Implications of GLP-1 Receptor Antagonists on Diabetic Foot Ulcerations

These are potential mediators in limb salvage efforts.

BY ZANIB CHEEMA, DPM, MS AND STEPHANIE WU, DPM, MSC

Diabetes is the eighth leading cause of death in the United States1. It has led to an estimated 327 billion dollars in medical costs in the U.S. alone,[1] with 37.3 million people being diagnosed with diabetes in 2019. It was estimated that roughly 96 million individuals older than eighteen were diagnosed with pre-diabetes,[2] raising concern for its prevalence in a younger demographic. People with diabetes are at risk for the development of foot infections, with a 7% yearly risk[3] and 25% lifetime risk.[2,4] The annual incidence of diabetic foot ulcers (DFUs) worldwide is between 9.1 and 26.1 million.[5] With such a large group of individuals being affected by the condition, it is imperative to take measures to prevent formation of DFUs, and providing effective care is necessary to minimize chances of infection and associated limb loss.

Standard of care for DFUs consists of ensuring adequate vascularity to the wound area, bioburden control, moist wound healing, debridement of the wound; along with offloading for pressure mitigation.[6] What hasn't been assessed is the use of therapeutic drugs, specifically, glucagon like peptide-1 receptor agonist (GLP-1 RA) medications in the treatment of DFUs, and management of diabetic peripheral neuropathy (DPN), a condition that in most cases is a precursor to the development of DFUs.

The American Diabetes Association (ADA) created practice guidelines in the pharmacological approach to the treatment of diabetes.[7] These recommendations when developing a treatment plan include taking into consideration patient-specific factors such as comorbid conditions. For most people with diabetes, first line pharmacologic treatment has been the use of metformin and promoting lifestyle changes. As an additive measure GLP-1, or sodium glucose transporter-2 (SGLT-2) inhibitors, can be administered with or without metformin. These medications have shown to be efficacious as appropriate initial therapy for patients with type 2 diabetes mellitus with comorbid atherosclerotic cardiovascular disease[7]

GLP-1 Receptors

GLP-1 receptors were first discovered in 1923 by Charles Kimball and John Murlin.[8] In 1959, Roger Unger developed an antibody that could be used to detect glucagon in tissue samples using a radioimmunoassay.[8] Unger further discovered that L cells in the gastrointestinal (GI) tract secreted GLP-1.[8] In the 1980s, Joel Habner[8] discovered glucagon-related peptides that are now known as glucagon-like peptides 1 and 2. Glucagon-like peptide-1 is composed of a 30-31 long amino acid sequence. The peptide hormone activates a seven-transmembrane G protein-coupled receptor, or GLP-1R. These receptors are expressed in pancreatic beta islet cells.[8] The receptor can then be coupled to Gs or Gq proteins in beta cells of the pancreas and activate cyclic AMP, thus increasing intracellular calcium levels. This results in the up-regulation and activation of protein kinase A, exchange protein activated by cAMP-2 (Epac-2), phospholipase C, ERK 1 and 2 signaling, and the phosphoinositide 3 kinase (PI3K) transduction pathways.[8] This pathway and its regulatory proteins are essential in cell cycle regulation,[9] and in wound healing promote recruitment of growth factors in the extracellular matrix.

The Hopton Study

In a retrospective observational study[10] from Hopton, et al., patients from the Veteran's Affairs health centers were identified who were on a pre-existing basal bolus insulin regimen and were prescribed a GLP-1 receptor agonist. The medications prescribed included: liraglutide, exenatide, albiglutide, and dulaglutide. A majority of the population consisted of males (94.2%) with a mean age of 63 years old, and a mean baseline A1c of 9%. Patients were assessed at baseline, 3 months, 6 months, and 1 year following the implementation of GLP-1 agonist therapy in addition to their existing insulin regimen.

