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The Addition of DPP4-Inhibitors to Metformin Therapy in the Long-term Management of Type II Diabetes Mellitus

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PERMISSION

Title The Addition of DPP4-Inhibitors to Metformin Therapy in the Long-term Management of Type II Diabetes Mellitus

Department Nursing

Degree Master of Science

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Abstract

This paper explores dipeptidyl peptidase-4 (DPP-4) inhibitors as an additional treatment option for patients with type II Diabetes Mellitus (DM) who are not controlled with metformin. The purpose is to look at the research indicating the efficacy and benefits of utilizing a DPP-4 inhibitor as an oral method for management of type II DM. Many patients with type II DM are often resistant to use an injectable medication, like insulin as part of their treatment plan. Many would like to continue to treat their diabetes with oral medications and the use of DPP-4 inhibitors may make that possible. Current studies look at the preservation of beta cell function and improved insulin sensitivity with the use of DPP-4 inhibitors, as well as the ability to effectively manage type II DM without insulin therapy (Utzschneider et al., 2017). By utilizing the DPP-4 inhibitors, the hope is to be able to offer this patient population a safe and effective way to manage their diabetes while prolonging the transition and possibly avoiding the need for insulin therapy.

Background

D. is a 60 year old Caucasian female who came to the clinic with a history of hypertension, hyperlipidemia, and type II DM. She was diagnosed with type II DM approximately 10 years prior. She has been managed on 500mg of Metformin twice daily. She was unsure of what her previous Hemoglobin (Hgb) A1C had been in the past. In the clinic, it was found that her DM was no longer controlled with a single oral medication and an adjustment would have to be made in order to improve her long-term health. This patient was willing to transition to insulin therapy if advised, which often times is not the case for diabetic patients.

There are other oral treatment options aside from metformin for individuals who are unable to or are not ready to transition to insulin or other injectable therapy while managing their diabetes. The option that will be addressed in this paper includes the use of DPP-4 inhibitors. DDP-4 inhibitors have been found not only to control blood sugars, but also to slow the decline of the beta cell function; which has been found to begin even prior to ones diagnosis of DM (Croxtall & Keam, 2008). DPP-4 inhibitors have shown to not be as effective as Metformin in terms of lowering Hgb A1C; however they have been found to be very effective as a combination therapy (Croxtall & Keam, 2008). Metformin tends to work in many different areas in the physiologic process of diabetes. These mechanisms include decreasing hepatic glucose production and intestinal absorption as well as increasing the peripheral glucose uptake and utilization (Woo & Robinson, 2016). Metformin is often utilized as first line therapy because of the efficacy it has in lowering the Hgb A1C, decreasing weight, and it's positive effect on lipid levels (Woo & Robinson, 2016). If the goal of the patient is to utilize oral agents for as long as possible and the patient is not achieving their Hgb A1C goal with Metformin alone, the DPP-4 inhibitor drug class may be an option.

Monotherapy with any oral medication is often unsuccessful in managing patient's long term with type II diabetes (Yoon et al., 2011). Yoon et al. (2011) state that the biggest drawback to starting a patient on a single oral medication is that while titrating oral dosages, patients are exposed to prolonged periods of hyperglycemia. This predisposes them to an increased risk of vascular disease. Initiating a combination therapy at the time of diagnosis will get a higher proportion of patients to goal versus the initiation of monotherapy (Yoon et al., 2011). A better long term management of diabetes will help

sustain the beta cell function in an individual, therefore increasing the efficacy of oral treatments as well as decreasing the chronic effects of diabetes such as neuropathy, retinopathy, and cardiovascular events.

Case Report

D. was in to the clinic on 3/10/2017 with the chief complaint of acute fatigue. She had been in the diabetic educator's office the week prior who suggested she be seen by primary care. She was last seen by her primary care providers about six months ago and states she is seen on a yearly basis. She has a history of hyperlipidemia, hypertension, and type II DM. She reported it has been 10 years since she was first diagnosed with diabetes. She has no neuropathy complaints; she gets annual eye exams and states that her primary will do yearly foot exams. She does not personally examine her feet nor was taught to do so. D.'s diabetes was managed with 500mg Metformin twice daily, her hypertension is managed with Lisinopril 20mg daily, her hyperlipidemia is managed with 20mg Atorvastatin daily and she also takes 81mg aspirin daily as well as a daily multivitamin. She is allergic to Penicillin; the specific reaction was not noted. She reported never having smoked or been around second hand smoke in the home. D. stated that she generally checks her blood sugar twice a week and noticed that it had been running between 150-200mg/dL. D. reported sleeping well, feeling refreshed in the morning and was not aware of any snoring or apnea. D. also denied any recent weight gain or constipation.

