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Oral Pharmacotherapy for Patients with Diabetic Kidney Disease: An Update

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Abstract Diabetes mellitus is the leading cause of chronic kidney disease (CKD) that usually progresses to end stage renal disease (ESRD) requiring dialysis or kidney transplantation. CKD is also associated with cardiovascular morbidity and mortality. Optimum control of blood sugar is the most important intervention to prevent or delay the progression of early stage diabetic kidney disease (DKD) to ESRD and to prevent cardiovascular events. Currently there are few antidiabetic drugs that are totally safe in a patient with DKD. The role of this review paper is to explore the safety and renoprotective effect of oral antidiabetic drugs used in patients with DKD. Traditionally, insulin has been considered the ideal choice for treating diabetic patients with CKD. Recently, new oral drug options have become good alternatives in the management of DKD. Sodium-glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin, canagliflozin, and empagliflozin) and certain dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, alogliptin, and linagliptin) have been reported to improve renal outcomes by reducing the amount of albuminuria and preventing GFR loss in patients with type 2 diabetes. The renoprotective effect along with reduction in HbA1c levels, indicates the potential therapeutic effect of SGLT2 inhibitors and some DPP4 inhibitors in DKD.

Keywords Diabetes Mellitus, Diabetic Kidney Disease, Chronic Kidney Disease, Oral Antidiabetic Drugs

1. Introduction

Diabetic kidney disease (DKD) is a global health problem; a substantial proportion will proceed to end stage renal disease (ESRD) requiring dialysis or renal transplantation with reduced quality of life. DKD is also a high risk for the development of cardiovascular (CV) events (angina, myocardial infarction, hypertension, stroke or death). As a cause of ESRD, diabetes ranks first both globally and nationwide; in Malaysia 58% of new patients of ESRD requiring dialysis in 2012 was due to type 2 diabetes mellitus (T2DM) [1]. Optimum glycaemic control is one of the most important intervention to prevent progression or reduction of early stage chronic kidney disease (CKD) in patients with diabetes and to prevent morbidity and mortality directly related to diabetes.

However, there are insufficient data and trials regarding the ideal glycaemic target in patients with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 (CKD stage 3 or more). Intensive or tight glycaemic control are associated with higher risk of hypoglycaemia and hypoglycaemia related CV events in patients with DKD especially who are elderly, having substantial comorbidities and receiving insulin or sulphonylureas. Diabetes-related hypoglycaemic episodes have been reported to induce acute cerebrovascular disease, myocardial infarction, neurocognitive dysfunction, retinal cell death/ blindness and raise quality of life issues by interrupting sleep, driving, employment, and recreational activities (e.g., exercise, travel) [2]. Moreover, the benefits of tight glycaemic control in patients with long-standing diabetes and advanced CKD are not yet fully known. Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) recommends that patients who are at risk for hypoglycaemia should not be treated to an HbA1c <7% and that the target HbA1c may be >7% in individuals who have comorbidities or limited life expectancy and who are at risk for hypoglycaemia [3, 4]. Among ESRD, some authors target an HbA1c goal of 7-8%, with the specific goal in individual patients based upon the risk of hypoglycaemia and presence of comorbid conditions [5, 6]. Levels above 8% or below 7% carry increased risks of all-cause and CV death.

For optimum glycaemic control, most of the patient having DKD will require antidiabetic agents. But all the drugs are not absolutely safe in a patient having DKD; they are at increased risk of hypoglycaemia and also other adverse effects of antidiabetic drugs at standard doses. This is due to impaired renal gluconeogenesis from lowered kidney mass and impaired metabolism/ clearance of some antidiabetic drugs. Therefore, for safe use, renal factors

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should be considered when selecting antidiabetic medications for individual patients with DKD. For patients with eGFR <60 ml/min/1.73m^2, (CKD stage 3) certain drug dose adjustment or discontinuation may require to avoid the risk of hypoglycaemia and adverse effects [7].

2. Aim

This review paper focuses on the updates of safe use, limitations and renoprotective effects of oral antidiabetic drugs in patients with DKD. The treatment of diabetes in patients with kidney transplant recipients is out of scope in this literature.

3. Methods

Related original studies and reviews were explored that were published through Jan 2001 to Jan 2018 on the management of diabetes in CKD correlating our topics and were identified in google search engine and Medline by using keywords that included DKD, CKD, and oral antidiabetic drugs.