The results showed a 0.5%, 0.7%, and 0.7% reduction in A1c from 9%

Continued on page 90

GLP-1 (from page 89)

in the intent-to-treat group at the 3-, 6-, and 12-month mark, respectively. In patients who had an A1c of < 8% at the time of GLP-1 RA initiation, the A1c levels were unchanged or even increased over time. Mean weight reductions in the intent-to treat group were 1.2kg, 2.3 kg, and 2.9kg from a mean baseline of 120.6kg at the 3-, 6-, and 12-month marks.

The authors concluded that initiating GLP-1 RAs in patients on a pre-existing basal bolus insulin regimen can result in a reduction of A1c levels in patients with an A1c greater than or equal to 9% and promote weight loss. The results of this study suggest that patients with diabetes may benefit from the administration of GLP-1 receptor agonists in regulating A1c levels and preventing the formation of excessive advanced glycosylation end products that could result in damage to peripheral nerves, and subsequently cause diabetic foot ulcer formation.

The Wolak and Nagae Studies

Wolak and colleagues assessed the efficacy of the GLP-1 RA exendin-4, aka exenatide, on wound healing in human skin in vitro, based on normo- and hyperglycemic conditions. In chronic, hard-to-heal wounds, there is an excess of matrix metalloproteinase-9 (MMP-9) and insufficient production of tissue inhibitor metalloproteinase concentrations (TIMP). MMP's in excess can degrade fibrous proteins of the extracellular matrix (ECM), while TIMPs suppress the activity of MMPs11. An imbalance of the two regulatory proteins can result in impaired or delayed wound healing.[8] Hyperglycemia places cells at a higher risk for apoptosis due to improper tissue repair.

Wolak, et al. found in their study that exendin-4 can be used to assist with up-regulation of the ECM, collagen, and glycosaminoglycans, and promote growth factors in a normoglycemic state. Unfortunately, these findings were not applicable to the simulated hyperglycemic environment in vitro. The authors suggest that this could have been due to mitochondrial dysfunction, overproduction of reactive oxygen species, or abnormal expression of chaperone proteins in the presence of increased glucose.

In another study[12] from Nagae, et al., liraglutide was assessed to see if there was facilitated healing by activation of the PI3K/Akt pathway in keratinocytes. The authors identified HaCaT cells from diabetic mice using real time quantitative reverse transcriptase PCR (qRT-PCR) and immunoblotting assays to assess the effect on wound closure. The results of the study demonstrated that keratinocytes expressed liraglutide at the mRNA and protein levels. Exogenous liraglutide promoted keratinocyte migration in vitro and facilitated wound closure in these mice. The up-regulatory capacity was mediated through the PI3K/Akt pathways. The authors thus concluded that administration of the GLP-1 mimetic facilitates wound closure. Since GLP-1 agonists are already recommended for treatment in patients with diabetes, this patient population may be able to supplement standard of care practices with this drug class to further promote wound healing.

Aside from the potential benefits in assisting wound closure, GLP-1 analogs have displayed a neuroprotective effect in research studies.

The Ponirakis Study

Aside from the potential benefits in assisting wound closure, GLP-1 analogs have displayed a neuroprotective effect in research studies.[13] GLP-1 is secreted by neurons in the nucleus of the solitary tract of the brainstem.[8] Since the peptide hormone is produced in the brainstem, it can cross the blood brain barrier, as well as its analogs. The receptors in the brain are expressed in regions of the hypothalamus including the paraventricular nucleus, the dorsal medial nucleus of the hypothalamus, and the arcuate nucleus.[8] In a randomized controlled trial, Ponirakis, et al.[14] assessed the use of exenatide and pioglitazone combination therapy versus basal bolus insulin on diabetic peripheral neuropathy in patients with poorly controlled type 2 diabetes mellitus. Outcome measures included results from the DN4 questionnaire, vibration perception threshold, sudomotor function, and the effects of these treatments on diabetic retinopathy. Diabetic peripheral neuropathy was assessed using corneal confocal microscopy (CCM).

The results of the study showed that treatment with the combination therapy or basal bolus insulin demonstrated improvements in corneal nerve regeneration, but there was no change in neuropathic symptoms or sudomotor functions at the one-year follow-up. However, there were improvements in the A1c levels. In the exenatide and pioglitazone treatment group, there was a reduction of 3.8% in the A1c level; and in the basal bolus insulin group, there was a reduction of 2.7%.

