Glycaemic control and glucose-lowering therapy in diabetic patients with kidney disease

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Introduction

Chronic kidney disease (CKD) is a common condition that affects approximately more than 50 million people worldwide.[1] Diabetes mellitus, one of the chronic non-communicable diseases is of increasing prevalence worldwide including in developing countries where it was previously a disease of less importance.[2] This rapid increase in prevalence has been attributed to rapid population growth, ageing, urbanisation, and increasing prevalence of obesity and sedentary lifestyles.[2] The use of antiretroviral therapy for the treatment of human immunodeficiency virus (HIV) has been shown to increase the risk of diabetes by causing insulin resistance and metabolic syndrome.[3] It is estimated that by the year 2030 the number of people with diabetes mellitus worldwide will be approximately double the number in 2000.[2] Diabetes has been implicated as one of the causes of renal diseases.[4] It is estimated that in up to 45% of patients with renal failure, diabetes is the cause.[5] Studies show that 15 to 24% of patients with diabetes also have moderate to severe CKD,[6–8] although a higher prevalence of 40% was found in one stud.[9] Scientific evidence shows that patients with a combination of diabetes and CKD (especially associated with albuminuria) have higher mortality rates compared with those with diabetes alone.[10–12]

Definition and diagnosis of CKD

Until recently, CKD resulting from diabetes has been referred to as diabetic nephropathy. Currently CKD resulting from diabetes is generally referred to as diabetic kidney disease (DKD) after review by the Diabetes and Chronic Kidney Disease Working Group of the National Kidney Foundation. Diabetic nephropathy is currently reserved for renal disease attributed to diabetes with histopathological injury from renal biopsy.[13,14] Regardless of the underlying pathology, CKD is defined as kidney damage or impaired renal function for 3 months or more.[14] Proteinuria has been shown to be an important marker of impaired renal function.[15] In patients with type 1 diabetes who are found to have proteinuria, CKD is most likely caused by diabetes because studies have shown that there is a strong correlation between proteinuria and typical histological findings on renal biopsy.[16] Microalbuminuria, however, is less associated with typical pathological lesions, but still indicates a risk of progression to CKD, especially when a patient has co-morbidities such as hypertension.[17] In type 2 diabetes, microalbuminuria is less associated with DKD,[18,19] however patients with retinopathy and microalbuminuria are strongly suggestive of DKD, with a sensitivity over 90%.[19]

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Measurement of glycaemic control

Glycated haemoglobin (HbA_{1c}) is used as a measure of glycaemic control for patients with diabetes. The recommended target value for patients with diabetes is <7.0%, including those with DKD.[20] Studies have shown that there is no significant difference between the correlation of the level of HbA_{1c} and the level of blood glucose between patients with CKD not requiring dialysis and those with diabetes without CKD.[21] With such evidence therefore, the same target value of HbA_{1c} of <7.0% can be used in this population.[20] For patients with CKD on dialysis, however, the correlation between HbA_{1c} and the level of blood glucose is unclear. Some studies suggest that HbA_{1c} provides an underestimate of glycaemic control,[21,22] while others suggest that it provides an overestimation.[5,23] One of the studies suggests that continuous glucose monitoring is more effective for the evaluation of glycaemic control in patients on haemodialysis as compared to HbA_{1c}.[24] Alternatives as markers for glycaemic control in this group of patients may be glycated albumin (GA) or glycated fructosamine.[22] However, one study showed glycated fructosamine was not reliable in uraemic patients.[21]

Choice of medications in diabetic patients with CKD

In patients with type 2 diabetes, tight glycaemic control has been shown to reduce the risk of microvascular complications.[9,25,26] The Diabetes Control And Complications Trial (DCCT) proved that in type 1 diabetes, tight glycaemic control reduces the risk for microvascular complications.[27] It is therefore important to attain glycaemic control to the target value as far as is possible, to avoid the complications associated with poor glycaemic control.

