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DRUG-INDUCED AUTOIMMUNE-LIKE HEPATITIS AND CHOLELITHIASIS ASSOCIATED WITH DULAGLUTIDE AND SEMAGLUTIDE USE IN A YOUNG ADULT: A CASE REPORT AND REVIEW OF LITERATURE

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Abstract
Only few cases of liver injury induced by liraglutide (glucagon-like peptide-1 receptor agonist) with complete recovery after drug discontinuation and administration of corticosteroid have been reported. This report presents the case of a 29-year-old Saudi female patient who presented to the emergency department complaining of acute right upper quadrant abdominal pain for three days. She was an occasional smoker
for the past 10 years with no relevant medical or surgical history. The young female developed autoimmune- like hepatitis due to the intake of Dulaglutide and Semaglutide, which are medications used for type-2 diabetes. Studies regarding the effects and association of dulaglutide and Semaglutide to cholelithiasis and autoimmune-like hepatitis are very limited. This case report shows a possible association of these drugs with developing autoimmune-like hepatitis and cholelithiasis.

Keywords: glp-1 receptor agonists, semaglutide, hepatitis, cholelithiasis, dulaglutide

Introduction
Glucagon-like peptide (GLP), an incretin hormone generated by the L cells of the small intestine, decreases blood sugar level by increasing insulin secretion and suppressing glucagon release from the pancreatic cells in a glucose-dependent way [1]. However, some of these drugs may cause adverse gastrointestinal effects such as nausea, vomiting, diarrhea and an elevated risk of hypoglycemia [2,3]. Dulaglutide actsprimarily by boosting insulin production in response to a high blood sugar levels, lowering glucagon secretion,and prolonging gastric emptying to reduce postprandial glucose levels [4,5]. Nausea, abdominal pain, diarrhea, decreased appetite, dyspepsia, and tiredness are the usual adverse reaction of dulaglutide observed in 5% or more of patients. Cholelithiasis has been associated with the use of (GLP1-RA), the possible mechanisms of which are weight loss, the agonistic effect on biliary secretion, and/or a drug-induced alteration of gallbladder motility [6,7]. Prolonged usage of GLP-1 may cause decreased gallbladder contraction, resulting in the accumulation of biliary sludge and gallstones, leading to an increased risk of cholelithiasis and cholecystitis [8].

Drug induced autoimmune-like hepatitis (DIAILH) is a complex, not well understood, inflammatory destructive disease directed against hepatocytes [9]. It is characterized by elevation in both serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, typically 5 to 20 times higher than the normal range [9,10]. The most commonly reported DIALH agents are interferons, statins, methylprednisolone, imatinib, adalimumab, and diclofenac [11]. It also shares many characteristics with idiopathic Autoimmune Hepatitis (AIH), including autoimmune features and histological findings, making diagnosis and differentiation difficult [11,12]. Although, DIALH is similar to idiopathic AIH, DIALH typically resolves completely after the responsible drug has been discontinued.

Recovery from DIALH may be gradual, and may need a short course of corticosteroid therapy, and the lack of relapse after the withdrawal of immunosuppressive medications, which is the only feature that differentiated patients with DIALH from idiopathic AIH patients [9,11].

There have been a few cases reported of liraglutide (GLP1-RA) induced liver injury, with complete recovery after drug discontinuation and administration of corticosteroid [13]. This case report aimed to determine the association of dulaglutide and semaglutide to DIALH and cholelithiasis in young female patient.

Case Presentation

A 29 year old Saudi female patient presented to the emergency department complaining of sudden right upper quadrant abdominal pain for three days, described as sharp pain, radiating to the epigastric region, 7 out of 10 in severity, associated with nausea and three episodes of non bloody, bilious vomiting. pain started after injecting Dulaglutide 1.5mg, which was used for weight reduction, as our patient is medically free.

Pain was relieved by nonsteroidal anti-inflammatory drugs (NSAIDs).