The authors acknowledged that a limitation in the findings of this study was that the participants were not blinded to the therapy that they were receiving. The authors did mention that the investigator was blinded to the intervention administered in the two treatment groups. The results of this study suggest that although there were no improvements in neuropathic symptoms, GLP-1 agonist combination therapy may have beneficial effects on reducing blood A1c levels.

The Qi and Pandey Studies

Although the results of the previously mentioned study didn't demonstrate neuroprotective effects, Qi, et al.[15] found a different result with the use of liraglutide. Neuroblastoma SH-SY5Y cells administered with methylglyoxal, a byproduct of glucose metabolism, can be used to mimic diabetic neuropathy. Qi, et al.[15] showed that use of liraglutide in SH-SY5Y cells decreased superoxide dismutase (SOD) and reactive oxygen species

Continued on page 92

GLP-1 (from page 90)

(ROS), suggesting that liraglutide reduced oxidative stress in methylglyoxal induced SH-SY5H cells.

Pandey, et al.[16] further analyzed these cells with the use of exenatide and discovered that exendin-4 elevated the level of protein kinase B (Akt) and B-cell lymphoma 2 (Bcl-2); this suppressed the level of Bax and lowered the level of cellular oxidative stress. Since decreased levels of oxidative stress and formation of ROS can prevent cellular apoptosis, the use of GLP-1 agonists may prove to be beneficial in preventing or slowing down neurodegeneration in the treatment of diabetic peripheral neuropathy, in addition to its therapeutic effects in regulating hyperglycemia.

The STARDUST Clinical Trial

Liraglutide was administered in patients diagnosed with type 2 diabetes mellitus with concomitant peripheral arterial disease in the STARDUST (effects of the GLP-1 Receptor Agonist Liraglutide on Lower Limb Perfusion in People with Type 2 Diabetes and Peripheral Artery Disease) open-label randomized clinical trial.[17] A total of 55 individuals were recruited in the study. The mean age of the patients was 67 years old, and 43 of the 55 patients were male (78%). The patients were randomly assigned to the treatment and control groups. Of the 55 patients, 27 were assigned to the liraglutide treatment, and 28 of the patients were assigned to the control group. The mean A1c of the patients was 6.9% ranging anywhere from 6.5%-7.8%. Transcutaneous oxygen pressure (TcPO2) measurements were taken with the mean TcPO2 being 40.3 mmHg.

The authors assessed if liraglutide would improve TcPO2 levels. The results of the study demonstrated that there was an increase of 10% in TcPO2 measures in 24 participants receiving liraglutide treatment (89%) and in 13 participants (46%) in the control group. This increase in peripheral perfusion was noted after six-months' duration of treatment. The authors suggest that based on the findings of this study, liraglutide can be used to prevent the clinical progression of peripheral arterial disease in patients with type 2 diabetes mellitus. Increasing oxygen levels for this patient population can prevent the formation of reactive oxygen species that prevent wound healing, and in patients who already have DFU formation can potentially promote angiogenesis and prevent lower extremity amputation.

The LEADER Study

The therapeutic benefits of liraglutide were further assessed in the LEADER (liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results) study. The results showed that patients with diabetes managed with liraglutide had a 35% lower risk of diabetic foot ulceration-related lower extremity amputations when compared with use of a placebo.[17,18] Werkman, et al.[19] found a similar outcome when comparing the risk of lower extremity amputation rates with the use of SGLT-2 inhibitors or GLP1-RAs versus sulfonylureas. The results of the study found that GLP1-RAs were associated with a lower risk of lower extremity amputation when compared to use of sulfonylureas. The authors also suggested that increasing the duration of use of GLP1-RAs could further lower the amputation risk.

Since decreased levels of oxidative stress and formation of ROS can prevent cellular apoptosis, the use of GLP-1 agonists may prove to be beneficial in preventing or slowing down neurodegeneration in the treatment of diabetic peripheral neuropathy, in addition to its therapeutic effects in regulating hyperglycemia.