4. Oral Antidiabetic Drugs

Currently, 9 unique classes of oral drugs are available for the treatment of patients with T2DM in most countries. The glycaemic control in T2DM is achieved with some agents that predominantly lower the fasting plasma glucose (metformin and sulfonylureas); with others that primarily lower postprandial plasma glucose excursions (meglitinides, and α-glucosidase inhibitors); and with still others that do both (thiazolidinediones and dipeptidyl peptidase-4 inhibitors) [8]. Traditionally, insulin has been considered the safe choice for treating diabetic patients with CKD. Recently, new oral drug options have become good potential alternatives in the management of DKD with their prescription and dosages regularly reviewed.

4.1. Metformin

The only drug of biguanide class available now is metformin; it is renally cleared, it does not cause hypoglycaemia but lactic acidosis though rare is a serious side effect in patients with renal impairment [9, 10]. The United States Food and Drug administration (US FDA) recommends that metformin should not be initiated for patients with an eGFR <45 ml/min/1.73m^2 [11]. Patients currently on metformin, having an eGFR 30-45 ml/min/1.73m^2 needs assessment of risk/ benefit. The American diabetes association (ADA) in their standards of medical care 2018, specifies no dose adjustment is required in patient with eGFR >45 ml/min/1.73m^2 [12]. In 2016, US FDA has contraindicated the use of metformin in patients with an eGFR <30 ml/min/1.73m^2 [11]. It is recommended that metformin should be stopped in the presence of situations that are associated with hypoxia or an acute decline in kidney function such as dehydration, sepsis/shock, hypotension, acute myocardial infarction, and use of other nephrotoxic agents [13, 14]. Metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30-60 ml/min/1.73m^2 [11]. Renal protective effects of metformin are being evaluated by various studies. Metformin is effective and safe, is inexpensive, and may reduce risk of CV events and death [12]. A recent systematic review has supported the use of metformin as first line given its additional beneficial effect by reducing CV mortality in patient with T2DM [15].

4.2. Sulfonylureas

Most of the sulfonylureas and their active metabolites are renally cleared. Studies have shown that there is an increased risk of hypoglycaemia as GFR declines. Glyburide (glibenclamide) should be avoided with eGFR <60 ml/min/1.73m^2 as at this stage hypoglycaemia is greatly increased [16]. Gliclazide should be avoided if the GFR falls to <45 mL/min/1.73m^2 [3, 17]. Glimepiride is primarily metabolized by the liver, the active metabolites of the drug formed by the liver is renally excreted [18]. Glimepiride should be used with caution if the eGFR is <60 ml/min/1.73m^2 and not be used with eGFR <30 ml/min/1.73m^2 [16]. Glipizide is metabolized by the liver; it is cleared renally in small amounts (less than 10%) and can still be used with caution with an eGFR <30 ml/min/1.73m^2 [19, 20]; dose adjustments are not necessary in patients with CKD. Therefore, glipizide and glimepiride are the sulfonylureas of choice in patients with CKD [7, 21, 22].

4.3. Meglitinides

Meglitinides, such as repaglinide or nateglinide, are sulfonylurea-like agents that stimulate insulin secretion and control postprandial hyperglycaemia [18]. Nateglinide should be initiated conservatively at lower dose of 60 mg with eGFR <30 ml/min/1.73m^2 [12]. The active metabolite of nateglinide is cleared by haemodialysis; it can be used in those undergoing dialysis [23]. Repaglinide is mainly metabolized by the liver, with less than 10 percent renally excreted [18]. Repaglinide appears safe in individuals with CKD, but should be used with caution in those with an eGFR <30 ml/min/1.73m^2, and started at the lowest dose (0.5 mg) with slow upwards titration [24, 25].

4.4. Thiazolidinediones

Thiazolidinediones such as pioglitazone or rosiglitazone, increase insulin sensitivity in the adipose tissue, skeletal muscle, and liver and do not cause hypoglycaemia [26]. They are metabolized by the liver and can be used in CKD. No dose adjustment is needed in DKD [12]. However, fluid retention is a major side effect and these drugs should be avoided in a patient with symptomatic heart failure and in those with advanced CKD [27].

4.5. Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors control postprandial hyperglycaemia by inhibiting small intestine brush-border alpha-glucosidases, thereby slowing degradation of complex carbohydrates into glucose as well as reducing the rate of glucose absorption. Acarbose is metabolized nearly completely within the gastrointestinal tract and less than 2% of an oral dose is renally excreted. On the other hand, greater amount of miglitol is absorbed systemically and excreted unchanged in the urine with increased accumulation in patients with CKD [18]. Due to their modest efficacy in glycaemic control and lack of long-term studies in patients with CKD, these medications should be avoided in CKD stages 4 and 5 [27, 28]. The ADA 2018, in their guidance has recommended to avoid acarbose at eGFR <30 ml/min/1.73m^2 and miglitol at eGFR <25 ml/min/1.73m^2 [12].

