

Review

Side Effects Associated with Liraglutide Treatment for Obesity as Well as Diabetes

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Liraglutide is a glucagon-like peptide-1 receptor agonist used as a treatment for type 2 diabetes mellitus, which has been expanded for use at a higher dose in weight control. Therefore, it is necessary to consider adverse reactions of the drug at high doses as well as at lower doses after the indication has been expanded. Body mass index criteria for patients prescribed the drug in the real world tend to be applied less rigorously, which may increase the number of adverse reactions due to over-prescription. Liraglutide treatment was found effective and safe in some studies, while others have warned about its risks. Therefore, this review summarizes the current data available on side effects associated with liraglutide.

Key words: Liraglutide, Glucagon-like peptide-1 receptor, Drug side effect, Adverse drug reaction, Adverse drug event, Diabetes mellitus, Obesity

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INTRODUCTION

Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is primarily used to treat type 2 diabetes mellitus (T2DM), but it has also been used to control weight.¹ While a dose of 1.8 mg is usually administered to treat T2DM, a higher dose of 3.0 mg is prescribed for weight control. Hence, studying adverse reactions of the high dose as well as those of a lower dose of liraglutide is necessary to develop strategies for rational prescription.

A previous study reported that liraglutide had a greater weight loss effect at 52 weeks compared to other weight control drugs, but it also had more drug discontinuations due to adverse reactions among overweight or obese adults.² However, according to another study, liraglutide treatment is effective and safe for weight loss in obese individuals without diabetes.³

Unlike the subjects' high body mass index criteria, which were applied in clinical trials related to liraglutide, the body mass index criteria for patients prescribed the drug in the real world tend to be applied less rigorously, which may increase the number of adverse reactions due to over-prescription. Many clinical trials have been carried out that studied liraglutide followed by subsequent meta-analyses of their data. This review draws on those data and summarizes the latest information on side effects associated with liraglutide.

ACUTE PANCREATITIS

Side effects related to liraglutide use are summarized in Table 1. In patients with T2DM, treatment with incretin-based therapies (GLP-1 receptor agonists and dipeptidyl peptidase 4 [DPP-4] inhibitors) was associated with increased odds of hospitalization due

Table 1. Side effects summary

Variable	Liraglutide dose	Side effect	Other consideration
Serum lipase and amylase level	1.8 and 3.0 mg	Increase ^{4,5}	-
Acute pancreatitis	1.2–3.0 mg	The absolute risk is numerically higher. ^{5,6}	-
Gallbladder or biliary disease	0.6–3.0 mg	Increase ^{7,8}	-
Liver disease	0.9–1.8 mg	Improve liver histology and reduce aminotransferase levels. ^{9,10}	Elevation of liver enzymes and development of cholestasis and hepatitis have been reported during post-approval use. ¹ Case reports: elevations of liver enzymes ^{11,12} and development of autoimmune hepatitis ¹²
Kidney disease	1.2 and 1.8 mg	Reduce proteinuria, improve renal function, produce an anti-inflammatory effect and ameliorate lipid metabolism. ^{13,14}	Dehydration resulting from nausea, vomiting, and diarrhea, increased serum creatinine, and acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis have been reported during post-approval use. ¹ Case reports: elevation of serum creatinine and development of acute kidney injury ^{15,16}
Heart rate	1.2 and 1.8 mg	Increase ^{17,18}	
Gastrointestinal symptom	0.6–3.0 mg	Increase ^{3,13,19,23}	
Hypoglycemia	0.6–1.8 mg	No increase ^{19,22,24,25}	Co-administered antidiabetic drugs should be adjusted according to glucose monitoring results and hypoglycemic risk. ¹

to acute pancreatitis (AP), increased risk of AP, and increased levels of serum lipase and amylase.^{26,27} While one study found no consistent trend for risk of pancreatitis with DPP-4 inhibitors,²⁸ other meta-analyses observed a positive trend towards increased risk for pancreatitis with DPP-4 inhibitors.^{29,30}

With GLP-1 receptor agonists, liraglutide 1.8 mg-treated patients with T2DM showed a 28% increase in serum lipase levels and a 7% increase in serum amylase levels compared with the placebo group, in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial.⁴ During this trial, 0.4% of liraglutide-treated and 0.5% of placebo patients developed AP.

