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Managing Diabetes Mellitus in Chronic Kidney Disease: Approaches

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Abstract

The main objective of this article is to review the medical management of the disease known as "diabetes mellitus" and its general consequences. To assess the risks and benefits of intensive glycemic control in patients with diabetic kidney disease, the search was refined using the following specific terms: "diabetic nephropathy" and "kidney disease", as well as "diabetes management" and "antidiabetic agents" or "oral hypoglycemic agents". A unique challenge. Due to changes in insulin production, glucose transport and metabolism, impaired renal function is associated with hyperglycemia and hypoglycemia. Management of hyperglycemia is more difficult in patients with diabetic nephropathy, which often requires a change in the treatment regimen. When changing diabetes medications and insulin regimens, healthcare teams responsible for the care of these patients must be vigilant and organized to make such changes.

Keywords: Diabetes, Kidney, Anti-Diabetic, Insulin

Introduction

Diabetes is the primary symptom of peripheral vascular disease and a significant worldwide health issue (Kim et al. 2017). Regrettably, the correlation between diabetes and hypertension is linked to higher rates of cardiovascular disease-related morbidity and death. (Matheuse and others, 2013). It might be challenging to manage hyperglycemia in diabetic people. (Perone et al.2023).

The rising incidence of hyperglycemia in patients with chronic renal disease is concerning, in part because of the patients' poor response to therapy and in part because there is no data demonstrating the advantages of strict glycemic control in this patient group. When selecting a course of therapy, systemic risk factors such as obesity and an elevated risk of cardiovascular disease should also be taken into account (Cercato et al., 2019). Anti-diabetic medications: According to recent recommendations, insulin is the most effective course of therapy for those with diabetes and high blood pressure. However, new and promising oral therapy alternatives have lately surfaced, and the safety and effectiveness of antidiabetic medications are being reassessed. The next section discusses a few of these therapies. (Babiker and others, 2017).

Biguanide – Metformin

The cornerstone of treatment for type 2 diabetes is often metformin. It reduces the liver's synthesis of glucose, increases the end organs' use of glucose, improves insulin sensitivity (DeFronzo et al. 2016). Metformin is permitted for individuals with a glomerular filtration rate (GFR) of 30 mL/min/1.73 m2 according to current UK recommendations for type 2 diabetes (T2DM), with dosage modifications for a GFR of 45 mL/min/1.73 m2.

In the US, males who have a creatinine level higher than 1.5 mg/dL or women who have a creatinine level higher than 1.4 mg/dL should not use metformin (Philbricket al. 2009). Recent research indicates that for people with end-stage renal disease (CKD) or chronic kidney disease, the advantages of metformin exceed the hazards. However, because metformin increases the risk of lactic acidosis, it should be avoided in individuals with

CKD stages 3–5. However, new research using cell culture models has shown that metformin may have renal consequences.

By reducing the activity of the enzyme NADPH oxidase, metformin has been demonstrated to prevent glucose-induced oxidative stress in podocytes. This may strengthen the autophagic defense mechanisms by lowering the levels of 8-hydroxydeoxyguanosine (8-OHdG), a marker of overall oxidative stress and DNA damage in the body (Gao et al. 2019).

Tolazamide (Tolinase):

One medication that promotes endothelial cell release is tolazamide. This medication may result in hypoglycemia. particularly when paired with conditions like elevated insulin levels. Limit or control your consumption of carbohydrates. excessive drinking. One or more of the enzymes may build up as a result of infection, heart failure, stress, age, or a response to some medications that release sulfonylureas from protein binding sites. Blood sugar levels rise as a result of this. There are several medications in this class. The liver breaks down glipizide into other inactive metabolites. Glipizide dosage does not need to be changed in people with chronic kidney disease (CKD). Glipizide is therefore the recommended sulfonylurea (SU) for those suffering from chronic renal disease (Abe et al. 2011).

The kidneys and urine are where glibenclamide is broken down and eliminated. One should not undervalue the physiological effects of hypoglycemia. Patients with grade 3 or more severe renal illness (glomerular filtration rate < 60 ml/min) should not use this medication. Glibenclamide is also broken down by the kidneys into two main metabolites, one of which lowers blood sugar. Schizophrenia patients may acquire these elements. Glibenclamide lowers thrombocytopenia, however people with renal impairment shouldn't use it. (Flow rate in circulation < 60 milliliters per minute)

In conclusion, glibenclamide and Diabezidum, another diuretic, are linked to a higher prevalence of hypoglycemia. Diabezidum also possesses a weak metabolite that is eliminated in the urine in considerable quantities (80%). The right dosage should be followed when taking this drug. Those with neurological conditions should use this drug with care. However, if the GFR is less than 40 ml/min, it should not be used (Arnold et al. 2016).

