EJCRIM
European Journal
of Case Reports
in Internal Medicine

# RHABDOMYOLYSIS ASSOCIATED WITH THE USE OF TIRZEPATIDE

Kunal Sonavane[1], Pallavi Shirsat[2], Gautam Agrawal[3], Bhawna Agarwal[4]

[1] Willis Knighton Medical Center, Bossier City, USA
[2] Minden Medical Center, Minden, USA
[3] Independence Health System, Greensburg, USA
[4] University of Pittsburgh Medical Center, McKeesport, USA

**Corresponding author's e-mail:** sonavanekunal@gmail.com

**Received:** 30/03/2025
**Accepted:** 08/04/2025
**Published:** 23/04/2025

**Conflicts of Interests:** The Authors declare that there are no competing interests.
**Patient Consent:** Written informed consent from patient for this publication has been obtained and is available on request.


**How to cite this article:** Sonavane K, Shirsat P, Agrawal G, Agarwal B. Rhabdomyolysis associated with the use of tirzepatide. *EJCRIM* 2025;**12**:doi:10.12890/2025_005392

## ABSTRACT

*Introduction:* Tirzepatide is one of the commonly used combined glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) agonists for weight loss in recent years. There are significant advantages of these medications for weight reduction, improved glycaemic control and cardiorenal benefits. However, these medications come with serious adverse events and need closer monitoring once they are initiated.

*Case description:* We present a case of a 35-year-old female with no comorbidities taking tirzepatide for weight loss. She developed severe rhabdomyolysis that required hospitalisation; muscle biopsy revealed necrotising myopathy. Her rhabdomyolysis resolved after stopping tirzepatide and conservative management with intravenous fluids. Since no other contributing factor could be identified, we believe tirzepatide may have increased her risk of rhabdomyolysis.

*Conclusion:* In patients presenting with rhabdomyolysis, consideration should be given to GLP-1 agonists as a potential contributing factor for the development of rhabdomyolysis.

## KEYWORDS

Tirzepatide, rhabdomyolysis, GLP-1 receptor agonist, necrotising myopathy, muscle damage

## LEARNING POINTS

- Clinicians need to be aware of unusual side effects of glucagon-like peptide-1 (GLP-1) agonists like rare occurrence of rhabdomyolysis potentially associated with the use of tirzepatide.
- Risks versus benefits of these medications should be discussed in detail with patients before prescribing.
- Close patient follow-up and monitoring for adverse events is necessary, especially after prescribing relatively newer medications such as GLP-1 agonists with evolving knowledge of adverse event profile.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

## INTRODUCTION

Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has gained a wide popularity in recent years for weight loss in adult patients with obesity with or without type 2 diabetes[1,2]. Tirzepatide also showed robust improvements in glycaemic control and bodyweight, without increased risk of hypoglycaemia[3]. Just like any other medication, tirzepatide comes with its own set of adverse events. The majority of adverse events from tirzepatide use are gastrointestinal (nausea, vomiting, diarrhoea, constipation)[4]. There are a few reported cases of pancreatitis, cholelithiasis, injection site reactions and some animal studies showing risk of thyroid cancer[4].

Rhabdomyolysis is a condition caused by the breakdown and necrosis of muscle tissue and the release of intracellular content into the bloodstream. Medications (statins, macrolide antibiotics, antihistamines, antipsychotics to name a few) remain an important cause of rhabdomyolysis[5]. Diagnosis is confirmed when the serum creatine kinase (CK) level is > 1,000 U/l or at least 5× the upper limit of normal[6]. One of the most feared complications of rhabdomyolysis is acute renal failure and the need for renal replacement therapy in some patients. To our knowledge, there has been only one reported case showing potential association between semaglutide and rhabdomyolysis[7].

We present a case of a young female patient with no known past medical history, who developed severe rhabdomyolysis requiring hospitalisation. She had been on tirzepatide for weight loss for the previous few months.

## CASE DESCRIPTION

A 35-year-old female with no past medical history presented to our emergency room with acute onset of pain and swelling of both upper extremities, limiting range of motion for two days. The patient reported no history of recent trauma, severe exercise or immobility. She reported no history of alcohol or illicit drug use, including binging on alcohol. The patient was having an active lifestyle and at her usual state of health when the symptoms occurred.

She explicitly denied any exertional activity or being outside in heat for a prolonged duration, since this happened during the winter months. There was no change in her level of hydration. She was not on any prescription medications other than tirzepatide, especially statins. She also denied taking any supplements, herbs or any other over-the-counter medications.

