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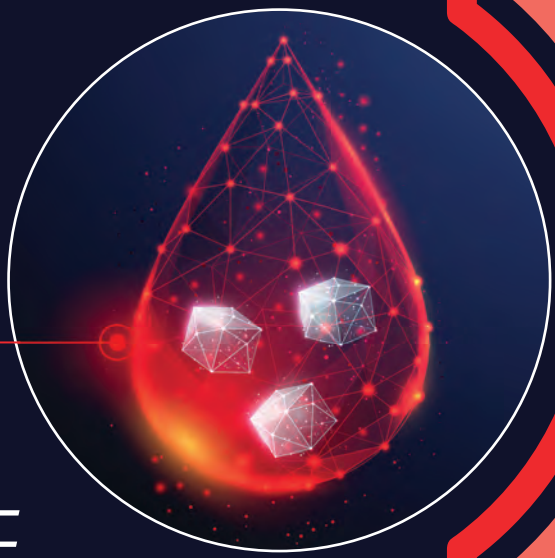

THYROID EYE DISEASE

MULTIDISCIPLINARY MANAGEMENT OF TREATMENT-ASSOCIATED HYPERGLYCEMIA

FACULTY



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ACTIVITY DESCRIPTION AND PURPOSE

This educational activity is intended to help clinicians identify patients with thyroid eye disease (TED) who require intervention for elevated blood glucose levels prior to treatment for TED with the insulin-like growth factor 1 receptor antagonist teprotumumab. Clinicians will also learn to apply evidence to manage patients who require intervention for glycemic control during treatment for TED with teprotumumab. The desired results of this activity are for eye care professionals to use a multidisciplinary approach to increase their ability to identify and manage hyperglycemia in patients who require treatment of TED.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists, oculoplastic surgeons, and neuro-ophthalmologists.

LEARNING OBJECTIVES

After completing this activity, participants will be better able to:

- Identify patients with thyroid eye disease who require intervention for elevated blood glucose prior to treatment
- Apply evidence to manage patients who require intervention for glycemic control during treatment of thyroid eye disease

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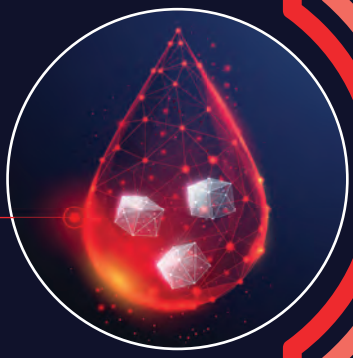
THYROID EYE DISEASE



MULTIDISCIPLINARY MANAGEMENT OF TREATMENT-ASSOCIATED HYPERGLYCEMIA

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INTRODUCTION

Thyroid eye disease (TED), otherwise known as Graves orbitopathy or Graves ophthalmopathy, is a rare, progressive, autoimmune inflammatory condition of the orbit associated with thyroid disorders.[1-3] This disease is most common in patients with hyperthyroidism, occurring in approximately 30% to 40% of patients with Graves disease.[4] TED, however, can occur in the setting of hypothyroidism or euthyroidism in approximately 10% of cases.[5]

TED can cause dry eye, blurred vision, photophobia, diplopia, proptosis, eyelid retraction, orbital pain, extraocular muscle (EOM) restriction, permanent orbital/facial changes, optic nerve dysfunction, and loss of vision.[6,7] TED typically begins with an acute inflammatory phase lasting 6 to 36 months.[5] Inflammation then subsides, leading to a chronic noninflammatory phase. Despite the resolution of inflammatory signs, structural changes, such as proptosis and EOM enlargement, often persist long term.[5,8]

Patients with TED have an increased risk for depression and anxiety, which is often associated with their having to deal with disfigurement and related changes in self-image, social interactions, and changes in their ability to work.[9] Even patients with mild disease have reported quality of life scores that are on par with those who have a life-threatening illness.[10]

Treatment selection for TED must take into account various factors, including clinical findings, disease severity, medical comorbidities, patient preferences, and cost effectiveness.[7] Mild cases can often be treated with selenium supplementation, ocular lubrication, and modification of risk factors such as smoking cessation.[1,5] More moderate to severe cases of TED that are in the chronic noninflammatory phase can be treated with rehabilitative surgery. For patients in the acute inflammatory phase, off-label medical treatments include corticosteroids, rituximab, mycophenolate, and tocilizumab; orbital radiation has also demonstrated efficacy for early inflammatory TED.[7] These agents have well-established adverse event profiles, but varying degrees of effectiveness. Typically, they help dampen the inflammatory response and halt the progression of disease; off-label medical therapies, however, fall short of improving proptosis and other disfiguring changes caused by TED.

In 2020, the US Food and Drug Administration (FDA) approved teprotumumab, currently the only agent approved to treat TED.[7,11,12] Teprotumumab has been shown to improve proptosis, diplopia, and quality of life in patients with active moderate to severe TED.[11-13] A recent phase 4 randomized controlled trial demonstrated improvement in proptosis with teprotumumab in patients with long-duration noninflammatory disease, which led to an expansion of its

> *We need to select our patients carefully after weighing the risks, benefits, and alternatives. With so much new information coming out, what is most important is to educate our patients and walk this road with them.*
>
> *–Andrea Kossler, MD, FACS*

indication.[11,14] Therefore, teprotumumab treatment may be considered in carefully selected patients with long-standing and noninflammatory TED.[14]

In pivotal trials that led to the approval of teprotumumab, hyperglycemia was found to be present in 10% of patients receiving teprotumumab compared with 1% of those receiving placebo.[11,13,15] More recent data, however, have led to a modification in the prescribing information of teprotumumab to include monitoring for elevated blood glucose levels as part of the Warnings and Precautions[11]:

> *Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with teprotumumab.[11] Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving teprotumumab.*

This has left many eye care professionals with the need to understand more about hyperglycemia and diabetic ketoacidosis (DKA) associated with teprotumumab. They also need to learn how to effectively comanage treatment and monitoring with endocrinologists.