Repaglinide: Repaglinide and nateglinide are members of the repaglinide family, a class of sulfonylureas with limited efficacy and a fast onset of action that promotes the synthesis of

insulin. They work particularly well to reduce blood sugar levels after meals. In individuals with severe liver illness, the metabolite nateglinide becomes an active metabolite and should be taken cautiously (Scheen et al.2023). GFR is maintained at 30 ml/min/1.73 m2 until repaglinide medication is discontinued. In patients with advanced renal illness, repaglinide therapy should be started with a dosage increase to 0.5 mg in order to prevent hypoglycemia (Stompóret al. 2020).

Alpha-glucosidase inhibitors: By decreasing lipid peroxidation, alpha-glucosidase inhibitors lessen lipid peroxidation. Less than 2% of the oral dosage of acarbose is eliminated as the medication itself, and its metabolites are also eliminated in the urine. Acarbose is completely absorbed. After entering the liver, the leftover form of metformin is eliminated unaltered. Patients with stages 4 and 5 chronic renal disorders should not use this medication due to the low response rate to insulin treatment and the lack of long-term research in kidney disease patients (Kalantar-Zadehet al.2021).

Rosiglitazone; Diabetes is treated with rosiglitazone maleate. It is an intriguing narrative that is intricate and multifaceted. Adipose tissue, skeletal muscle, and the liver are among the tissues that have these receptors and are essential for the action of insulin. The expression of many insulin signaling pathways in lipid and adipose tissue homeostasis is modulated by activation of the nuclear receptor PPAR-γ. It has been demonstrated that pioglitazone works just as well for individuals with advanced renal disease who do not require dialysis (Satirapojet al. 2018). The PROactive research, which looked at the effectiveness of pioglitazone in patients, found that it considerably reduced blood total creatinine more than rosiglitazone (0.8 ml/min/1.73 m2 annually). However, patients with heart disease or severe renal disease and low GFR should use these medications cautiously since they may cause fluid retention (Clark et al. 2019).

Dipeptidyl Peptidase-4 Inhibitors

Inhibitors of dipeptidyl peptidase-4 (DPP-4) stimulate the secretion of glucose-dependent insulin by preventing the breakdown of the incretin hormone DPP-4 (Pechman et al., 2024). Sitagliptin is one of five DPP-4 inhibitors; each has unique pharmacological characteristics as well as distinct mechanisms for absorption and disposal.
• With the right dosage modification, sitagliptin (Januvia), which is eliminated unaltered in the urine, can be utilized to treat chronic kidney disease. Patients with minor renal impairment should take 50 mg per day instead of 100 mg. The dosage should be lowered to

25 mg per day for individuals who need dialysis due to end-stage renal disease (ESKD) or stage 4 chronic kidney disease.

• About 25% of vildagliptin (Gallus) is eliminated unaltered in the urine after being converted to inactive metabolites in the liver. Vildagliptin dosages for people with type 2 diabetes or moderate to severe chronic renal disease should be lowered to 50 mg per day.
• An active metabolite of saxagliptin (Onglyza) is produced and eliminated in the urine. The recommended daily dosage of 5 mg should be lowered to 2.5 mg in individuals with renal impairment. Patients with end-stage renal disease (ESRD) who need hemodialysis must have their doses adjusted.

Linagliptin (Tradjenta) is the best option for people with renal insufficiency, particularly stage 5 chronic kidney disease (GFR <15 mL/min/1.73 m2), since it is the only DPP-4 inhibitor that is eliminated in the bile.

• At a dosage of 25 mg per day, alogliptin (Nikina) is eliminated unaltered in the urine. The dosage should be lowered to 12.5 mg/day for individuals whose creatinine clearance is between 30 and 60 ml/min, and to 6.25 mg/day for patients who have renal disease or are receiving hemodialysis.

DPP-4 inhibitors and heart failure DPP-4 inhibitors may aid in heart failure, according to recent data. When compared to a placebo, a meta-analysis of 59 randomized controlled studies with 36,620 patients receiving DPP-4 inhibitors for 24 weeks revealed a substantial decrease in hospitalizations owing to heart failure. A greater incidence of heart failure is linked to risk factors such N-terminal B-type natriuretic peptide (NNNP), GFR below 60 ml/min, and pre-existing heart failure. Results pertaining to heart failure may be impacted by the combination of DPP-4 inhibitors with other medications, such as ACE inhibitors and BNP P antagonists (Schüttet al.2024).