She reported no family history of any neuromuscular or autoimmune condition, or strenuous exercise. On presentation, she had normal vitals, weighed 72.12 kg with a BMI 25.72. Pertinent physical examination showed generalised oedema and severe tenderness to palpation of both upper extremities. She had no rash or palpable nodules, any axillary lymphadenopathy or joint swelling. The remainder of the physical examination was unremarkable; she did not have sepsis. Her laboratory findings are reported in *Table 1*. The urine analysis was unremarkable except for 3+ occult blood, 0–3 urine red blood cells (RBC); a urine drug screen was negative. Other laboratory findings, including rheumatoid factor, antinuclear antibody, SS-A/Ro IgG antibody, SS-B/La IgG antibody, Sm (Smith) antibody, SM/RNP IgG antibody, acute hepatitis panel were all negative. A biopsy was obtained from the right triceps muscle, which showed necrotising myopathy *(Fig. 1)*.

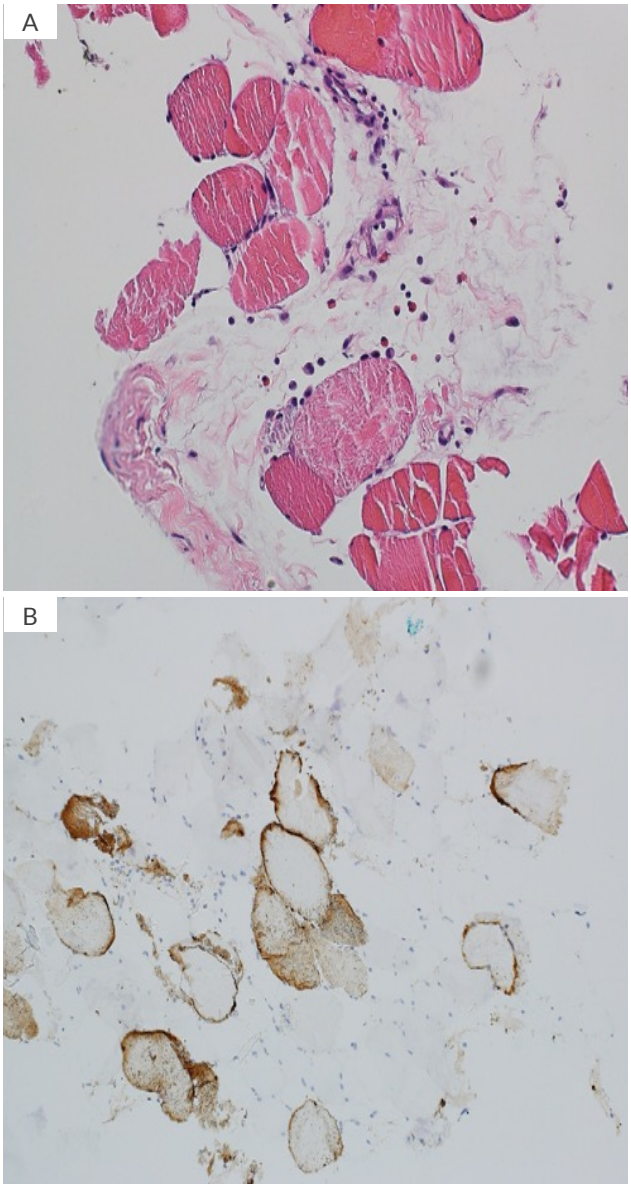


*Figure 1. Histological evaluation showing: A) Scattered pale-staining early necrotic muscle fibres (haematoxylin and eosin-stained formalin-fixed paraffin embedded tissue section 400× original magnification); B) The presence of frequent necrotic muscle fibres was confirmed with immunohistochemical stain for C5b-9 (membrane attack complex 200× original magnification).*

Our patient's CK level started to trend downwards after starting intravenous fluids *(Fig. 2)*. She did not develop acute renal failure and had near total resolution of symptoms at the time of discharge and was advised to discontinue tirzepatide. Upon a follow-up call two months after discharge, she revealed she had stopped tirzepatide use and was symptom-free and continued to feel well.

