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CASE STUDY: UNCONTROLLED TYPE-2 DIABETES IN CHRONIC KIDNEY
DISEASE & REVIEW OF ORAL GLYCEMIC OPTIONS

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An Independent Study

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PERMISSION

Title

Department: Nursing

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Abstract

The pathologic effects of type-2 diabetes on organ systems contribute to dyslipidemia, hypertension, cardiac and vascular remodeling, and kidney disease increasing the risk of heart attack, stroke (Cheng et al., 2012). Appropriate management of diabetes can delay onset of organ dysfunction, decreasing mortality, and improving quality of life (Nashar & Egan, 2014). The guidelines set by the American Diabetes Association (2016) indicates a therapeutic A1c value to be <6.5 percent in type-2 diabetics. However, co-morbidities, such as renal failure and heart disease, as well as patient wishes play a key role in goals of treatment. The purpose of this clinical case study is to identify appropriate second-line therapy in addition to metformin in a type 2 diabetic patient exhibiting clinical signs of progressive kidney disease. A case presentation of an adult female with type 2 diabetes and kidney disease will be addressed in this independent project. Lastly, a literature review and discussion of appropriate prescribing practices of some of the newer anti-diabetic medications for a patient with decreased renal function will then be conclude the case.

Keywords: type-2 diabetes, pharmacological, treatments, chronic kidney disease, metabolic syndrome, pharmacotherapy

Background

In 2014 twenty-one million or 9.3 percent of Americans have been diagnosed with diabetes, and over eight million are believed to be living with this condition undiagnosed (CDC, 2014). According to the American Diabetes Association (ADA, 2016) about 1.7 million people in the United States were newly diagnosed with diabetes contributing to heart, kidney, metabolic, and vascular dysfunction leading to increased

mortality. Also, about ninety percent of the diabetic population has type 2 diabetes also identified as insulin resistance (ADA, 2016).

The American Diabetes Association (2016) and U.S Preventative Service Task Force (2015) guidelines recommend screening for people the age of 40 every three years through assessment of fasting plasma glucose $>126\text{mg/dL}$, or HgbA1c $> 6.5\%$. Increased blood glucose and A1c levels are directly associated with decreased kidney function over time and diagnosed through albuminuria, and impaired glomerular-filtration rate (GFR) (ADA, 2014). Tight glucose control has several physiologic benefits including minimizing damage to arteries and preserving adequate renal blood flow (Nashar & Egan, 2014). Syndrome X was first noted in 1929, now labeled as metabolic syndrome originally was identified with clinical findings of three or more of the following five risk factors including abdominal obesity defined by waist circumference (men $>102\text{ cm}$; women 88 cm), triglycerides $>150\text{ mg/dL}$, low high-density lipoprotein (HDL) cholesterol levels (men $>40\text{ mg/dL}$; women $>50\text{ mg/dL}$), blood pressure $>130/85\text{ mmHg}$, and fasting glucose $>100\text{ mg}$ (Nashar & Egan, 2014). In several studies reviewed by Nashar, and Egan, (2014) diagnosis of metabolic syndrome has been linked to increased mortality due to multiple organ dysfunction including complicating diagnosis and treatment. Therefore a multisystem approach is necessary to appropriately manage metabolic syndrome including clinical evaluation and intervention of blood glucose, cholesterol, blood pressure, and body-mass. As an example, Thomas & Atkins (2006) explains the role of how hypertension influences renal function. Blood sugar control is one of the parameters necessary for maximizing health in diabetes (Nashar & Egan, 2014).

Primary care providers have an opportunity and obligation to recognize clinical findings of diabetes and metabolic syndrome and intervene to minimize the risk of organ damage due to elevated blood glucose. Screening for kidney function, dyslipidemia, hypertension, and diabetes as recommended by the U.S. Preventative Services Task Force (USPSTF, 2015), and the American Diabetes Association (ADA, 2016) encourages early diagnosis of individuals high-risk for chronic debilitating disease. Early diagnosis and intervention of type-2 diabetes aims at keeping blood glucose values as close to normal as possible without the patient having symptoms of hypoglycemia (ADA, 2016).

