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## Case Report

# A Novel Case of Hyperglycemic Hyperosmolar State After the Use of Teprotumumab in a Patient With Thyroid Eye Disease

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### ABSTRACT

**Background/Objective:** Teprotumumab, a novel treatment for thyroid eye disease (TED), which blocks the insulin-like growth factor 1 receptor, has been associated with improvement in proptosis and inflammatory ocular symptoms. In the original trials, hyperglycemia was reported in 5% to 12% of patients; however, none required hospitalization. We report a case of hyperglycemic hyperosmolar state after the first infusion of teprotumumab.

**Case Report:** A 56-year-old woman with Graves' disease, severe thyroid eye disease, and prediabetes presented with polyuria, polydipsia, nausea, abdominal pain, headache, dizziness, and a fall to the emergency department 3 weeks after her first teprotumumab infusion. She was noted to have serum glucose levels of 939 mg/dL, serum bicarbonate levels of 28 meq/dL, serum osmolality of 324 mOsm/kg, and trace ketones in urine. She was treated with intravenous fluids and insulin with subsequent improvement in clinical status and biochemical profile. She was then discharged on multiple daily injections of insulin.

**Discussion:** Hyperglycemia is a known adverse effect of insulin-like growth factor 1 receptor inhibitors like teprotumumab. The incidence of hyperglycemia in the original trials was 5% to 12%. Most cases were mild and resolved with titration of current diabetes medications. No cases of hospitalization due to severe hyperglycemia or hyperglycemic hyperosmolar state have been reported until now.

**Conclusion:** We intend to highlight the severity of hyperglycemia that could occur with the use of teprotumumab and the need for research to evaluate the true incidence of this condition.

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## Introduction

Thyroid eye disease (TED), also known as Graves' ophthalmopathy, is a multifactorial autoimmune condition mostly associated with hyperthyroidism secondary to Graves' disease.<sup>1</sup> The therapies for TED were limited to glucocorticoids, radiation, and surgery until the advent of teprotumumab, an insulin-like growth factor 1 (IGF-1) inhibitor. Hyperglycemia has been reported as a side effect in phase 2 and phase 3 trials; however, is usually mild and managed with adjustment of diabetes medications.<sup>2,3</sup> We report a case of hyperosmolar hyperglycemic state (HHS) after the use of teprotumumab.

## Case Report

A 56-year-old woman with a history of Graves' disease, TED, and prediabetes presented to the Emergency Department with nausea,

vomiting, abdominal pain, headache, dizziness, unsteady gait, and a fall 1 day before admission. Her symptoms began about 3 weeks after her first infusion of teprotumumab, which included persistent polyuria, polydipsia, and nausea. She reported a history of prediabetes for about 3 years, and her most recent hemoglobin A1C (HbA1C) was 6.1% (43 mmol/mol), 1 month before her infusion of teprotumumab. She denied any recent oral, topical, or injectable glucocorticoids. Significant laboratory findings included a point-of-care glucose levels of 576 mg/dL, plasma glucose levels of 939 mg/dL, HbA1C levels of 11.1% (98 mmol/mol), anion gap of 19 mmol/L (normal, 9–16 mmol/L), serum bicarbonate levels of 28 meq/dL (normal, 21–31 meq/dL), serum osmolality of 324 mOsm/kg (normal, 275–300 mOsm/kg),  $\beta$ -hydroxybutyrate levels of 1.70 mmol/L (normal, 0.02–0.27 mmol/L), trace ketones in urine and a venous blood gas pH of 7.34. On physical examination, she was found to have proptosis, lid lag, dry mucous membranes, and abdominal tenderness. She met the diagnostic criteria for HHS and was treated with aggressive intravenous fluids and insulin infusion. This led to improvement in her clinical status and laboratory findings. She was then transitioned to a subcutaneous insulin regimen where she required a dose of 0.75 units/kg of subcutaneous insulin given as a basal-bolus regimen. Her glucose level was

**Abbreviations:** HbA1C, hemoglobin A1C; HHS, hyperglycemic hyperosmolar state; IGF-1, insulin-like growth factor 1; TED, thyroid eye disease.

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maintained in the range of 140–180 mg/dL during her hospitalization. Given the history of Graves' disease, she was screened for latent onset autoimmune diabetes of adults with glutamic acid decarboxylase antibody and islet cell antibody, which were both negative. It is most likely that teprotumumab was the cause of her worsening glycemic control and HHS. At her 3-month follow-up visit, her HbA1C improved to 6.9% (52 mmol/mol) while she was continued on insulin as well as teprotumumab infusions.