PATHOPHYSIOLOGY OF TED AND THE ROLE OF TEPROTUMUMAB

The pathophysiology of TED is complex and not fully understood. An autoimmune response of thyroid-stimulating immunoglobulins (TSIs) binding to orbital tissues expressing the thyroid-stimulating hormone (TSH) receptor (TSHR) is thought to be involved **(Figure 1)**.[1,7] In addition, the insulin-like growth factor 1 receptor (IGF-1R) forms a signaling complex with TSHR on orbital fibroblasts.[7] Thus, IGF-1R is activated alongside TSHR.[1] This triggers orbital fibroblast proliferation and differentiation into adipocytes, release of proinflammatory mediators, and production of hyaluronan. The result is enlargement and edema of the orbital tissues. Teprotumumab binds to IGF-1R, blocking its effects and that of the IGF-1R–TSHR signaling complex.[3]

In the OPTIC phase 3 trial, a proptosis reduction of ≥ 2 mm at 24 weeks was achieved by 83% of patients receiving teprotumumab vs 10% of those receiving placebo.[15] In addition, a greater proportion of patients in the teprotumumab group had a Clinical Activity Score (CAS) of 0 or 1 and an improvement in diplopia. The OPTIC-X extension study included patients initially treated with placebo, those who did not respond to the first course of teprotumumab, and those who experienced disease relapse after treatment.[16] Of the patients enrolled in the OPTIC-X study, 89% had a proptosis response at week 24. Of the 5 patients who were initially nonresponders to teprotumumab, 40% had a response to re-treatment. TED relapse was noted to occur in 10 patients (~30%) from the OPTIC study who had been previously treated with teprotumumab. Five of these 8 patients (62.5%) who were treated with an additional course of teprotumumab responded to re-treatment. The adverse events reported in the teprotumumab clinical trials were generally mild or moderate, and included muscle spasm, nausea, alopecia, hearing loss, and hyperglycemia **(Table 1)**.[15,17]

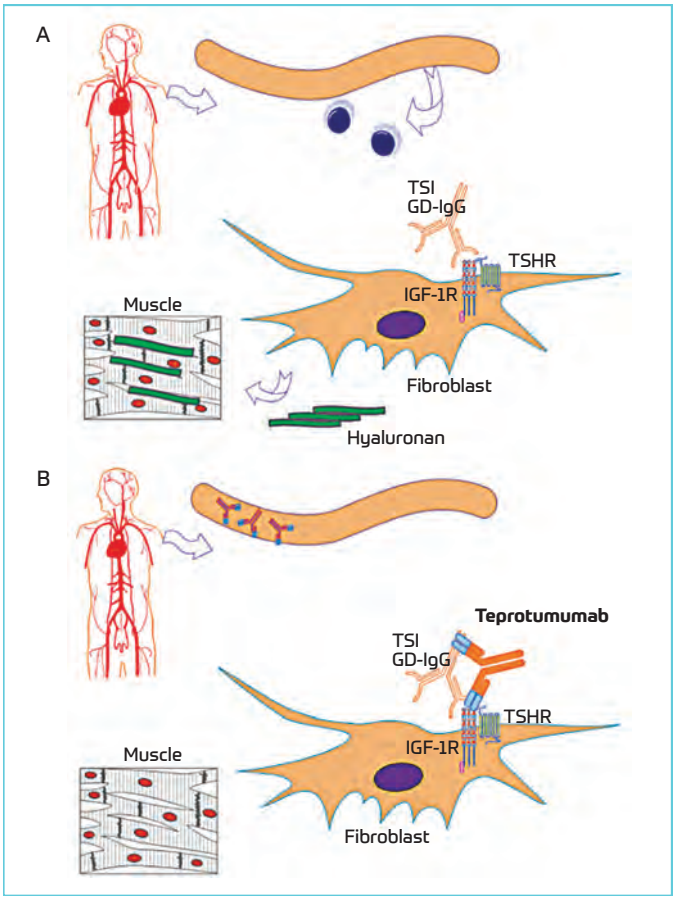

Figure 1. Pathophysiology of thyroid eye disease and mechanism of teprotumumab.[3] (A) Autoantibodies stimulate orbital fibroblasts, leading to production of hyaluronan and proinflammatory mediators. (B) Teprotumumab blocks insulin-like growth factor 1 receptor, preventing autoantibodies from binding.

Abbreviations: GD, Graves disease; IGF-1R, insulin-like growth factor 1 receptor; IgG, immunoglobulin G; TSHR, thyroid-stimulating hormone receptor; TSI, thyroid-stimulating immunoglobulin.

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Table 1. Adverse Events Occurring in ≥ 5% of Patients Treated With Teprotumumab From a Pooled Analysis of the Phase 2 and 3 Trials[17]

Adverse Event	Number of Patients (%)	
	Teprotumumab (n = 84)	Placebo (n = 86)
Muscle spasms	21 (25)	6 (7)
Nausea	14 (17)	8 (9)
Alopecia	11 (13)	7 (8)
Diarrhea	10 (12)	7 (8)
Fatigue	10 (12)	6 (7)
Hyperglycemia	**8 (10)**	**1 (1)**
Hearing impairment	8 (10)	0
Dysgeusia	7 (8)	0
Headache	7 (8)	6 (7)
Dry skin	7 (8)	0
Rash	5 (6)	5 (6)

In this educational activity, endocrinologist Sonalika Khachikian, MD, and oculoplastic surgeons Andrea Kossler, MD, and Lilly Wagner, MD, will discuss their experiences with teprotumumab, with a focus on teprotumumab-related hyperglycemia. These experts in TED will also provide their perspectives on patient selection for the treatment and management of this adverse event in their clinical practices. The goals of the discussion are to more easily identify patients with TED who may require intervention for hyperglycemia and to highlight practical recommendations for teprotumumab-related hyperglycemia management.

