OPEN

Liraglutide with Lifestyle Intervention in Adolescents with Overweight/Obesity, Nonalcoholic Fatty Liver Disease, and Type II Diabetes Mellitus

Taisa Kohut, MD, and Jennifer Panganiban, MD

Abstract: There is a strong interplay between nonalcoholic fatty liver disease (NAFLD), obesity, insulin resistance, and type II diabetes mellitus (T2DM). Liraglutide, a glucagon-like-peptide-1 (GLP-1) analogue, is FDA approved for T2DM in children 10 years or older and more recently approved for chronic weight management in children 12 years or older with obesity. GLP-1 analogues have also been shown to reduce liver enzymes and improve liver histology. We report two adolescent females with T2DM and biopsy proven nonalcoholic steatohepatitis (NASH) refractory to lifestyle intervention who were safety treated with liraglutide with associated weight loss and liver enzyme improvement. This is the first case series reporting use of liraglutide in pediatric NASH. Liraglutide should be considered in pediatric patients with overweight/obesity, NAFLD, and T2DM.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children with increased prevalence with obesity (1, 2). Prediabetes and type II diabetes mellitus (T2DM) have been associated with more severe histologic disease in NAFLD (3). Native glucagon-like peptide-1 (GLP-1) has potent blood glucose-lowering abilities, including inducing insulin secretion and reducing glucagon secretion, suppressing appetite, and delaying gastric emptying, that can induce weight loss and improved insulin sensitivity (4). Endogenous GLP-1 is degraded within minutes, whereas liraglutide is a long-acting human GLP-1 analogue shown to cause weight loss, lower systolic blood pressure, decrease hemoglobin A1C (HbA1c), and improve beta cell function (5, 6). Victoza (liraglutide dosed up to 1.8 mg daily) was FDA approved in 2019 for the treatment of T2DM in children 10 years or older (7–9), and Saxenda (liraglutide dosed up to 3.0 mg daily) was approved in 2020 for chronic weight management among pediatric patients aged 12 years or older with obesity (10). GLP-1 analogues have also been shown to reduce liver enzymes and improve liver histology in murine models of NASH (11).

Received February 21, 2021;accepted October 8, 2021.

From the Division of Gastroenterology, Hepatology, and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

The authors report no funding and conflicts of interest.

Correspondence: Taisa Kohut, MD, The Children's Hospital of Philadelphia 34th and Civic Center Boulevard, Wood Building, 3rd Floor, Philadelphia, PA 19104. E-mail: kohuttj@chop.edu.

JPGN Reports (2021) 2:4(e141)
ISSN: 2691-171X
DOI: 10.1097/PG9.0000000000000141

CASE REPORT NO. 1

The patient is a 17-year-old black female with severe obesity, hypertension, hypertriglyceridemia, low high density lipoprotein (HDL), and poorly controlled T2DM (hemoglobin A1c [Hb A1c] 9.1) on metformin and insulin, who presented to the NAFLD Program clinic in July 2018 for elevated liver enzymes since 2014 with a presenting alanine aminotransferase (ALT) of 213 and aspartate aminotransferase (AST) 195. Evaluation was negative for other chronic liver diseases. Right upper quadrant (RUQ) ultrasound demonstrated hepatic steatosis. Despite initially losing weight with lifestyle modification (i.e., increased aerobic physical activity and choosing foods low in fructose and carbohydrates), over 6 months of attempted lifestyle change, she had difficulty with maintenance and liver enzymes remained elevated. She underwent a core needle biopsy revealing steatosis, inflammation, ballooning, and sinusoidal fibrosis consistent with nonalcoholic steatohepatitis (NASH), with NAFLD activity score (NAS) of 5/8 and Fibrosis score 2 (Fig. 1). In collaboration with her endocrinologist, liraglutide was initiated at 0.6 mg daily and increased after 1 week to 1.2 mg daily and maintained at this dose. Six months after initiation of liraglutide in conjunction with lifestyle modification, the patient had a weight loss of 2.1 kg with improvement of BMI z score of 0.11. ALT and AST significantly improved to 71 and 40, respectively (Table 1). Weight regain and worsening of liver enzymes occurred in the setting of a prolonged period of noncompliance, however, after reestablishing care with the NAFLD Program clinic 2 years later and with improved liraglutide compliance, her weight, BMI z score, and liver enzymes again improved. She reported no side effects from use of liraglutide.