She also complained of headache and fever for 10 days. Headache was intermittent and accompanied by tightness (described as mild to moderate pain that feels like a tight band around the head), she denied any association of aura, light or noise sensitivity. Moreover, the fever was subjective, every six hours, not accompanied with chills, sweating or rigors, and was improving with paracetamol the patient's mother noticed a yellowish discoloration over patient's sclera and skin for the past 10 days. The patient herself noticed that her urine was red in color. She developed an unpleasant taste and loss of appetite for five days so she developed constipation and could not pass stool. Other systemes review were essentially unremarkable. No history of alcohol or any herbal medication intake, no history of antibiotic use.

The patient was allergic to beta-lactam antibiotic (cephalosporin). She was an occasional smoker for 10 years. She has no relevant medical or surgical history, no previous hospital admissions and no family history for the same complaint.

She gave family history of gallbladder stones and obesity, since one of her siblings had gastric sleeve surgery and cholecystectomy due to the presence of gallbladder stones at the time of surgery, and the other is using GLP1 agonist for weight reduction.

Our patient used Semaglutide 0.25mg weekly for a month, and then she increased the dose to 0.50mg weekly for another month. Subsequently, she stopped taking Semaglutide for three months. Over these five months, she lost approximately 16 kg. Patient was not satisfied yet with the weight loss, so she resumes dulaglutide 1.5mg for one month prior to her presentation. She was adherent to the medication without skipping doses.

Her BMI at presentation was 31.12 after losing 16 kg and using 8 doses of Semaglutide and 4 dosses

of Dulaglutide, on presentation, her temperature was 36.7 °C, blood pressure 142/64 mmHg, heart rate 74 beats/minute, respiratory rate 18 cycles/minute, and her oxygen saturation was 99% on room air.

On physical examination, she was awake, alert, and not in distress. She had yellowish skin, sclera, and mucus membrane, with no scratch marks. On abdominal examination, she possessed a guarded upper abdomen, with tenderness in the right upper quadrant and epigastric region, and a positive Murphy's sign (which is performed by palpating the subcostal region during inspiration, If pain is evoked and suddenly stops their inspiration this considered a positive Murphy's sign) [14]. On abdominal percussion, the liver span was 14cm, with no sign of ascites, or spleen or kidney enlargement. Other physical examinations conducted did not reveal any remarkable findings.

Upon admission, chest x-ray was unremarkable. Abdominal ultrasound showed partially contracted gallbladder with intra-luminal sludge, negative sonographic Murphy's sign, no intra or extra hepatic biliary duct dilation, common bile duct (CBD) caliber was 0.27cm and portal vein was patent (Fig.1).

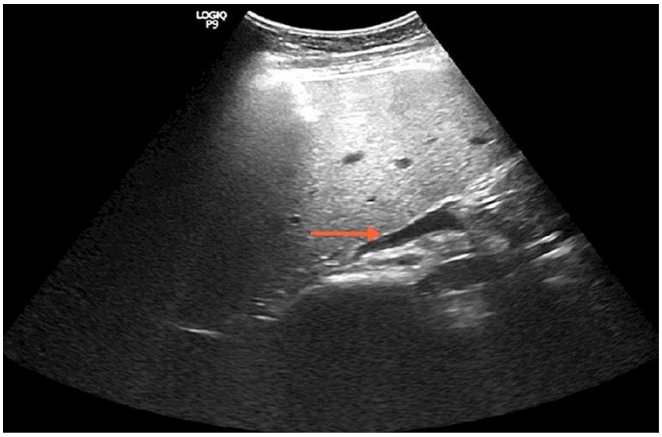

FIGURE 1: Abdominal ultrasonography showing partially contractedgallbladder with intraluminal sludge.

Her Total bilirubin was 9.91 mg/dl at presentation (Fig. *2*), direct bilirubin 9.05 mg/dl (Fig. *3*), alkaline phosphatase (ALP) 390 U/L, (AST) 175.8 U/L, (ALT) 229 U/L, no leucocytosis, and negative human immunodeficiency virus antibody HIV Ab, hepatitis B surface antigen HBsAg, hepatitis C virus antibody HCV Ab, and hepatitis B-core Igg HBcAb, positive serology test for Cytomegalovirus and Epstein-Barr virus
(Table *1*).

