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Case Report

Combined GLP-1 Receptor Agonist and Amylin Analogue Pharmacotherapy to Treat Obesity Comorbid With Type 1 Diabetes

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Abstract

Type 1 diabetes mellitus (T1DM) with obesity is increasingly common, prompting effective clinical interventions to induce weight loss in this population. We present 3 patients with T1DM and obesity prescribed a glucagon-like peptide 1 receptor agonist (GLP-1RA) and pramlintide. **Case 1:** A 32-year-old male with obstructive sleep apnea (OSA) who lost −20.9 kg (−16.1% of total body weight [TBW]) over 10 months on semaglutide and pramlintide. **Case 2:** A 68-year-old female with diabetic retinopathy, coronary artery disease, hypertension, hypothyroidism, and depression/anxiety initially treated with topiramate, losing −8.4 kg, but experiencing weight plateau. After adding dulaglutide and pramlintide, she lost an additional −12.8 kg (−14.0% TBW) over 7 months, with total weight loss of −21.2 kg (−23.1% TBW). **Case 3:** A 49-year-old female with hypertension, hypothyroidism, and depression who lost −14.6 kg (−17.9% TBW) over 6 months on semaglutide and pramlintide. No significant side effects were experienced. All patients reported decreased insulin requirements on pramlintide, and hemoglobin A1c levels remained constant or decreased throughout the treatment period. Pramlintide and GLP-1RA resulted in excellent weight loss in our patients with obesity and T1DM. This combination may have a synergistic effect on the gut-brain axis. More research is required to substantiate these findings.

Key Words: anti-obesity medications, medical weight loss, weight management, type 1 diabetes, type 2 diabetes, amylin, pramlinitide, semaglutide

Abbreviations: BMI, body mass index; CAD, coronary artery disease; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin; HTN, hypertension; OSA, obstructive sleep apnea; T1DM, type 1 diabetes mellitus; TBW, total body weight.

Introduction

Although type 1 diabetes mellitus (T1DM) was historically viewed as a lean disease, obesity has become an increasingly common comorbidity in this population [1]. This increase in prevalence is likely a reflection of an overall increase in obesity prevalence in the general population [2], and a consequence of the current approach to the management of hyperglycemia in this population. Intensive insulin therapy in T1DM patients has been shown to increase incidence of overweight and obesity. A study by Conway et al found that the prevalence of obesity in T1DM patients increased by a factor of 7 over an 18-year period, and that intensive insulin therapy was a predictor of weight gain [3]. In addition to the known weight-gaining effect of insulin therapy, dysregulation of biologic mechanisms controlling satiety and appetite in T1DM may also contribute to weight gain. The effect of incretins such as glucagon-like peptide-1 (GLP-1) have been shown to be attenuated in T2DM, and to a lesser extent, in T1DM. Additionally, the beta-cell destruction that characterizes T1DM leads to a deficiency of amylin, a pancreatic beta-cell peptide hormone co-secreted with insulin [4]. Amylin is released postprandially as a satiety signal and is an important regulator of energy homeostasis. It may also function as an adiposity signal and reduce the reward value of food [5].

Randomized controlled trials have demonstrated the weight loss effectiveness of GLP-1 receptor agonists (GLP-1RAs) in obese populations, including in populations with T1DM, although more data exist from the T2DM population [6]. Pramlintide, an amylin analog, has been demonstrated in clinical trials to induce weight loss. Clinical trials have also demonstrated that cagrilintide, a long-acting amylin analog, induces significant weight loss. In the T1DM population, amylin analogs reduce insulin requirements, improve glycemic targets, and induce modest weight loss [7]. Outcomes evidence of combined amylin analog and GLP-1RA therapy for weight loss is incomplete; however, preclinical mouse models have demonstrated a synergistic weight loss effect with this combination [8]. We present 3 clinical cases of patients with obesity and T1DM treated with combination GLP-1RA and pramlintide pharmacotherapy, resulting in significant weight loss and reduced insulin requirements.