ASA and SPAQI Recommendations

People with diabetes are at a high risk for the development of DFUs and foot infections.[20] In those who may need to have urgent or emergent surgery, it is imperative to understand risk factors associated with GLP1-RA use that could influence pre- and post-operative outcomes. Blood glucose and A1c levels are commonly utilized to assess perioperative risk management and patient outcomes. The American Society of Anesthesiologists (ASA) have created guidelines for the management of GLP-1 agonists in the perioperative period. The recommendations state that GLP-1 receptor agonists should be stopped one day prior to surgery in patients who are on daily dosing, and for patients who are on weekly dosing should discontinue its use one week prior to surgery.[21]

The society for perioperative assessment and quality improvement recommends discontinuing GLP-1 RAs on the day of surgery.[22] If a patient does not stop taking their medication, then a decision should be made on performing a guided gastric ultrasound to assess the volume of gastric contents.[23] This could possibly delay surgery. In the event of an urgent case, anesthesiologists should proceed with full stomach precautions.[23] Per the ASA guidelines, if a GLP-1 agonist is held pre-operatively for an extended period of time, consulting an endocrinologist would be beneficial to bridge these patients and prevent hyperglycemia.[24] If bridging does not occur, the patient may also be at risk for developing adverse cardiovascular events.[23]

Delayed Gastric Emptying

In a case study from Fujino, et al.,[24] the authors discovered that a 31-year-old female diabetic patient, with multiple comorbidities and on semaglutide, had increased gastric contents once she presented for her esophagogastroduodenoscopy

Continued on page 93

GLP-1 (from page 92)

(EGD) procedure. The authors suggested that the patient adhere to a liquid diet for 36 hours prior to her repeat EGD that was scheduled for one month after her initial procedure. The patient was also instructed to withhold semaglutide for 7 days prior to the procedure. The results of the second EGD demonstrated that there were no gastric food contents present. Based on these findings the authors suggested that the delayed gastric emptying from semaglutide can result in retention of solid gastric contents and could present as a potential risk for pulmonary aspiration during operative procedures.

The recommendation was that patients should consider stopping semaglutide prior to surgery, adhere to a liquid diet prior to EGDs, or administer prokinetic drugs such as, metoclopramide or erythromycin, to promote gastric emptying. The findings of this study were similar to that of a retrospective study performed by Silveira et, al.[25] Silveira and colleagues noted in 404 patients undergoing elective EGD procedures that there was an increase in residual gastric contents in patients taking semaglutide for diabetic management or weight loss when compared to the control subjects. Therefore, it may be pertinent to consider temporary cessation or bridging therapies for patients on semaglutide, prior to surgical intervention to prevent delayed gastric emptying.

Conclusion

GLP-1 receptor agonists are widely used to regulate hyperglycemic effects in patients with type 2 diabetes. Due to its positive effects on decreasing A1c levels, it may potentially prevent the formation of diabetic peripheral neuropathy or slow its progression. GLP-1 receptor agonists' effects on weight loss may further aid in regulating A1c levels. There are also studies demonstrating that these drugs may have a neuroprotective effect that can potentially prevent damage in nerves and promote cellular regeneration. This may prove to be beneficial in preventing the formation of diabetic foot ulcers and, in turn, decrease the incidence of diabetic foot infections and lower extremity amputations. Additional research to further assess the therapeutic effects of GLP-1 receptor agonists in wound healing and as a potential mediator in limb salvage efforts is warranted. **PM**

References

[1] National Diabetes Statistics Report | Diabetes | CDC. (2022, June 29). https://www.cdc.gov/diabetes/data/statistics-report/index.html

[2] Mutluoglu M, Uzun G, Turhan V, Gorenek L, Ay H, Lipsky BA. How reliable are cultures of specimens from superficial swabs compared with those of deep tissue in patients with diabetic foot ulcers? J Diabetes Complications. 2012 May-Jun;26(3):225-9. [PubMed].