| | Day of admission | Day of discharge | Reference range |
|---|---|---|---|
| White blood cells ($10^3$/µl) | 9.7 | 5.8 | 3.7–10.6 |
| Haemoglobin (g/dl) | 16 | 12.5 | 11–14.9 |
| Haematocrit (%) | 46.2 | 37.2 | 32.6–43.4 |
| Platelet count ($10^3$/µl) | 240 | 206 | 130–351 |
| Sodium (mmol/l) | 136 | 137 | 137–145 |
| Potassium (mmol/l) | 3.5 | 3.7 | 3.5–5.1 |
| Chloride (mmol/l) | 102 | 104 | 98–107 |
| Carbon dioxide (mmol/l) | 30 | 30 | 21–32 |
| Blood urea nitrogen (mg/dl) | 11 | 6 | 7–20 |
| Creatinine (mg/dl) | 0.76 | 0.58 | 0.52–1.04 |
| Glucose (mg/dl) | 83 | 87 | 70–109 |
| Calcium (mg/dl) | 9.5 | 8.8 | 8.4–10.2 |
| Total bilirubin (mg/dl) | 1.2 | 0.6 | 0.2–1.3 |
| Aspartate aminotransferase (U/l) | 709 | 1,260 | 3–45 |
| Alanine aminotransferase (U/l) | 159 | 404 | 0–35 |
| Alkaline phosphatase (U/Ll) | 56 | 42 | 38–126 |
| Albumin (g/dl) | 4.6 | 3.4 | 3.5–5.0 |
| Creatine kinase (U/l) | 57,014 | 20,814 | 25–192 |

*Table 1. Laboratory values during hospitalisation.*

## DISCUSSION

We present a young, healthy Caucasian female patient with no known past medical history who developed severe rhabdomyolysis with her CK level peaking at >76,000 U/l (range 25–192 U/l). The patient had been on tirzepatide for the previous few months for weight reduction. Muscle biopsy showed necrotising myopathy *(Fig.1)*; she reported no recent strenuous physical activity or exertion and maintained good oral intake. Due to the lack of any other contributing factors, tirzepatide was considered to be potentially associated with the development of rhabdomyolysis in our patient.

Naranjo et al. created a systematic method for estimating the probability of adverse drug reactions, referred to as the Naranjo scale[8]. This scale consists of 10 questions and the scores range from −4 to +13. An adverse drug reaction is considered definite if the score is 9 or higher, probable if the score is between 5 and 8, possible if between 1 and 4, and doubtful if 0 or less. In this case, the score was 7, demonstrating a probable association between rhabdomyolysis and the use of tirzepatide.

Tirzepatide and other GLP-1 agonists have shown efficacy in weight loss, improving glycaemic control and providing cardioprotective effects[3,9]. However, it is important to also pay attention to their adverse events. There is sufficient data around GLP-1 agonists causing gastrointestinal side effects[10] but the overall state of evidence around tirzepatide and other GLP-1 agonists increasing the risk of rhabdomyolysis remains sparse.

Besides being primarily found in the pancreas, GLP-1 receptors are also found in skeletal muscles[11]. GLP-1 agonists act by promoting glucose uptake in a PKB-independent, PI3K-dependent mechanism in muscle cells[11]. This in turn leads to glycogen synthesis in myocytes. However, in hyperglycaemic states, myocytes become resistant to both insulin and GLP-1, thereby suppressing the uptake of glucose and glycogen synthesis[11]. Direct injury to muscle cells or failure of glycogen synthesis in myocytes can cause rhabdomyolysis. Factors such as underlying medical comorbidities, strenuous exercise or dehydration may also play a role. We believe this may be a plausible mechanism for a correlation between use of tirzepatide and other GLP-1 agonists causing rhabdomyolysis.

Adverse events related to tirzepatide, and other GLP-1 agonists remain an evolving area of research. The US FDA Adverse Events Reporting System (FAERS) database review revealed an astounding increase in the number of reported adverse events, as the use of tirzepatide has increased over the past 2–3 years. *Fig. 3* reveals the number