In the Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) trial, 3.0 mg of liraglutide versus placebo showed a 31% increase in serum lipase levels and a 7% increase in serum amylase levels.⁵ In addition, the absolute risk of AP in this evaluation was numerically higher in liraglutide (0.4%, 2.65 events/1,000 person-years of observation) versus placebo (< 0.1%, 0.44 events/1,000 person-years of observation).

A previous study suggested that there was not enough evidence to support an association between liraglutide (0.1–1.8 mg) and AP, when used in the treatment of T2DM.³¹ According to a claim-based study, there was no excess risk of AP associated with liraglutide relative to other antidiabetic drugs.³² However, a pooled analysis suggested a tendency to slightly increased risk of pancreatitis

with GLP-1 receptor agonists.²⁸ In addition, a review suggested that the incidences of reported AP and chronic pancreatitis were numerically greater with liraglutide (1.2 and 1.8 mg) than with comparators in patients with T2DM.⁶ GLP-1 receptor agonists are likely to cause subclinical pancreatic inflammation, leading to an elevation in enzyme levels, which may explain the increased lipase and amylase blood levels due to liraglutide.⁵

GALLBLADDER OR BILIARY DISEASE

In the LEADER trial, the risk of acute gallbladder or biliary disease was higher with liraglutide (1.8 mg) compared to placebo.⁷ A recent updated meta-analysis suggested a significant increase in the risk of cholelithiasis in patients treated with liraglutide (0.6–3.0 mg).⁸ GLP-1 suppresses the secretion of cholecystokinin after a meal in normal subjects and patients with type 1 diabetes mellitus (T1DM).³³ This suppression attenuates the gallbladder contractility, therefore, offering an explanation for the increased risk of adverse gallbladder events.

LIVER DISEASE

Individual patient-level data meta-analysis of the Liraglutide Effect and Action in Diabetes program suggested that treatment with 1.8 mg of liraglutide significantly reduced alanine aminotransferase

in patients with T2DM and abnormal baseline alanine aminotransferase and showed a trend towards improving hepatic steatosis.⁹ Studies suggest that in patients with non-alcoholic steatohepatitis, particularly those with diabetes, GLP-1 receptor agonists (including 0.9 and 1.8 mg of liraglutide) may improve liver histology and reduce aminotransferase levels from baseline.¹⁰

Animal studies suggest that liraglutide attenuates non-alcoholic fatty liver disease by (1) downregulating the expression of inflammatory signaling mediators in the tumor necrosis factor- α pathway,³⁴ (2) upregulating an antioxidant protein (Sestrin2)-mediated nuclear factor-erythroid 2-related factor 2/heme oxygenase-1 pathway,³⁵ (3) regulating the local renin-angiotensin system,³⁶ and (4) bringing about structural changes in gut microbiota associated with hepatic steatosis.³⁷

However, elevations of liver enzymes and development of cholestasis and hepatitis have been reported during post-approval use of liraglutide.¹ There have been case reports of elevations of liver enzymes^{11,12} and development of autoimmune hepatitis¹² in patients treated with liraglutide (1.2 mg).

KIDNEY DISEASE

Liraglutide (1.2 mg) appears to be effective in reducing proteinuria, improving renal function, producing an anti-inflammatory effect, and ameliorating lipid metabolism in patients with T2DM and early-stage nephropathy.¹³ In a Scandinavian cohort study, use of GLP-1 receptor agonists was associated with risk reduction in serious renal events compared with DPP-4 inhibitors.¹⁴

Liraglutide also enhances lipolysis and reduces lipid synthesis to

inhibit renal ectopic lipid deposition in diabetic nephropathy rats by promoting adenosine monophosphate-activated protein kinase phosphorylation.³⁸ In addition, GLP-1 receptor agonists are known to have a reno-protective effect by reducing blood sugar, blood pressure, and body weight, but are thought to have additional effects that preserve renal function by an unknown mechanism.³⁹

However, dehydration due to nausea, vomiting, and diarrhea, increased serum creatinine, and acute renal failure have been reported during post-approval use of liraglutide.¹ There have been case reports of elevation of serum creatinine and development of acute kidney injury in patients treated with liraglutide (1.8 mg¹⁵; dosage not reported¹⁶). One of these cases was thought to be caused by dehydration due to progressively worsening nausea, vomiting, and diarrhea for several weeks,¹⁵ and the patient even received hemodialysis treatment.