FOCUS ON TEPROTUMUMAB: PATIENT SELECTION

Various factors, such as disease severity, chronicity, and activity, must be considered in patient selection for treatment with teprotumumab **(Table 2)**.[5,18-20] The teprotumumab clinical trials were limited to patients with active moderate to severe TED with symptom onset within the previous 9 months.[5,15] Although there is some evidence for improvements in mild TED with teprotumumab, the risks may outweigh the potential benefits.[5] In addition, retrospective studies have suggested that patients with chronic TED (with symptom onset > 1 to 2 years before treatment) may also benefit from teprotumumab treatment.[18] Further study is needed in this area.[5] A CAS of ≥ 4, designating active disease, was also required in the clinical trials, and may be required by some insurance carriers.[15] Therefore, the best candidates for teprotumumab treatment have active moderate to severe TED with relatively recent onset.

Other patient-specific factors should be considered. Significant improvements were seen in proptosis and diplopia in the teprotumumab clinical trials.[15] Therefore, this medication should be considered as a first-line therapy for properly screened and selected patients with these characteristics.[5] Patients with dysthyroid optic neuropathy were not included in the clinical trials for teprotumumab.[15] Although observational studies and case reports have suggested that teprotumumab may be effective for dysthyroid optic neuropathy, additional study is needed in this area.[5,18] Ideally, thyroid function should be maintained in the normal range prior to initiating teprotumumab.[5] Antithyroid medication may be started concurrently with treatment if necessary.

Finally, there are some contraindications and precautions for patients with certain preexisting medical conditions. Two patients with preexisting inflammatory bowel disease (IBD) demonstrated serious exacerbations in the teprotumumab clinical trials.[17] Active IBD is considered a contraindication to treatment with teprotumumab.[5] Pregnancy and lactation are additional contraindications. Uncontrolled diabetes with HbA_{1c} ≥ 9% is a relative contraindication.[5,20] Special considerations for patients with diabetes will be discussed subsequently. Finally, hearing evaluation is recommended before, during, and after treatment with teprotumumab.[11] Caution is advised in patients with preexisting hearing loss.[5]

Dr Kossler: What type of patients do you think are good candidates for teprotumumab, and why?

Dr Wagner: I do not know if we have identified the perfect candidate yet. In general, I strongly consider teprotumumab in patients with proptosis and double vision because they could potentially get the most bang for their buck. These were the 2 TED manifestations that improved in the initial clinical trial.[15] Then, in terms of insurance coverage, we oftentimes still need that CAS of ≥ 4.

Dr Kossler: New evidence can become known at any time and potentially adjust who we think the ideal candidate is. The active moderate to severe patients seem to be that sweet spot for teprotumumab. What types of patients are not good candidates for teprotumumab, and why?

Dr Wagner: They are the opposite of my good candidates. For example, I would really recommend against using teprotumumab in patients who have, as a main manifestation, just dry eyes without proptosis or any diplopia and motility restriction. I do not feel that the risk-benefit profile is good for them.

Dr Khachikian: Teprotumumab is a great medication for the right patient. If somebody does not have moderate to severe disease and just wants to try it, he/she is not the right candidate.

Table 2. Aspects for Consideration in Treatment Selection for Teprotumumab

Characteristic	Good Candidates	Poor Candidates
Disease severity and activity	Active moderate to severe TED (CAS ≥ 4)	Mild or inactive TED (CAS < 4)
Symptoms/Signs	Proptosis and diplopia[5]	• No proptosis or diplopia • +/- DON (possible benefit; further study needed)[5,18]
Thyroid function	Ideally in normal range, but can start thyroid medication concurrently with teprotumumab[5,19]	Abnormal or fluctuating significantly not ideal, but can manage concurrently during treatment[5,19]
Medical history	No systemic contraindications	Warnings and contraindications[5]: • Active IBD • Pregnancy • Lactation Relative contraindications[5,20]: • Uncontrolled diabetes (HbA_{1c} ≥ 9, but treatment may be considered under certain circumstances) Precautions[5]: • Preexisting hearing loss

Abbreviations: CAS, Clinical Activity Score; DON, dysthyroid optic neuropathy; IBD, inflammatory bowel disease; TED, thyroid eye disease.

Dr Kossler: I completely agree. What we are trying to say here is that we need to select our patients carefully after weighing the risks, benefits, and alternatives. With so much new information coming out, what is most important is to educate our patients and walk this road with them.