CASE REPORT NO. 2

The patient is a 17-year-old White female with overweight, low-grade supracellar astrocytoma status postchemotherapy, T2DM on metformin (Hb A1c 6.3), precocious puberty, and hypothyroidism who presented to the NAFLD Program Clinic in November 2019 for elevated liver enzymes since 2015 with a presenting ALT 87 and AST 65. Evaluation was negative for other chronic liver diseases. RUQ ultrasound demonstrated hepatic steatosis. Hepatic magnetic resonance elastography (MRE) showed an elevated fat fraction of 31.9% (<6% is normal) and normal liver stiffness. She underwent core needle biopsy revealing steatohepatitis (macrovesicular steatosis occupying 50–60%) with NAS 3/8 and Fibrosis score 0. Lifestyle intervention was recommended but over 6 months of attempted change she had difficulty with dietary management and liver enzymes remained elevated. In collaboration with her endocrinologist, liraglutide was initiated at 0.6 mg daily, increased after 2 weeks to 1.2 mg daily, and increased after 2 months to 1.8 mg daily. Eight months after initiation of liraglutide in conjunction with lifestyle modification, the patient had a total weight loss of 7.4 kg with improvement in BMI z score of 0.37. Liver enzymes stabilized and then significantly improved (Table 2). The patient maintained her weight with improved liver enzymes at over 1 year after starting liraglutide. Repeat hepatic