CANCER

Cancer-related side effects of liraglutide are summarized in Table 2. A recent study found no reported cases of pancreatic or thyroid cancer within a year in patients with T1DM taking insulin treated with liraglutide (0.6–1.8 mg) or placebo.¹⁹ Another study observed no increase in cancer with the use of GLP-1 receptor agonists (including 0.9–3.0 mg of liraglutide) in patients with T2DM.⁴⁰ In a previous study of patients with T2DM, use of liraglutide (0.1–1.8 mg) increased the risk of cancer by 35%, but was not statistically significant.³¹ However, the cancer risk became statistically significant when only high-quality methodological studies were considered.

Table 2. Cancer-related side effects summary

Variable	Liraglutide dose	Side effect	Other consideration
Cancer	0.1–1.8 mg	Increase when only methodological studies of high quality were considered. ³¹	-
Thyroid cancer	0.1–1.8 mg	No increase ³¹	Cases of medullary thyroid carcinoma have been reported during post-approval use. ¹
Pancreatic cancer	1.2 and 1.8 mg	No increase ^{32,41,42}	Pancreatic cancer was more commonly reported among patients with T2DM who took GLP-1 receptor agonists. ⁴³
Breast cancer	1.8 and 3.0 mg	No increase ⁴⁴	Significant increase in breast cancer risk was identified in patients using GLP-1 receptor agonists for 2–3 years. ⁴⁵
Prostate cancer	-	No reports to date relating liraglutide to an increased risk of prostate cancer	-

T2DM, type 2 diabetes mellitus; GLP-1, glucagon-like peptide-1.

Thyroid cancer

Medullary thyroid tumors have been reported more commonly in rodent toxicology studies using liraglutide compared to human trials, as in the latter, there is a controversy over the relationship between GLP-1 receptor agonists (including 0.6–1.8 mg of liraglutide) and thyroid cancer.⁴⁶

The results of one study indicated no increase in thyroid cancer with the use of liraglutide (0.1–1.8 mg) in patients with T2DM.³¹ Medullary thyroid carcinomas rarely express the GLP-1 receptor *in vitro*, while papillary thyroid cancers do not express the receptor.⁴⁷ Therefore, only GLP-1 receptor-positive medullary thyroid carcinomas can be candidates for *in vivo* GLP-1 receptor targeting. Cases of medullary thyroid carcinoma have been reported during post-approval use of liraglutide.¹

Pancreatic cancer

According to a claim-based study, there was no increased risk of pancreatic cancer with liraglutide compared to other antidiabetic drugs.³² However, pancreatic cancer has been reported more commonly among T2DM patients taking GLP-1 receptor agonists or DPP4 inhibitors compared to other therapies.⁴³ Recent studies have suggested that GLP-1 receptor agonists (including 1.2 and 1.8 mg of liraglutide) do not increase the risk for pancreatic cancer when compared to other treatments⁴¹ or placebo⁴² in T2DM patients.

In a human pancreatic cancer cell study, GLP-1 receptor activation had an antitumor effect on human pancreatic cancer via inhibition of the phosphoinositide 3-kinases/protein kinase B pathway.⁴⁸ As normal ductal epithelial cells, pancreatic intraepithelial neoplasia 3, or ductal pancreatic carcinomas do not express the GLP-1 receptor, it seems that the receptors are not involved in the neoplastic transformation in the pancreas.⁴⁷

