use of Premixed Insulin, Metformin, and a Glucagon-Like Peptide 1 Receptor Agonist as a Therapeutic Approach for Uncontrolled Type 2 Diabetes

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OBJECTIVE I To explore the use of premixed insulin, a glucagon-like peptide 1 (GLP-1) receptor agonist, and metformin as combination therapy for type 2 diabetes.

DESIGN AND METHODS I All adult patients with type 2 diabetes who had been prescribed premixed insulin and a GLP-1 receptor agonist simultaneously at our outpatient clinic were selected for retrospective review. We reviewed A1C, weight, cumulative daily insulin dose, and adverse events over 12 months.

RESULTS I A total of 72 patients received premixed insulin and a GLP-1 receptor agonist, of which 32 met inclusion criteria. The average duration of type 2 diabetes for these patients was 14.2 ± 7.1 years. Mean A1C at baseline was 10.5 ± 2.1%. At 12 months, mean A1C was 8.3 ± 1.9%. The change in mean A1C after 12 months was −2.2% (95% CI −3.433 to −1.014, P < 0.0001). At 12 months, the mean cumulative insulin dose was 33.3 units less than before the therapy change (CI −57.13 to −9.46, P = 0.0030). Average weight change at 12 months was −2.2 kg (95% CI −27.6 to 37.6, P = NS). After 12 months, 61% of included patients (19 of 31) had an A1C ≤8%. Six additional patients were not included in analysis because they stopped the regimen after <3 months because of adverse events.

CONCLUSION I Despite a decreased cumulative daily dose of insulin, patients with historically uncontrolled type 2 diabetes using metformin, premixed insulin, and a GLP-1 receptor agonist in combination experienced improved glycemic control over 12 months. Prospective randomized trials are needed to better assess the potential benefit of this combination therapy.

Glycemic control improves both microvascular and macrovascular outcomes in patients with type 2 diabetes (1). A1C levels >6.5% are associated with increased diabetes-related complications (2,3). Unfortunately, fewer than half of Americans with diabetes reach their A1C goal despite newer oral agents, injectable insulin-sparing agents, and insulin products becoming available during the past decade (4).

In uncontrolled type 1 diabetes, basal insulin is traditionally the initial type of insulin prescribed. It may be escalated to a dose ≥1.0 unit/kg, but increases beyond 0.5 units/kg have a diminishing additional impact on glycemic control while increasing the risk of weight gain and hypoglycemia (5,6). Overall, newer basal insulin analogs have failed to show a reduction in severe hypoglycemia or conclusively demonstrate a significant glycemic benefit over NPH insulin (7–10).

When premixed insulin and a basal-bolus insulin regimen are compared in clinical trials, glycemic control typically improves more with basal-bolus insulin (7). However, the costs associated with this type of regimen, its requirement of four to five daily injections, and general issues with insulin compliance are all common barriers to successful basal-bolus insulin therapy (11–14).

Both the American Diabetes Association (ADA) and European Association for the Study of Diabetes recommend considering the addition of prandial insulin or a glucagon-like peptide 1 (GLP-1) receptor agonist if the total basal insulin dose is >0.5 units/kg (15,16). GLP-1 receptor agonists when combined with basal insulin have yielded significant glycemic benefit and are especially appealing given their potential cardiovascular (CV) and renal benefits, especially in people with established CV disease (CVD).
Medication nonadherence is one of the main reasons for patients not attaining their A1C goal (4). In an effort to simplify the medication regimen for our obese patients with poorly controlled type 2 diabetes on high-dose basal or basal-bolus insulin therapy and to limit their required daily injections, we implemented the use of premixed insulin, metformin, and a GLP-1 receptor agonist in our clinic. We report the results here.

Design and Methods

This retrospective chart review was approved by the institutional review board of George Washington University.

Patient Selection

All patients who presented to the George Washington University Department of Endocrinology and Diabetes outpatient center between 1 January 2013 and 1 November 2017 and were given a prescription for premixed insulin (70/30 insulin aspart protamine and insulin aspart or 75/25 insulin lispro protamine and insulin lispro) were identified. Electronic medical records were reviewed in detail, and all patients who were prescribed a GLP-1 receptor agonist while on premixed insulin were then selected. Patients on premixed insulin who were never given a GLP-1 receptor agonist, were not taking a GLP-1 receptor agonist and premixed insulin concomitantly, or did not have >3 months of follow-up data we excluded, as well those taking any additional diabetes medications other than metformin and those who stopped taking premixed insulin or a GLP-1 receptor agonist after <3 months.