For patients with both diabetes and CKD however, achieving glycaemic control is not a straightforward issue. Treatment options are limited in this group of patients because with the reduced glomerular filtration

rate (GFR), there is accumulation of the drugs used or their metabolites, some of which are active.[28] There are important considerations that need to be made in choosing the correct medications to use in this patient group. Here we will review the commonly used hypoglycaemic agents to aid the right choice of medications in this patient group.

Insulin

Exogenous insulin is mainly eliminated by the kidneys. In patients with renal insufficiency, the degradation of exogenous insulin is impaired leading to prolongation of the half-life of insulin.[29] Several studies have shown that in patients with renal insufficiency there is decreased renal clearance of insulin with one study showing that there is 30–40% decreased clearance of short-acting insulins.[30] Because of this, there are more episodes of hypoglycaemia in patients on insulin with renal insufficiency compared with those without renal insufficiency,[31] especially when the GFR falls to <60 ml/min.[32] It has been shown that in patients with renal insufficiency, there is a reduced insulin requirement because of the decreased clearance.[33,34] In one study, however, it was found that despite decreased clearance of regular insulin there was also a reduction in its effect.[30] In a more recent study, it has been shown that reducing the dose of insulin in diabetic patients with renal insufficiency reduced the episodes of hypoglycaemia while having the same effect on glycaemic control as compared with those receiving standard doses.[35] Another study showed that higher weight-based insulin doses were associated with a higher risk of hypoglycaemia as compared with lower doses.[36] The American College of Physicians recommends a 25% decrease in the dose of insulin when the GFR is between 10 and 50 ml/min and a 50% decrease of the dose when the GFR is <10 ml/min.[37] Therefore in patients with renal insufficiency, insulin dose should be calculated based on the level of GFR to avoid episodes of hypoglycaemia. In all cases, an 'estimated' GFR (eGFR) can be used.

Oral hypoglycaemic agents general conditions

Clearance of many of the oral hypoglycaemic drugs or their metabolic products (like that of insulin) is reduced in diabetic patients with renal insufficiency. As a result of such effects, patients will be exposed to higher levels of respective drugs or their metabolites potentiating side-effects. This has been found to be serious in patients with CKD stages 3 to 5 (eGFR <60 ml/min).

Sulphonylureas

These drugs are insulin secretagogues and increase the level of endogenous insulin. Because of their effect in increasing the level of endogenous insulin, these drugs have the potential to cause significant hypoglycaemia, especially in patients with renal insufficiency.[38] These are one of the commonest prescribed group of medications in diabetic patients, with one study showing that up to 33% of the prescriptions for hypoglycaemic drugs in America were for sulphonylureas.[39] Clearance of sulphonylureas and their metabolites is dependent on renal function. Studies have shown a high prevalence of hypoglycaemic episodes in dialysis patients using sulphonylureas.[38] The risk of hypoglycaemia is reduced when shorter-acting agents are used. First-generation sulphonylureas should be avoided in CKD stages 3 to 5. Of the second-generation sulphonylureas, glipizide is recommended with no dose adjustment being necessary because its metabolites are not active and there is a lower potential for the development of hypoglycaemia.[14,40] The major metabolites of glipizide are products of aromatic hydroxylation that have no hypoglycaemic activity. Glibenclamide undergoes hepatic metabolism to two weakly active metabolites. In patients with renal insufficiency, these accumulate and increase the risk of hypoglycaemia.[38, 41-43] Another of the second-generation sulphonylureas glimepiride also undergoes hepatic metabolism into two metabolites which are excreted in urine and faeces. The major metabolite is renally excreted and has a weak hypoglycaemic effect and may accumulate in renal insufficiency, increasing the risk for hypoglycaemia.[44–46] However, low doses have been shown to be safe in CKD.[44] With this evidence, glipizide is the sulphonylurea of choice in CKD. It has been shown to have the least risk in causing hypoglycaemia compared with the other sulphonylureas.[47]

Biguanides (metformin)