[3] Pitocco, D., Spanu, T., Di Leo, M., Vitiello, R., Rizzi, A., Tartaglione, L., Fiori, B., Caputo, S., Tinelli, G., Zaccardi, F., Flex, A., Galli, M., Pontecorvi, A., & Sanguinetti, M. (2019). Diabetic foot infections: a comprehensive overview. European review for medical and pharmacological sciences, 23(2 Suppl), 26–37. https://doi.org/10.26355/eurrev_201904_17471

[4] Tchanque-Fossuo, C. N., Ho, D., Dahle, S. E., Koo, E., Li, C. S., Isseroff, R. R., & Jagdeo, J. (2016). A systematic review of low-level light therapy for treatment of diabetic foot ulcer. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society, 24(2), 418–426. https://doi.org/10.1111/wrr.12399

[5] Oliver TI, Mutluoglu M. Diabetic Foot Ulcer. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from:https://www.ncbi.nlm.nih.gov/books/NBK537328/

[6] Dreifke, M. B., Jayasuriya, A. A., & Jayasuriya, A. C. (2015). Current wound healing procedures and potential care. Materials science & engineering. C, Materials for biological applications, 48, 651–662. https://doi.org/10.1016/j.msec.2014.12.068

[7] American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2022. Diabetes Care 1 January 2022; 45 (Supplement_1): S125–S143. https://doi.org/10.2337/dc22-S009

[8] Mehdi, S. F., Pusapati, S., Anwar, M. S., Lohana, D., Kumar, P., Nandula, S. A., Nawaz, F. K., Tracey, K., Yang, H., LeRoith, D., Brownstein, M. J., & Roth, J. (2023). Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent. Frontiers in immunology, 14, 1148209. https://doi.org/10.3389/fimmu.2023.1148209

[9] Kong, T., Liu, M., Ji, B., Bai, B., Cheng, B., & Wang, C. (2019). Role of the Extracellular Signal-Regulated Kinase 1/2 Signaling Pathway in Ischemia-Reperfusion Injury. Frontiers in physiology, 10, 1038. https://doi.org/10.3389/fphys.2019.01038

[10] Hopton, O. M., Waterbury, N. V., Egge, J. A., & Lund, B. C. (2022). Clinical Impact of GLP-1 receptor agonists in veterans receiving basal-bolus insulin. Pharmacotherapy, 42(1), 45–52. https://doi.org/10.1002/phar.2648

[11] Wolak, M., Drobnik, J., & Bojanowska, E. (2021). Exendin-4 differentially modulates essential functions of human dermal fibroblasts under normoglycemic and hyperglycemic conditions. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society, 72(3), 10.26402/jpp.2021.3.14. https://doi.org/10.26402/jpp.2021.3.14

[12] Nagae, K., Uchi, H., Morino-Koga, S., Tanaka, Y., Oda, M., & Furue, M. (2018). Glucagon-like peptide-1 analogue liraglutide facilitates wound healing by activating PI3K/Akt p pathway in keratinocytes. Diabetes research and clinical practice, 146, 155–161.https://doi.org/10.1016/j.diabres.2018.10.013

[13] Liu, C., Wu, T., & Ren, N. (2024). Glucagon-like peptide-1 receptor agonists for themanagement of diabetic peripheral neuropathy. Frontiers in Endocrinology, 14. https://doi.org/10.3389/fendo.2023.1268619

[14] Ponirakis, G., Abdul-Ghani, M. A., Jayyousi, A., Almuhannadi, H., Petropoulos, I. N., Khan, A., Gad, H., Migahid, O., Megahed, A., DeFronzo, R., Mahfoud, Z., Hassan, M., Al Hamad, H., Ramadan, M., Alam, U., & Malik, R. A. (2020). Effect of treatment with exenatide and pioglitazone or basal-bolus insulin on diabetic neuropathy: a substudy of the Qatar Study. BMJ open diabetes research & care, 8(1), e001420. https://doi.org/10.1136/bmjdrc-2020-001420

[15] Qi L, Gao R, Chen Z, Lin D, Liu Z, Wang L, et al. Liraglutide reduces oxidative stress and Improves energy metabolism in methylglyoxal-induced SH-SY5Y cells. Neurotoxicology (2022) 92:166–79. doi: 10.1016/j.neuro.2022.08.007