CASE STUDY IN TREATMENT SELECTION: NEWLY DIAGNOSED THYROID EYE DISEASE AND GRAVES DISEASE

From the Files of Lilly Wagner, MD

*A 70-year-old man presented with eyelid edema he has had for the past 6 weeks **(Figure 2A)**. TSH level was undetectable, TSI level was elevated, free T4 level was 2.2, and there was mild EOM enlargement on computed tomography. He was diagnosed with new active TED and Graves disease. After discussion with a collaborating endocrinologist, he was seen within 2 weeks and started on antithyroid treatment. He was treated with a course of intravenous methylprednisolone for his TED and had a good response to treatment **(Figure 2B)**.*

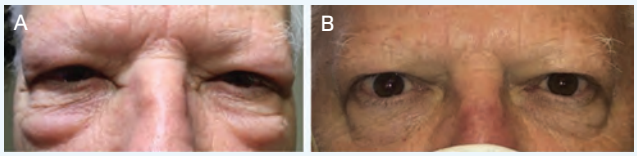

Figure 2. Images of the patient presented in the case study at presentation (A) and after treatment with a course of intravenous methylprednisolone for thyroid eye disease, with improvement in periocular edema (B)

Images courtesy of Lilly Wagner, MD

Dr Wagner: With the patient having no proptosis and no diplopia, I did not feel that teprotumumab was the very best option for him. The patient also wanted to do whatever was easiest and fastest, and could be done locally. We ended up starting him on a course of intravenous corticosteroids. He got much better, was really happy with his result, and had no flareup after steroids were discontinued. He was started on methimazole by his endocrinologist, resulting in correction of his thyroid hormone levels.

Dr Khachikian, if a patient has zero comorbidities, such as this patient, what baseline testing would you recommend?

Dr Khachikian: The only other test I would add is free T3. This is somebody whom I would likely start on antithyroid medication. Obviously, radioactive iodine is not a good option. There is some thought that if you do a thyroidectomy, the antigenic response goes down and you will have some improvement in the patient's eye disease. Most experts, however, believe that the risk of surgery outweighs the benefits. For this type of patient, pick up the telephone and call your endocrinologist. There is not a single endocrinologist who cannot find a spot to see a patient such as this, especially when you have done all the legwork. It is important to talk to the patient about treatment options. It is also important to start the patient on antithyroid medication immediately.

KEY TAKEAWAYS

- Baseline studies in patients with a possible or new diagnosis of TED include TSH, free T3, free T4, TSI, thyrotropin receptor antibody, and orbital computed tomography
- For patients with a new diagnosis of Graves disease and TED, timely consultation and comanagement with endocrinology is indicated
- Patients with active moderate to severe TED with proptosis and/or diplopia should be considered for treatment with teprotumumab
- Active IBD, pregnancy, and lactation are contraindications for teprotumumab treatment, and uncontrolled diabetes (HbA_{1c} > 9%) is a relative contraindication. Caution is advised in patients with hearing loss.
- In patients with active moderate to severe TED without proptosis and diplopia, intravenous glucocorticoids can be considered as an alternative to teprotumumab

EVIDENCE: HYPERGLYCEMIA WITH TEPROTUMUMAB

Several studies have investigated the occurrence of hyperglycemia during treatment with teprotumumab. In a pooled analysis of the phase 2 and 3 trials, 8 patients (10%) treated with teprotumumab developed hyperglycemia compared with 1 patient (1%) treated with placebo.[17] In the OPTIC-X extension study, 3 patients experienced hyperglycemia during the treatment period, and 2 patients developed new-onset type 2 diabetes.[16]

> *If I have a new patient with TED who does not have an endocrinologist, the first thing I do is refer the patient to our endocrinologist here.*
>
> *–Lilly Wagner, MD*

Smith et al performed a post hoc analysis of the data from the phase 2 and 3 trials, including the 8 patients (10%) with hyperglycemia who were treated with teprotumumab.[21] Of these 8 patients, 5 were noted to have preexisting diabetes. Mean HbA_{1c} increased by 0.22% from baseline to week 24 in the teprotumumab group compared with 0.04% in the placebo group. Most hyperglycemic events resolved during the treatment period and were controlled with medical treatment. No patients withdrew from the study owing to hyperglycemia.

Additional studies and case reports have since posed the possibility that teprotumumab-induced hyperglycemia may be more frequent, and, in some instances, more severe than that reported in clinical trials.[20,22,23] Amarikwa et al performed an observational study of 42 consecutive patients treated with teprotumumab at a single academic center.[20] In this study, hyperglycemia developed in 52% of patients. The mean increase in HbA_{1c} at 12 weeks after beginning teprotumumab was 0.5%. Greater increases in HbA_{1c} were noted in patients with preexisting prediabetes or diabetes **(Figure 3)**. Nevertheless, 41% of patients without either of these diseases developed prediabetes during the course of treatment. Of these, only one-third had resolved by the last follow-up.

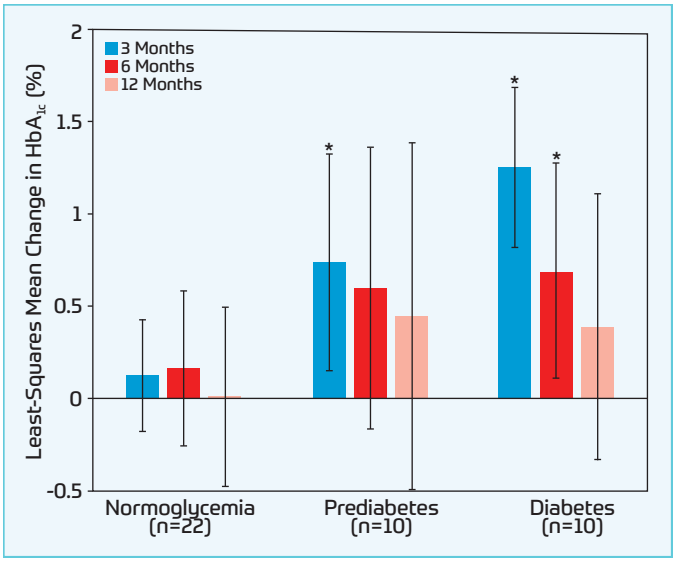

Figure 3. Hyperglycemia in an observational study of 42 consecutive patients treated with teprotumumab.[20] Least-squares mean change in HbA_{1c} is shown in relation to baseline values at 3 months (blue), 6 months (red), and 12 months (pink) after initiating treatment.