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Case Presentation

Case 1

A 32-year-old male with T1DM treated with an insulin pump, microalbuminuria, obstructive sleep apnea (OSA), and restless leg syndrome presented to the obesity clinic weighing 129.3 kg with a body mass index (BMI) of 47.43 kg/m^2 (class 3 obesity) and a body fat percentage of 63.6%. He had struggled with weight since childhood, with the majority of his weight gain occurring in his twenties. His hemoglobin A1c (HbA1c) was 7.8% at presentation. Along with intensive lifestyle modifications, he was prescribed semaglutide (0.25 mg/week increasing to 1 mg/week over a 2-month period) and pramlinitide (15 mcg pre-meal injections 3 times a day). At his 2-month follow-up assessment, he had lost −8.3 kg (−6.4% total body weight [TBW]) and reported decreased insulin requirements with no increased incidence in hypoglycemic events. At 3.5 months from the initial encounter, he had lost −10.9 kg (−8.4% TBW), with his most recent HbA1c at 7.6%. At 10 months from the initial encounter, he had lost a total of −20.9 kg (−16.1% TBW) and a body fat percentage of 48.4%. His low-density lipoprotein (LDL) cholesterol remained constant over the same 10-month period. He tolerated semaglutide without issue and experienced tolerable nausea on pramlintide.

Case 2

A 68-year-old female with T1DM on an insulin pump, with diabetic retinopathy, coronary artery disease (CAD), hypertension (HTN), hypothyroidism, and depression/anxiety presented to the obesity clinic weighing 91.6 kg with a BMI of 34.6 kg/m^2 (class 1 obesity) and a body fat percentage of 44.6%. Her total daily dose of insulin was 36 units/day. Her surgical history included quadruple coronary bypass surgery and cholecystectomy. She struggled with stress and emotional eating, particularly during the COVID-19 pandemic, which led to more weight gain. Her HbA1c was 7.8% at presentation. Along with lifestyle modifications, she was prescribed topiramate 50 mg daily to help control craving and emotional eating. She lost −8.4 kg (−9.1% TBW) on topiramate but experienced a plateauing of her weight loss and an increase of HbA1c to 7.6%. Dulaglutide (starting dose 0.75 mg/weekly increasing to 4.5 mg/weekly over a five-month period) and pramlintide (60 mcg pre-meal injections 3 times a day) were added to her pharmacotherapy. Over the next 7 months, she lost an additional −12.8 kg (−14.0% TBW), bringing her total loss to −21.2 kg (−23.1% TBW). Additionally, her HbA1c decreased to 7.1% after 7 months of dual therapy and her basal insulin requirement decreased from 22 units/day to 20 units/day. There was no change to the incidence of hypoglycemia on her glucose monitor between the start and conclusion of the treatment period (1% at start and 0% at conclusion). Her LDL cholesterol decreased from 78 to 49 mg/dL over the same period. She experienced tolerable nausea, including 2 instances of emesis, while taking dulaglutide and pramlintide.

Case 3

A 49-year-old female with T1DM on an insulin pump, with HTN, hypothyroidism, and depression presented to the obesity clinic weighing 81.7 kg with a BMI of 30.9 kg/m^2 (class 1 obesity) and a body fat percentage of 42.3%. She had struggled to maintain her weight throughout childhood and had been unable to lose weight despite diet and exercise. Her HbA1c was 7.9% at presentation and she was on an average of 43 units of total daily insulin. Along with lifestyle modifications, she was prescribed semaglutide (0.5 mg weekly injections) and pramlintide (15 mcg pre-meal injections 3 times a day increasing to 30 mcg after 6 months). Over a 6-month period, she lost −14.6 kg (−17.9% TBW) and her body fat percentage decreased to 37.3%. Her HbA1c also decreased to 7.0% and she reported a decrease in her basal insulin requirement from 23 units/day to 18 units/day. She reported no hypoglycemic events. Her LDL cholesterol remained constant over this same period. She did not experience side effects with either medication.