The kidneys are responsible for elimination of a majority of drugs and it is the responsibility of all healthcare providers to recognize and make appropriate adjustments in medication therapy based on organ function (Liles, 2011). Type 2 diabetes management choices should be individualized, taking into account patient comorbidities, and wishes when considering treatment (Tierney, 2012, p.2). Medication adjustments and close monitoring are required for several medications used to treat diabetes in the presence of renal disease, and some are not indicated to prescribe in the presence of renal disease (Fravel, et al., 2011). The elderly are also at risk for undesirable effects of diabetic management. Reduced dosage and careful monitoring are suggested in this population (Fravel, et al., 2011). Lack of renal dose adjustments of most medications can lead to undesired increased potency and increased toxicity which can be harmful to patients (Liles, 2011).

Case Report

Chief Concern

Mrs. Jones presented to the clinic today after being referred by the clinic diabetic educator for evaluation of her diabetes. She was noted to be having pre-prandial blood sugar readings ranging from 150-200mg/dl. She is a new patient to me and is here today to establish with a primary care provider. Besides her elevated blood sugar, she has some mild exercise intolerance and has noticed minor lower-leg edema. She indicates her health has been otherwise good.

Review of systems and past medical history

She is a sixty-five year-old retired teacher who appears younger than her stated age and does not appear to be in acute distress at the time of examination. She has been married for 40 years and her husband lives at home with her. They are both in good health. Her past medical history includes hypertension, type-2 diabetes, and hypercholesterolemia. She has had “elevated blood sugars” during previous annual visits and has started metformin therapy about six months ago and she indicates she felt like she was gaining control of her blood sugars. Recently her blood sugars have been slowly climbing. She understands her goal is to get her blood sugars down as close to 110-140mg/dl however she has been unsuccessful. Mrs. Jones denies headaches, nausea, visual changes, fluctuations in weight, nausea or vomiting, palpitations, chest pain or heaviness, shortness of breath, pain in her abdomen, numbness or tingling in lower extremities, lesions on feet, sensory changes, and sexual dysfunction. She has been following the suggestions of the dietician and diabetic educator and has not gained control of her blood sugars with three months of metformin therapy. She regularly sees a

Dentist and an Ophthalmologist and she indicates no problems with her eyes or her teeth. She is post-menopausal and had a vaginal exam with a negative pap smear she believes was 2 years ago and denies any vaginal issues today. She denies any stressors at home or with family. She had a stent placed about two years ago. She has had no other surgeries. She has not had a colonoscopy. She is up to date on her immunizations including pneumonia, flu, tetanus, and shingles. Indicates regular bowel movements and urinary patterns without pain, bleeding, or signs of infection.

- Vital Signs: BP 122/64mm/Hg, HR 64, BMI 25
- Past Medical History
 - Uncontrolled type-2 diabetes on metformin therapy
 - Hypertension controlled with Lisinopril 20mg and Furosemide 20mg daily.
 - Hyperlipidemia, on Atorvastatin 20mg daily.
 - Coronary Artery Disease with history of stent placement. On Plavix 75mg daily.
 - Lower extremity edema and taking Furosemide 20mg daily
- Allergies: Penicillin

Physical Assessment

- HEENT: Facial symmetry normal. Scalp clean and dry without lesions or irregularities. PERRLA, Fundoscopic eye exam shows normal red-reflex without lesions in posterior chamber. Tympanic membrane pearly-grey without redness or effusion, normal light reflex at 5 O'clock (right) and 7 O'clock (left) respectively. No prominent lymph nodes in submandibular, maxillary, axillary, suprasternal,

anterior or posterior cervical chains noted. Oral cavity normal moist intact mucous membranes without lesions. Teeth are in good condition. Thyroid palpated without noting abnormal or irregular lumps.

- Skin: Color good throughout. Intact without cuts, scrapes, lesions, rashes, or discoloration. Minor bilateral non-pitting edema.
- Heart/ vascular: Regular rate and rhythm without appreciating rubs, gallops, or murmurs. Equal regular pulses present in upper and lower extremities.
- Lungs clear bilaterally with good air exchange.
- Musculoskeletal: Good range of motion in all major joints without pain. Deep tendon reflexes normal patellar, and Achilles. Determination of proprioception normal. Lower extremity vibratory and filament test shows normal sensation, motion, and pulses bilaterally. Skin intact without signs of injury or infection.