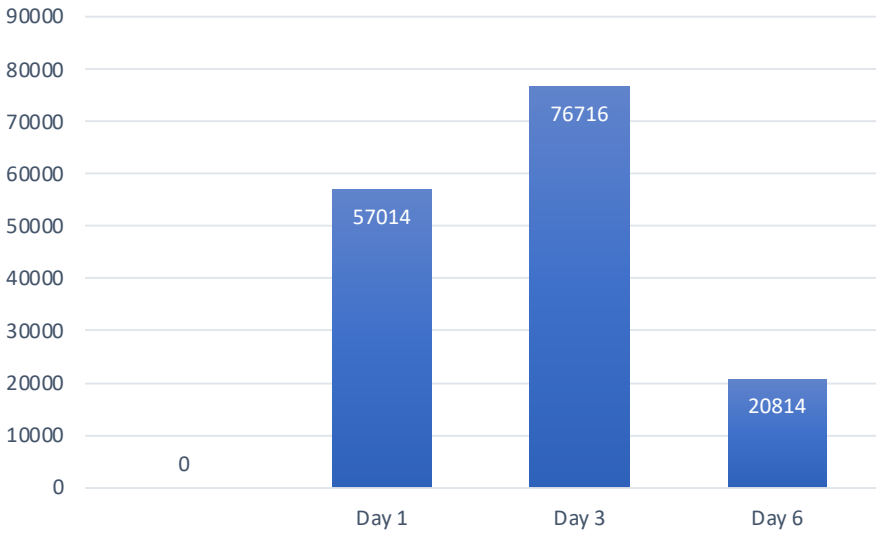


*Figure 2. Creatine kinase (CK) level during hospitalisation.*

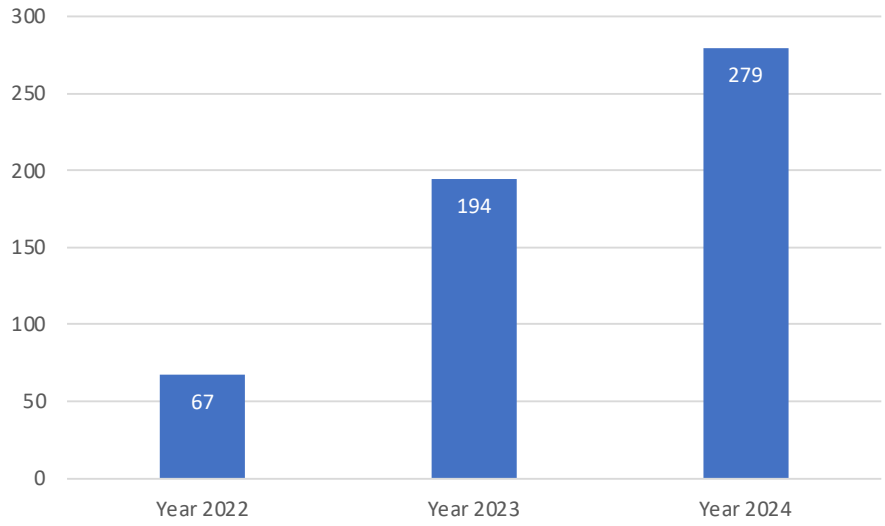


*Figure 3. US FDA Adverse Events Reporting System (FAERS) – musculoskeletal and connective tissue disorders related adverse events from use of tirzepatide for years 2022–2024.*

of musculoskeletal and connective tissue-related adverse events reported to the FAERS database from the use of tirzepatide. Studies need to be performed to understand the exact mechanism of rhabdomyolysis due to GLP-1 agonists. It remains unknown though whether rhabdomyolysis is potentially a class effect of GLP-1 agonists or linked to specific medication within that group.

To our knowledge, there has been only one reported case of semaglutide-related rhabdomyolysis[7]. Similar to that reported case, our patient's symptoms completely resolved after stopping tirzepatide. Clinicians need to be aware of the potential association between GLP-1 agonists and rhabdomyolysis and need to implement appropriate monitoring. Patients taking GLP-1 agonists also need to be warned about the potential occurrence of rhabdomyolysis.

## CONCLUSION

The benefits of GLP-1 agonists in appropriate patient groups remain significant. In patients presenting with rhabdomyolysis, consideration should be given to GLP-1 agonists as a potential cause of rhabdomyolysis. Clinicians need to be aware of this potential adverse event, caution and educate their patients, and consider discontinuing the drug to prevent serious complications associated with rhabdomyolysis.

## REFERENCES


1. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. SURMOUNT-1 investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;**387**:205–216.
2. Garvey WT, Frias JP, Jastreboff AM, le Roux CW, Sattar N, Aizenberg D, et al. SURMOUNT-2 investigators. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2023;**402**:613–626.
3. Rosenstock J, Wysham C, Frias JP, Kaneko S, Lee CJ, Fernández Landó L, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* 2021;**398**:143–155.
4. Yin DG, Ding LL, Zhou HR, Qiu M, Duan XY. Comprehensive analysis of the safety of semaglutide in type 2 diabetes: a meta-analysis of the SUSTAIN and PIONEER trials. *Endocr J* 2021;**68**:739–742.
5. Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine (Baltimore)* 1982;**61**:141–152.
6. Zimmerman JL, Shen MC. Rhabdomyolysis. *Chest* 2013;**144**:1058–1065.
7. Billings SA, Felix HM, Prier CC, Hedges MS. Rhabdomyolysis associated with semaglutide therapy: a case report. *Cureus* 2023;**15**:e50227.
8. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–245.
9. Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes. *Circulation* 2022;**146**:1882–1894.
10. Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse effects of GLP-1 receptor agonists. *Rev Diabet Stud* 2014;**11**:202–230.
11. Green CJ, Henriksen TI, Pedersen BK, Solomon TP. Glucagon like peptide-1-induced glucose metabolism in differentiated human muscle satellite cells is attenuated by hyperglycemia. *PLoS One* 2012;**7**:e44284.