D.'s physical exam revealed good blood pressure control at 120/80 and a pulse of 64 beats per minute. She was afebrile and reported no recent fevers or chills. Her neck was supple; no masses were felt. She has a regular heart rhythm, no murmurs or rubs, and a normal respiratory effort without any crackles or wheezes present upon auscultation. Her

abdomen was soft, non-tender and bowel sounds present in all four quadrants. There was no lymphadenopathy felt; she was alert and orientation x4, skin was warm, dry, no abrasions, rashes, or lesions noted. She was noted to have full range of motion in all extremities and she had a normal mood and affect. When doing her foot exam, she had good sensation in all areas. She had no breakdown or callousing noted and good skin condition between joints and phalanxes.

To assist in the management and diagnosis for the etiology of her fatigue, it was decided to obtain some diagnostic lab work. A complete blood count was ordered to look for anemia, a comprehensive metabolic count was ordered to assess electrolyte imbalances, fasting blood glucose, and hydration status. A Hgb A1C was ordered to assess her overall management of diabetes in approximately the past three months. Due to her hyperlipidemia and the possible long terms effects due to her comorbidities; a fasting lipid panel was drawn. This will help assess for the need for lifestyle or medication changes. Lastly, a thyroid stimulating hormone was drawn to assess for thyroid function. If her thyroid was not producing enough hormone; it could help to diagnosis a deficiency and point to a possible source for her fatigue.

The only lab that was out of normal limits was her Hgb A1C at 8.3%. According to Cefalu (2017), the goal is somewhere between 6.5% and 7% depending on the patient and the practitioner. D.'s Hgb A1C indicated that her diabetes mellitus was in an uncontrolled state. Since she was diagnosed with diabetes 10 years prior and has been on an oral antihyperglycemic agent, lifestyle choices and changes were reinforced but were unable to be the sole intervention. At this point in her care, it was important to discuss what she would like to include in her pharmacological management. She was given the option of

either pursuing another oral medication or starting a basal rate of insulin. Due to her 10 year history of diabetes, her age of 60 years and her fairly elevated Hgb A1C of 8.3%; a basal insulin was encouraged, but the decision was ultimately left up to the patient. D. was very receptive to starting a basal rate of insulin and decided that she was open to the lifestyle changes associated with it.

D. was instructed to continue her same medication management, including the metformin, but she now will add in a nightly insulin injection of Glargine. She will start with a dose of five units nightly and increase it by one unit every two days if her blood sugars continue to be above 150mg/dL. It was also asked that she check her blood sugar twice daily, once in the morning and once in the evening and to keep a log of her results with pertinent information. This included different snacks, meals, and/or exercise that may have affected her glucose. She will plan to return to the clinic in 1 week for a re-evaluation of her management and a possible adjustment of her insulin. A large portion of this visit was centered around education in using the insulin pens, effects of insulin, signs and symptoms of hypoglycemia as well as how to handle low blood sugars. She was given an instruction sheet with a summary of the visit, a plan of care and how to take her insulin and titrate it up to goal. All her questions were answered and she was given the clinic phone number to call if any questions arise so that she can talk to the nurse or myself for instructions. She was also advised to follow up with her primary care at least every three months for now while managing her diabetes; if she would like to establish with myself for management she was encouraged to do so. She was instructed on “red flag” symptoms and to return to the clinic sooner with any acute changes or new concerns. Please refer to Appendix A for the full progress note.

Literature Review

Type II DM is a chronic disease that involves glycemic control, but also involves managing comorbidities such as hypertension, obesity and dyslipidemia (Kasper et al., 2014). Obtaining control of diabetes is very important to prevent damage to organs that are necessary for living such as the kidneys. While some individuals are very receptive and open to starting insulin like in D.'s case, others are not and an acceptable and effective alternative treatment plan should be offered and utilized. It is important to consider the individual's own physiologic ability to either make insulin or be receptive to it.

