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Case Series

Polyneuropathy Temporally Associated with Tirzepatide Use in Patients with Pre-Existing Risk Factors: Two Cases

Hira Shakeel, MD[1*], Ehtesham Khalid, MD[2]

[1]Quaid-e-Azam Medical College, Bahawalpur, Pakistan.
[2]Ochsner Medical Center, New Orleans, USA.

***Corresponding Author:** Hira Shakeel, MD, Quaid-e-Azam Medical College, Bahawalpur, Pakistan.

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Abstract

Tirzepatide, a GLP-1 receptor agonist, used in the treatment of diabetes and weight loss is found to be associated with polyneuropathy. We encountered two cases with multiple co-morbidities in our clinical practice who were started on tirzepatide, and they reported neuropathic symptoms afterwards. Peripheral neuropathies are attributed to different factors like metabolic, endocrine and autoimmune conditions. Through these 2 cases, we tried to evaluate the link between onset, progression and continuity of neuropathy after commencement of tirzepatide.

Keywords: *Tirzepatide, Polyneuropathy, Diabetes Mellitus, Bariatric Surgery, Vitamin B12, Dysautonomia*

Introduction

An early diagnosis often shapes the entire course of a patient's medical care. Tirzepatide, a combination glucagon-like peptide-1 (GLP-1)/gastric inhibitory peptide or glucose-dependent insulinotropic peptide (GIP) (GLP-1/GIP) agonist, was approved by the US Food and Drug Administration (FDA) in recent years for the treatment of type 2 diabetes mellitus (T2DM) and obesity. As a newly approved therapy, it remains at the forefront of scientific research regarding its long-term safety and potential adverse effects. [1][2]

A recent pharmacovigilance study by Chen et al. evaluated neurologic adverse events associated with glucagon-like peptide-1 receptor agonists, including tirzepatide, using data from the FDA Adverse Event Reporting System through the third quarter of 2024. The authors identified multiple neurologic adverse events associated with GLP-1 receptor agonists at the class level, with variability across individual agents. Tirzepatide was statistically not associated with any neurologic adverse events; however, its interpretation is limited due to the relatively recent approval and the shorter duration of post-marketing surveillance. [3]

In this context, case reports remain pivotal for identifying potential neurological adverse events related to tirzepatide use. Cases of central nervous system complications have been temporally linked, along with isolated instances of peripheral nerve injuries, including "slimmer's paralysis." [4-8]

We present two cases of polyneuropathy temporally associated with the use of tirzepatide in the past 3-4 months. To our knowledge, there have been no previous reports linking this association, further emphasizing the need to understand tirzepatide's neurological safety profile.

Case Presentation

Case # 1;

A 59 years-old female with past medical and surgical history significant for Roux-en-Y gastric bypass surgery greater than 25 years ago, lumbar spinal stenosis following lumbar laminectomy in July 2024, and type 2 diabetes since 2023 who presented with bilateral upper and lower limb distal paresthesias with loss of sensation and difficulty ambulation since February 2024. She developed some fatigue and tiredness in May 2024 but after laminectomy, she developed worsening paresthesias in the hands and feet, loss of distal sensation beside progressive weakness in lower extremities and inability to ambulate. B12 and B6 were normal; Zinc level was low but normalized with supplement. ANA was positive with a speckled pattern; SPEP showed no monoclonal peaks. She denied bowel/bladder dysfunction or recent illness.

In a recent follow up with the patient, she mentioned that tirzepatide was started in January 2024 and she lost 56.2 kg in 6 months, then she stopped taking tirzepatide before surgery in July 2024. It was difficult to go upstairs for her in the late february. No neuropathy was noted before surgery. She started to use walker few days after surgery. She found no recovery after stopping tirzepatide. She didn't suffer any bladder issues in the whole course of worsening of paresthesias. Clinically, she was unable to stand without support due to sensory ataxia, impaired deep tendon reflexes, impaired pin prick and vibratory senses in asymmetric fashion in lower extremities. Her work up revealed low zinc (47 ug/dl) and selenium (42 mcg/ l) levels, nerve conduction consistent with sensorimotor axonal polyneuropathy and bilateral median mononeuropathy. Despite comprehensive evaluation, no unifying cause was identified.

Case # 2:

A 49 years old female presented with a prior medical history that was significant for rheumatoid arthritis with probable new onset dysautonomia and a recent diagnosis of type 2 diabetes mellitus since 2021. Dysautonomia symptoms included recurrent palpitations and fatigue with an onset that occurred before she started tirzepatide therapy for diabetes. The patient lost ~26 kg while on tirzepatide. Her HbA1c levels dropped from 9.3% to 5.3% in four months from May to September in 2024 by using GLP-1 agonist only. The neurologic examination revealed loss of vibratory and pinprick sensation in both feet, while deep tendon reflexes were intact. Vitamins B1 (34ug/L) and B6 (2ug/L) levels were low, while the remaining workup was negative, including the nerve conduction study. Skin biopsy showed evidence of length-dependent paucity of small fibers consistent with small fiber neuropathy. In a recent follow-up with the patient, she mentioned that she had undergone a spinal surgery in January 2025 and stopped taking tirzepatide since one year with no noticeable change in her neurological symptoms.

