EJCRIM
European Journal
of Case Reports
in Internal Medicine

TIRZEPATIDE-RELATED ACUTE LIVER INJURY

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Received: 12/08/2024
Accepted: 12/08/2024
Published: 02/09/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Available.
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How to cite this article: Abdullah I, El-Ghousain H, Alenezi M. Tirzepatide-related acute liver injury. *EJCRIM* 2024;**11**:doi:10.12890/2024_004813

ABSTRACT

Tirzepatide, a modified protein containing 39 amino acids, acts as a dual agonist at the gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, showing great promise in weight-loss treatment. While rare, there have been reports of hepatotoxicity associated with tirzepatide use, and the exact mechanism of liver injury remains unclear. This case report highlights the experience of a 24-year-old female schoolteacher who started her weight-loss journey with tirzepatide. Despite its potential, she developed an idiosyncratic drug-related liver injury after escalating doses of tirzepatide prescribed by a private doctor. Her symptoms of recurrent vomiting, nausea and abdominal pain, initially indicative of hypoglycaemia and mild metabolic disturbances, ultimately revealed acute hepatitis and impaired coagulopathy. This case underscores the need for further research and frequent following of liver enzymes when using tirzepatide for weight loss.

KEYWORDS

Liver injury, tirzepatide

LEARNING POINTS

- Tirzepatide should be used cautiously, with regular monitoring of liver function tests.
- If patients develop severe gastrointestinal symptoms or worsening abdominal pain, immediate hospital admission is necessary for further work-up, including a CT abdomen.
- Daily liver function tests, renal function tests and international normalised ratio (INR) tests should be conducted to identify and manage potential complications.

INTRODUCTION

Tirzepatide is currently being used as a potential weight-loss agent for overweight or obese individuals without diabetes, available in weekly doses of 2.5 to 15 mg administered subcutaneously[1]. Adverse effects of tirzepatide therapy include non-specific gastrointestinal complaints such as nausea, vomiting, diarrhoea, decreased appetite, dyspepsia and abdominal discomfort. It is common practice to see cases of drug-induced pancreatitis in patients regularly taking tirzepatide, possibly influenced by the recent popularity of the self-prescription trends of Mounjaro treatment[2,3]. There are very few cases documenting mild hepatotoxicity associated with tirzepatide spillage of aspartate transferase (AST) and alanine transaminase (ALT) that is reversible on

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smc media srl

cessation of the drug that have been reported, but it has not been known to cause acute liver injury before[4].

CASE DESCRIPTION

A 24-year-old female schoolteacher, non-diabetic with a body mass index (BMI) of 34 kg/m^2, was treated with tirzepatide as a part of her weight reduction programme, which started in February 2024. She presented to our casualty department with recurrent episodes of vomiting, nausea and non-specific abdominal pain. Her initial admission was on 5 July 2024, where she exhibited symptoms of hypoglycaemia alongside nausea, vomiting and abdominal discomfort. Initial laboratory tests showed high anion gap metabolic acidosis (pH 7.33 and $HCO_3$17 mmol/l), AG 19 mEq/l and hypokalaemia (potassium 3 mmol/l) but her liver function tests were normal. She responded well to intravenous fluids, proton pump inhibitors and antiemetics, and was discharged in a stable condition with all laboratory parameters within normal limits. However, she was readmitted just two days later with recurrence of symptoms and hypoglycaemia with blood sugar at 3.5 mmol/l. A computed tomography (CT) abdomen scan was performed and showed a normal appearance of the common bile duct, pancreas, spleen, kidneys, adrenals and visualised bowel loops, and a mildly enlarged fatty liver. There was no radiological evidence of acute appendicitis, but her liver enzymes were alarming *(Table 1)*. However, her renal function test results (urea and creatinine) were within normal ranges throughout. She presented with severe abdominal pain and hypotension with blood pressure of 90/50 mmHg, necessitating intensive care unit admission for close monitoring and management. Treatment included fresh frozen plasma transfusion, vitamin K injections, lactulose, rifixamin and ursodeoxycholic acid (Ursofalk®), with ongoing daily evaluations by the gastroenterology team and consultations with the liver transplant team due to the severity of her condition. She was offered a liver biopsy, but she refused. The serum paracetamol level was negative. Serological tests for hepatotropic viruses (hepatitis A, B, C and E, cytomegalovirus, herpes simplex 1 and 2, Epstein-Barr and varicella-zoster) were negative. Anti-nuclear, anti-mitochondrial, anti-LKM and anti-smooth muscle antibodies were negative.Over the course of ten days, her liver enzymes gradually decreased *(Fig. 1 and 2)* and her international normalised ratio (INR) normalised *(Table 1)*. Throughout her hospital stay, she remained conscious and oriented, with additional evaluations including an unremarkable chest X-ray and normal troponin levels; an electrocardiogram (ECG) showed a sinus rhythm with T-wave inversion. She had been using the Mounjaro treatment for weight loss continuously for the past seven months, between 15 February 2024 and 26 June 2024. She discontinued oral contraceptive pills (Gynera) in the month of June, which she had been using since the birth of her first child one year previously. There is no family history of autoimmune diseases or malignancies, and she has no history of alcohol