When looking at the pharmacological management of this disease, it is important to consider the physiological process that is taking place. DM type II involves a decreased sensitivity to endogenous insulin as well as degradation of the beta cell function. This is key in producing the insulin that is needed to drive the glucose into the body's cells (Kasper et al., 2014). Mu et al. (2006) observed that a class of medications, the DPP-4 inhibitors, works as a key regulator in the incretin hormones. Incretins work in response to a meal by stimulating insulin production and glucagon release, decreasing gastric emptying and increasing satiety. These advantageous incretin hormones are ultimately destroyed by dipeptidyl peptidase-4. By utilizing DPP-4 inhibitors, we are able to slow incretin degradation, and ultimately increase mealtime insulin production, glucagon release, and satiety. This will in turn decrease the overall blood glucose of an individual (Aschner et al., 2006).

While it may not be traditionally done, DPP4-inhibitors have the possibility of being utilized as a first line treatment in type II DM. Aschner, P. et al. (2006) looked at utilizing the DPP-4 inhibitor class as a monotherapy. It was noted that a once daily dose of

Sitagliptin (DPP-4 inhibitor) of at least 100mg inhibited plasma activity of the DPP-4 hormone by greater than 80%. That equates to an increase of two to three times more active incretin hormone, increased insulin and decreased plasma glucose. By blocking the hormones that lower insulin production and glucose release, there is an ability to decrease the plasma glucose levels. This works primarily on post parandial glucose management, which will help decrease an individual's susceptibility to hypoglycemia episodes while on this medication. Orally administered DPP4-inhibitors alone can decrease a hemoglobin A1C by 0.5%-1.0% (Drucker & Nauck, 2006). For those who need more of a decrease to obtain a goal Hgb A1C, one might need an additional therapy. While it is not yet supported in literature to utilize the DPP-4 inhibitors as first line monotherapy; it might be a medication that is utilized in the future for those who are unable to tolerate the use of metformin for various reasons.

The most common agent to combine DPP4-inhibitors with is metformin. This is the current standard of care (American Diabetes Association, 2017). Patients are commonly started on metformin as monotherapy when they start to show signs and symptoms of type II DM and their Hgb A1C is above 6.5%. As their Hgb A1C starts to rise, their dose of Metformin will be increased as tolerated until their diabetes is controlled, or until they reach a maximum dose of 2550 mg per day (Woo & Robinson, 2016). When additional intervention is needed to control their hyperglycemia, supplementary treatment options are looked at. Insulin therapy may not appeal to a diabetic patient, especially in the early stages of treatment. It is now being found that earlier treatment can possibly prevent or minimize the loss of beta cell function. (Mudaliar, S., 2013). Undoubtedly lifestyle changes are the preferred way to prevent type II DM. While some people are able to treat or control

their DM2 this way, for others additional treatment or intervention is needed. It is possible that starting individuals on a dual therapy early in their treatment for diabetes is beneficial. Yoon et al. (2011) state that an initial combination therapy may have a greater benefit on the B-cell function and help an individual maintain a long-term glycemic control without insulin. By utilizing two different antihyperglycemic agents, you will target different physiological processes and therefore be more effective at lowering the plasma glucose level. In utilizing a DPP-4 inhibitor you will increase the amount of active incretin hormones in the body. The DDP-4 inhibitor drug class has been shown to have an apoptotic and pro-proliferative effects on the B-cells. Another class of antihyperglycemics, the thiazolidinediones, have an agonistic effect on receptors and have been shown to increase B-cell structure and their ability to function as well as increasing the hepatic glucose output and decreasing the insulin resistance. Through this method you might be able to utilize the complimentary actions of oral agents and achieve a target Hgb A1C more effectively.

It is known that certain risk factors pre dispose some people to type II DM such as physical inactivity, first degree relatives with type II diabetes, certain ethnic groups, hypertension, hyperlipidemia, polycystic ovarian syndrome, and a history of cardiovascular disease (American Diabetes Association, 2017). There also are screening guidelines as well, which is secondary prevention. The American Diabetes Association (2017) recommends that fasting blood glucose screening should begin at age 45 and if results are normal, testing should be repeated every three years. What experts are not as concrete on is what occurs physically during the prodromal period of development of diabetes. How early or how late before diagnosis does the beta cell function start to decline? Would treatment with a DPP4-inhibitor before diagnosis (those with a high enough risk) benefit?

If this process can be identified, medication therapy can potentially be utilized to prevent or prolong the development of type II DM with early recognition. An article by Tabak et al. (2009) attempted to look at the pathological process and timing of impaired glucose tolerance, insulin sensitivity, and insulin secretion in type II diabetes. These individuals found that beta cell function has an abrupt and short-lived elevation between years three and four prior to the diagnosis of type II DM. After that small spike in productivity, the function of the beta cells begins to decrease and hyperglycemia becomes evident. This will continue until a diagnosis of type II DM is made. Knowing this trend, it is possible that in the future this will be a target for therapy in the prevention or prolongation of type II diabetes.