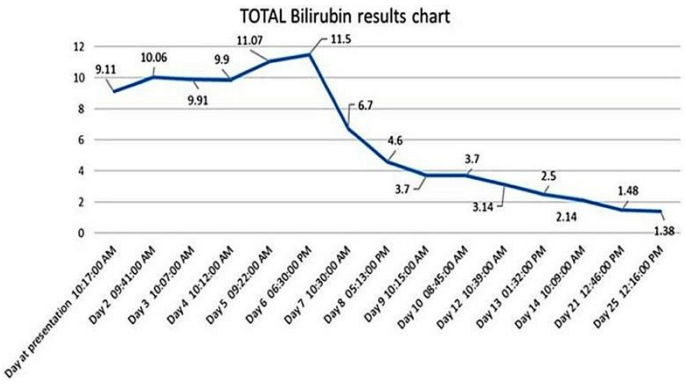

FIGURE 2: Patient's Total Bilirubin upon presentation to discharge.

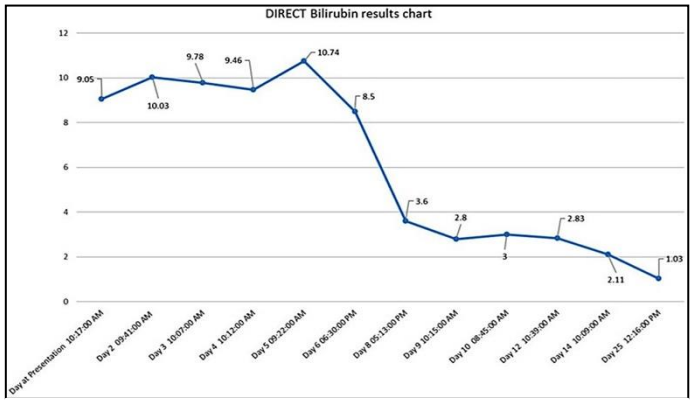

FIGURE 3: Patient's Direct Bilirubin upon presentation to discharge.

Labs	20-07-2022 Day at presentation	Day 2	Day 4	Day 5	Day 12	Day 13	Day 14	Day 21
ALP (U/L)	390	420	465	555	350	269	245	135
GGT (U/L)	-	226	248	292	-	117	-	55
AST (U/L)	175.8	223.4	149.8	191.2	39.6	37.8	27.7	16.8
ALT (U/L)	229	245.8	178.2	208.8	132	112.8	92.7	40.8
WBCs (×109 /L)	-	8.6	None	6.02	9.42	9.03	-	-
Hemoglobin (g/dl)	-	11.6	-	10.8	13	11.4	-	-
Platelet (×109 /L)	-	190	-	256	556	446	-	-

Our patient was admitted as a case of Obstructive jaundice and was treated conservatively with intravenous fluid and antibiotics. Her bilirubin level and liver enzymes showed no improvement, she underwent endoscopic retrograde cholangiopancreatography (ERCP) with no intra or extra hepatic biliary duct
stones were observed, and sphincterotomy was performed. An iatrogenic perforation occurred during ERCP, although patient was vitally stable and her abdomen was soft and lax upon examination, she was kept NPO (nill per os) for 48 hours and a nasogastric tube (NGT) was inserted. She was treated conservatively with no remarkable findings, then started feeding and NGT was removed.

However, post ERCP, her bilirubin level had not improved (Fig. *2*, *3*), therefore, she underwent magnetic resonance cholangiopancreatography (MRCP) and it showed minimal gallbladder sludge with no sign of cholecystitis, no intra or extra hepatic biliary duct or CBD stones.