Fasting labs ordered and reviewed this visit

- **CBC:** WBC 8.92K/uL; RBC 5.04 M/uL; Hemoglobin 12.5g/dL; Platelets 351K/uL.
- **Basic Metabolic Panel:** BUN 22mg/dL; Sodium 139mmol/L; Potassium 3.9mmol/L; Chloride 102mmol/L; CO2 27.3mmol/L; Glucose 151; Creatinine 1.3mg/dL; Calcium 9.8mg/dL; GFR 49 (L); Albumin 4g/dL; Alkaline Phosphate 88U/L; Total Protein 7.4g/dL.
- **Urinalysis:** positive for protein <300mg/dL (otherwise normal findings).
- **Lipid panel:** Triglycerides 231(H); Cholesterol 199; HDL 38(L); LDL 95; Cholesterol-HDL Ratio 3.5.
- **HgbA1c** – 9.7mg/dl

Diagnosis and plan

Uncontrolled type 2 diabetes mellitus. Reviewed HgbA1c level and blood sugars with her and discussed the consequences of poor control of her blood sugars such as heart, kidney, retinal and vascular disease. With her HgbA1c at 9.7 she will most likely need additional medication possibly insulin to reach goal of A1c <7. Discussed options with Mrs. Jones included increasing Metformin, adding another anti-diabetic agent such as a second oral agent or insulin. It is unlikely increasing her HgbA1c to goal of 6.5-7 mg/dl will happen with increasing her metformin. Initiating a DPP-4 inhibitor would assist in lowering blood sugars through elimination in the urine. So stopping the metformin and adding Janumet 25/1000 BID would likely show improvement in the glucose levels. Continue visits to see the diabetic educator.

Hypertriglyceridemia. Currently she is on 20mg of Atorvastatin. Discussed the possibility of recurrent coronary artery disease with elevated triglycerides and low-normal HDL. Mrs. Jones agrees to an increase her Atorvastatin to 40mg daily for cholesterol control.

Stage 3a chronic renal disease with proteinuria. Discussed the findings of her lab work including protein in the urine and creatinine in the blood indicating moderate kidney disease. Repeat testing will need to be done to confirm chronic renal disease. I explained this is due to some of her conditions such as hypertension and diabetes damaging the small vessels in her kidneys and therefore protein is able to spill into the urine. However, with continued blood pressure control and improved management of blood sugar I hope to see an improvement in this during her next appointment. If she is

still having moderate amounts of protein in her urine I will send her to Nephrology for a consult.

Lower extremity edema. Non-pitting minor swelling bilateral lower extremities with mild increased shortness of breath with activity. This still remains to be a concern for the client. Offered to increase Lasix for a few days to see if this helps with the swelling and mild dyspnea with activity. Will double Furosemide dosage to 40mg daily for 3days. Then she is to return to original 20mg daily dosage.

Follow-up. Will have her return to see me in four weeks for a basic metabolic panel and in three months for A1c, Basic Metabolic Panel, and Urinalysis. Discussed signs and symptoms of hypoglycemia, infection, and hyperglycemia. She should return to the clinic or call if she has any questions or concerns about her care.

Literature Review

Search strategies

Review of the literature in support of the topic I electronically accessed the Harley E. French Library of the Health Sciences at the University of North Dakota, utilizing two search engines, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PubMed. Literature search focused on management of type-2 diabetes in the presence of chronic renal failure, and metabolic syndrome. “All text” search terms included “chronic kidney disease”, “type-2 diabetes”, “treatment”, “pharmacology”, and “metabolic syndrome”.

Filters applied to the search included “English”, “academic journals only” and “results within the last 8 years” elicited 223 articles matching the search. Filters

“pharmacotherapy” were then applied yielding 34 articles. Of these journal articles, ten were selected for critical analysis.

Findings

There are several studies relating to the diagnoses and management of renal disease in diabetes and metabolic syndrome focusing on pharmacotherapies such as antihypertensive management, blood glucose control, statin therapy, and modifiable risk factors such as tobacco use, obesity, and dietary restrictions.