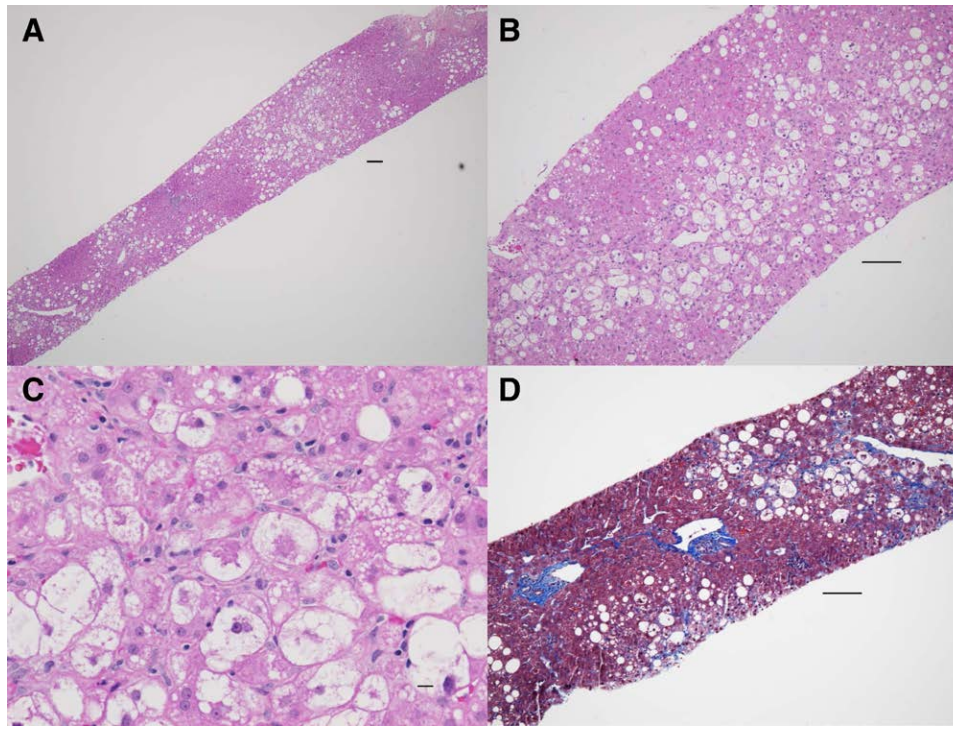

FIGURE 1. H&E and trichrome stains revealing steatosis, inflammation, ballooning, and sinusoidal fibrosis consistent with a diagnosis of NASH with NAS of 5/8 and Fibrosis score 2. The scale bar is 100 μm for 4× and 10× images; 10 μm for 40× image. (A) 4× H&E, (B) 10× H&E, (C) 40× H&E, and (D) 10× trichrome stain. NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis.

TABLE 1. Change from baseline for anthropometrics, liver enzymes, and hemoglobin A1C for patient no. 1 after starting liraglutide

	Baseline	S/p 2 months liraglutide	S/p 6 months liraglutide	Change from baseline	>24 months post liraglutide
Weight (kg)	95.2	95.8	93.1	–2.1	95.7
BMI (kg/m²)	35.3	35.6	34.4	–0.9	35.33
BMI %	98.8	98.8	98.4	–0.4	98.0
BMI z score	2.25	2.23	2.14	–0.11	2.05
ALT (U/L)	213	157	71	–142	69
AST (U/L)	195	98	40	–55	51
HbA1c	9.1	6.4	5.7	–3.4	10.0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index.

TABLE 2. Change from baseline for anthropometrics, liver enzymes, and hemoglobin A1C for Patient #2 after starting liraglutide

	Baseline	Liraglutide increased 1.2 mg daily	Liraglutide increased 1.8 mg daily	S/p 8 months Liraglutide	Change from Baseline	>12 months post Liraglutide
Weight (kg)	86.6	84.5	81.2	79.2	–7.4	78.2
BMI (kg/m²)	29.4	28.8	27.7	26.7	–2.7	26.22
BMI %	94.8	93.9	92.0	89.4	–5.4	86.44
BMI z score	1.62	1.54	1.39	1.25	–0.37	1.10
ALT (U/L)	87	87	94	51	–36	48
AST (U/L)	65	65	55	27	–38	25
HbA1c	6.3	6.3	6.1	5.5	–0.8	5.5

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index.

MRE at this time demonstrated fat fraction improved to 18.9%. She reported no side effects from use of liraglutide.

DISCUSSION

There is a strong association between NAFLD, obesity, insulin resistance, and T2DM. Increased adiposity and insulin resistance contribute to increased levels of free fatty acids and carbohydrates leading to hepatic lipid accumulation, cell injury, inflammation, and fibrosis. As such, therapies under investigation for NASH include the gut-derived incretin hormone, GLP-1, that induces weight loss and insulin sensitivity (12). Liraglutide (dosed up to 1.8 mg daily), a GLP-1 analogue, is licensed for glycemic control in adults with T2DM and gained FDA approved for T2DM in children greater than 10 years of age (7–9). Liraglutide (dosed up to 3.0 mg daily) has been FDA approved since 2014 for chronic weight management in adults with obesity and recently gained approval in 2020 for chronic weight management in adolescents with obesity (10, 13). Liraglutide (1.8 mg daily) was shown to lead to histologic resolution of NASH and attenuate fibrosis in a randomized, placebo-controlled clinical trial in overweight adults with NASH (12). A more recent clinical trial in adults with biopsy-proven NASH showed that another GLP-1 analogue, semaglutide, also led to histologic resolution of NASH (14). Liraglutide (1.2 mg daily) led to significantly reduce liver fat content and ALT level in a study of adults with uncontrolled diabetes, and this effect was mainly driven by body weight reduction (15).