After 3 days she developed rash all over her body after using paracetamol-codeine-caffeine soluble tablets (Solpadine) for a headache and was treated with corticosteroids and antihistamine (diphenhydramine) after dermatology consultation.
After using corticosteroid to treat her skin condition there was a significant improvement in her bilirubin and liver enzymes levels (Fig. *2*, *3*). This raised the suspicion of AIH. Therefore, an Immunology workup was performed which showed negative antinuclear antibodies (ANA) and Anti smooth muscle antibody (ASMA). She had normal levels of Immunoglobulin-G4 (IGG4) and total Immunoglobulin G (IGG). Liver biopsy showed the portal tract with moderate infiltration and inflammation, and mild interfac hepatitis and mixed inflammation, which was predominantly lymphocytes with occasional neutrophils (Fig. *4*, *5*, *6*).

Patient's last bilirubin level was 1.48 mg/dl. And she was discharged on prednisolone, with and OPD follow up and a plan to perform an elective laparoscopic cholecystectomy once her liver profile normalized.

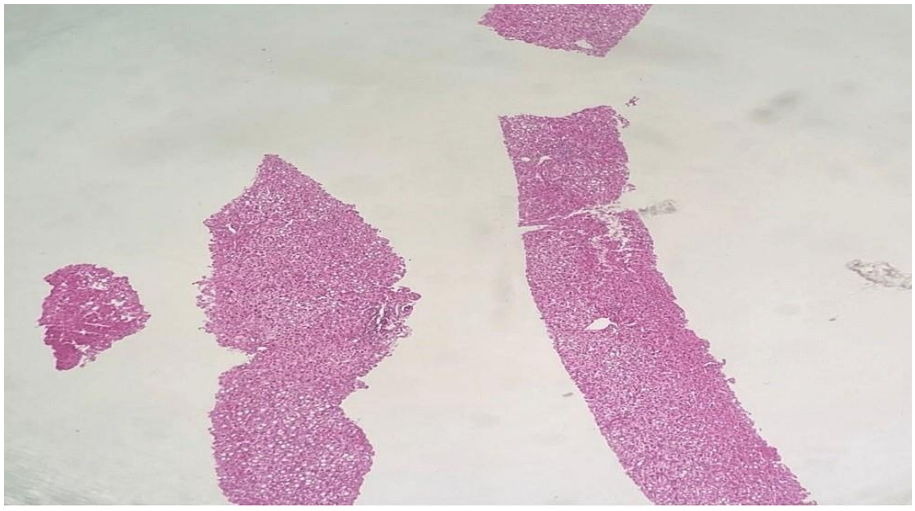

FIGURE 4: Liver Tissue biopsy showing portal tract with moderate infiltration with inflammation, and mild interphase hepatitis and mixed inflammation (Magnification power: 40)

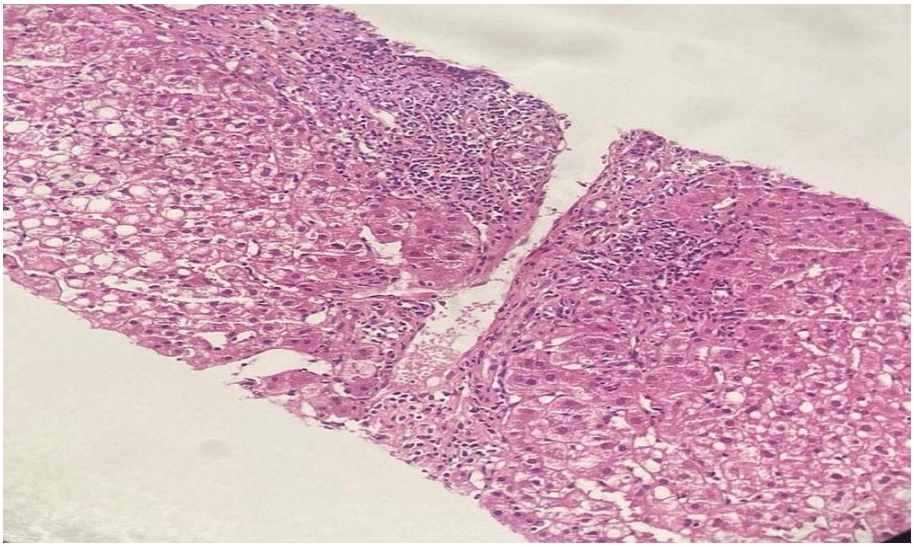

FIGURE 5: Portal tract showing moderate infiltration with inflammation and mild interphase hepatitis (Magnification power: 100)