Test	Admission result	Discharge result	Normal range
Albumin (g/l)	32	23.5	35–52
Alanine transaminase (IU/l)	6,212	562	5–37
Aspartate transferase (IU/l)	6,712	41	5–34
Alkaline phosphatase (IU/l)	132	123	35–105
Total bilirubin (µmol/l)	124	71	2.5–22
Gamma-glutamyl transferase (IU/l)	287	120	7–40
Ammonia (µmol/l)	148	83	11–51
International normalised ratio (INR)	9	1	1
White blood count (×10^9/l)	16.7	6.1	4–10
Haemoglobin (g/l)	127	107	120–150
Blood urea nitrogen (mmol/l)	2.29	0.53	2.14–7.14
Creatinine (µmol/l)	60	43	44–80

Table 1. Laboratory results.

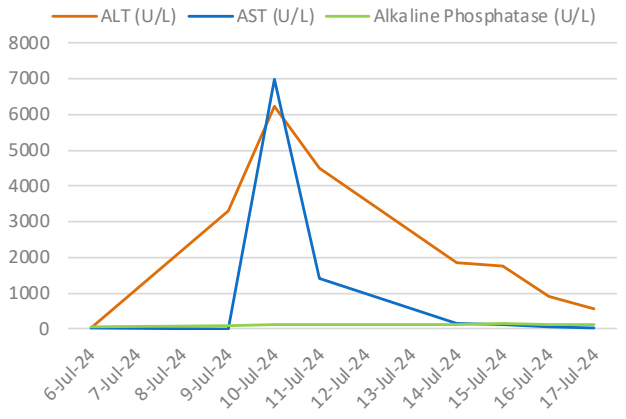


Figure 1. Kinetics of liver enzymes during hospitalisation.

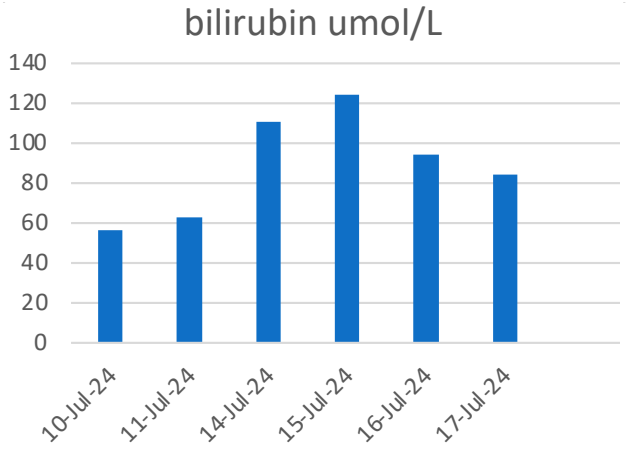


Figure 2. Trend of in-patient bilirubin levels.

Factors	Case	Score
Time of onset from the beginning of drug use	> 90 days	+1
Change in ALT levels between peak and stopping drug use	>50% improvement in 30 days after withdrawal	+2
Risk factors		
1) Age > 55	No	0
2) Alcohol/pregnancy	No	0
Concomitant drug use	Unknown hepatotoxicity	0
Exclusion of other causes	Ruled out all causes of Groups 1 and 2	+2
Previous information on hepatotoxicity	Unknown	0
Response to re-administration	Doubling of ALT with the drug alone	0
Total score	Possible	5

Table 2. RUCAM Score.

consumption, psychotropic drug use or smoking. She was discharged from gastroenterology care on 19 July 2024, with a weight of 58 kg and a BMI of 25 kg/m^2.

DISCUSSION

The rapid onset and severity of liver injury observed in this case raise concerns about the safety profile of tirzepatide, while the exact mechanisms underlying tirzepatide-induced acute liver injury remains unclear.

Idiosyncratic drug-induced liver injury (DILI) has emerged as the second leading cause of acute liver failure after acetaminophen hepatotoxicity. Unlike acetaminophen hepatotoxicity, which typically exhibits dose-dependency, idiosyncratic DILI can occur unpredictably and has a highly variable latency period from ingestion to the onset of symptoms, depending on the offending agent. Once the diagnosis is established, the suspected drug should be discontinued immediately and subsequent care is predominantly supportive[5].

In our case, the patient started weekly injections of tirzepatide, escalating from 2.5 mg, 5 mg, 7.5 mg, 10 mg to 12 mg in June. Following the last dose of 12 mg, the patient experienced repeated admissions to the casualty department with symptoms including abdominal pain and vomiting. The half-life of tirzepatide is approximately five days, suggesting that the drug remained in the bloodstream for an extended period, potentially contributing to the observed liver injury[6]. A RUCAM score of 5 *(Table 2)* and the temporal relationship of tirzepatide with acute liver injury makes it likely the susceptible cause[7].

Another proposed mechanism could be rapid defatting of liver along with its high dose, as in this patient it could have caused direct cytotoxic injury, thus contributing to acute liver injury[4].

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