# The Expanding Role of GLP-1: From Diabetes Management to Cancer Treatment

Areeba Fareed and Aariz Hussain

Karachi Medical and Dental College, Karachi, Karachi City, Sindh, Pakistan.

Clinical Medicine Insights: Endocrinology and Diabetes
Volume 16: 1–2

DOI: 10.1177/11795514231213566

Sage

**RECEIVED:** June 28, 2023. **ACCEPTED:** October 17, 2023.

**TYPE:** Letter to the Editor

**FUNDING:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**COMPETING INTERESTS:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**CORRESPONDING AUTHOR:** Areeba Fareed, Karachi Medical and Dental College, Block M North Nazimabad Town, Karachi, Karachi City, Sindh 74700, Pakistan. Email: areebafareed201@gmail.com

Dear Editor,

Glucagon-like peptide 1 (GLP-1) is a gastrointestinal peptide released in response to food consumption. The main effects of GLP1 are mediated by GLP1 receptors in the pancreas, intestine, stomach, and the sensory and central nervous systems, heart, pituitary, lung, and kidney. In the β cell of the pancreas, GLP1 augments glucose-induced membrane depolarization and therefore serves a significant function in maintaining glucose balance by enhancing insulin secretion in response to glucose and suppressing glucagon release. Additionally, GLP-1 is suggested to exert an influence on satiety. Supporting this proposition, the administration of GLP-1 peripherally has been observed to restrain food consumption.[1] For this reason, GLP-1 is also used to control obesity by increasing satiety and decreasing hunger stimuli to help avoid overeating.[2] Furthermore, GLP-1 has shown great results for Diabetes Mellitus Type 2 and Obesity in a recent clinical study. The study revealed the GLP-1 receptor agonist reveals promising outcomes in terms of glycemic control and weight reduction among individuals diagnosed with type 2 diabetes.[3]

In recent years, our understanding of the underlying cellular and molecular processes contributing to the development of hepatocellular carcinoma (HCC) in Non-Alcoholic Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver Disease (NAFLD) has expanded. This has brought attention to GLP-1 receptor agonists (GLP-1 RAs), initially designed for diabetes management, as potential treatment options for HCC. Animal studies have indicated that GLP-1 RAs may regulate key molecular pathways involved in the initiation and progression of HCC, such as inflammation, tumor cell growth, and oxidative stress. However, further research is necessary to evaluate the potential benefits and risks of using GLP-1 RAs in HCC patients. This includes studying their combined administration with chemotherapy, assessing gastrointestinal side effects in a high-risk population, and managing weight loss in individuals with poor nutritional status and cancer-related cachexia.[4]

However, concerns have arisen regarding the safety of GLP-1 analogs and cancer risk among patients receiving these medications. The leading cause for uncertainty stems from animal studies demonstrating that treatment with liraglutide, a GLP-1 analog, activated GLP-1 receptors in C cells, thereby increasing the susceptibility to medullary thyroid carcinoma (MTC).[5] Consequently, the use of these drugs is contraindicated in individuals with a personal or family history of MTC or multiple endocrine neoplasia type 2. Moreover, evidence indicates that the GLP-1 receptor is expressed in neoplastic lesions of thyroid C cells in humans.[6]

GLP-1 receptor agonists (GLP-1RAs) do not exhibit an elevated risk of breast cancer or benign neoplasms, making them suitable as an adjunct to diet and exercise for individuals with type 2 diabetes, as well as those without diabetes but who are overweight. Given that excessive weight and type 2 diabetes are known risk factors for breast cancer,[7] it becomes imperative to conduct further research to determine whether pharmacological intervention with GLP-1RAs in high-risk populations could benefit primary and secondary breast cancer prevention.[8]

One study detected GLP-1R expression in samples of human prostate cancer tissue and cell lines. It demonstrated that Ex-4, a GLP-1R agonist, could attenuate prostate cancer growth by inhibiting ERK-MAPK activation.[9] According to other experimental findings, it was observed that GLP-1 receptor analogs: exenatide and liraglutide effectively suppressed the proliferation of LNCap cell lines and induced apoptosis in these cells. Exenatide exhibited a dose-dependent increase in the Bax/Bcl-2 ratio within the range of 1 to 100 nmol/L, while liraglutide only demonstrated an increase in the Bax/Bcl-2 ratio at a concentration of 10 nmol/L. Furthermore, this research revealed that GLP-1 analogs activate the p38 signaling pathway in LNCap cells without affecting the ERK1/2 or AKT pathways. Additionally, the presence of classical GLP-1 receptors was detected in LNCap cells.[10] LNCap cells can be further sensitized by physodic acid.[11]