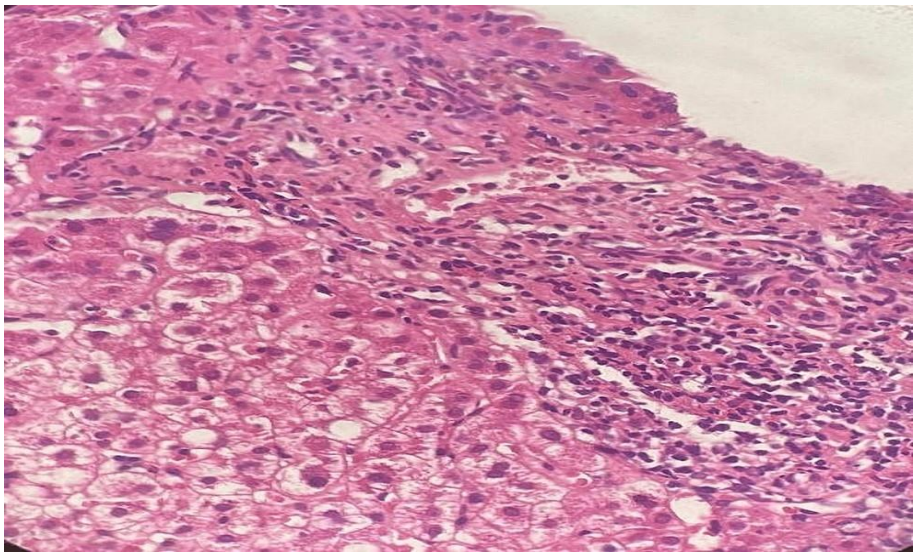

FIGURE 6: Mixed inflammation which is predominantly lymphocytes with occasional neutrophils (Magnification power: 400)

Discussion

In response to the increasing development of new medication and the escalating prevalence of chronic medical conditions, Idiosyncratic DILI has becoming more common since the liver is considered the primary site for the first-pass metabolism of drugs [15]. GLP-1 agonists (Dulaglutide, Liraglutide and Semaglutide) are promising treatment options for those with type 2 diabetes With a 97% amino acid sequence similar to human GLP-1, it is a recombinant human GLP-1 analogue [10]. They have several unfavorable side effects, including nausea, diarrhea, constipation, flatulence, and vomiting. Cholelithiasis, along with pancreatitis and gastroparesis, is one of the potentially serious adverse effects of (GLP1-RA) [16]. The pharmaceutical label mentions the elevation of liver enzymes based on postmarketing experiences, despite the fact that the mechanism of liver damage caused by GLP1 medication use is unknown [17]. Clinical manifestations and laboratory evidence can help to define Drug-induced hepatitis. It can be described and confirmed by histological findings using a liver biopsy [16]. Our patient was admitted because of cholelithiasis which is reported to be associated with (GLP1-RA). During ERCP, it was discovered that the patient has iatrogenic injury, which is usually acquired from receiving a medical therapy, medication, or the use of medical technology that has nothing to do with the primary condition [18]. Possible that iatrogenic injury may be caused by the mediations or medical concentrations she's taken.

Upon presentation her laboratory results showed high total (9.91 mg/dl) and direct bilirubin (9.05 mg/dl), ALP (390 U/L), AST (175.8 U/L) and ALT (229 U/L). According to the study, DIALH is described by moderate serum aminotransferase elevations, 200 to 800 IU/L which is 5 to 20 times of upper limit of the normal range (ULN) and a minor elevation in alkaline phosphatase levels(230 U/L: 2 ULN) mg/dL [10]. Bilirubin levels are generally between 0.3 and 1.0, It is considered abnormal if bilirubin levels is above 1.2 mg/dL.