Patient no. 1 is a black female with severe obesity, uncontrolled blood glucose despite metformin and insulin, and histological evidence of NASH with fibrosis, who was losing weight with lifestyle intervention but having difficulty maintaining weight loss, while patient no. 2 is a white female with overweight, relatively better blood glucose control on metformin alone, and histological evidence of NASH without fibrosis, who was struggling with lifestyle management and weight loss. Both patients had T2DM and persistently elevated liver enzymes nonresponsive to metformin, prompting the decision to initiate therapy with liraglutide. While different clinical circumstances surrounded the NASH diagnosis in each patient, they both tolerated liraglutide without side effects, lost weight, and liver enzymes improved. These two cases highlight the safe use of liraglutide in conjunction with lifestyle modification to promote weight loss and liver enzyme improvement in pediatric patients with overweight/obesity, NAFLD, and T2DM.

This is one of the reports of the application of liraglutide in pediatric NASH. Lifestyle modification using diet and exercise to promote weight loss remains the primary treatment for pediatric NAFLD. Liraglutide, used in conjunction with lifestyle changes, can help induce and maintain weight loss and improve insulin sensitivity; therefore, helping to improve NAFLD in pediatric patients with overweight/obesity and T2DM. Liraglutide may be an especially attractive alternative in patients with severe obesity when lifestyle modification is unsuccessful or only partially effective and more invasive and risky treatment options such as metabolic and bariatric surgery would like to be avoided or at least postponed. These two cases provide preliminary evidence that calls attention to consideration of liraglutide for pediatric patients with overweight/obesity, NAFLD, and T2DM. Further studies investigating the safety and efficacy of liraglutide for pediatric NAFLD are needed.

ACKNOWLEDGMENTS

The parents of both patients provided informed consent for publication of the case details. The authors are grateful to Dr. Benjamin Wilkins for providing histologic images.

REFERENCES

1. Skinner AC, Perrin EM, Moss LA, et al. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med.* 2015;373:1307–1317.
2. Schwimmer JB, Deutsch R, Kahen T, et al. Prevalence of fatty liver in children and adolescents. *Pediatrics.* 2006;118:1388–1393.
3. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. *JHEP Rep.* 2019;1:312–328.
4. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology.* 2007;132:2131–2157.
5. Henry RR, Buse JB, Sesti G, et al. Efficacy of antihyperglycemic therapies and the influence of baseline hemoglobin A(1C): a meta-analysis of the liraglutide development program. *Endocr Pract.* 2011;17:906–913.
6. Astrup A, Rössner S, Van Gaal L, et al; NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet.* 2009;374:1606–1616.
7. Klein DJ, Battelino T, Chatterjee DJ, et al; NN2211-1800 Study Group. Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *Diabetes Technol Ther.* 2014;16:679–687.
8. Petri KC, Jacobsen LV, Klein DJ. Comparable liraglutide pharmacokinetics in pediatric and adult populations with type 2 diabetes: a population pharmacokinetic analysis. *Clin Pharmacokinet.* 2015;54:663–670.
9. Tamborlane WV, Barrientos-Pérez M, Fainberg U, et al. Liraglutide in children and adolescents with type 2 diabetes. *N Engl J Med.* 2019;381:637–646.
10. Kelly AS, Auerbach P, Barrientos-Perez M, et al; NN8022-4180 Trial Investigators. A randomized, controlled trial of liraglutide for adolescents with obesity. *N Engl J Med.* 2020;382:2117–2128.
11. Trevaskis JL, Griffin PS, Wittmer C, et al. Glucagon-like peptide-1 receptor agonism improves metabolic, biochemical, and histopathological indices of nonalcoholic steatohepatitis in mice. *Am J Physiol Gastrointest Liver Physiol.* 2012;302:G762–G772.
12. Armstrong MJ, Gaunt P, Aithal GP, et al; LEAN trial team. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet.* 2016;387:679–690.
13. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med.* 2015;373:11–22.
14. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med.* 2021;384:1113–1124.
15. Petit J-M, Cercueil J-P, Loffroy R, et al. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes. The Lira-NAFLD study. *J Clin Endocrinol Metab.* 2017;102:407–415.