These are insulin sensitisers. They have no effect on the level of insulin, they rather lower hepatic gluconeogenesis and increase insulin-mediated glucose uptake by insulin -sensitive peripheral tissues. Metformin is the only available drug in this group. Metformin is one of the most efficacious oral hypoglycaemic agents and is associated with favourable clinical outcomes.[48] Metformin is recommended as the drug of choice in patients with type 2 diabetes.[49] Metformin does not exhibit the high risk of hypoglycaemia associated with other drugs used to treat diabetes, it is excreted unchanged in urine. Guidelines discourage the use of metformin in patients with CKD because of its alleged potential to cause lactic acidosis.[14] However, some studies challenge this by showing that metformin has less risk of causing lactic acidosis than previously thought. Metformin has been shown to have no effect on intracellular lactate production.[50–52] Even in patients with renal failure, the use of metformin was not associated with significant rise in lactate levels.[53–54] Diabetic patients on metformin developed significant lactic acidosis only when they had other co-morbidities such as hypotension, hypoxaemia, acute kidney injury, or other acute pathophysiological insults.[55–57] CKD has been shown to cause insulin resistance;[58] being an insulin sensitiser metformin may improve this as well. Researchers have shown that metformin is safe to be used in patients with CKD provided that dose adjustments

are made according to the level of renal function.[54] A review article on the use of metformin in patients with CKD has shown that its use is beneficial with respect to cardiovascular outcomes and metabolic parameters in patients with diabetes and CKD.[59,60] The long-time belief that metformin use in patients with CKD is highly associated with lactic acidosis may be exaggerated based on recent evidence by investigators.

Though the evidence for lactic acidosis-risk and CKD may be weak, it is generally agreed that the drug should not be used, or the dose reduced, in significant CKD. An old system was to discontinue the drug if the serum creatinine rose above 150 mmol/l, but current guidelines use the estimated GFR (eGFR). One simple system is to use metformin freely if the eGFR is >45; use with caution (and in lower doses) when the eGFR is 30–45, and not to use at all if the eGFR is <30.[61]

Thiazolidinediones (pioglitazone)

Thiazolidinediones enhance insulin action in insulin target tissues through binding to peroxisome proliferator-activated receptor gamma. Pharmacologically, these drugs have glycaemic efficacy proven to be equivalent to sulphonylureas and biguanides with less hypoglycaemic episodes. Thiazolidinediones are metabolised by the liver to products that have either very weak action as in rosiglitazone or moderate activity as in pioglitazone. These drugs have been shown to be effective without increasing the risk of hypoglycaemia in patients with renal insufficiency.[62–64] Some studies have suggested that the use of thiazolidinediones in diabetic patients with renal insufficiency may have renoprotective effects. Thiazolidinediones have been shown to either prevent or slow progression of DKD independent of glycaemic control.[65] Other studies have shown that the use of thiazolidinediones is associated with reduction in urinary excretion of albumin, essential for slowing progression of DKD.[66] The pharmacokinetics of thiazolidinediones has not been shown to change even when there is decreasing renal function and therefore no dose adjustment is required when they are used in treating diabetes in patients with CKD.[67] However, this group of drugs has a known side-effect of fluid retention which may be accentuated in patients with renal failure. Also, due to concerns over increased risk of cardiovascular disease, rosiglitazone has been withdrawn. Pioglitazone is thus now the only glitazone available. As mentioned, because of its hepatic metabolism, it can be safely used in all grades of CKD. However, because of lack of information, the manufacturers do not recommend its use for patients on dialysis. Additionally, there have been recent concerns over a possible association with bladder cancer, and pioglitazone should not be used in those with a previous diagnosis of bladder neoplasms, or with unexplained haematuria.

Incretin-based insulin secretagogues

This is the new group of drugs for the treatment of type 2 diabetes. It has been developed following improved understanding of the incretin effect in the pathophysiology of type 2 diabetes. In this group, we have glucagon-like peptide 1 receptor analogues and selective dipeptidyl peptidase 4 inhibitor is approved for use.