Table 1. Summary of the 3 cases

	Case 1	Case 2	Case 3
Age	32	68	49
Sex	Male	Female	Female
Comorbidities	T1DM w/microalbuminuria, OSA, restless leg syndrome	T1DM w/diabetic retinopathy, CAD, HTN, hypothyroidism, depression, and anxiety	T1DM, HTN, hypothyroidism, and depression
Pharmacotherapy	Semaglutide 1.0 mg weekly Pramlintide 3x/day 15 mcg	Topiramate 50 mg daily Dulaglutide 4.5 mg weekly Pramlintide 3x/day 60 mcg	Semaglutide 0.5 mg weekly Pramlintide 3x/day 30 mcg
Time in Program	10 months	14 months	6 months
Weight			
Start	129.3 kg	91.6 kg	81.7 kg
End	108.4 kg	70.4 kg	67.1 kg
Loss	20.9 kg (16.1% TBW)	21.2 kg (23.1% TBW)	14.6 kg (17.9% TBW)
HbA1c			
Start	7.8%	6.9%	7.9%
End	7.6%	7.1%	7.0%

All cases presented with obesity comorbid with T1DM and were treated with combination GLP-1RA and pramlintide.
Abbreviations: CAD, coronary artery disease; HbA1c, glycated hemoglobin; HTN, hypertension; OSA, obstructive sleep apnea; T1DM, type 1 diabetes mellitus; TBW, total body weight.

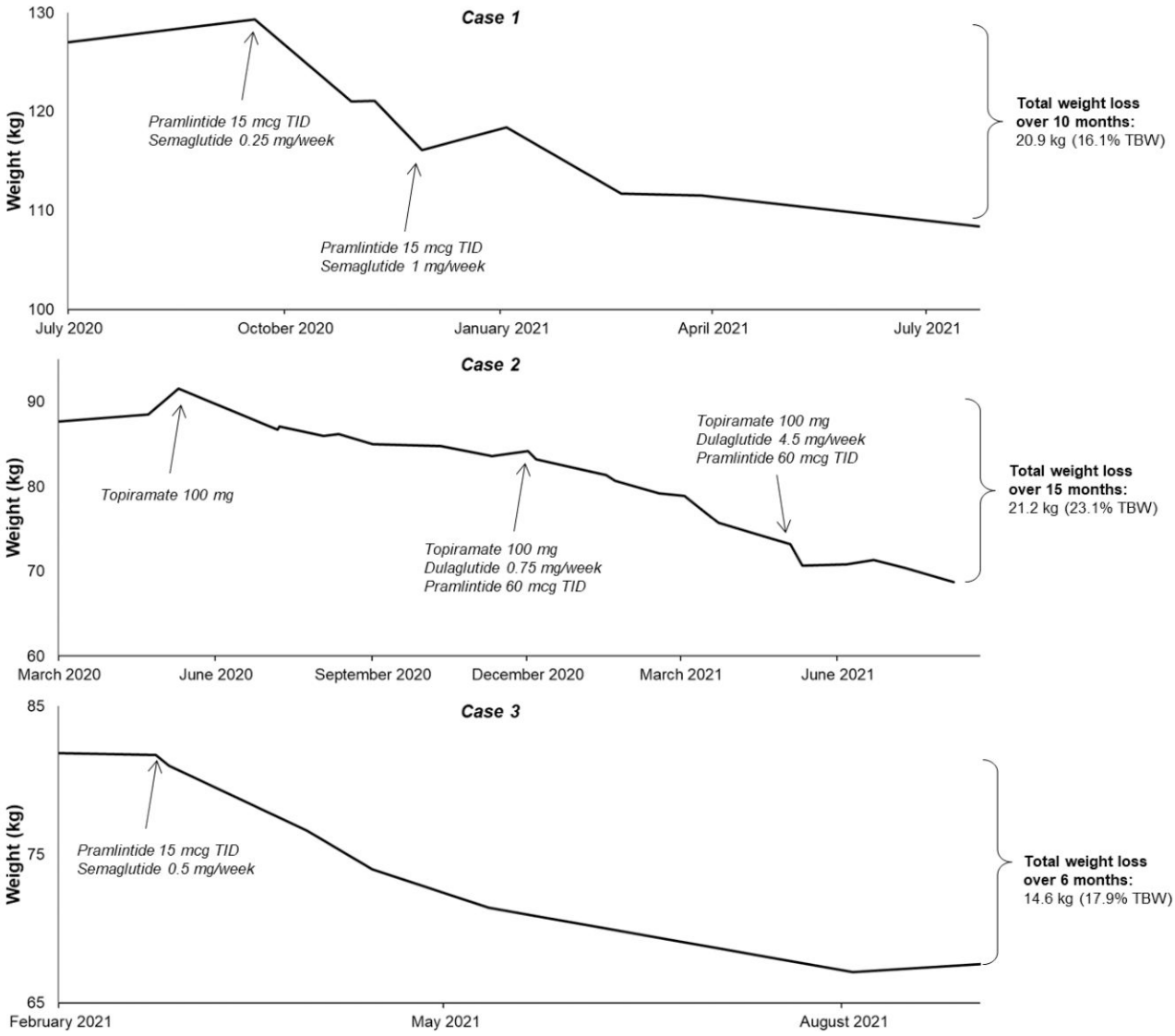

Figure 1. Summary of weight loss for each of the 3 cases.