Breast cancer

Liraglutide may have a role in the inhibition of proliferation as well as promotion of apoptosis in human breast cancer cells (MCF-7) by inhibiting microRNA-27a and subsequently increasing the expression of adenosine monophosphate-activated protein kinase catalytic subunit $\alpha 2$ protein.⁴⁹ However, a prospective cohort study suggested that there is no association between liraglu-

tide (1.8 and 3.0 mg) use and female breast cancer in a real-world setting.⁴⁴ According to a similar study, as compared with DPP-4 inhibitors, the risk of breast cancer increased in patients treated with GLP-1 receptor agonists for 2–3 years, although the use of GLP-1 receptor agonists did not increase the risk of breast cancer overall.⁴⁵ GLP-1 receptors have been located on human breast tissue, and the interaction between GLP-1 receptor agonists and the fibroblast growth factor 7/fibroblast growth factor receptor 2 axis could stimulate proliferation of a subset of early breast cancers.⁴⁵

Prostate cancer

Liraglutide attenuates prostate cancer growth through regulation of the p38 pathway by binding with the GLP-1 receptor *in vitro*.⁵⁰ Forced expression of GLP-1 receptor attenuates prostate cancer cell proliferation by inhibiting cell cycle progression *in vitro* and *in vivo*.⁵¹ A recent study also showed that an anticancer drug and liraglutide decreased the viability of prostate cancer cells (LNCaP) synergistically.⁵² To date, there are no reports relating liraglutide to an increased risk of prostate cancer.

HEART RATE

Liraglutide (1.2 and 1.8 mg) is associated with increased heart rate for patients with T2DM.^{17,18} This increase may be a mechanism of compensation for the hypotensive effect of GLP-1 receptor agonists. It is more likely that the increase in heart rate results from a direct GLP-1 receptor effect on myocytes in the human heart sinoatrial node and/or the sympathetic nervous system stimulation related to inhibition of the autonomic nervous system.⁵³

GASTROINTESTINAL SYMPTOMS

According to a recent study, liraglutide (0.6–1.8 mg) as an adjunct to insulin in patients with T1DM significantly increased gastrointestinal adverse reactions (nausea and vomiting).¹⁹ Earlier reports found that the most commonly observed adverse reactions associated with liraglutide (0.6–1.9 mg) were gastrointestinal symptoms including nausea, vomiting, dyspepsia, constipation, and diarrhea compared to other therapies or placebo in patients with T2DM.^{13,20-23} A dose of 3.0 mg of liraglutide for the treatment

of obesity in non-diabetic individuals led to higher incidence of nausea compared to placebo.³

HYPOGLYCEMIA

Various studies have evaluated the use of liraglutide in both T1DM and T2DM patients. The results of one such study suggested that there were no differences in severe hypoglycemia between liraglutide (0.6–1.8 mg) and placebo or any other comparator as adjunct to insulin in patients with T1DM.¹⁹ Another study of Japanese adults with uncontrolled T2DM, who were prescribed 0.9 mg of liraglutide or DPP-4 inhibitors, found that the treatments were not statistically differentiable with respect to risk of hypoglycemia.²⁴

The use of liraglutide (0.6–1.8 mg) in T2DM combined with metformin also did not increase the risk of hypoglycemia.^{22,25} No excess of hypoglycemia was even observed between GLP-1 receptor agonists and placebo in patients with T2DM with or without established cardiovascular disease.⁴⁸ However, it is recommended that co-administered antidiabetic drugs such as sulfonylurea or insulin be adjusted according to glucose monitoring results and hy-

poglycemic risk.¹

CONCLUSION

Fig. 1 shows a graphical summary of adverse reactions associated with liraglutide. Liraglutide is associated with an increase in serum lipase and amylase levels. The absolute risk of AP compared to placebo was numerically higher for liraglutide. Liraglutide may also lead to an increased risk of acute gallbladder or biliary disease. Although it does not seem to play an active role in the development of cancer, liraglutide may be associated with an increased risk of thyroid, pancreatic, and early breast cancer considering its post-approval use and the location of GLP-1 receptors.

The most commonly observed adverse reactions associated with liraglutide were gastrointestinal symptoms, and it also may increase the heart rate of T2DM patients. Although liraglutide does not seem to increase the risk of hypoglycemia, it is essential to adjust the doses of co-administered antidiabetic drugs according to glucose monitoring results and the hypoglycemic risk of patients.

