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Strategies of Hyperglycemia Management among Patients with Diabetic Nephropathy, Renal Impairment, Hypertension and Lipid Disorders

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Abstract

Diabetic nephropathy, a microvascular complication, usually starts by the development of incipient nephropathy (microalbuminuria), then proteinuria, reduced glomerular filtration rate and finally renal impairment or Chronic Kidney Disease (CKD). CKD if untreated may lead to End Stage Renal Disease (ESRD). Hence, tight glycemic control, and management of hypertension and dyslipidemia is often required to prevent morbidity and mortality. However, this strategy is usually challenging as most of the anti-diabetic therapies need adjustments, modifications or alterations to prevent adverse events and hypoglycemia with CKD. Hence, the aim of the present review is to discuss the up to date existing literature for the management of hyperglycemia with oral agents or insulin among diabetic patients with nephropathy and CKD, while at the same time managing diabetic dyslipidemia and hypertension.

Keywords: Type 2 diabetes mellitus, Glomerular filtration rate, Microalbuminuria, End-Stage Renal Disease, Chronic Kidney Disease

Introduction

Diabetes mellitus is one of the main causes of nephropathy, rising creatinine levels or Chronic Kidney Disease (CKD), and ultimately leading to End-Stage Renal Disease (ESRD) [1,2]. It is important to notice that, in most of cases, Diabetic Kidney Disease or CKD is often present at the time of diabetes diagnosis [3]. The earliest clinical manifestation of diabetic nephropathy and CKD is Microalbuminuria (MA), also known as incipient nephropathy, which is defined as ≥ 30 mg per 24 hours of albumin excretion [4,5]. Annual testing for MA in diabetic subjects is established by the American Diabetes Association's guidelines [4] with 3 methods of screening: measurement of albumin-to-creatinine ratio in a random spot urine collection, 24-hour collection with creatinine allowing for simultaneous measurement of creatinine clearance, and timed collection of urine.

However, management of diabetic subjects with CKD still remains a challenge to diabetologists since pharmaceutical agent's metabolism is usually affected by serum creatinine levels and serious adverse events, such as hypoglycemia and hyperkalemia, are usually present with these patients [5]. Therefore, the aim of the present review was to summarize the existing literature data regarding simultaneous management of subjects with Type 2 Diabetes Mellitus (T2DM) with nephropathy, CKD, hypertension with co-existing diabetic dyslipidemia [6].

Towards this aim, we performed a systematic search in the PubMed and EMBASE databases using the terms 'Type 2 Diabetes Mellitus', 'Glomerular Filtration Rate', 'Microalbuminuria', 'End-Stage Renal Disease' And 'Chronic Kidney Disease' alone and in combination to retrieve available data.

Lifestyle Modifications

Smoking

The role of smoking in the development and progression of CKD is well established [7,8]. A lot of studies have showed that smoker diabetics have higher prevalence of MA, macroalbuminuria and reduced GFR compared with their nonsmoking counterparts [7,8]. On the other hand, smoking cessation has been showed to be effective at preventing progression of early nephropathy in subjects with T2DM [9]. Therefore, it is of great importance the recommendation of smoking cessation to all diabetic subjects with CKD according to the current guidelines [7].

Weight loss

Obesity is independently related to increased CKD risk in diabetics [10]. Weight loss has been shown to reduce proteinuria and MA while it stabilizes kidney function in subjects with T2DM [11]. These findings are related to the observed reduction in Blood Pressure (BP) in these patients [11]. The National Kidney Foundation recommends a target Body Mass Index (BMI) of 18.5 - 24.9 kg/m^2 for diabetics with CKD [2]. Weight management programs should comprise dietary restriction and increased physical activity, coupled with appropriate counseling [12]. Bariatric surgery should be considered only for patients with T2DM and BMI > 35 kg/m^2 [12].

Dietary modifications

Protein restriction has been shown to slow the progression of albuminuria, the decline in GFR, and the development of ESRD [2,12]. Patients with early-stage CKD should be advised to limit their protein intake to 0.8 g/kg body weight per day; the target for those with late-stage CKD is 0.8 g/kg or lower per day [12]. The reduction of sodium intake (≤ 2.4 g/d of sodium or ≤ 6 g of salt) and alcohol consumption (≤ 2 drinks/day for most men or 1 drink/day in women and lighter-weight individuals) will have a positive effect on BP [13]. Dietary changes to improve diabetic dyslipidemia should comprise reductions in saturated fat, trans fat, and cholesterol intake, together with increases in omega-3 fatty acids, viscous fiber, and plant stanols/sterols [12].