Important to include in consideration for treatment in an individual with type II diabetes is the degree of exhaustion in the beta cells. While our case study, D., was diagnosed with diabetes 10 years prior, her beta cell function most likely started the decline about 13 years ago. She made the choice to begin injection therapy with insulin, which was encouraged by her practitioner. While the DPP-4 inhibitor is another option and one that is worth a try, you may not see as good of results as with insulin due to the possible exhaustion of her beta cells.

Some of the attractions to using a DPP-4 inhibitor in patients are that they essentially work to augment a natural hormone or process that already exists. Many times synthetic products are created that are suitable for pharmacological therapy. The downside is that they may have multiple side effects or interactions. The DPP4-inhibitors tend to not have many side effects due to this natural augmentation. There can be some gastrointestinal side effects such as nausea and vomiting, but these side effects do tend to

recede after therapy has been stabilized. The most important thing to remember is to start low and go slow with titration (Svec, 2010). Another side effect that should be recognized is unexplained joint aches and pains. These can occur at the start of treatment or unprecedented a year later. According to Lowes (2015), this pain will recede within a month of cessation of the medication. With a DPP4-inhibitor, the degradation of DPP-4 is prevented. It is theorized that through this mechanism, another enzyme that degrades something in the inflammatory process is inhibited, therefore leading to these aches and pains. Zhong et al. (2015) reported that the DPP-4 enzyme may affect cardiovascular function through the regulation of inflammation. The authors state that the DPP-4 enzyme is highly present on many of the inflammatory cells, such as the T cells, and that it generally will control their function. In some individuals, inhibition of this enzyme may cross over to their joints and cause pain as a side effect. While D. does not have any rheumatologic concerns or chronic pain, individuals that do have these comorbidities may not be appropriate candidates for this choice of therapy.

Diabetes has multiple complications, one of them being cardiovascular disease. Because of this, Nga et al. (2011) researched the effects that DPP4-inhibitors have on the cardiovascular system. It was found that DPP-4 inhibitors reduced the amount of atherosclerotic lesions that were present in diabetic mice. The importance of this finding is that while utilizing DPP4-inhbitors to manage diabetes, atherosclerotic lesions are being reduced, and therefore the amount of diabetic complications is decreased.

When examining the effect that DPP-4 inhibitors have on the development of atherosclerotic plaques, it does make sense that individuals who have higher levels of incretin hormones in the body tend to have lower levels of cardiovascular disease.

Matsbubara et al. (2012) state that DPP-4 inhibitors work to phosphorylate the nitric oxide produced by the epithelium and therefore reduce the amount of atherosclerosis that accumulates over time and in diseased states. This process is one of the main components in diabetic complications, and many individuals tend to face multiple comorbidities that put them at high risk. In the case study of D., it would be ideal to utilize a DPP-4 inhibitor to not only manage her hyperglycemia but also to combat her comorbidities of hypertension and hyperlipidemia. Reducing atherosclerotic plaques in her vasculature system will help to reduce the progression of her comorbidities as well as prevent the development of other complications such as small vessel disease in the form of neuropathy, nephropathy, or retinopathy.

Learning Points

- DPP4-inhibitors are starting to be studied as a monotherapy agent in the control of diabetes. They have not been found to be more effective than metformin, however they may be an alternative if metformin is not an option.
- Dual therapy with two oral agents earlier in treatment may better effectively manage diabetes and prolong the time until insulin is needed.
- While beta cell function has been found to decline about three years prior to diagnosis of diabetes, DPP4-inhibitors have been found to increase the function of the beta cells as well as reduce the amount of apoptosis that occurs.
- An attraction to DPP-4 inhibitors over other pharmacological interventions is that they augment a natural process instead of utilizing a synthetic product. They are also weight neutral, they have a low propensity for hypoglycemia, and they have a low interaction rate with other medications.

- DPP-4 inhibitors affect on the cardiovascular system by reducing the amount of atherosclerosis present. They work to phosphorylate the nitric oxide and stabilize the epithelium that is preset in the vasculature. This should decrease and prolong the diabetic associated comorbidities such as hypertension and hyperlipidemia.

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Appendix A

Progress Note for D.