The data presented in a study for pancreatic cancer and GLP-1 demonstrate for the first time that liraglutide alone exhibits notable anti-tumor effects on gemcitabine-resistant human pancreatic cancer cells. Furthermore, it enhances the therapeutic efficacy of gemcitabine by modulating the NF-κB signaling pathway and downstream ABCG2.[12] These findings suggest that GLP-1 receptor agonists hold promise as safe and beneficial treatments for patients with pancreatic cancer and diabetes, particularly for those with gemcitabine resistance.[13]

In conclusion, glucagon-like peptide 1 (GLP-1) and its receptor agonists have shown significant potential in various areas of medical research. GLP-1 plays a crucial role in glucose balance by enhancing insulin secretion and suppressing glucagon release, making it beneficial for managing type 2 diabetes. It also has implications for obesity treatment by increasing

satiety and reducing hunger. Additionally, GLP-1 receptor agonists have been studied for their potential in hepatocellular carcinoma, breast cancer, prostate cancer, and pancreatic cancer. While further research is needed to evaluate the benefits and risks, GLP-1 receptor agonists show promise in regulating key molecular pathways involved in these cancers. However, safety concerns exist regarding their association with medullary thyroid carcinoma. Overall, GLP-1 and its receptor agonists present exciting avenues for medical intervention but require careful evaluation and monitoring in specific contexts.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Author contributions*

Areeba Fareed: Conceptualization; Writing – review & editing.
Aariz Hussain: Data curation; Writing – original draft.

### *Acknowledgements*

None

### *Availability of data and materials*

No new data was generated.

## ORCID iDs

Areeba Fareed https://orcid.org/0000-0001-5906-9852
Aariz Hussain https://orcid.org/0000-0003-0555-5032

## REFERENCES

1. D'Alessio D. Is GLP-1 a hormone: whether and when? *J Diabetes Invest*. 2016;7 Suppl 1:50-55.
2. Grill HJ. A role for GLP-1 in treating hyperphagia and obesity. *Endocrinology*. 2020;161(8):bqaa093.
3. Nauck MA, Quast DR, Meier JJ. Another milestone in the evolution of GLP-1-based diabetes therapies. *Nat Med*. 2021;27:952-953.
4. Arvanitakis K, Koufakis T, Kotsa K, Germanidis G. How far beyond diabetes can the benefits of glucagon-like peptide-1 receptor agonists go? A review of the evidence on their effects on hepatocellular carcinoma. *Cancers*. 2022;14:4651.
5. Knudsen LB, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology*. 2010;151:1473-1486.
6. Gier B, Butler PC, Lai CK, et al. Glucagon like peptide-1 receptor expression in the human thyroid gland. *J Clin Endocrinol Metab*. 2012;97:121-131.
7. Boyle P, Boniol M, Koechlin A, et al. Diabetes and breast cancer risk: a meta-analysis. *Br J Cancer*. 2012;107:1608-1617.
8. Piccoli GF, Mesquita LA, Stein C, et al. Do GLP-1 receptor agonists increase the risk of breast cancer? A systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2021;106:912-921.
9. Nomiyama T, Kawanami T, Irie S, et al. Exendin-4, a GLP-1 receptor agonist, attenuates prostate cancer growth. *Diabetes*. 2014;63:3891-3905.
10. Li XN, Bu HM, Ma XH, et al. Glucagon-like peptide-1 analogues inhibit proliferation and increase apoptosis of human prostate cancer cells in vitro. *Exp Clin Endocrinol Diabetes*. 2017;125:91-97.
11. Cardile V, Graziano ACE, Avola R, Madrid A, Russo A. Physodic acid sensitizes LNCaP prostate cancer cells to TRAIL-induced apoptosis. *Toxicol In Vitro*. 2022;84(21):105432.
12. Beutel AK, Halbrook CJ. Barriers and opportunities for gemcitabine in pancreatic cancer therapy. *Am J Physiol Cell Physiol*. 2023;324:C540-C552.
13. Zhao HJ, Jiang X, Hu LJ, et al. Activation of GLP-1 receptor enhances the chemosensitivity of pancreatic cancer cells. *J Mol Endocrinol*. 2020;64:103-113.