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Glucagon - Like Peptide – 1 Receptor Agonists to Reduce the Risk of
Nephropathy in the Uncontrolled Type 2 Diabetic Patient

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GLUCAGON-LIKE PEPTIDE – 1 RECEPTOR AGONISTS TO REDUCE THE RISK OF NEPHROPATHY IN THE UNCONTROLLED TYPE 2 DIABETIC PATIENT

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Glucagon - Like Peptide – 1 Receptor Agonists to Reduce the Risk of Nephropathy in the Uncontrolled Type 2 Diabetic Patient

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Abstract

The rise in the prevalence of Type 2 diabetes mellitus (T2DM) worldwide has become a major health care issue due to associated increases in patient morbidity and mortality secondary to cardiovascular and renal disease complications (Leiter et al., 2014). Nephropathy is a common comorbidity in patients with T2DM, with the reported overall prevalence of chronic kidney disease (CKD) (GFR<60) ranging from 25-30 percent in patients with T2DM (Scheen, 2015). Current treatment options for glycemic control are significantly limited for patients with T2DM and CKD, which often leads to the start of insulin and sulfonylureas (Leiter et al., 2014). Incretin-based therapies, including glucagon-like peptide-1 (GLP-1) receptor agonists, are being used increasingly for the management of T2DM and have been shown to have favorable renal effects (Scheen, 2015). A case outlined below demonstrates the wide variety of treatment options available for Type 2 diabetics, including GLP-1 receptor agonists, as well as the effects GLP-1 receptor agonists have on T2DM and other systems of the body. This case study and literature review will outline the benefits of GLP-1 to reduce the risk of nephropathy in the T2DM patient.

Background

The prevalence of T2DM in the United States continues to rise remarkably (Ajiboye & Segal, 2017). It has increased from 26 million in 2010 to 36 million in 2015, meaning that about one in eight Americans live with T2DM (Ajiboye & Segal, 2017). Diabetic nephropathy is a microvascular complication that occurs in about 40 percent of patients within 20-25 years following the onset of T2DM (Ajiboye & Segal, 2017). Nephropathy is a strong predictor of

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mortality in diabetic patients and is the most common cause of end-stage renal disease (Ajiboye & Segal, 2017). Nephropathy also places patients at a higher risk of strokes, peripheral artery disease and cardiovascular mortality (Ajiboye & Segal, 2017). Due to these alarming statistics, there is a huge need to prevent and manage T2DM to reduce the risk of nephropathy (Nasri & Rafieian-Kopaei, 2015).

Pharmacologic intervention is almost always required to slow the progression of nephropathy in the T2DM patient (Ajiboye & Segal, 2017). Choosing the correct medication and treatment in a patient with T2DM and nephropathy is often difficult due to the major role the kidneys play in the clearance of drugs (Scheen, 2015). This introduces the purpose of the report; GLP-1 receptor agonists are injectable medications that have been introduced for the treatment of T2DM as well as slow the progression of nephropathy. GLP-1 lowers blood glucose levels without producing hypoglycemia by stimulating insulin secretion from pancreatic beta-cells (Lee & Jun, 2014). In addition to helping control T2DM, GLP-1 receptor agonists inadvertently reduce the decline in nephropathy (Tuttle et al., 2018).

The case report will introduce a 65-year-old obese female who has a history of T2DM, hyperlipidemia and hypertension. She has no concerns regarding her diabetes and is tolerating her medications well. However, her lab results indicate that her T2DM is no longer controlled by her current medication regimen. These factors put her at high risk for developing complications such as nephropathy. Other medications and interventions must be completed to prevent these complications from occurring. The case study will illustrate the clinical role of the nurse practitioner in the treatment and management of a patient with T2DM, including the introduction of a GLP-1 receptor agonist to achieve glycemic control and to prevent nephropathy.