Mimetic Increments:

The phrase "potentiator mimetic" describes a class of glucagon-like peptide-1 (GLP-1) agonists and analogs that inhibit glucagon production, raise insulin release in an insulin-dependent manner, and lower the risk of hypoglycemia (Ja'arah et al., 2021). Through internal physiological changes, the mimetics also decrease stomach emptying, which lowers appetite and causes weight reduction. Nonetheless, nausea and vomiting are the most frequent adverse effects. Glomerular filtration is primarily responsible for eliminating this phenomenon, which is also prevalent in individuals with end-stage renal disease (ESRD),

however removal is a little slower in those with mild to moderate renal failure. Additionally, glomerular filtration removes lixisenatide, which is then reabsorbed and undergoes metabolic breakdown to produce amino acids and short polypeptides needed for protein synthesis. There is a dearth of information on people with renal illness, though. Pharmacokinetics and safety in non-diabetic individuals are unaffected by mild to severe renal impairment. Nonetheless, individuals with renal failure had longer medication clearance, indicating that dosage modification is required for this patient group. Lastly, liraglutide is not linked to any one organ and is processed similarly to big proteins. There are currently few guidelines for moderate to severe renal impairment, and its usage in individuals with renal illness is restricted (Farrington et al. 2016).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors:

About 90% of the glucose that is expelled is reabsorbed by the sodium-glucose cotransporter 2 (SGLT2) protein, which is found in the kidney's proximal tubules. In individuals with hyperglycemia, a class of medications known as SGLT2 inhibitors drastically lowers blood glucose levels by inducing glycosuria and osmotic diuresis. When a patient's estimated glomerular filtration rate (eGFR) is higher than 45 mL/min/1.73 m2, this class is authorized to treat type 2 diabetic mellitus (T2DM). Canagliflozin has only been investigated in individuals with renal illness thus far, and it has been shown to be safe and effective in a group of patients with stage 3 renal failure (Simeset al. 2019).

Insulin Therapy:

Through specialized channels that are separate from the general circulation, the kidney plays a crucial role in controlling insulin. The primary route involves the metabolism of insulin in proximal tubular cells by endocytosis and glomerular filtration. The second channel involves the diffusion of insulin through peritubular capillaries, where cells, particularly those in the distal portion of the renal corpuscle, are bound by the luminal membrane (Bagga et al., 2016). The last metabolic products are created during this phase by transporting glucose to the cytoplasm, where it is transformed into carbonic acid and released into constructed blood vessels. The kidney plays a part in insulin clearance and is crucial for insulin processing and storage in individuals with renal impairment because exogenous glucose does not take part in the liver's first-pass metabolism. Numerous additional issues, such as insulin and glucose metabolism, are linked to chronic kidney disease. Because renal failure lowers insulin clearance, hypoglycemia is less likely to occur.

enhanced insulin uptake by proximal tubular cells and enhanced glucose reabsorption capacity initially offset this decrease in insulin clearance (Mathieu et al.2021).

References

Abe, M., Okada, K., & Soma, M. (2011).Antidiabetic agents in patients with chronic kidney disease and end-stage renal disease on dialysis: metabolism and clinical practice. *Current drug metabolism*, *12*(1), 57-69.

Arnold, R., Issar, T., Krishnan, A. V., &Pussell, B. A. (2016).Neurological complications in chronic kidney disease. *JRSM cardiovascular disease*, *5*, 2048004016677687.

Bagga, A., Srivastava, R. N., Gupta, A. K., Jana, M., Bal, C. S., Thergaonkar, R. W., &Khandelwal, P. (2016). Renal Anatomy and Physiology. *Paediatric Nephrology*, 1.

Babiker, A., & Al Dubayee, M. (2017). Anti-diabetic medications: How to make a choice?. *Sudanese journal of paediatrics*, *17*(2), 11.

Cercato, C., & Fonseca, F. A. (2019). Cardiovascular risk and obesity. *Diabetology& metabolic syndrome*, *11*, 1-15.

Clark, A. L., Kalra, P. R., Petrie, M. C., Mark, P. B., Tomlinson, L. A., &Tomson, C. R. (2019). Change in renal function associated with drug treatment in heart failure: national guidance. *Heart*, *105*(12), 904-910.