CC
D. is a 60yr of female who presents today for diabetes recheck. She saw her diabetes educator last week and was encouraged to follow up in the clinic.

HPI
D. is a new patient who presents today for a follow up on diabetic care. She saw her diabetic educator approximately 1 week ago who encouraged her to schedule a follow up in the clinic. She reports that her last follow up with her primary was about 6 months ago and that she is seen in the clinic on a yearly basis for management. She states that she has been a diabetic for about 10 years and has been "well managed" during that time period. She states she does get annual eye exams and her most recent was in May 2016. She does not routinely examine her feet but states that her primary does this during her yearly visits. She does report checking her sugars about twice a week and they are currently running anywhere between 150-200mg/dL. She does not check them at a consistent time during the day. She is not a smoker, she is not exposed to second hand smoke, nor has she ever smoked in the past. Currently her only symptom that she has noticed recently, is she is more fatigued. She reports sleeping well, feeling refreshed in the morning, and does not report any observed snoring or apnea. She is unaware if she has ever had her thyroid checked; however she denies any recent weight gain, or constipation.

Medications
Metformin 500mg twice daily
Aspirin 81mg daily
Lisinopril 20mg daily
Atorvastatin 20mg daily
Multivitamin daily

Allergies
Penicillin

PMH/Problem List
Dyslipidemia, Hypertension, Diabetes Mellitus type 2

Social History
D. lives independently in a private home with a significant other. She continues to have a job where she works 40 hours a week. She does have living children.

ROS
See HPI

Physical Exam

BP 120/80 **Pulse** 64 **Temp** 98.3 **SpO2** 90% on Room Air

Constitutional: Patient is well groomed, in no acute distress, does not appear ill.
HENT: Head normocephalic, atraumatic, nasal mucosa pink, no septal deviation, no rhinorrhea, oropharynx clear and moist, posterior pharynx without edema or exudate
Eyes: PERRLA, conjunctivae without injection, no discharge
Neck: supple, no masses, trachea midline
Cardiovascular: Regular rhythm, S1 and S2 normal. Exam reveals no S3 or S4. No murmur, rubs, or gallop. Brisk capillary refill. No peripheral edema.
Pulmonary/Chest: Effort normal, symmetric unlabored respirations, no respiratory distress, no crackles or wheeze, no chest tenderness
GI: soft, non-tender to palpation, bowel sounds present x4, no splenomegaly
Lymphadenopathy: No retropharyngeal, submental, submandibular, preauricular, post auricular, cervical, occipital, or supraclavicular lymphadenopathy appreciated.
Neurological: Alert and oriented x 3
Skin: Warm and dry, no abnormal lesions or rashes
Musculoskeletal: full range of motion without pain
Psychiatric: Normal mood and affect.

Differential Diagnoses
Hypothyroidism
Sleep Apnea
Uncontrolled Diabetes Mellitus type 2

Lab data/Diagnostics
CMP unremarkable
CBC unremarkable
Fasting Lipid Panel unremarkable
TSH unremarkable
Hgb A1C = 8.3

Course/Plan
Diagnostics ordered as above

A discussion was had with D. concerning her lab data and diagnostics. Her tests were unremarkable aside from an elevated Hgb A1C at 8.3. Her current medication regimen of Metformin 500mg BID is no longer controlling her diabetes mellitus type 2. She was educated on current lifestyle changes and management with inclusion of exercise and diet modification. It was discussed whether she would like to increase or add on another oral medication; or if she would like to start daily dosing of a basal rate insulin. Due to her 10-year history of diabetes mellitus, age of 60 years and possible declining beta cell function, basal rate insulin was recommended as first line therapy. D. was very agreeable to starting a basal rate of insulin at this time. She was instructed to continue her metformin at 500mg BID and to start nightly Glargine at 5units. She is going to check her sugars twice daily in the morning and then at night, and keep a log along with pertinent foods and comments that surround either high or low blood sugars. She is going to increase her Glargine by 1

unit every 2 days if her blood sugars remain above 150mg/dL. She was educated on the signs and symptoms of hypoglycemia and how to manage at home. I will plan to see her back in the clinic in 1 week for an evaluation of her management and a recheck of a fasting blood sugar. It was discussed that she should be seen by a primary more often and a Hgb A1C monitoring at least every 3 months until we are at a more stable control, if she does not have an appointed primary she is welcome to establish with myself. She was advised to return to the clinic sooner if she has any increasing symptoms or acute changes. D. verbalized an understanding and was agreeable to the plan of care.