Case Report

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A.B. is a 65-year-old obese female with a 10-year history of Type 2 diabetes who presents for a 6-month diabetes follow up. She denies any concerns or complications, including chest pain, leg swelling, palpitations, shortness of breath, nausea, vomiting, diarrhea, abdominal pain, numbness/tingling in her extremities, or sores on her feet. She also denies polyuria, nocturia, and hematuria. She has been tolerating her medications well and has been checking her blood glucose about two to three times a week at random times throughout the day. She did not bring in her blood glucose log; however, she states her glucose values usually range from 170-220 mg/dL, with no episodes of hypoglycemia. She cannot remember what her highest glucose has been since her last visit.

A.B. is currently using glipizide 10 mg and Janumet 50-1000 mg BID to treat her T2DM. She also takes lisinopril 10mg daily, metoprolol 50 mg daily and aspirin 81 mg for hypertension, and simvastatin 20 mg daily for hyperlipidemia. She has tolerated these medications well and adheres to her daily schedule. She has no allergies to medications. Besides hypertension and hyperlipidemia, her past medical history includes a colon polyp (2013), carpal tunnel, obesity, and cataracts. Her only pertinent family history includes her father, who had arthritis and died from “heart issues.” A.B.’s mother is alive and is in good health; she is unsure of any major health concerns.

In her free time, A.B. likes to spend time with her husband and their two daughters. She is a retired school teacher, but sometimes helps her husband in the “shop.” She has been wanting to lose weight. Though she has started walking four times a week for 30 minutes, she has been unsuccessful in losing weight. Her diet includes a wide range of different foods, including fruits, vegetables, meats, and carbohydrates with pasta being her favorite food. A.B. and her husband go out to eat 2-3 times a week, mostly on the weekend. She drinks a glass of wine or two on the

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weekends with her husband, has never been a smoker, and does not use illicit drugs. She has seen a diabetic counselor and dietician in the past, but this was many years ago. She does not remember any of the education. Her last eye examination was about six months ago, and she has never needed to see a podiatrist.

A complete physical examination was completed following obtaining the patient's history. A.B.'s vital signs included a of weight 122 kg (269 lbs) making a BMI of 36.5 kg/m, blood pressure 138/80, pulse 72, and respirations 18. She is an alert and oriented female with a normal gait. Red reflex present bilaterally, with her pupils equal, round and reactive to light and fundi were clear and with no arteriovenous nicking or retinopathy. Her thyroid was nonpalpable and her lungs were clear to auscultation with even and unlabored respirations. S1S2 were heard and the heart rate and rhythm were regular with no extra heart sounds, murmurs, gallops or rubs. The vascular assessment was within defined limits with no carotid bruits or thrills, and the femoral, popliteal, and dorsalis pedis pulses plus-2 bilaterally. Her abdomen was soft, nondistended, nontender, and rounded. Lastly, she had full sensation to all four extremities, no sores or lesions, with full vibratory, and monofilament sensed throughout bilateral feet, and plus-2 ankle reflexes.

Fasting labs were obtained the morning of the office visit and were as follows: glucose 324 mg/dL *, A1C 9.5%*, creatinine 0.92 mg/dL, BUN 16 mg/dL, sodium 139 mg/dL, potassium 4.3 mg/dL, cholesterol 133 mg/dL, triglyceride 167 mg/dL*, HDL 39 mg/dL*, LDL 61 mg/dL, AST 19 U/L, ALT 30 U/L, and microalbumin 22/17 mg/L.

Based on A.B.'s medical history, physical exam and lab results, her diagnoses include uncontrolled Type 2 diabetes without complications and obesity. Interventions need to be completed to achieve glycemic hemostasis and to promote weight loss. The first intervention is

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to start a GLP-1 receptor agonist to help decrease her A1C, weight loss, achieve better glycemic control, and to reduce her risk of developing nephropathy. Liraglutide will be started at 0.6 mg sub-1 once daily for 1 week, then increase to 1.2 mg once daily. If we are not at an A1C goal of <7 percent after 3 months, we will then increase to 1.8 mg once daily. Due to starting a GLP-1 receptor agonist, we will stop her Janumet 50-1000 mg BID as dipeptidyl peptidase four inhibitors as not recommended with GLP-1 receptor agonists (American Diabetes Association, 2019). We will, however, continue her metformin at 1000 mg BID as she tolerated this well and has weight loss and renal protective properties. She will also continue her glipizide at 10 mg daily.