* $P < .05$

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Hyperglycemia is a known and common adverse effect among other IGF-1R inhibitors used in oncologic treatment.[24] Several mechanisms may be involved **(Figure 4)**.[25] IGF-1R is partially homologous to the insulin receptor. Therefore, IGF-1R inhibitors may also inhibit the insulin receptor, leading to hyperglycemia. In addition, IGF-1R inhibition leads to increased levels of growth hormone release from the pituitary. This promotes insulin resistance and gluconeogenesis, adding a potential second mechanism for hyperglycemia.

We need to closely follow patients who are high risk, such as Asian, African American, and Hispanic patients, and those who are overweight or have a family history.

–Sonalika Khachikian, MD

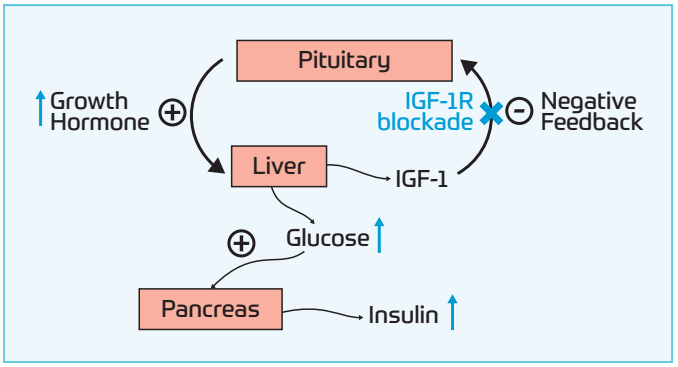

Figure 4. Mechanism of hyperglycemia with insulin-like growth factor 1 receptor inhibition.[25] Blockade of the insulin-like growth factor 1 receptor leads to decreased negative feedback inhibition of the pituitary. This results in increased levels of circulating growth hormone and increased gluconeogenesis.

Abbreviations: IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor.

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Dr Khachikian: Hyperglycemia is important because it is something that we are seeing in patients with diabetes and in a small subset of patients who are not diabetic but are on the cusp of having diabetes.

Dr Kossler: I can speak only for myself, but as an oculoplastic surgeon, when blood sugar levels are uncontrolled, I get very concerned. It is essential that patients be comanaged by their endocrinologist or primary care physician to ensure their blood sugar level and other systemic comorbidities are properly managed.

Dr Wagner: As ophthalmologists, we are quite familiar with ocular complications of diabetes, but we are definitely not familiar with all the new noninsulin drugs for controlling blood sugar. What kind of regimen should patients be on? How often should they monitor their blood sugar level at home? When should they have to be started on insulin? If I have a new patient with TED who does not have an endocrinologist, the first thing I do is refer the patient to our endocrinologist here.

Dr Kossler: Patients who have thyroid dysfunction are already at risk for hyperglycemia. If someone who may already have uncontrolled hyperglycemia is given a drug that can exacerbate it, then bad things can happen. The FDA label for teprotumumab clearly states that hyperglycemia is a warning and precaution.[11] It states that we need to assess for elevated blood glucose and symptoms of hyperglycemia prior to each infusion, and to continue to monitor while patients are on treatment with teprotumumab. Also, per the FDA label, we need to ensure that patients who have preexisting hyperglycemia or diabetes are under appropriate glycemic control while they are receiving the drug. We really need to heed those warnings.

ASK THE ENDOCRINOLOGIST

How Often Are You Seeing Teprotumumab-Related Hyperglycemia in Your Practice?

Dr Kossler: In a pooled analysis of the phase 3 trials, 10% of patients who received teprotumumab developed hyperglycemia compared with only 1 patient who received placebo.[17]

Are you seeing this number in your everyday practice, or is it higher or lower than this?

Dr Khachikian: I think in patients who have diabetes, the number is higher than that, more like 90%. If a patient has diabetes and is borderline controlled, he/she is going to have an elevation in glucose values. We need to closely follow patients who are high risk, such as Asian, African American, and Hispanic patients, and those who are overweight or have a family history. A patient with prediabetes is in a higher risk category. I would tell such a patient, "You are already at risk. Now I'm giving you a medicine that's going to exacerbate your prediabetes. We need to talk about ways that you're going to monitor your numbers." I think with diabetes—100%, with prediabetes—probably, and if the patient does not have diabetes, then I just need to monitor.

Dr Kossler: In the study by Amarikwa et al, most patients (52%) treated with teprotumumab developed hyperglycemia.[20] Patients with prediabetes had a significant increase in their HbA_{1c}; patients with preexisting diabetes had an even more robust increase in their HbA_{1c}. We are seeing that there is a significant increase in patients' HbA_{1c} over time, but this increase really does have a predilection for patients who have prediabetes and diabetes.

Dr Wagner: This study reassures clinicians, especially ophthalmologists or optometrists who do not have an endocrinology background, that they are relatively safe treating someone who does not have diabetes or prediabetes. Conversely, if patients have diabetes or prediabetes, the eye care professional has a genuinely good reason to reach out to either the patient's primary care physician or an endocrinology physician and say, "Hey, I really need your help with this" because this person is most likely going to run into trouble.

Dr Khachikian: I will say that when I further analyzed the Amarikwa study, I think the numbers were a little bit higher than, perhaps, those of the normal population. I think that may have to do with having higher Hispanic and Asian populations. I do not think it undermines what you are saying.