The most common symptom of elevated bilirubin levels is jaundice which describes by yellowing of skin and eyes [11]. In this case, patient developed a rash all over her skin after taking Solpadine, a pain killer containing paracetamol/codeine/caffeine, and was treated with corticosteroids and antihistamines. After taking corticosteroids, bilirubin levels improved significantly. With this, an immunology workup was done. Previous studies showed that corticosteroid therapy is effective in treating AIH [13,19]. Prednisolone used alone or combined with azathioprine relieves the majority of patients' symptoms. In the context of the recently started GLP-1 medicine, our patient had a

hepatocellular pattern of liver disease. We hypothesized that GLP-1 medications caused liver harm based on the temporal correlation between the usage of Dulaglutide and Semaglutide and the emergence of liver damage. Table *2*. Summarizes the review of literatures associated with GLP-1. According to that, a different symptoms may presents the liver function tests returned to normal once the patient's medication was stopped, supporting our judgment that the patient's liver damage was caused by the GLP-1 medications.

First Author	Study type	Sample size	Gender	Age(Years)	TypE ofmedication	Symptoms	Duration ofsymptoms	DiagnosIs
Neahusan et al., 2021 [20]	Case report	N=1	Female	53	Dulaglutide	Diffuse pruritus	2 weeks	DILI andAIH
Kern et al., 2013 [21]	Case repost	N=1	Female	29	Liraglutide	Nausea, vomiting and acutehepatitis	-	DILI
Patel et al., 2019 [22]	Case report	N=1	Male	64	Dulaglutide	Dark urine and pruritus	2 weeks	DILI
Enslin et al., 2021 [23]	Case report	N=1	Male	79	Semaglutide	Dehydration and fatigue	4 weeks	DILI

TABLE 2: Review of the literature on GLP1-RA.

Conclusions

A young female patient developed DIAILH due to intake of dulaglutide and semaglutide which are medications used for Type 2 diabetes. Studies that address the effects and association of GLP1-RA to cholelithiasis and DIAILH are very limited. However, this case report showed possible associations between these drugs and AIH and cholelithiasis. We recommend more researches on GPL-1 medication side effect because nowadays it becomes more popular and commonly used medication.