Along with the changes to her medications, referrals to a diabetic counselor and a dietician were placed. She will see the diabetic counselor in three days, and the dietician in one week. She was also set up with a local exercise program for Type 2 diabetic patients to help them get started on a gentle exercise program to promote weight loss and well-being. Glycemic goals were reviewed including an A1C of 8.0 percent and fasting blood sugars of 130. She was encouraged to start taking her blood sugars at least four times daily while changing diabetic medications and to bring these values in at our next appointment, which was scheduled for three months from now. Labs, including A1C and CMP, will be completed prior to next appointment to see improvement of glycemic control. She will also call clinic next week to inform us of how she is tolerating her new medication regimen and update the NP of blood sugars after starting liraglutide.

Literature Review

Problem Formulation

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Diabetic nephropathy (DN) is a common Type 2 diabetes mellitus (T2DM) complication that is associated with an increased risk of adverse outcomes (Boye, Botros, Haupt, Woodward, & Lage, 2018). DN is the leading single cause of end-stage kidney disease, with clinical features including elevated urinary albumin excretion, impaired glomerular filtration rate, and progressive decline in kidney function (Ding & Choi, 2015). In the United States, more than 40 percent of the 36 million patients with T2DM have diabetic kidney disease (Doshi & Friedman, 2017). Patients with comorbid nephropathy and T2DM are at significant risk of cardiovascular events as well as all-cause morbidity and mortality (Goldenberg et al., 2018). The presence of diabetic kidney disease also increases the complexity of T2DM treatment due to the pharmacokinetic aspects of drugs cleared by the kidney can be influenced by renal impairment (Boye et al., 2018). Glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to significantly slow the decline in nephropathy while providing a large reduction in A1C in the T2DM patient.

Literature Search

A literature review was completed to survey adequate articles, results and other sources relevant to impact of GLP-1 receptor agonists to reduce nephropathy in the patient with T2DM. This will give an overview of the ideas, theories and significant literature published on the topic of GLP-1 receptor agonists to reduce nephropathy. The literature review will also provide a description, summary, and evaluation of the references used in relation to GLP-1 receptor agonists in lowering A1C. The most common database that was used for this literature review was CINAHL (Cumulative Index to Nursing & Allied Health), provided from the UND School of Medicine and Health Sciences online resources.

The first key words that were used in CINAHL were “kidney disease” and “Type 2 diabetes,” which provided 2,280 search results. To narrow this large number of results, a refined

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search was completed by asking for only current articles (years of 2014 to 2019) and English-language results. A smaller, more recent date range was used to make sure the data was current, relevant and the evidenced-based. The English language parameter was used to eliminate articles that could not be translated or understood. This search unfortunately continued to yield many articles, so another key word was added, “GLP-1.” This brought the results down significantly, to 16 results, making the selection of references and sources much easier to review. When viewing CINAHL with these parameters and using the three key terms provided, four of the 12 articles that were used are shown. This includes the articles by Aldrich & Ashjian (2019), Goldenberg et al., (2018), Scheen (2015), and Stanton (2014). These first four articles were used to provide the background of the research, including excellent information, data and statistics regarding nephropathy and GLP-1 receptor agonists in helping achieve glycemic control. All four articles were peer-reviewed, published academic journals.

Other resources that were used to find pertinent articles included PubMed, American Diabetes Association and UpToDate. PubMed searches were focused on biomedical and clinical literature, while the American Diabetes Association provided statistics and current guideline recommendations for practice regarding T2DM medication management. PubMed was useful in finding research regarding pathophysiology and causes of diabetic nephropathy. These articles included Ajiboye & Segal (2017), Ding & Choi (2015), and Nasri & Rafieian-Kopaei (2015). UpToDate provides practice recommendations by synthesizing the most recent medical information. While not using UpToDate directly for information for this literature search, UpToDate provided many references and other sources that were used for the search, including Lee & June (2014), Leiter et al. (2014), Mann et al. (2017), and Tuttle et al. (2018). These articles were crucial in the information regarding how GLP-1 reduce the risk of nephropathy.

