http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v11i6.06

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Article

Gall stone Disease after starting Liraglutide, Is it reversible?

Authors
Dr Jayesh Kalbhande, Dr Mayank Chaudhary

Abstract

Objective: *Liraglutide is known to cause gall stones and its related complication. They are often subjected to cholecystectomy. We describe a case of Liraglutide induced cholelithiasis and cholecystitis which was managed conservatively. The gall stones resolved after stopping Liraglutide. This is only second such case report of complete resolution of gall stones after discontinuation of Liraglutide.*

Case Description: *A 66 years old female patient, Diabetic and Hypertensive, who was on Inj. Liraglutide for her diabetes presented with complaints of fever, right side hypochondriac pain and few episodes of vomiting. Upon clinical examination, patient was vitally stable and necessary blood investigations were done. Her CT scan of abdomen and pelvis showed layered grain size hyperdense opacities in Gall bladder lumen. She was put on I.V. antibiotics and nil per orally. Her Inj. Liraglutide was discontinued and started on Basal Glargine insulin with intermittent Human Regular insulin for control of blood sugars and continued monitoring was done. She showed significant improvement showing no pain and tenderness in right hypochondriac region and her blood and serum reports showed considerable improvement. She remained asymptomatic and subsequent USG reports showed normal gall bladder with no evidence of calculus or sludge seen.*

Conclusion: *Gall stones associated with Liraglutide treatment is a reversible disease after stopping treatment of Liraglutide. The use of GLP-1 analogues was associated with an increased risk of bile duct and gallbladder disease. Physicians should be aware of this potential adverse event when prescribing these drugs.*

Introduction

GLP 1 receptor agonist Liraglutide was approved for treatment of Diabetes by FDA in year 2010. It gained popularity because of multiple beneficial effects such as increasing early satiety, weight loss, reducing all-cause mortality, cardioprotective effect and improved glycemic control without increasing risk of hypoglycemia. Liraglutide is associated with side effects such as nausea, vomiting and new incidence of gall stone disease. In this case report we discuss a case of Liraglutide induced symptomatic gall stone disease caused by cholecystitis. It was managed conservatively. The gall stones resolved completely after discontinuation of Liraglutide. This is only second such case report showing complete resolution of

gall stone disease after discontinuation of Liraglutide.

Case Report

A 66 yrs old Diabetic and Hypertensive female presented with complains of Fever since 3 – 4 days, Severe pain in right hypochondriac region associated with 7 – 8 episodes of vomiting and feverfor1 day. She had peculiar history of being started on Inj. Liraglutide from 9 months prior to this episode of pain in abdomen. Her routine USG abdomen done two years back had shown normal gall bladder with no evidence of any gall stones.

On presentation she was vitally stable – Her Pulse was 84 /min and Blood pressure of 130/80 mm of Hg. On Per abdomen examination, there was tenderness in right hypochondriac region. Rest of the abdomen was soft. Her blood investigation done on admission showed Hb 10.9 gm/dl, WBC count 9,300/cmm. Urine routine was normal. Total Bilirubin was 3.3 mg/dl, Direct Bilirubin was 2.2 mg/dl, SGOT 132 U/L, SGPT 232 U/L, Serum Creatinine was 0.6 mg/dl, Serum Sodium was 139 meq/L, Serum Potassium was 4.4 meq/L and Serum Chloride was 97 meq/L, Serum Amylase was 26 U/L, INR was 0.98, Serum Alkaline Phosphatase was 174 U/L (Normal Range 39 – 117 U/L), Her USG abdomen done showed small gall bladder calculi with probe tenderness in right hypochondriac region which may suggest cholecystitis. Her CT scan of abdomen and pelvis done It showed layered grain size hyperdense opacities in Gall bladder lumen.The common bile duct was normal. She was kept nil per orally. She was Started on Intravenous Ceftriaxone 1 gm twice a day and Metronidazole 500 mg three times a day. Her Inj. Liraglutide was discontinued and she was started on Basal Glargine insulin and intermittent Human Regular insulin for control of blood sugars. Her blood sugars were regularly monitored in hospital and were kept in normal range.

She showed significant symptomatic improvement after treatment and her pain and tenderness in right hypochondriac region subsided. Her Investigation done on 4th day of admission showed Total Bilirubin was 0.9 mg/dl, Direct Bilirubin was 0.4 mg/dl, SGOT 82 U/L, SGPT 52 U/L, Serum Alkaline Phosphatase was 161 U/L (Normal Range 39 – 117 U/L). She was discharged from hospital. She followed up after 1 month when her investigation showed Total Bilirubin of 0.5 mg/dl, Direct Bilirubin of 0.3 mg/dl, SGOT 31 U/L, SGPT 22 U/L, Serum Alkaline Phosphatase was 99 U/L (Normal Range 39 – 117 U/L)

She remained asymptomatic for any abdominal complaints thereafter. She later on followed up after 3 years when her routine USG abdomen showed Normal Gall bladder with no evidence of calculus or sludge.