Measurements

Demographic data collected included patients’ age, sex, race/ethnicity, weight, BMI, insurance status, baseline insulin dose, duration of diabetes, other diabetes medications, and presence of chronic kidney disease (CKD; with estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²) or CVD (Table 1).

Clinical data were collected at time of initiation of combination therapy, 6 months after initiation, and 12 after initiation. These included A1C, weight, insulin types, total daily insulin dose, insulin units/kg, GLP-1 receptor agonist type (once-daily vs. once-weekly administration), other oral diabetes medications, and adverse events. AtC values were also reviewed for the 2 years prior to initiation of combination therapy, if available. The primary outcomes were changes in A1C, weight, and total insulin dose on the combination of premixed insulin and a GLP-1 receptor agonist.

Statistical Analysis

Descriptive statistics were calculated for the demographic data and expressed as mean ± SD or n (%). We examined distributions of continuous variables for nonnormality or outliers and log-transformed if necessary, to produce approximate normality. Paired t tests were used to compare mean A1C, total insulin dose, weight, and insulin dose per kg across time points. Associations of change in A1C with change in total insulin dose and change in weight were examined with Spearman correlations, which provide an index of the strength of the monotonic relationship between two continuous variables. Between-groups t tests were used to compare the degree of change in A1C, total insulin dose, and weight by sex, previous use of either a GLP-1 receptor agonist or premixed insulin, and presence of CKD. ANOVA and the Kruskal-Wallis test were used to compare changes in A1C, total insulin dose, and weight by race/ethnicity. Data analysis was performed with SAS v. 9.4 software (SAS Institute, Cary, NC) with P < 0.05 considered significant.

Results

A total of 72 patients were selected based on having received a prescription for premixed insulin during the study period. Of those, 17 were never prescribed a GLP-1 receptor agonist, 2 never started the premixed insulin, 7 were lost to follow-up, 1 had been recently started on the GLP-1 receptor agonist (<3 months ago), and 7 were taking other diabetes medications (3 empagliflozin, 1 glipizide, 1 glimepiride, and 2 lunchtime prandial insulin). Four patients stopped the GLP-1 receptor agonist and two stopped the premixed insulin because of adverse effects within the first 3 months. This left 32 patients to be included in the analysis.

Participant Characteristics

Of the 32 patients remaining, 31 patients had 12-month data. Twenty-five (78.1%) were female, 23 (71.9%) were African American, 6 (18.8%) were Caucasian, and 3 (9.4%) were Hispanic. The mean age was 53.1 ± 9.6 years, and the mean diabetes duration was 14.2 ± 10 years. Most common insurance types were Medicare 12 (37.5%) and both Medicare and Medicaid 11 (34.4%) (Table 1).
Data are mean ± SD or n (%). MDI, multiple daily injection.

The mean A1C of our population 6 months before starting the combination therapy was 10.6 ± 2.1%, with a mean total daily insulin dose of 108.8 ± 49.8 units. The mean A1C at baseline was 10.5 ± 2.1%. Mean weight at baseline was 110 ± 25 kg, with a mean BMI of 38.2 ± 7.5 kg/m².

Nine patients (28.1%) had previously taken a GLP-1 receptor agonist before their insulin was changed to premixed insulin. These prescriptions were for various GLP-1 receptor agonist agents, with 19 patients (59.4%) taking a once-weekly formulation and 13 (40.6%) taking a once-daily formulation. The mean number of daily injections decreased from 3.4 to 2.8, with 59% of patients only taking 2 daily injections because their GLP-1 receptor agonist was a once-weekly formulation. Use of metformin was standard, with only one patient not previously on metformin.

Eight patients (25.0%) had CKD (eGFR < 60 mL/min/1.73 m²), whereas none had known CVD at baseline.

### Changes in A1C and Cumulative Insulin Dose

Mean A1C declined significantly from 10.5 ± 2.1% at baseline to 8.6 ± 2.1% at 6 months and 8.3 ± 1.9% at 12 months (both P < 0.0001) (Figure 1). The change in mean A1C was −2.3% at 12 months (95% CI −3.183 to −1.437). At 12 months, 61% of the patients (19 of 31) had an A1C ≤8%, 23% (7 of 31) had an A1C ≤7% (Table 2 and Figure 1). There was no significant difference in baseline A1C between those who did or did not previously take a GLP-1 receptor agonist (9.7 vs. 10.9%, P = NS). Mean A1C decreased after 6 months and was sustained at 12 months on the combination therapy. However, subgroup analysis showed that the group that was previously on a GLP-1 receptor agonist did not have a statistically significant reduction in A1C drop (n = 9, P = NS) likely because of the small sample size. The subgroup who had not previously taken a GLP-1 receptor agonist had statistically significant decrease (n = 23, P < 0.0001), perhaps detected as a result of the larger sample size.