The following articles in this independent study will give insight into second-line treatment options in type-2 diabetes in the presence of chronic kidney disease. Mrs. Jones as presented in the clinical case presents with increased fasting blood glucose, A1c of 9.7mg/dL and is in moderate renal impairment with marked proteinuria and elevated triglycerides. Drug selection will include consideration of the fact her A1c goal should be around 6.5-7.5mg/dL, and she is in stage 3a renal disease. Other considerations for drug selection will focus on lowering triglycerides, and increasing HDL cholesterol. Learning points of the literature review regarding diabetic treatment options for Mrs. Jones will follow each drug class.

Glucagon-like peptide (GLP-1) receptor agonists / incretin therapy. These are also known as incretins have demonstrated weight reductions 4.4% so they are recommended in patients with a BMI > 35kg/m², and offer cardiovascular benefits such as systolic blood pressure reduction (Tierney, 2012). GLP-1 antagonists are predominantly eliminated by filtration so patients with a GFR between 30-50ml/min need small dosage increases at 5 to 10mcg increments and monitoring for increased renal failure (Hamilton, 2012). GLP-1 receptor agonists such as exenatide and liraglutide, have

a significant effect over many therapies with an effect of lowering A1c 1.5%. and this drug requires minimal monitoring for renal function (Fleury, E. 2009). Liraglutide is designed to need minimal monitoring in the presence of renal disease. GLP-1 receptor agonists are resistant to the DPP-4 enzyme and provide direct stimulation of GLP-1 receptors (Capaldi-Milfort, B. 2012).

The GLP-1 receptor agonists Liraglutide would work in conjunction with metformin therapy well for Mrs. Jones due to the low chance of her renal dysfunction causing toxicity. The benefit of a reduction of 1.5% in her A1c would help, however she needs to come down at least two points in her A1c. Increasing her metformin to 1000mg BID in collaboration with Liraglutide may be enough to bring her A1c to goal however her creatinine is borderline.

Biguanides. Metformin is an anti-hyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes and acts by lowering both basal and postprandial plasma glucose and is recommended for patients with a body mass of at least 25Kg/meter squared (Hamilton, 2012). Biguanides decrease hepatic production of glucose, decrease intestinal uptake of glucose, and increase insulin sensitivity by enhancing peripheral glucose uptake and utilization and has a very low chance of producing hypoglycemia (Hamilton, 2012). Due to their effectiveness and minimal adverse side effects, Biguanides (metformin) are the mainstay of first line anti-diabetic treatment. Caution is recommended in patients with estimated glomerular filtration rates less than 45ml/min or serum creatinine > 1.4 (woman) and > 1.5 (men) because in significant renal impairment, there is a chance of lactic acidosis (0.03 cases per 1,000 patient years) (Hamilton, 2012). Research by Shaw, Wilmot, & Kilpatrick, (2007) has

shown that metformin is safe in renal impairment as long as the estimated glomerular filtration rate is > 30 ml/min.

Mrs. Jones was on this medication previously and she was taking 500mg BID. An increase in this medication would benefit her A1c and fasting glucose. Her creatinine being borderline elevated warrants careful watching of her renal functions but should be safe to increase to 1000mg twice daily.

Thiazolidinediones. Pioglitazone is a thiazolidinedione and primarily excreted in feces via the liver and can be used in patients with CKD creatinine clearance >4 ml/min and has an effect of 1.5-2.1% decrease on A1c levels, however is associated with minor weight gain (Derosa, 2014). Rosiglitazone, another thiazolidinedione, was removed by the FDA in 2013 due to the belief that it was associated with cardiovascular events such as heart attack and stroke (Derosa, 2014). It was reinstated in 2015 due to lack of findings linking the medication to possible cardiovascular side effects.

Pioglitazone would be a good medication for her as it gives up to a 2% reduction in her A1c and can be used in renal disease without risk of toxicity because the medication is metabolized in the liver and excreted in the stool. Given the fact that her liver panel was the only lab that was perfect this may be a good choice as well.