## Discussion

TED is a debilitating condition that can significantly affect a patient's quality of life. The therapies for TED have been quite limited, and associated with uncertain outcomes at the cost of adverse effects, until the discovery of teprotumumab.<sup>2</sup> In vitro studies have revealed overexpression of IGF-1 receptors by orbital fibroblasts in patients with TED, which led to inflammation, edema, and fibrosis. Inhibition of the IGF-1R with teprotumumab leads to mitigation of the effects of IGF-1 and other autoantigens involved in the pathogenesis of TED.<sup>4</sup> Following the OPTIC Trial in 2020,<sup>3</sup> teprotumumab was approved by the FDA for its use in moderate to severe thyroid-associated ophthalmopathy. We reviewed the current literature for studying the reported adverse events with the use of teprotumumab, particularly hyperglycemia.

The phase 2 trial published in 2017<sup>2</sup> involved 88 patients who were randomized to receive teprotumumab versus placebo every 3 weeks over a period of 24 weeks. Adverse events in the teprotumumab group included nausea, diarrhea, muscle spasm, dysgeusia, hearing impairment, headache, weight loss, alopecia, and hyperglycemia. Hyperglycemia was reported in 12% of patients in the teprotumumab group versus 5% in the placebo group. It was described as a mechanism-based side effect from the inhibition of the IGF-1R. Glycemic control was measured by HbA1C at time zero and weeks 12, 24, 36, and 72. There was no significant change in HbA1C at the end of the trial in the teprotumumab group compared to baseline. Upon further review of the published supplementary data, it was noted that the baseline HbA1C in the teprotumumab group ranged between 5.9% (41 mmol/mol) to 7.4% (57 mmol/mol) and between 5.8% (40 mmol/mol) to 7.7% (61 mmol/mol) at the end of the trial (72 weeks) with a maximum change of 0.3%, which was not statistically significant. However, no cases of diabetic ketoacidosis or HHS were reported. The phase 3 trial<sup>3</sup> included 83 patients who were randomized to receive a placebo versus teprotumumab. Out of 41 patients in the teprotumumab group, only 2 patients (less than 5%) had hyperglycemia, and both cases were reported to be mild; however, no objective description of the glucose parameters was mentioned in the trial. Horizon Therapeutics, the manufacturer of teprotumumab, stated in the prescriber information<sup>5</sup> that the incidence of hyperglycemia is about 10%, and prescribers should monitor symptoms of hyperglycemia during treatment, and that when it does occur, it should be controlled with medications. Lee et al<sup>6</sup> wrote a letter to the editor in July 2021, recognizing hyperglycemia as a mechanism-based side effect due to the partial homogeneity of the IGF-1R and the insulin receptor. IGF-1R inhibitors block the insulin receptor preventing insulin binding to the receptor and thus inhibiting glucose uptake in cells, resulting in hyperglycemia.<sup>7</sup> They discussed specific screening and monitoring guidelines for managing hyperglycemia while being on teprotumumab, such as monitoring fasting and postprandial blood glucose daily after initiation and weekly follow-up visits with their diabetes provider for adjustment of diabetes medications. Most importantly, they emphasized the need for prescriber awareness and close communication between the patient, prescriber, and endocrinologist.

To date, no cases of HHS/diabetic ketoacidosis associated with teprotumumab have been reported in the literature. Our patient

## Highlights

- Teprotumumab is a novel therapeutic agent in the treatment of thyroid eye disease.
- Hyperglycemia is a known side effect of this insulin-like growth factor 1 receptor inhibitor due to inhibition of insulin receptor.
- In the original trials, hyperglycemia was reported as mild with about 5% to 12% incidence, with no cases of hospitalizations or hyperglycemia hyperosmolar state (HHS).
- Our patient, however, experienced symptoms of hyperglycemia 3 weeks after the first infusion of teprotumumab and was eventually hospitalized with an episode of HHS. Given the temporality of the events, a recognized mechanism-based side effect in the current literature, we believe that teprotumumab led to worsening of her glycemic control and resulting in HHS.
- To date, there are no established guidelines that can help prescribers manage hyperglycemia from teprotumumab.

## Clinical Relevance

By reporting this case of HHS after the use of teprotumumab in our patient, we intend to highlight the severity of hyperglycemia that could occur with the use of Teprotumumab, and the need for research to evaluate the true incidence of this condition.

had prediabetes at baseline, which was managed with lifestyle modifications for years, experienced symptoms of hyperglycemia 3 weeks after the first infusion of teprotumumab, and was eventually hospitalized with an episode of HHS. Given the temporality of the events, a recognized mechanism-based side effect in the current literature, we believe that teprotumumab led to worsening of her glycemic control and resulted in HHS.

## Conclusion

Hyperglycemia is a reported adverse reaction of IGF-1 receptor inhibitors. The current literature suggests that the magnitude of hyperglycemia from teprotumumab is mild; however, this case highlights the possibility that teprotumumab could cause severe hyperglycemia and HHS. More studies are needed to better understand the incidence of severe hyperglycemia and HHS after initiation of teprotumumab.

## Disclosure

The authors have no multiplicity of interest to disclose.

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