There have been several instances of withdrawal or discontinua-

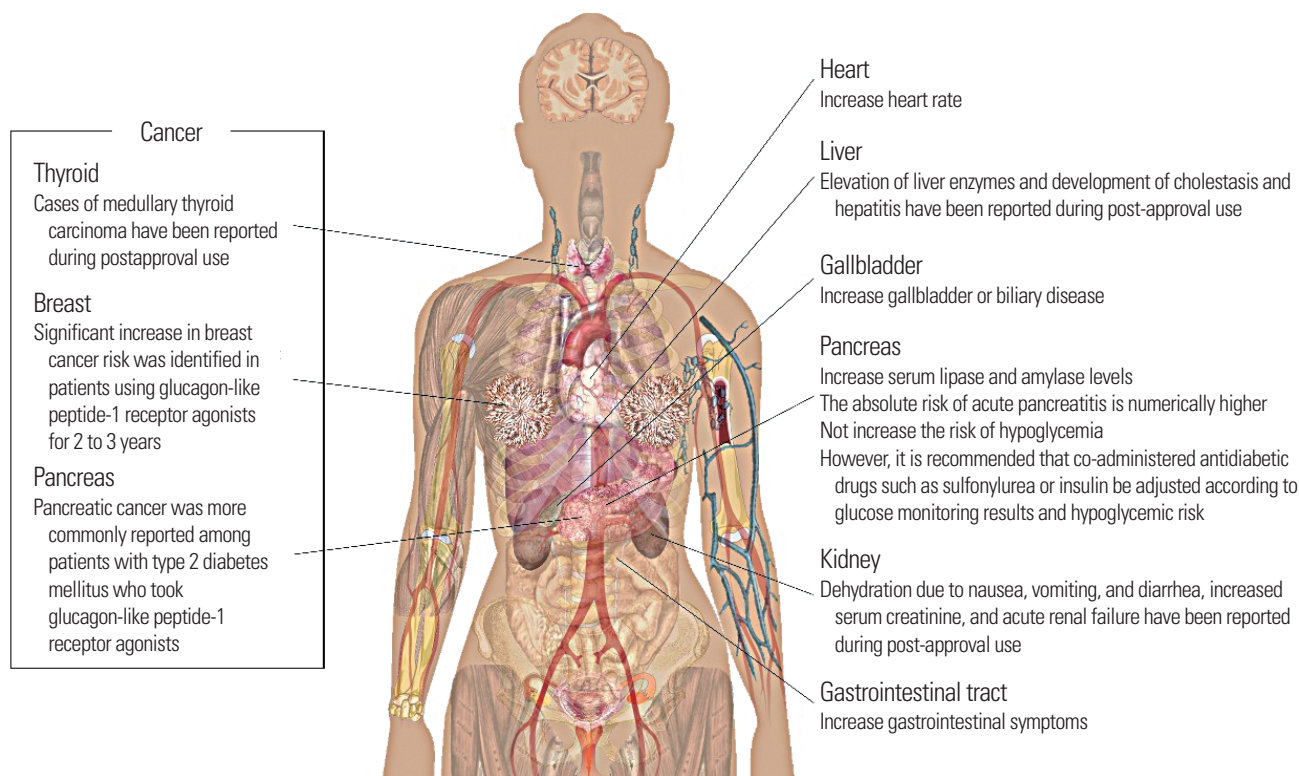


Figure 1. Graphical summary of adverse reactions associated with liraglutide.

tion of liraglutide prescription due to adverse reactions. Therefore, it is important to exercise precaution and refrain from over-prescribing the drug considering only its efficacy, and to administer liraglutide in accurate doses according to the patient's health condition. Monitoring adverse reactions in patients is equally necessary to minimize any long-term damage to patient health.

CONFLICTS OF INTEREST

Young-Gyun Seo is the Editorial Board member of the *Journal of Obesity & Metabolic Syndrome*. However, he is not involved in the peer reviewer selection, evaluation, or decision process of this article. Otherwise, no other potential conflicts of interest relevant to this article were reported.

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