The mean total daily insulin dose before starting premixed insulin was 108.8 ± 49.8 units/day, which declined significantly to 80.8 ± 25.8 units/day (P = 0.0064) at the start of combination therapy, a 26% average decrease. The mean cumulative insulin dose further declined by 4% to 75.5 ± 37.1 units/day after 12 months (P = NS). The reduction in mean total daily insulin dose from baseline to 12 months was 33.3 units/day (P = 0.0019) (Table 2). The insulin dose decreased by a mean 0.3 units/kg (P = 0.0022) from that during the original therapy. Being on a GLP-1 receptor agonist before adding premixed insulin was not related to the change in A1C, total insulin dose, or weight (P = NS), and A1C dropped significantly in all patients.

### Weight Change

Overall change in weight after the combination therapy was not significant (P = NS). However, 36% (11 of 31) lost >2.2 kg, 29% (9 of 31) lost >5% body weight, and 10% (3 of 31) lost >10% body weight. Overall, 45% of patients (14 of 31) either lost or did not gain weight (Table 2).

### Intolerance to Therapy/Adverse Events

Thirty-two patients were included in the analysis, but an additional six patients had received intervention therapy but stopped either the GLP-1 receptor agonist or the premixed insulin within the first 3 months secondary to
adverse events; these patients were excluded from the analysis given their short duration on the combination therapy. Two patients stopped therapy secondary to nausea and vomiting from the GLP-1 receptor agonist, one for pancreatitis, and one for leg cramps. One patient stopped insulin therapy secondary to hypoglycemia, and one stopped after having a skin reaction to the premixed insulin.

Discussion

We sought to use a novel combination treatment approach of premixed insulin with a GLP-1 receptor agonist in a group of patients with historically difficult-to-control type 2 diabetes and to assess their glycemic control while on this therapy.

Multiple randomized control trials have shown the benefits of basal insulin and GLP-1 receptor agonist therapy (22–24). Several small studies with the GLP-1 receptor agonist liraglutide as an add-on to multidose insulin therapy have shown reductions in A1C, weight, and insulin dose (25–27), even in those with extreme insulin resistance taking U-500 regular insulin (28). One of these studies using liraglutide did include 15 patients on premixed insulin but also included other oral agents for diabetes, and the cumulative daily insulin dose at baseline was <0.5 units/kg (25). In this study, 30% of patients were able to stop insulin use with the addition of a GLP-1 receptor agonist.

There have been two other small studies (26,27) with populations more similar to ours in which patients were initially on multidose insulin at >1.5 units/kg daily. In one of these studies, 14 patients in the add-on group were on premixed insulin. Those on premixed insulin showed improvements in A1C and reduced insulin requirements; however, there was no reduction in the number of daily injections (insulin only), with a mean number of 3.8 injections per day in both groups (26).

Overall, there are very few studies involving people on multidose insulin and a daily GLP-1 receptor agonist (25–28) and three case reports that have also shown significant A1C improvement on a combination therapy regimen of high-dose or U-500 insulin and a daily GLP-1 receptor agonist (29–31). There have been no randomized controlled trials examining the use of a GLP-1 receptor agonist in conjunction with premixed insulin and only one recent case report that included the use of a once-weekly GLP-1 receptor agonist (32). Furthermore, to our knowledge, our study, with data at 12 months, is the only one to assess the effects of this combination therapy regimen for >6 months.