References

1. Kieffer TJ, Habener JF: The glucagon-like peptides. . Endocrine Reviews. 1999 Dec, 20:876-913. 10.1210/edrv.20.6.0385
2. Collins L, Costello RA: Glucagon-Like Peptide-1 Receptor Agonists . 2023 Jan 13,
3. Perez-Montes DE Oca A, Pellitero S, Puig-Domingo M: Obesity and GLP-1. Minerva Endocrinol. 2021 Jun, 46:168-176. 10.23736/s2724-6507.20.03369-6
4. Grunberger G, Chang A, Garcia Soria G, Botros FT, Bsharat R, Milicevic Z: Monotherapy with the once- weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycaemic control in a randomized, double-blind, placebo-controlled study. Diabet. Med. 2012 July, 29:1260-1267. 10.1111/j.1464-5491.2012.03745.x
5. Mirabelli M, Chiefari E, Tocci V, et al.: Clinical effectiveness and safety of once-weekly GLP-1 receptor agonist dulaglutide as add-on to metformin or metformin plus insulin secretagogues in obesity and type 2 diabetes. J. Clin. Med. 2021, 10:985. 10.3390/jcm10050985
6. Liyun He, Jialu Wang, Fan Ping, et al.: Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-analysis of Randomized Clinical Trials . JAMA Intern Med . 2022 March , 182:513-519. 10.1001/jamainternmed.2022.0338
7. Nreu B, Dicembrini I, Tinti F, Mannucci E, Monami M : Cholelithiasis in patients treated with Glucagon- Like Peptide-1 Receptor: An updated meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 2020 Mar, 161:108087. 10.1016/j.diabres.2020.108087
8. Di Ciaula A, Garruti G, Wang DQ, Portincasa P: Cholecystectomy and risk of metabolic syndrome. Eur J Intern Med. 2018 Jul, 53:3-11. 10.1016/j.ejim.2018.04.019
9. Czaja AJ: Drug-induced autoimmune-like hepatitis . Dig Dis Sci. 2011 Apr, 56:958-76. 10.1007/s10620-011- 1611-4
10. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet] . National Institute of Diabetes and Digestive and Kidney Diseases. 2012,
11. Björnsson ES, Medina-Caliz I, Andrade RJ, Lucena MI: Setting up criteria for drug-induced autoimmune-like hepatitis through a systematic analysis of published reports. Hepatol Commun. 2022 Aug, 6:1895-1909. 10.1002/hep4.1959
12. Sebode M, Schulz L, Lohse AW: Autoimmune(-Like)" Drug and Herb Induced Liver Injury: New Insights into Molecular Pathogenesis. Int J Mol Sci. 2017 Sep, 18(9):1954. 10.3390/ijms18091954
13. Parvataneni S, Ramachandran R, Then E, Grantham T: An Exceedingly Rare Case of Liraglutide-Induced Liver Injury. Case Rep Gastrointest Med. 2021 Aug, 23:6306149. 10.1155/2021/6306149
14. Musana K, Yale SH: John Benjamin Murphy (1857 - 1916) . Clin Med Res. 2005 May, 3:110-2. 10.3121/cmr.3.2.110
15. Reuben A, Koch DG, Lee WM: Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010 Dec, 52:2065-76. 10.1002/hep.23937
16. Dong YH, Wu JH, Chang CH, Lin JW, Wu LC, Toh S: Association between glucagon-like peptide-1 receptor agonists and biliary-related diseases in patients with type 2 diabetes: A nationwide cohort study. Pharmacotherapy. 2022 Jun, 42:483-494. 10.1002/phar.2688
17. Buse JB, Garber A, Rosenstock J, et al.: Liraglutide treatment is associated with a low frequency and magnitude of antibody formation with no apparent impact on glycemic response or increased frequency of adverse events: results from the Liraglutide Effect and Action in Diabetes (LEAD) trials. J Clin Endocrinol Metab. 2011 Jun, 96:1695-702. 10.1210/jc.2010-2822
18. Gilbert Lau MBBS: Iatrogenic Injury: A Forensic Perspective . Forensic Pathology Reviews. 2005, 3:351-439.
19. Czaja AJ: Rapidity of treatment response and outcome in type 1 autoimmune hepatitis . J Hepatol. 2009 Jul, 51:161-7. 10.1016/j.jhep.2009.02.026

20. Neahusan, Emma BS; Williams, Carson BS; Lee, Melissa MS, DO; Sadowski, Brett MD: Autoimmune Hepatitis-like Drug Injury of the Liver Associated with the Glucagon-like Peptide 1 (GLP-1) Agonist Dulaglutide. Am J Gastroenterol. October 2021, 116:S1189. 10.14309/01.ajg.0000785004.17193.b9
21. Kern, Emily MD; VanWagner, Lisa MD, MS; Rinella, Mary MD, FACG: Drug-induced Liver Injury Associated with the Glucagon-like Peptide 1 (GLP-1) Agonist Liraglutide. Am J Gastroenterol. October 2013, 108:S335- S336.
22. Patel AV, Jotwani PM, Lee TP: Drug-Induced Liver Injury Due to Dulaglutide Use . Am J Ther. 2019 Sep/Oct, 26(5):e620-e622. 10.1097/mjt.0000000000000826
23. Enslin, Sarah PA1; Bartell, Nicholas MD1; Kaul, Vivek MD, FACG2: The First Reported Case of Drug-Induced Liver Injury Caused by Semaglutide.. Am J Gastroenterol. October 2021, 116:S1141. 10.14309/01.ajg.0000784440.97741.d2