Discussion

We present 3 cases of individuals with obesity and T1DM who experienced significant weight loss while taking dual GLP-1RA and amylin analog therapy (Table 1 and Fig. 1). Over treatment periods of less than 1 year, our 3 patients lost −16.1%, −23.1%, and −17.9% of their TBW. All 3 patients had decreased total daily insulin requirements. HbA1c decreased in 2 patients and remained stable in the third patient over the treatment period. These cases demonstrate dual GLP-1RA and amylin analog therapy is effective for inducing meaningful weight loss in patients with obesity and T1DM; in fact, the weight loss results were remarkable enough to postulate these gut peptide hormone analogs in combination may have synergistic effects.

Amylin is a polypeptide hormone synthesized and secreted by pancreatic beta-islet cells. The autoimmune destruction of beta cells in T1DM leads to deficient fasting and postprandial levels of amylin [4]. Amylin has several properties that make it an effective target for weight loss. First, amylin decreases the rate of gastric emptying. Second, amylin induces a satiety signal to the brain. Amylin has been shown to directly bind the area postrema, which can signal the lateral parabrachial nucleus to mediate appetite suppression. The lateral parabrachial nucleus is also neurally connected to the central amygdala, which mediates signals to many of the key energy controlling areas of the brain, including the hypothalamus, nucleus tractus solitarius, nucleus accumbens, and ventral tegmental area. GLP-1RA have also been shown to affect brain circuitry in regions overlapping with amylin, including the area postrema, hypothalamus, parabrachial nucleus, ventral tegmental area, and nucleus tractus solitarius, to increase satiety and decrease the reward effect of food [9]. We hypothesize that amylin and GLP-1RA act synergistically along these pathways, accounting for the substantial weight loss in our cases, although more research is required to elucidate their specific combined response. Although the weight loss response of our 3 patients suggests a synergistic effect between amylin analogs and GLP-1RAs, there are limitations. On all 3 patients in this report, GLP-1RAs were initiated simultaneously with amylin analogs. Weight loss could be therefore be

attributable to strong response to GLP-1RAs alone rather than a synergistic effect.

Clinically, both amylin analogs and GLP-1RA have separately been demonstrated to induce weight loss in populations with obesity, including those with T1DM [6, 7]. Their combined effect on obesity in patients with T1DM is not well-studied. Preclinical models have suggested additive and potential synergistic effects, and there are ongoing clinical trials examining combined effects in the general patient population [8]. Both medications are generally well-tolerated by patients The most common side effect of pramlintide is nausea, which was observed in one our cases at a tolerable level. Pramlintide is not associated with any major long-term side effects. Pramlintide decreases blood glucose and therefore insulin should be decreased to prevent hypoglycemia, although long-term studies of its use do not show increased rates of hypoglycemia [10]. GLP-1RAs are also not associated with any major long-term side effects. The most common side effects are nausea, vomiting, and diarrhea. Based on favorable side effect profiles and proven effectiveness when taken individually, combined therapy with amylin analog and GLP-1RA therapy combined may be an excellent therapeutic regimen for the treatment of obesity comorbid with T1DM.

Learning Points

- Dual pharmacotherapy with pramlintide and GLP-1RAs can result in significant weight loss in patients with obesity and T1DM.
- Theoretical models of the mechanisms of action of GLP-1RAs and amylin analogs suggest they might act synergistically for weight loss.
- More research is required to determine if combination GLP-1RA and pramlintide is an effective treatment for patients with T1DM for treatment of obesity.

Contributors

G.W., E.M.G., and G.S. conceptualized, wrote, and edited the manuscript. G.W. and E.M.G. collected and analyzed the data. G.S. confirmed authenticity of the data. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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