Discussion

Glucagon like peptide 1 is secreted by intestinal endocrine cells and it acts on GLP 1 receptors in islets of pancreas to increase secretion of post prandial insulin and decrease secretion of post prandial Glucagon. GLP 1 receptor agonist act on GLP 1 receptors in islets of pancreas resulting in control of post prandial rise in blood sugars. It has many favourable properties such as causing early satiety, inducing weight loss, preventing hypoglycaemia. GLP 1 receptor agonist reduces gastric emptying which may resulting in fullness of abdomen, early satiety, nausea and vomiting which is seen as important side effect of GLP 1 receptor agonist.[(1)]

After the launch of Liraglutide in 2010, the evidence for gall stones induced by Liraglutide started pouring in from year 2015. In this year, there was a case report which suggested possibility of Gall stone formation linked to use of Liraglutide.[(2)] In the same year 2015, a randomized controlled trial for use of Liraglutide in nondiabetic patients for weight loss showed that in addition to significant weight loss they also had increased incidence of Gall stone formation and Cholecystitis as compared to placebo arm. There was an interesting observation in this study that most patients in Liraglutide group who developed

gall stone disease underwent surgery of cholecystectomy.[3] Then came an observational study initially suggested that there is associated in between Gall stone formation and use of Liraglutide,[4] A study showed that Liraglutide was found to increase the time required for maximum ejection of bile from Gall bladder – suggesting possible mechanism of diminished contractility of gall bladder as a cause of formation of gall stones.[5] A Double blind randomised controlled, LEADER trial, which was originally designed to compare cardiovascular outcomes in liraglutide vs placebo group. The analysis of data of LEADER trial showed that there was statistically significant increase in incidence of acute gallbladder disease or biliary disease in liraglutide group as compared to placebo.[6]It was followed by Metaanalysis of multiple trials which once again confirmed association of gall bladder disease and treatment with Liraglutide.[7]

Our patient was found not having any gall stone disease before the index episode of acute cholecystitis. The episode occurred after starting of treatment with Liraglutide. There was resolution of symptoms after conservative treatment. The gall stones resolved completely after stopping of Liraglutide. She had raised liver enzymes and raised bilirubin without any biliary obstruction, which returned to normal after stopping treatment of Liraglutide. We found that this was only second such case report which showed that there was complete resolution of gall stones after stopping Liraglutide. In First such case reported, a 75 years old female developed symptoms of acute calculus cholecystitis after starting Liraglutide, she was managed conservatively and Liraglutide was stopped, on follow up she had complete resolution of gall stones after stopping Liraglutide.[2]

The exact mechanism of gall stone formation after treatment with Liraglutide is not known. There are multiple theories. Decreased gall bladder functioning resulting in inadequate emptying of gall bladder, altered bile acid secretion and weight loss may be factors contributing to formation of gall stones. It was found that many times patients developing gall stones after initiating treatment of Liraglutide are subjected to surgery of cholecystectomy.[3] Our case report suggests that simple discontinuation of Liraglutide can bring reversal of gall stone and thus completely avoiding morbidity and mortality caused by surgical intervention.

Conclusion

GLP 1 receptor agonist such as Liraglutide is associated with increased gall stone formation. There is a possibility that Gall stones associated with Liraglutide treatment is a reversible disease after stopping treatment of Liraglutide. This fact itself can help avoid gall stone related surgery in patients developing new gall stone disease after treatment with Liraglutide.

References

1. Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78–107-amide) inhibits gastric and pancreatic functions in man. Digestive diseases and sciences. 1993 Apr;38(4):665-73.
2. Korkmaz H, Araz M, Alkan S, Akarsu E. Liraglutide-related cholelithiasis. Aging clinical and experimental research. 2015 Oct;27:751-3.
3. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, Le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. New England Journal of Medicine. 2015 Jul 2;373(1):11-22.
4. Faillie JL, Oriana HY, Yin H, Hillaire-Buys D, Barkun A, Azoulay L. Association of bile duct and gallbladder diseases with the use of incretin-based drugs in patients with type 2 diabetes mellitus. JAMA internal medicine. 2016 Oct 1;176(10):1474-81.

5. Nexøe- Larsen CC, Sørensen PH, Hausner H, Agersnap M, Baekdal M, Brønden A, Gustafsson LN, Sonne DP, Vedtofte L, Vilsbøll T, Knop FK. Effects of liraglutide on gallbladder emptying: A randomized, placebo- controlled trial in adults with overweight or obesity. Diabetes, Obesity and Metabolism. 2018 Nov;20(11):2557-64.
6. Nauck MA, MuusGhorbani ML, Kreiner E, Saevereid HA, Buse JB, LEADER Publication Committee on behalf of the LEADER Trial Investigators. Effects of liraglutide compared with placebo on events of acute gallbladder or biliary disease in patients with type 2 diabetes at high risk for cardiovascular events in the LEADER randomized trial. Diabetes care. 2019 Oct 1;42(10):1912-20.
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 research and clinical practice. 2020 Mar 1;161:108087.