Dr Kossler: In the Smith et al post hoc analysis of the clinical trials, there was a change in HbA_{1c} of only 0.2% at 24 weeks.[21] Smith et al did a very good job of making sure that patients who were included in the studies were euthyroid. Patients had to have HbA_{1c} < 9%, but they also could not have had any changes to their blood glucose treatment in the prior few months before starting treatment.[15,21] The study by Amarikwa et al demonstrated an increase in HbA_{1c} of 0.5%.[20]

Dr Khachikian, please comment on the difference between the 2 studies?

Dr Khachikian: I think the truth lies somewhere between these 2 studies. I think the takeaway point is that hyperglycemia associated with teprotumumab is real.

KEY TAKEAWAYS

- There are 2 possible mechanisms for teprotumumab-related hyperglycemia:
  1. Sequence homology between IGF-1R and insulin receptor
  2. Elevated growth hormone levels and resulting increased gluconeogenesis
- Hyperglycemia is listed as a warning and precaution on the FDA label for teprotumumab
- Hyperglycemia occurred in 10% of patients in the teprotumumab phase 2 and 3 trials
- Two-thirds of patients experiencing hyperglycemia in the clinical trials had preexisting diabetes or impaired glucose tolerance
- Observational studies have suggested that hyperglycemia may be more frequent and more severe than that reported in the clinical trials

MANAGEMENT OF TEPROTUMUMAB-RELATED HYPERGLYCEMIA

No formal guidelines currently exist for the screening and monitoring of hyperglycemia during teprotumumab therapy, although several different recommendations have been published.[20,26,27] There are several commonalities among the existing recommendations: screening with HbA_{1c} at baseline, ongoing blood glucose monitoring during therapy, and educating patients on the symptoms of hyperglycemia.

Differences exist in the recommendations in regard to HbA_{1c}. Amarikwa et al suggested that patients with HbA_{1c} < 7% proceed with therapy, and those with HbA_{1c} > 9% delay therapy.[20] They additionally recommended that HbA_{1c} testing be repeated at 12 weeks. Lee et al recommended that patients with HbA_{1c} < 8% to 8.5% proceed with therapy.[26] Finally, Stan and Krieger recommended that patients with HbA_{1c} < 8% proceed with treatment and to repeat HbA_{1c} testing at the third and sixth infusions.[27]

Although glucose monitoring during treatment is universally recommended, the frequency and type of testing varies. Amarikwa et al recommended blood glucose testing before each infusion for all patients and daily blood glucose testing in patients with diabetes **(Table 3)**.[20] Lee et al recommended weekly fasting glucose testing for 3 months in patients without diabetes and daily fasting glucose in patients with diabetes.[26] They additionally suggested immediate evaluation for any symptoms of hyperglycemia or genital-urinary tract infection.[26] Finally, Stan and Krieger recommended glucose testing before infusions and for symptoms of hyperglycemia, with more frequent testing in patients with diabetes.[27]

If [patients] are not checking blood glucose values, we clinicians need to make sure that we start doing that. If they are on the cusp of needing medication for diabetes, maybe we need to start that medication. If patients are on oral medication and not well controlled, it is a good time to talk about insulin.

–Sonalika Khachikian, MD

Dr Kossler: In the Amarikwa et al study, we recommended that all patients must have their baseline glycemic status checked before starting teprotumumab **(Table 3)**.[20,28] That is the only way we are really going to understand their true risk for this condition. We also recommended that blood glucose levels be checked before each teprotumumab infusion and that HbA_{1c} be repeated every 12 weeks during therapy. Most importantly, we need to educate our patients on the risk of hyperglycemia and on the signs of hyperglycemia. Finally, as an ophthalmologist, I always comanage my patients with endocrinology or their primary care physician.

Table 3. Recommendations for Managing Hyperglycemia in Patients Treated With Teprotumumab[20]

1	Check baseline glycemic status (HbA_{1c}) prior to initiating treatment.
2	Recheck HbA_{1c} every 12 weeks during treatment.
3	Check blood glucose level at least before each teprotumumab infusion (more frequently for patients with diabetes).
4	Educate patients on risk and signs of hyperglycemia.
5	Comanage patients with endocrinology.*

* Primary care physicians, nurse practitioners, and physician assistants may also have a role in monitoring and managing hyperglycemia[28]

I think that although the numbers may differ according to where your patient population lives, the takeaway point is the same: patients should be screened at baseline for their blood glucose control. It seems that all the studies agree that a patient can be treated with teprotumumab.[20,26,27] Of course, you want to monitor the patient's HbA_{1c}, work with an endocrinologist, and continue to check blood sugar levels. Now, if a patient has HbA_{1c} that is not controlled, it makes sense to get the diabetes under control first, weighing the risks and benefits of the severity of the patient's TED. For patients with diabetes, we want to talk to them about checking their fasting blood sugar level before infusions and checking their own glucose level at home. Finally, I think all the studies at least agree that patients should be seen by both ophthalmology and endocrinology so that they get the best of both worlds.

Dr Khachikian: I think the providers taking care of the patient need to have a discussion because not every patient is the same.

I think all the studies at least agree that patients should be seen by both ophthalmology and endocrinology so that they get the best of both worlds.

–Andrea Kossler, MD

ASK THE ENDOCRINOLOGIST

When Is Hyperglycemia a Contraindication to Starting Treatment With Teprotumumab?

Dr Kossler: Should a patient with HbA_{1c} of 8% receive teprotumumab therapy?

Dr Khachikian: I think in terms of everyday management of patients, what would be more ideal than measuring HbA_{1c}, but not necessarily always possible, is a continuous glucose monitor. This is a device worn on the arm that shows blood sugar levels on an every-5-minute basis. Thus, one can see what the trend is in terms of when the patient gets a first infusion, and when the numbers rise.

Dr Kossler: I love that you mentioned the continuous blood glucose monitor. I agree with you that if you are just checking blood sugar at one point in time, you may be getting a false sense of security and safety.