In our retrospective study, after starting the premixed insulin in combination with a GLP-1 receptor agonist, A1C improved in the majority of the patients by ≥2%. After 12 months, 66% (19 of 31) had an A1C ≤8%, and 23% (7 of 31) reached an A1C <7% (Figure 1). Glycemic control improved in the majority of the patients despite a decrease in cumulative insulin dose by 30% from baseline, a long history of uncontrolled diabetes (A1C >9.0%), and obesity.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Changes in A1C, Weight, and Insulin Dose Over Time With Combination Therapy</th>
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<tbody>
<tr>
<td></td>
<td>Baseline on Original Therapy (n = 32)</td>
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<tr>
<td>A1C, %</td>
<td>10.6 ± 2.1</td>
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<tr>
<td>A1C change, %</td>
<td>–</td>
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<tr>
<td>Weight, lb</td>
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<tr>
<td>Insulin dose, units/kg</td>
<td>1.04 ± 0.6</td>
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<tr>
<td>Total daily insulin dose (units)</td>
<td>108.8 ± 49.8</td>
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Data are mean ± SD. Analysis was with ANOVA repeated measures and paired t tests. *Insulin doses were compared between baseline and the 12-month time point.
Because this was a retrospective analysis, we can only hypothesis about why there was a large reduction of insulin (mean 26%) at baseline with the therapy change, but we but suspect that when then regimen was initiated, the cumulative insulin dose was reduced to limit the risk for hypoglycemia. There was then only a modest (4%) further reduction of insulin dose by 12 months.

This improvement in A1C despite a reduction in cumulative insulin may be associated with simplification of treatment; 59% of patients were only on two daily injections, and patients went from a mean 3.4 to 2.8 shots a day (including those on a daily GLP-1 receptor agonist). All patients took medication only twice daily; metformin, premixed insulin, and GLP-1 receptor agonist were given in the morning, and metformin and insulin were given at dinner. No injections were required at lunch, a time typically more challenging for patients who work or have busy schedules.

Improved glycemic control also likely occurred because prandial insulin was added at the time people tend to be more insulin resistant (morning) and with the largest meal, which is typically dinner. This addition of prandial insulin targeted postmeal blood glucose more than basal insulin. As noted earlier, studies have shown that further escalation of basal insulin >0.5 units/kg may have limited benefits and increased risks.

The sustained glycemic improvement also may have been, in part, because combination treatment with premeal insulin and a GLP-1 receptor agonist helps target the physiology and natural progression of type 2 diabetes. Longer duration of diabetes may result in β-cell dysfunction, in turn resulting in relative insulinopenia (33), especially after meals. Additionally, patients with obesity and type 2 diabetes also may possess some degree of incretin deficiency (34), and up to 70% of overall postprandial insulin response to glucose is mediated by the incretin hormones (35). In individuals with diabetes, especially of long duration, the α-cells are not suppressed by hyperglycemia, and plasma glucagon concentrations are increased. Thus, both postprandial and fasting glucose levels rise (34). GLP-1 receptor agonists are incretin mimetics that stimulate insulin secretion and prevent postprandial glucagon release. Therefore, they help with both fasting insulin levels and postprandial insulin release and target the glucagon pathway, which could lead to more substantial glycemic improvement. Preprandial insulin likely also helps support the relative insulinopenia of the patients with a longer duration of diabetes. Additionally, as was seen in a study with the GLP-1 receptor agonist exenatide, GLP-1 receptor agonists may improve β-cell function (36). Exenatide significantly improved β-cell function during 1 year of treatment compared with basal insulin (36).

Finally, a GLP-1 receptor agonist may also be desirable as an adjunct to premixed insulin therapy given the newer data on CVD and renal benefits (18–22,37). Despite having a long duration of diabetes, the average age of patients in our study was 53 years, so none of our 31 patients had had an initial CV event at baseline. However, 28% had renal involvement. The REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) study (37) recently showed that GLP-1 receptor agonists may be beneficial for primary prevention for CVD. Thus, their use in this high-risk, obese population is desirable given that GLP-1 receptor agonists have a lower risk for hypoglycemic episodes, may promote weight loss, and offer have potential CV and renal benefits (18–22,37).

Weight

It is well established that insulin is associated with weight gain. In the UK Prospective Diabetes Study (33,38), the group receiving intensive insulin therapy gained an average of 4.0 kg compared with patients in the conventional therapy group. Weight gain may be secondary to many factors such as decreased glycosuria after improvement in glycemic control, the anabolic effects of insulin itself, and decreased metabolic rate. However, in our population of participants with an original mean A1C >10%, no weight gain occurred despite improvement in A1C to <8% in 61% of the participants. In our study, 42% of patients (13 of 31) had weight loss or no weight gain. Only 29% (9 of 31) gained >2.2 kg. In fact, 36% of patients (11 of 31) lost >2.2 kg, and 29% (9 of 31) lost ≥5% of body weight.

Although it has been noted that 30% of patients experience no weight loss while taking a GLP-1 receptor agonist (39), these agents may cause weight loss in many by slowing gastric emptying and improving satiety (40). In studies using GLP-1 receptor agonists as monotherapy or add-on therapy, weight reduction of 1–5 kg has been seen and is often sustained (40–46).