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Data Evaluation

GLP-1 receptor agonists are an attractive option for the treatment of T2DM because they effectively lower A1C and produce weight loss without posing the risk of hypoglycemia (Trujillo, Nuffer, & Ellis, 2015). GLP-1 is an incretin hormone that is naturally released from intestinal L-cells in the small intestine and colon in response to food ingestion (Lee & Jun, 2014). GLP-1 lowers blood glucose by stimulating insulin secretion from pancreatic beta-cells in a glucose-dependent manner (Lee & Jun, 2014). All GLP-1 receptor agonists have been shown to reduce A1C by an average of 1-1.2 percent after a duration of 8-30 weeks (Trujillo et al., 2015).

GLP-1 also works on the beta-cells by preserving their function. These medications have been shown to produce beta-cell proliferation, beta-cell neogenesis and prevention of beta-cell apoptosis (Lee & Jun, 2014). This is incredibly beneficial due to beta-cell function progressively declining in the typical T2DM patient, which often leads to necessitating an increase to current treatments or adding new medications (Trujillo et al., 2015). GLP-1 also promotes glucose homeostasis by slowing gastric emptying, suppressing appetite, reducing plasma glucagon, and stimulating glucose removal (Lee & Jun, 2014). This leads to an overall weight reduction for the patient, which inadvertently reduces blood sugar over time.

Although rates of adverse effects differ between the different types of GLP-1 receptor agonists, the most common adverse effects are gastrointestinal related, including nausea, vomiting, and diarrhea (Trujillo et al., 2015). There are currently five GLP-1 receptor agonists approved for use in the United States, including exenatide, liraglutide, albiglutide, dulaglutide, and lixisenatide (Trujillo et al., 2015). The main differences between the several GLP-1 receptor agonists include the dose, administration, storage, tolerability, cost, and patient satisfaction (Trujillo et al., 2015).

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GLP-1 receptor agonists reduce the risk and rate of decline of diabetic nephropathy.

Although renal GLP-1 receptors have been found, their exact localization and physiological role are not fully understood (Scheen, 2015). Activation of GLP-1 receptors in the kidney leads to diuretic and natriuretic effects, possibly through direct actions on renal tubular cells and sodium transporters (Scheen, 2015). This also may explain why GLP-1 receptor agonists have antihypertensive effects (Scheen, 2015). GFR is also regulated by GLP-1, but these effects are complex and further depend on glycemic conditions (Scheen, 2015). Lastly, atrial natriuretic peptide and the renin-angiotensin system may be involved in the signaling of GLP-1 mediated renal actions (Scheen, 2015). This may influence the water and electrolyte balances, further protecting the kidney. Overall, GLP-1 therapy is kidney protective and reduces albuminuria, glomerulosclerosis, oxidative stress, inflammation, and fibrosis in the kidney, slowing the risk and decline of nephropathy (Scheen, 2015).

Analysis and Interpretation

GLP-1 receptor agonists have been proven to be an effective antihyperglycemic therapy. Results of a meta-analysis of clinical studies showed that treatment with GLP-1 receptor agonists is associated with a significant A1C reduction from baseline (Hinnen, 2017). In studies of GLP-1 receptor agonists used alone or with other oral antihyperglycemic medications, mean changes in A1C ranged from -0.6 percent to 1.7 percent, depending on the type of GLP-1 used (Hinnen, 2017). Other studies, including Trujillo et al. (2015), Aldrich & Ashjiah (2019), Goldenberg et al. (2018) and Boye et al. (2018), found similar findings with an average reduction in A1C in the T2DM patient of around 1 percent. Due to providing the T2DM patient an effective treatment to help lower blood glucose, the American Diabetes Association recommends GLP-1 receptor agonists as an add-on therapy for patients who do not achieve their A1C target after three months

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of metformin therapy (American Diabetes Association, 2019). GLP-1 receptor agonists are also recommended as first-line therapy as an alternative to metformin in patients who cannot tolerate or are contraindicated for metformin (American Diabetes Association, 2019).