When does hyperglycemia preclude a patient from being a candidate for initiation of teprotumumab, if ever?

Dr Wagner: What I have learned from my endocrinology colleagues—who taught me so much about this—is that there is no patient who absolutely cannot have teprotumumab because of blood sugar status. He/she may need very tight monitoring and very aggressive glycemic control, but if the medication is really needed, and there is no good alternative, then he/she can start it and we can manage the blood sugar level.

Dr Khachikian: I agree with that. I do not think uncontrolled diabetes is a reason to decline medical therapy with teprotumumab. I think that the patient and the medical team need to understand that there is going to be a little bit more involved for everyone if teprotumumab therapy is undertaken. If patients are not checking blood glucose values, we clinicians need to make sure that we start doing that. If they are on the cusp of needing medication for diabetes, maybe we need to start that medication. If patients are on oral medication and not well controlled, it is a good time to talk about insulin.

Dr Kossler: I might just summarize by observing that *hyperglycemia is important*. It is life threatening if not properly controlled, but it does not need to progress to that point. It should be evaluated at baseline to understand a patient's level of risk **(Table 4)**. In coordination with our

Table 4. Recommendations From Expert Discussion on HbA_{1c} Levels and Considerations for Teprotumumab Therapy

HbA_{1c} Level	Recommendation
< 7%	• Proceed with treatment if clinically indicated • Monitor blood glucose level and HbA_{1c} according to recommendations • Comanage with endocrinology
7%-8.9%	• Severity of disease should be weighed against risks of treatment • Must monitor closely in conjunction with endocrinology • May need medication adjustments or additional medications
≥ 9%	• Consider delaying treatment or alternative treatments • Treatment may be considered, if clinically indicated, with very close monitoring by an endocrinologist • Adjustment in medications and insulin therapy likely needed

outstanding endocrinology partners and other health care providers, the hyperglycemia can be properly monitored and managed throughout therapy. Therefore, so long as we are properly selecting patients, comanaging with endocrinology, educating our patients, and monitoring during therapy, we can decrease the risk of hyperglycemia in patients receiving teprotumumab.

KEY TAKEAWAYS

- Screen with baseline HbA_{1c} prior to initiating teprotumumab treatment in all patients
- Repeat HbA_{1c} testing at least every 12 weeks
- Monitor blood glucose level at each infusion in patients without diabetes and at least daily in patients with diabetes
- Patients with HbA_{1c} < 7% may proceed with therapy if clinically indicated
- Patients with HbA_{1c} of 7% to 8.9% may proceed with therapy; however, the risks of therapy should be weighed against the severity of disease. Management with endocrinology is needed.
- In patients with HbA_{1c} ≥ 9%, if appropriate, teprotumumab therapy may be delayed until better diabetes control is achieved. If needed, treatment may be considered with aggressive blood glucose control and very close monitoring by endocrinology.
- Consider a continuous glucose monitor for patients with diabetes who are being treated with teprotumumab
- Educate all patients on the signs of hyperglycemia
- All patients should be comanaged with endocrinology and ophthalmology for optimal care

HYPERGLYCEMIC HYPEROSMOLAR STATE AND DIABETIC KETOACIDOSIS IN TEPROTUMUMAB-TREATED PATIENTS

No cases of hyperglycemic hyperosmolar state (HHS) or DKA were reported in the teprotumumab clinical trials.[20] Despite this, case reports have emerged recently describing these conditions in patients treated with teprotumumab.[20,22,23]

One recent case report by Shah and Charitou described a patient with a history of prediabetes (baseline HbA_{1c} of 6.1%) who developed HHS 3 weeks into treatment with teprotumumab.[22] The patient was hospitalized and successfully treated with intravenous fluids and insulin. Shah and Charitou concluded that although the adverse events reported in the clinical trials were mild, the possibility exists that teprotumumab can cause severe hyperglycemia and HHS, and further study is needed.

In another recent case report by Carter et al, a patient with a history of prediabetes (baseline HbA_{1c} of 6.3%) developed DKA and new-onset diabetes after beginning treatment with teprotumumab.[23] The patient was treated successfully with insulin and intravenous fluids before being discharged on insulin. The patient opted to discontinue further teprotumumab treatment. Carter et al recommended glucose monitoring throughout treatment with a home glucometer.

Finally, in the longitudinal study by Amarikwa et al, 1 of the 42 patients included in the analysis developed DKA during teprotumumab treatment.[20] This patient is described in the following case study.

CASE STUDY: DIABETIC KETOACIDOSIS IN A PATIENT UNDERGOING TEPROTUMUMAB TREATMENT

From the Files of Andrea Kossler, MD, FACS

A 59-year-old female with a history of Graves disease, prediabetes, and obesity (body mass index of 35.2 kg/m^2) presented with a 1-year history of worsening proptosis and new intermittent double vision. She was well controlled for her thyroid disease with methimazole 10 mg, with some fluctuation in thyroid function. Her prediabetes was managed with diet and lifestyle interventions. At baseline, her TSH level was low at 0.01, her free T4 level was 1.2, free T3 level was 177, TSI level was elevated, and HbA_{1c} was 6.4%. She was diagnosed with active moderate to severe TED, with a CAS of 5.

The patient was started on teprotumumab, with monitoring of her blood glucose level before each infusion. Before her second infusion, she had a blood glucose level of 101 mg/mL. After 2 infusions, her pain, swelling and redness, and intermittent double vision improved, and even her proptosis slightly improved.