Typically, a GLP-1 receptor agonist in combination with insulin prevents significant weight gain and may still facilitate modest weight loss (46). One study in patients with poorly controlled diabetes and visceral obesity showed that add-on lixisenatide treatment significantly reduced mean body weight (by 5.62 kg, P <0.01), waist circumference (by 5.70 cm, P <0.01), BMI (by 1.93 kg/m², P <0.01), and daily total insulin dose (by 66%), whereas all these parameters significantly increased with insulin therapy intensification (25). In our study, we also saw on average reduction of 33.3

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units of total daily insulin, which may have helped with weight maintenance or loss.

**Hypoglycemia**

We did not see any documented episodes of severe hypoglycemia in our record review, nor did we see evidence of increased hospitalization or emergency room visits for low blood glucose. There was one case that led to cessation of therapy secondary to recurrent moderate hypoglycemia. However, this was only a retrospective chart review, and there was no objective way to determine rates of hypoglycemia.

In studies with basal insulin and GLP-1 receptor agonists, rates of hypoglycemia did not increase despite improved glycemic control (24,43–46), and one can speculate that reduction in the cumulative insulin dose with use of a GLP-1 receptor agonist and metformin helped reduce hypoglycemia. Recent studies have shown that combination GLP-1 receptor agonist and high-dose insulin therapy results in a statistically significant reduction in glycemic variability, as assessed by continuous glucose monitoring (27). However, further prospective research is needed in individuals taking premixed insulin.

**Side Effects and Discontinuation**

GLP-1 receptor agonists often cause gastrointestinal problems. Of our 38 patients, 2 discontinued the medication because of nausea, and 1 developed pancreatitis. These results are not surprising given the side effect profile that has been described in prospective studies of GLP-1 receptor agonists. A recent meta-analysis of GLP-1 receptor agonist therapy by Zheng et al. (47) found improvements in CVD risk and all-cause mortality (by 0.6 and 0.5%, respectively) but also a higher rate of side effects leading to withdrawal from the trials at higher rates than with sodium–glucose cotransporter 2 inhibitors or dipeptidyl peptidase 4 inhibitors. Most of these side effects were gastrointestinal events.

**Limitations and Future Directions**

This study was limited by its small sample size, lack of control subjects, heterogeneity in type of GLP-1 receptor agonist used, and retrospective design. Some patients were lost to follow-up and excluded secondary to a lack of serial A1C data, which could have affected the results. Furthermore, 15% of patients stopped the regimen after <3 months because of side effects and were therefore not included in the analysis. Another limitation is that we hypothesized that A1C improvement and maintenance resulted from both medication effects and improved compliance given the decreased number of required daily injections, but we were not able to objectively measure a change in compliance. Finally, hypoglycemia data were not well documented despite the significant risk of hypoglycemia associated with all diabetes therapies, and especially insulin.

We acknowledge these limitations; however, we believe that successfully sustaining an A1C <8.0% over 12 months without weight gain in >60% of a socioeconomically and ethnically diverse patient population with historically difficult-to-control diabetes remains noteworthy. Our findings have practical applications for clinical practice and highlight the need to think about the utility and potential benefits of combining older premixed insulin therapy with newer GLP-1 receptor agonist therapy. Prospective research is needed to further explore the use of premixed insulin in combination with a GLP-1 receptor agonist to better assess the effects of such a combination on long-term glycemic control.

**Conclusion**

The use of combined premixed insulin, metformin, and a GLP-1 receptor agonist is not common practice but may improve and sustain glycemic control by simplifying the treatment regimen and providing better targeting of postprandial hyperglycemia from both the GLP-1 receptor agonist and the prandial component of the premixed insulin formulation. Randomized controlled trials should be considered to evaluate the use of this combination in patients with obesity and a long duration of uncontrolled diabetes.

**DUALITY OF INTEREST**

No potential conflicts of interest relevant to this article were reported.

**AUTHOR CONTRIBUTIONS**

N.E. wrote the manuscript. S.F. researched and analyzed the data, contributed to discussion, and reviewed/edited the manuscript. S.R. researched the data and reviewed/edited the manuscript. R.A. analyzed the data and reviewed/edited the manuscript. N.E. is the guarantor of this research the data and reviewed/edited manuscript. R.A. analyzed the data and reviewed/edited the manuscript. S.R. contributed to discussion, and reviewed/edited the manuscript. S.F. researched and analyzed the data.

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