4.6. Colesevelam

The bile acid sequestrant colesevelam is used as an adjunctive therapy to improve glycaemic control in adults with T2DM. It binds to intestinal bile acids/ cholesterols, decreases blood low-density lipoprotein (LDL) cholesterols but unknown mechanism of lowering blood glucose for those with T2DM. Colesevelam shows no difference in efficacy or safety in those with an eGFR <50 ml/min/1.73m^2 but data are limited as it has not been adequately studied in more advanced CKD. No specific dose adjustment has been recommended by the manufacturer in a patient with DKD [12].

4.7. Bromocriptin

The dopamine-2 agonist bromocriptin is available in the US as an anti-diabetic agent. It activates brain dopamine D2 receptors to lower plasma levels of glucose. Bromocriptine has not been adequately studied in CKD. No specific dose adjustment has been recommended by the manufacturer in a patient with DKD [12].

4.8. Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors are novel class weight neutral oral anti-diabetic drugs for the treatment of T2DM with a low risk for hypoglycaemia. The available DPP-4 inhibitors (also known as gliptins) are sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin. Since most DPP-4 inhibitors are excreted by the kidneys, dose adjustments are recommended for patients with renal dysfunction [12]. Sitagliptin is mainly cleared by the kidneys, therefore it has been advised to reduce the usual dose of 100 mg/day, to dose at 50 mg/day with moderate renal impairment, and a dose of 25 mg once daily with an eGFR <30 ml/min/1.73m^2 [29, 30]. Saxagliptin needs a dose reduction; the normal dose (5 mg once daily) should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment [31]. Alogliptin also needs a dose reduction from dose of 25 mg daily to 12.5 mg daily with an eGFR <60 ml/min/1.73m^2 and then to 6.25 mg daily with an eGFR <30 ml/min/1.73m^2 [32]. Linagliptin is the only DPP-4 inhibitor that is eliminated nearly entirely via the bile; only a small amount of it is cleared renally. Linagliptin is a choice for patients with all stages of CKD, and even stage 5 (eGFR <15 ml/min/1.73m^2) without dose adjustments [33, 34]. Vildagliptin also appears to be effective in this population with limited studies [35]. Dose of vildagliptin has to be reduced by half (50 mg/day) both for moderate (eGFR ≥30 to ≤50 ml/min/1.73m^2) and severe CKD (eGFR <30 ml/min/1.73m^2) [35].

DPP-4 inhibitors also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo [36]. A recent cohort study demonstrated that DPP-4 inhibitor treatment could ameliorate diabetic nephropathy by reducing urine albumin excretion and mitigating the reduction of eGFR in T2DM patients [37]. Other previous studies have also shown that sitagliptin, alogliptin, and linagliptin are effective in reducing the amount of albuminuria in patients with T2DM [38-40]. Further long-term studies are required to define the renal outcomes of treatment with DPP-4 inhibitors.

The DPP4 inhibitors were proven to be neutral with regard to CV outcomes. However, concerns on the safety of heart failure have been raised with increase in the risk for heart failure hospitalization in diabetic patients treated with DPP-4 inhibitor saxagliptin [41]. Further studies are required to come to a conclusion on whether DPP-4 inhibitors result in increased risk of heart failure.

4.9. Sodium-Glucose Co-Transporter 2 Inhibitors

The sodium-glucose cotransporter 2 (SGLT2) inhibitors are another novel class of antidiabetic drugs that can effectively control blood sugar level without producing weight gain or hypoglycaemia. The available SGLT2 inhibitors are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin. The SGLT2, expressed in the renal proximal tubules, accounts for 90% of the glucose reabsorption filtered through the glomeruli. They selectively inhibit SGLT2, increase urinary excretion of glucose in patients with hyperglycaemia and lower plasma glucose levels in an insulin-independent manner [42]. They produce osmotic diuresis in diabetes with hyperglycaemia and are accompanied by modest blood pressure reduction, some weight loss and improved glycaemic control [43]. Side effects of SGLT2 inhibitors include significant increase of genitalia and urinary tract infection. A small increase in LDL-cholesterol levels have also been observed for this class [44]. Euglycaemic diabetic ketoacidosis (DKA) have been reported in patients with type 1 and T2DM with all SGLT2 inhibitors [45]. These drugs should be prescribed carefully in those patients with severe beta-cell insufficiency, latent autoimmune diabetes and in postsurgical patients [46]. The US FDA issued a warning about the risk of euglycaemic DKA ketoacidosis occurring in the absence of significant

hyperglycaemia in patients with diabetes treated with SGLT2 inhibitors. The US FDA has also issued a warning for canagliflozin related to reduced bone mineral density and increased risk of bone fracture [47].