DeFronzo, R., Fleming, G. A., Chen, K., &Bicsak, T. A. (2016). Metformin-associated lactic acidosis: Current perspectives on causes and risk. *Metabolism*, *65*(2), 20-29.

Farrington, K., Covic, A., Aucella, F., Clyne, N., De Vos, L., Findlay, A., ...& Van Den Noortgate, N. (2016). Clinical Practice Guideline on management of older patients with chronic kidney disease stage 3b or higher (eGFR< 45 mL/min/1.73 m2). *Nephrology Dialysis Transplantation*, *31*(suppl_2), ii1-ii66.

Gao, Q. (2019). Oxidative stress and autophagy. *Autophagy: biology and diseases: basic science*, 179-198.

Ja'arah, D., Al Zoubi, M. S., Abdelhady, G., Rabi, F., &Tambuwala, M. M. (2021).Role of glucagon-like peptide-1 (GLP-1) receptor agonists in hypoglycemia. *Clinical Medicine Insights: Endocrinology and Diabetes*, *14*, 11795514211051697.

Kalantar-Zadeh, K., Jafar, T. H., Nitsch, D., Neuen, B. L., &Perkovic, V. (2021).Chronic kidney disease. *The lancet*, *398*(10302), 786-802.

Kim, Y. J., Hwang, S. D., Oh, T. J., Kim, K. M., Jang, H. C., Kimm, H., ...& Lim, S. (2017). Association between obesity and chronic kidney disease, defined by both glomerular filtration rate and albuminuria, in Korean adults. *Metabolic syndrome and related disorders*, *15*(8), 416-422.

Mathieu, C., Martens, P. J., &Vangoitsenhoven, R. (2021). One hundred years of insulin therapy. *Nature Reviews Endocrinology*, *17*(12), 715-725.

Matheus, A. S. D. M., Tannus, L. R. M., Cobas, R. A., Palma, C. C. S., Negrato, C. A., & Gomes, M. D. B. (2013). Impact of diabetes on cardiovascular disease: an update. *International journal of hypertension*, *2013*(1), 653789.

Pechmann, L. M., Pinheiro, F. I., Andrade, V. F. C., & Moreira, C. A. (2024). The multiple actions of dipeptidyl peptidase 4 (DPP-4) and its pharmacological inhibition on bone metabolism: a review. *Diabetology& Metabolic Syndrome*, *16*(1), 175.

Perone, F., Pingitore, A., Conte, E., Halasz, G., Ambrosetti, M., Peruzzi, M., &Cavarretta, E. (2023, March). Obesity and cardiovascular risk: systematic intervention is the key for prevention. In *Healthcare* (Vol. 11, No. 6, p. 902).MDPI.

Philbrick, A. M., Ernst, M. E., McDanel, D. L., Ross, M. B., &Moores, K. G. (2009). Metformin use in renal dysfunction: Is a serum creatinine threshold appropriate?. *American journal of health-system pharmacy*, *66*(22), 2017-2022.

Satirapoj, B., Watanakijthavonkul, K., &Supasyndh, O. (2018). Safety and efficacy of low dose pioglitazone compared with standard dose pioglitazone in type 2 diabetes with chronic kidney disease: a randomized controlled trial. *PloS one*, *13*(10), e0206722.

Schütt, K. (2024). Rethinking the Impact and Management of Diabetes in Heart Failure Patients. *Current Heart Failure Reports*, *21*(1), 53-60.

Scheen, A. J. (2023). Pharmacokinetic, toxicological, and clinical considerations for the treatment of type 2 diabetes in patients with liver disease: A comprehensive update. *Expert opinion on drug metabolism & toxicology*, *19*(8), 543-553.

Simes, B. C., &MacGregor, G. G. (2019). Sodium-glucose cotransporter-2 (SGLT2) inhibitors: a clinician's guide. *Diabetes, metabolic syndrome and obesity: targets and therapy*, 2125-2136.

Stompór, T., Adamczak, M., Masajtis-Zagajewska, A., Mazanowska, O., Maziarska, K., Witkowska, A., &Więcek, A. (2020). Diagnosis and treatment of type 2 diabetes mellitus in patients with chronic kidney disease and eGFR< 60 mL/min—A position statement of the Polish Society of Nephrology Working Group on Metabolic and Endocrine Disorders in Kidney Diseases. *EndokrynologiaPolska*, *71*(1), 3-14.