The literature review confirmed that GLP-1 receptor agonists reduce the progression and risk of diabetic nephropathy in the T2DM patient. GLP-1 receptor agonists, including liraglutide, reduced the incidence new or worsening nephropathy, including new onset albuminuria >300 mg/day, doubling of creatinine, end-stage renal disease, and renal death in a large trial of patients with T2DM (Mann et al., 2017). This decline was predominantly due to a reduction in new-onset albuminuria, as it was shown that few patients in the GLP-1 group had albuminuria (Mann et al., 2017). Dulaglutide, another GLP-1, was proven to slow kidney disease progression and prevented worsening albuminuria in a trial of diabetic patients with chronic kidney disease (Mann et al., 2017). GLP-1 receptor agonists were also shown to slightly slower the decline in estimated GFR overtime (Mann et al., 2017). These studies showed that GLP-1 receptor agonists, especially liraglutide and dulaglutide, can be used not only to significantly reduce A1C and body weight, but also for slowing the onset and progression of nephropathy in the T2DM patient.

A similar study was completed by Boye et al. (2018), who collected data from electronic health records from 2012 to 2015. The study characterized the use of GLP-1 receptor agonists in patients with T2DM with and without renal impairment and examined the effects the medication had on GFR and A1C. The results showed similar findings to the Mann et al. (2017) study that was discussed earlier in that GLP-1 receptor agonists were associated with significantly smaller declines in GFR in patients with kidney disease, smaller likelihood of having new onset nephropathy, and a significant larger reduction in A1C (Boye et al., 2018). The study completed

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by Boye et al. (2018) again shows the significance that GLP-1 receptor agonists have on reducing the risk and rate of nephropathy in the T2DM patient. The limitation to this study was that laboratory results were not completed at the same interval time for all patients; however, a sensitivity analysis revealed the timing of these tests had no major impact on the results (Boye et al., 2018).

The last study to be discussed was the AWARD-7 trial, which was a multicenter, open label trial done at 99 sites in nine countries (Tuttle et al., 2018). The GLP-1 receptor agonist used was a once weekly injection, compared to the daily insulin injection. The T2DM patients of the trial were randomly prescribed a GLP-1 receptor agonist or insulin glargine. The results showed that the effects of GLP-1 receptor agonists on A1C were non-inferior to insulin glargine (Tuttle et al., 2018). The study also found that patients taking the GLP-1 receptor agonist had slower rates of decline in GFR compared to insulin users (Tuttle et al., 2018). In patients with T2DM and moderate-to-severe chronic kidney disease, once-weekly GLP-1 receptor agonists produced similar glycemic control compared to insulin, with reduced decline in GFR (Tuttle et al., 2018). The GLP-1 may be considered as a safe alternative as it does not produce hypoglycemic effects and once-weekly use compared to daily (Tuttle et al., 2018). The major limitation of this study was they only used one type of GLP-1 receptor agonist, dulaglutide, making it difficult to assume that all GLP-1 receptor agonists have the same results.

GLP-1 receptor agonists are an effective option for the treatment of T2DM because they effectively lower A1C and body weight while having a low risk of hypoglycemia (Trujillo et al., 2015). They have also been proven by multiple literature review, meta-analysis and randomized control trials to reduce the risk of developing new onset nephropathy, as well as slow the

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progression of kidney disease in the diabetic patient. GLP-1 should be considered as a treatment option by all advanced practice providers for the treatment of T2DM.

Learning Points

- GLP-1 receptor agonists have been found to effectively slow the progression of nephropathy as well as reduce A1C and facilitate weight loss without the risk of hypoglycemia.
- For patients with both CKD and T2DM, advanced practice providers should consider the use of a GLP-1 receptor agonist to reduce the risk of chronic kidney disease progression.
- GLP-1 receptor agonists can be used as an add-on therapy for patients who do not achieve their A1C target goal after three months of starting metformin. They are also recommended as first-line therapy as an alternative to metformin in patients who cannot tolerate or are contraindicated to metformin.

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