Exenatide is the glucagon-like peptide 1 receptor analogue. Pharmacologically, it has only modest glycaemic efficacy, but also has the advantage of causing weight loss, unlike most of the other glycaemic agents.[68] Exenatide is cleared primarily by the kidneys. Studies have shown that renal clearance of exenatide is significantly reduced in patients with CKD stages 4 to 5. Several case reports show that the use of exenatide is associated with acute kidney injury or progression of CKD.[69,70] Its use is therefore not recommended in patients with CKD stages 4 and 5.[20] The other available incretin mimetic, liragrutide, is fully metabolized elsewhere in the body and the kidneys are not a major organ in its elimination.[71] When used in single dosing, it has not been shown to cause any effect in patients with CKD stages 4 to 5;[70] however, there is not enough data on long-term use, hence it is not recommended when eGFR is <60 ml/min.[20]

The dipeptidyl peptidase (DPP-4) inhibitors work by decreasing the breakdown of endogenous incretin hormones, as a result improving postprandial and fasting blood glucose levels. This group includes drugs like sitagliptin, saxagliptin, vildagliptin, and linagliptin. They have been shown to be safe in the management of hyperglycaemia in patients with CKD.[72–74] However, with the exception of linagliptin, the rest require a downward dose adjustment with declining renal function.[20,73]

Alpha-glucosidase inhibitors

Other oral agents include alpha-glucosidase inhibitors (acarbose and miglitol). These act by inhibiting intestinal breakdown of oligosaccharides delaying digestion of ingested carbohydrates. Acarbose is metabolised nearly exclusively in the gastrointestinal tract (GIT) with only about 2% being systemically absorbed. Miglitol on the other hand is largely absorbed systemically and excreted unchanged in urine. There is not enough data to support the use of these drugs in patients with CKD, and their use is not recommended in patients with CKD stages 4 to 5.[20,47]

Meglitinides

Meglitinides are insulin secretagogues which act by binding to adenosine triphosphate (ATP) dependent potassium channels in beta cells in the pancreas. They have a potentially lower risk of hypoglycaemia than standard sulphonylureas in patients with CKD, but still need to be used with care.

In this group, repaglinide undergoes hepatic metabolism resulting in inactive bi-products with a small risk of hypoglycaemia in patients with CKD.[75,76] Another drug in the group nateglinide is mainly metabolised in the liver to weakly active metabolites, of which about 80% are excreted in urine and 20% in faeces; about 15% of

the drug is excreted unchanged in urine. With impaired renal function, there is accumulation of the drug and its active metabolites which may increase the risk of hypoglycaemia.[77,78] Nateglinide therefore should be used cautiously in patients with CKD. Studies have shown that repaglinide accumulation only occurs in severe renal dysfunction, but this is not associated with increased risk of hypoglycaemia.[75,76] Based on this evidence, it is recommended that both of these drugs be started at lower doses (0.5 mg for repaglinide and 60 mg for nateglinide, each with meals) in CKD.

Conclusions

Management of patients with diabetes and CKD is a challenging task because multiple factors in each condition may affect the other. Diabetes is a leading cause of CKD and a major source of morbidity and mortality in patients with established CKD. Loss of kidney function conspires to change glycaemic regulation in ways that can both worsen and improve blood glucose control. Despite the unique nature of diabetes in patients with CKD, there currently are no specific guidelines to direct glycaemic therapy in these patients. In summary, the majority of drugs available to treat hyperglycaemia, and especially first-generation sulfonylureas and alpha glucosidase inhibitors, are affected by kidney function and therefore should be either avoided or used in reduced doses for patients with CKD. The use of metformin is controversial because recent evidence shows it may not be as toxic as initially thought, but should be avoided when CDK is significant. Thiazolidinediones do not require dose adjustments for kidney disease and may have an independent beneficial impact on the progression of DKD, though only pioglitazone is now available, and other side-effects restrict its use. Overall, insulin remains the safest glucose-lowering treatment, when CDK in diabetes is associated with markedly low eGFR.

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