After her third infusion, she presented to the emergency room with dizziness, dry mouth, weakness, polyuria, decreased appetite, and decreased weight. Her random blood glucose level was 920 mg/mL, and her HbA_{1c} was 12.5%. She had a pH of 7.25 on venous blood gas, with bicarbonate of 17 and an anion gap of 30. She was treated for DKA with intravenous fluids and insulin, and teprotumumab was discontinued. She was discharged on insulin and transitioned to metformin after 6 weeks. At a 33-week follow-up, her HbA_{1c} had decreased to 5.6%.

Nine months later, she experienced a relapse of her TED. After discussion with her endocrinologist, retreatment with teprotumumab was recommended because her diabetes was felt to be very well controlled with medication. The patient agreed to check her blood glucose level multiple times per day and consistently report these values and maintain close follow-up with her endocrinologist. She was successfully treated with a full course of teprotumumab, with good response and no further adverse events. HbA_{1c} increased during treatment to 6.4%.

Dr Kossler: I wanted to present this case because this was the first patient who made me realize how incredibly scary hyperglycemia is. I was under a false impression that my patient had acceptable blood sugar control because her blood sugar level prior to her last infusion was good. I had a fantastic endocrinologist; we were comanaging. We had checked the HbA_{1c};

we had checked the blood sugar levels before infusions. And then, Boom! This really showed me how labile this can be.

Dr Khachikian: This is a classic example of a patient who is borderline diabetic. You have 3 different mechanisms in which there is increased insulin resistance: increased growth hormone, increased gluconeogenesis, and insulin receptor resistance. It is not unusual for patients to be like this. They need insulin to get rid of that insulin resistance. Once they overcome it, they can go on medications such as metformin. That is the best medicine that helps people who have insulin resistance. I think it goes to show you how much we are learning about teprotumumab.

Dr Kossler: What this case taught me is that we cannot be fooled by normal numbers right before patients' infusions. We need to educate our patients. We need to get on the telephone with the endocrinologist. We cannot have a false sense of security because the blood sugar level was okay and HbA_{1c} was < 7%. Conversely, with wonderful diabetic care, patients can do great even after such an event, as you can see in this patient's second round.

Dr Wagner: This patient had several risk factors that put her into a high-risk category. She had obesity. She was just diet controlled, which probably made her even higher risk because she was a borderline diabetic on no medication. It is good to have these check boxes in your head for low-, intermediate- or high-risk categories. I think it is great to see that once she was well controlled and under tight observation, she could successfully finish her treatment.

KEY TAKEAWAYS

- Although there were no instances of HHS or DKA in the teprotumumab clinical trials, several case reports have emerged since its approval
- HHS or DKA may occur even in patients with a baseline HbA_{1c} < 7%
- Patients who are borderline diabetic with only diet control may be at greater risk for HHS or DKA, but further study is needed
- With appropriate treatment and monitoring, even patients who have experienced HHS or DKA may be safely treated with teprotumumab

We hope you enjoyed this monograph and learned something new. If you have general questions on this topic, please email them to TED@mededicus.com. Questions will be collated, and responses will be posted quarterly throughout 2024. To see questions and answers, scan the QR code.

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1. A 64-year-old woman with a history of prediabetes presented with a 3-month history of proptosis and diplopia. CAS score was 4. Baseline laboratory testing revealed HbA_{1c} of 6.5%, elevated TSI level, low TSH level, and elevated free T3 and T4 levels. Treatment with teprotumumab was initiated. What additional management steps should be considered during the course of treatment?
    a. Repeat HbA_{1c} testing every 3 months, ensure blood glucose is monitored at every infusion and in between infusions, educate on the symptoms of hyperglycemia, and comanage with endocrinology
    b. Repeat HbA_{1c} testing every 6 months, ensure blood glucose is monitored at every infusion, educate on the symptoms of hyperglycemia, and comanage with endocrinology
    c. No additional laboratory testing is needed, but educate on the symptoms of hyperglycemia and ask the patient at each visit if she has had symptoms
    d. Have the patient wear a continuous glucose monitor during the course of teprotumumab and educate on the symptoms of hypoglycemia

2. A 64-year-old woman with a history of prediabetes presented with a 3-month history of proptosis and diplopia. CAS score was 4. TSI level was elevated. What additional baseline laboratory testing should be considered in the workup of this patient?
    a. HbA_{1c}, TSH, and free T3 and T4
    b. Serum creatinine, TSH, and free T3 and T4
    c. Free T3 and T4 and fasting blood glucose
    d. HbA_{1c}, serum creatinine, TSH, and free T3 and T4

3. A 61-year-old man with no history of diabetes or prediabetes presented with a 3-month history of proptosis and diplopia. CAS score was 4. Baseline laboratory testing revealed HbA_{1c} of 5.5%, elevated TSI level, low TSH level, and elevated free T3 and T4 levels. Treatment with teprotumumab was initiated. What additional management steps should be considered during the course of treatment?
    a. Repeat HbA_{1c} testing every 3 months, perform blood glucose testing at each infusion, educate on the symptoms of hyperglycemia, and comanage with endocrinology
    b. Repeat HbA_{1c} testing every 6 months, perform blood glucose testing every 3 months, educate on the symptoms of hyperglycemia, and comanage with endocrinology
    c. No additional laboratory testing needed, but educate on the symptoms of hyperglycemia and comanage with endocrinology
    d. No additional laboratory testing needed, but he should start selenium supplementation

4. Patients with diabetes or prediabetes who have a _____ should not initiate teprotumumab treatment without first being referred to an endocrinologist.
    a. Baseline HbA_{1c} of 6% and are controlled on 2 antidiabetic medications
    b. Baseline HbA_{1c} of 8% and are not receiving any antidiabetic medications
    c. History of prior HHS following an appendectomy 3 years ago
    d. All the above