[16] Pandey S, Mangmool S, Madreiter-Sokolowski CT, Wichaiyo S, Luangmonkong T, Parichatikanond W. Exendin-4 protects against high glucose-induced mitochondrial dysfunction and oxidative stress in SH-SY5Y neuroblastoma cells through GLP-1 receptor/Epac/Akt signaling. Eur J Pharmacol (2023) 954:175896. doi: 10.1016/j.ejphar.2023.175896

Continued on page 94

GLP-1 *(from page 93)*

[17] Caruso P, Scappaticcio L, Maiorino MI, Esposito K, Giugliano D. Up and down waves of glycemic control and lower-extremity amputation in diabetes. Cardiovasc Diabetol. 2021 Jul 6;20(1):135. doi: 10.1186/s12933-021-01325-3. PMID: 34229673; PMCID: PMC8261935.

[18] Dhatariya K, Bain SC, Buse JB, et al. The impact of liraglutide on diabetes-related foot u ulceration and associated complications in patients with Type 2 diabetes at high risk for cardiovascular events: results from the LEADER trial. Diabetes Care 2018; 41: 2229–2235.

[19] Werkman NCC, Driessen JHM, Stehouwer CDA, Vestergaard P, Schaper NC, van den Bergh JP, Nielen JTH. The use of sodium-glucose co-transporter-2 inhibitors or glucagon-like peptide-1 receptor agonists versus sulfonylureas and the risk of lower limb amputations: a nation-wide cohort study. Cardiovasc Diabetol. 2023 Jun 29;22(1):160. doi: 10.1186/s12933-023-01897-2. PMID: 37386427; PMCID: PMC10311702.

[20] Spampinato SF, Caruso GI, De Pasquale R, Sortino MA, Merlo S. The Treatment of Impaired Wound Healing in Diabetes: Looking among Old Drugs. Pharmaceuticals. 2020; 13(4):60. https://doi.org/10.3390/ph13040060

[21] Fezza, R., Rains, B., Fezza, T., & Fezza, J. P. (2023). Emerging Anesthesia Risks with Semaglutide. Plastic and reconstructive surgery. Global open, 11(11), e5427. https://doi.org/10.1097/GOX.0000000000005427

[22] Pfeifer KJ, Selzer A, Mendez CE, et al.. Preoperative management of endocrine, hormonal, and urologic medications: Society for Perioperative Assessment and Quality Improvement (SPAQI) Consensus Statement. Mayo Clin Proc 2021; 96:1655–1669.

[23] American Society of Anesthesiologists Consensus-Based Guidance on Preoperative Management of Patients (Adults and Children) on Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists. (n.d.). Retrieved July 23, 2024, from https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative

[24] Fujino, E., Cobb, K. W., Schoenherr, J., Gouker, L., & Lund, E. (2023). Anesthesia Considerations for a Patient on Semaglutide and Delayed Gastric Emptying. Cureus, 15(7), e42153. https://doi.org/10.7759/cureus.42153

[25] Silveira SQ, da Silva LM, de Campos Vieira Abib A, et al., Relationship between perioperative semaglutide use and residual gastric content: a retrospective analysis of patients undergoing elective upper endoscopy. J Clin Anesth 2023; 87:111091.

Dr. Cheema is currently a second-year podiatry resident at New York Community Hospital. She is involved with the American Podiatric Medical Association where she serves on several committees. She graduated from the Dr. William M. Scholl College of Podiatric Medicine. Prior to her podiatry career she received her Master's degree in Physiology and Biophysics from Georgetown University.

Dr. Wu is the Dean and Professor of Surgery at the Dr. William M. Scholl College of Podiatric Medicine, and Professor, Center for Stem Cell and Regenerative Medicine at the School of Graduate and Post-Graduate Studies at Rosalind Franklin University of Medicine in North Chicago. She is also Director of the Center for Lower Extremity Ambulatory Research (CLEAR).