Discussion

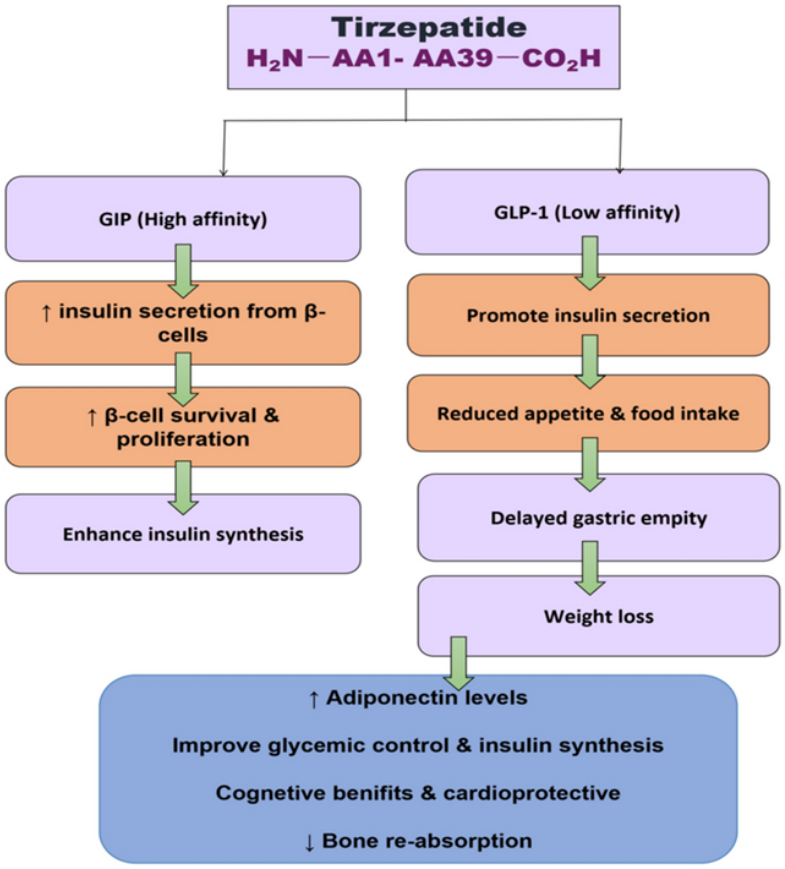
Peripheral neuropathies are a group of disorders of the peripheral nervous system, which includes the cranial nerves, spinal nerve roots and ganglia, nerve trunks and divisions, and the nerves of the autonomic nervous system. These pathologies may be categorized based on the extent and pattern of injury, ranging from mononeuropathies and multifocal neuropathies to polyneuropathies, with an axonal, demyelinating, or mixed pattern. [9]

In patients with multiple pre-existing risk factors predisposing them to peripheral neuropathies, the emergence or worsening of symptoms after starting a new therapy can pose a diagnostic challenge, particularly given the limited safety data of newly approved drugs. In our first case, there were pre-existing risk factors like gastric bypass, diabetes mellitus, exposure to anesthetics beside GLP-1 agonist and in second case there were pre-existing autoimmune condition, diabetes mellitus beside use of GLP-1 use to exacerbate preexisting neuronal injury.

Peripheral neuropathies are often multifactorial. Underlying etiologies may include metabolic and endocrine conditions (e.g., diabetes mellitus), nutritional deficiencies (e.g., vitamins B1, B6, and B12), autoimmune and inflammatory diseases (e.g., rheumatoid arthritis, vasculitis), infections, toxic or drug-induced exposures, neoplastic and paraneoplastic processes, hereditary disorders, or trauma. [9]

It is still not clear whether GLP-1 is the direct cause of neuropathic insult or secondary to weight loss with micronutrient loss but both cases highlight temporal association of worsening small and large fiber neuropathy which has either not been obvious or existed before adding GLP-1 to treatment regimen with poor recovery despite discontinuing GLP-1 therapy; which also makes it difficult to definitely associate it to GLP-1 therapy.

These cases highlight the diagnostic challenges in patients with overlapping nutritional, metabolic, and autoimmune conditions. The close link with tirzepatide initiation and rapid weight loss suggests a potential exacerbating role of GLP-1 therapy in neurological injury. Tirzepatide is considered to be a "twincretin" owing to its dual agonistic activity on the glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) receptors.[10] However, the exact mechanism by which tirzepatide causes paresthesias and polyneuropathy is not fully elucidated, but it may be related to metabolic changes affecting peripheral nerve function, rapid weight loss potentially leading to nutritional deficiencies that affect nerve health or possible effects on electrolyte balance that can influence nerve conduction. [11]



Mechanism of action (MOA) of Tirzepatide[10]

Conclusion

After bariatric surgery, the patients who receive GLP-1 agonists should be closely monitored by multidisciplinary evaluation teams and long-term nutritional support is essential. Further investigation is warranted to explore neuropathic side effects of tirzepatide therapies in high-risk populations. Nutritional deficiencies, most commonly involving iron, folate, and vitamin B12, often develop after bariatric surgery, particularly following malabsorptive procedures such as Roux-en-Y gastric bypass. Nutritional deficiencies in vitamins B1, B6, B12, D, E, and folate, as well as the minerals copper and zinc, are most commonly linked to neurologic complications. [12]

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Conflict of Interest

The authors declare that they have no competing interests.

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