Efficacy of SGLT2 inhibitors are dependent on renal function; their efficacy will decrease in reduced renal function and there is likely to be adverse effects of the drugs. In general, this therapeutic class should not be used for the treatment of patients with T2DM with an eGFR of <45 ml/min/1.73m^2 and they are contraindicated with an eGFR of <30 ml/min/1.73m^2, including patients with ESRD who are on dialysis [2, 48-50].

Canagliflozin, is safe and effective with 100 mg daily in patients having eGFR 45–59 ml/min/1.73m^2; no dose adjustment is required if eGFR >60ml/min/1.73m^2 [48, 51]. Its use should be avoided and discontinued if the eGFR is persistently <45 ml/min/1.73m^2 because of an increase in adverse events as well as reduced efficacy. Dapagliflozin is avoided for use if the eGFR is <60 ml/min/1.73m^2 and discontinued if eGFR <45 ml/min/1.73m^2 [12]. Dapagliflozin is contraindicated if eGFR <30 ml/min/1.73m^2. Empagliflozin can be used upto an eGFR of 45 ml/min/1.73m^2; it is contraindicated if eGFR <30 ml/min/1.73m^2 [12].

Several recent trials have evaluated the potential renoprotective effect of SGLT2 inhibitors in diabetic patients. SGLT2 inhibitors have direct effects on the kidney that are not mediated through glycaemia; they reduce intraglomerular pressure, albuminuria and GFR loss through mechanisms that appear independent of glycaemia [52-55]. In one trial, patients treated with canagliflozin had a decrease in the urinary albumin-creatinine ratio [56]; canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESRD, or death from ESRD by 40% [55]. In another trial involving diabetic patients with moderately decreased renal function, dapagliflozin showed favourable results in terms of reduced albuminuria [57]. Empagliflozin compared with placebo, reduced the risk of incident or worsening nephropathy by 39% and the risk of doubling of serum creatinine accompanied by eGFR 45 ml/min/1.73m^2 by 44% [58]. The renoprotective effect along with the combination of a reduction in HbA1c levels, decreased body weight and blood pressure, indicates the potential therapeutic effect of SGLT2 inhibitors in DKD [59, 60].

Patients with DKD are at high risk of CV events, and some SGLT2 inhibitors (canagliflozin and empagliflozin) have demonstrated CV benefits. Recent trials have revealed CV benefits of empagliflozin by reducing the risk of CV death in patients having diabetes and CVD [53, 58]. In 2016, December 2, the US FDA added a new indication for empagliflozin, to reduce the risk of CV death in adults with T2DM and CVD [61] based on data from the EMPA-REG OUTCOME study [58]. Trials have also revealed similar CV benefits of canagliflozin among participants with and without kidney disease at baseline [53, 55].

5. Conclusions

Optimum glycaemic control is one of the most important intervention to prevent or retard the progression of early stage CKD to advanced stage CKD in patients with diabetes. Tight glycaemic control also prevents morbidity and mortality directly related to diabetes. In DKD, there is impaired metabolism, transport and excretion of glucose, insulin and certain antidiabetic drugs favouring both hyperglycaemic peaks and hypoglycaemia. Additionally, in CKD there is reduced functioning renal mass affecting renal gluconeogenesis for glycaemic homeostasis. Moreover, the benefits of tight glycaemic control in patients with advanced CKD are not fully known. Intensive or tight glycaemic control are associated with higher risk of hypoglycaemia with hypoglycaemia related CV events and mortality in patients with DKD. The goals for glycaemic control in patients with renal impairment and a GFR of <45 ml/min/1.73m^2 have yet to be defined. Management of hyperglycaemia in patients with DKD is challenging, requiring regular assessment and adjustment of antidiabetic agents and their doses. The antidiabetic drugs should be used with care considering their safety in patients with DKD specially to avoid hypoglycaemia and drug related adverse effects. Recently several trials have indicated the potential renoprotective effect of SGLT2 inhibitors and certain DPP-4 inhibitors in diabetic patients. Further large trials of longer durations are needed to determine definitively whether specific glucose-lowering drugs improve renal outcomes.

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