DPP-4 inhibitors / incretin therapy . DPP-4 inhibitors reduce glucose levels with a low risk of hypoglycemia DPP-4 inhibitors are generally “weight-neutral”, have a low risk of hypoglycemia, and come as a combined medication with metformin which makes them a preferred treatment plan often (Tierney, 2012). Sitagliptin and Vildagliptin have significant side effects and cannot be administered with creatinine clearance <50 ml/min (Hamilton, 2012). Saxagliptin on the other hand, can be used with a

creatinine clearance of 5-49ml/min at a reduced dosage of 2.5mg per day (Hamilton, 2012) & (Plosker, 2014). All the DPP-4 inhibitors deliver a reduction in A1c of about 1.2-1.5% (Capaldi, 2012),

DPP-4 inhibitor Saxagliptin would be the only medication in this class that would be appropriate for this patient as it can be given in the presence of impaired kidney function. This is a medication provides a neutral weight and low risk of hypoglycemia, and would give a nice decrease in her A1c.

Sulfonylureas. Sulfonylureas are primarily excreted in the liver however metabolites from the breakdown of the medication are excreted via the kidney (Liles, 2011). Glyburide requires a creatinine clearance > 50ml/min, and Glimepiride requires a creatinine clearance > 22ml/min, and Glipizide requires no adjustment and could be utilized in hepatic impairment (Liles, 2011). Sulfonylureas are associated with weight gain (Capaldi, 2012). Fleury-Milfort, (2009) states incretin based sulfonylureas will deliver a 0.7% reduction in A1c values.

Glimepiride or Glipizide would work in a patient with decreased renal disease and give a modest reduction to A1c value. This medication may not give enough of a decrease in A1c value at 0.7%.

Insulin. Insulin is easily titrated and has excellent efficacy of reaching target A1c goals, however practitioners need to be aware that over half of the dosage of insulin is eliminated through the kidney making decreasing dosage necessary as renal function declines (Hamilton, 2012). Patients presenting with symptoms of hyperglycemia and A1c values >9.0% should initially use insulin therapy without delay because the consequences of uncontrolled hyperglycemia can be severe (Tierney, 2012). In the event of an acute

decrease in renal function the American College of Physicians recommends a 25% decrease in insulin dosage (Liles, 2011).

Insulin would give adequate coverage and ability to drive her A1c to goal as desired. Insulin is very helpful as it can be utilized in renal disease with easy manipulation of the dosage. The dosage can be adjusted daily or even more frequently as needed to endure adequate control. As discussed earlier in the paper a majority of people would probably be put on multiple oral agents than start injections of insulin. However as Mrs. Jones's renal disease progresses she will most likely need to start insulin. Having a brief discussion about the fact that she may need after some time will make the transition less traumatic.

Many of these newer agents offer important advantages over the traditional therapies. Most of the new diabetic classes have a medication that is designed for clients with renal impairment. Having multiple options to prescribe in different patient presentations is helpful as a provider because it helps me tailor the drug therapy to the patient needs. To understand the risks and benefits of each of classes of drugs allows me as a practitioner to better educate and safely prescribe in the clinic setting.

Conclusion

Metformin is clearly the first-line choice for type-2 diabetes management. Decisions for second-line treatment should include patient preference and desired HgbA1c goal. Options I would choose for this patient include additional oral therapy such as increasing her metformin and adding a DPP-4 inhibitor such as Januvia / Janumet. This medication would have the desired effect with minimal risk to renal function and her renal function is within guidelines to initiate this therapy. Discussion

about her renal impairment should be addressed with her during this and subsequent visits. The goal of diabetes management is to slow the progression of the disease in the microvascular compartment. With her creatinine at 1.4mg/dl she may experience increased renal failure and will need insulin to control her diabetes.

Recommendations for practice

Many options available to clinicians for the treatment of type-2 diabetes and most of the classes of medications have a formulary that is applicable to patients with renal impairment. Therefore oral therapy should continue to be the first-line treatment for these patients. Options for providers are somewhat limited in patients with severe renal impairment and discussion of insulin therapy in the presence of stage 3b to 4 renal failure should be discussed with patients and utilized. The standard monitoring for changes in oral therapy is the HgbA1c and is most accurate if only drawn every three months. However, having the patient back in to have renal function studies evaluated may be needed every two to four weeks to ensure renal function is still adequate in patients with a creatinine approaching high-normal. A multisystem approach to managing diabetes is necessary for preservation of organ function including blood pressure, lipids, as well as blood-sugar and should be worked into the plan of care.

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