T2DM Pharmacological Treatment

Biguanides

Metformin is globally accepted as the first choice in all therapeutic algorithms for diabetic subjects management. It is known that metformin is eliminated by the kidneys [14] and, therefore, reduction of GFR results to a reduction in the elimination of metformin by the kidneys increasing the risk of adverse events [15]. One of these is lactic acidosis, a rare but very dangerous side effect of metformin [16]. Risk factors for lactic acidosis by metformin are heart failure, advanced age, alcohol consumption and iodinated radiographic contrast media [14]. In the latter case, metformin should be stopped 2 days before the use of iodinated radiographic contrast media and can be given to patient only after renal function has returned to a normal baseline [17,18]. According to the current guidelines, metformin should not be administered in diabetic patients with creatinine levels above 1.4 mg/dl in women and 1.5 mg/dl in men.

Sulfonylureas

Second-generation sulfonylureas that are used in daily clinical practice are glipizide, glyburide, glimepiride and gliclazide. Glipizide is metabolized by the liver [19,20] and, therefore, reduction of GFR does not affect its dose in CKD subjects [21]. Glyburide is, also, metabolized by the liver [19,22,23], but its metabolites have hypoglycemic activity and, therefore, glyburide should use with caution according to the stage of CKD [23-25]. Glimepiride is, also, metabolized by the liver [23-26], but hypoglycemia has been reported with the use of glimepiride in CKD subjects and, therefore glimepiride should be used with caution in CKD subjects [19,27]. Its use is safe in GFR ≥ 60 ml/min and with a reduced dose of up to 30 ml/min. Gliclazide causes less hypoglycemia than other sulfonylureas and is safe for GFR levels ≥ 30 ml/min.

Meglitinides

Repaglinide is metabolized by the liver [28,29]. However, its elimination is diminished in subjects with reduced GFR [30-32] leading to the need for dose adjustment [32]. However, in CKD stages 4 and 5repaglinide can be used without dose adjustment. Nateglinide, despite its liver metabolism [33], can cause hypoglycemia in subjects with reduced GFR because of the reduction of plasma protein binding [34]. Therefore in stage 4 we adjust the dose of nateglinide because of the risk of hypoglycemia [35,36] while in CKD stage 5 we avoid its use.

Thiazolidinediones

Pioglitazone is hepatically metabolized, forming several metabolites that are not accumulated in CKD subjects [19,37]. The most worrisome side effect of pioglitazone is edema that can worst pre-exisitng heart failure in CKD subjects [38,39]. Pioglitazone does not need dose adjustment in CKD subjects. However, it should be used with caution because of risk of congestive heart failure [38,39]. The use of pioglitazone in CKD subjects is in decreased dose (15 mg once a day).

Alpha-glucosidase inhibitors

Acarbose is an alpha-glucosidase inhibitor that is absorbed from the gastrointestinal tract [19]. Its metabolites are secreted by the urine and in subjects with impaired renal function its elimination is diminished [19]. Therefore, in subjects with CKD stages 4 and 5 should not be used [19].

GLP-1 analogues

Exenatide, the first GLP-1 analogue used for the treatment of diabetes, is eliminated mainly by the kidneys [40,41]. Reduction in GFR has as a result an elevation in drug's half-life time [40]. Therefore, for GFR's levels between 30 and 50 ml/min a reduction of drug's dosage is recommended while for GFR's levels lower than 30 ml/min exenatide should not be used [40, 41]. Regarding liraglutide, another GLP-1 analogue [42,43], a recent meta-analysis showed that mild renal impairment had no effect on the efficacy and safety of liraglutide [44]. However, since there are not large clinical studies in patients with GFR < 60mL/min liraglutide cannot be used under these cut off point.

DPP-4 inhibitors

Sitagliptin, is mainly eliminated by the kidneys [45]. In subjects with moderate kidney disease sitagliptin can be used in dosage of 50 mg while for more severe kidney disease sitagliptin can be used in dosage of 25 mg [46,47]. Saxagliptin is mainly metabolized by the liver by cytochrome P450 3A4/5 [48]. According to recent data a dosage of 2.5 mg of saxagliptin is suggested for subjects with GFR <50 ml/min [48]. Vildagliptin, another oral DPP-4 inhibitor should be used with caution in subjects with CKD [49,50]. A 24-week study including subjects with T2DM and moderate or severe renal impairment, vildagliptin (50 mg once-daily) added to ongoing anti-diabetic therapy had a safety profile similar to placebo [51]. In patients with CKD stage ≥ 3, vildagliptin needs dose adjustment. For GFR < 50 mg/mL the dose of vildagliptin is 50 mg. Linagliptin is the newer oral DPP-4 inhibitor. Renal impairment has only a minor effect on linagliptin pharmacokinetics. Consequently, there is no need for adjusting the linagliptin dose in diabetics with CKD [52].

Insulin

Insulin is metabolized by the kidneys [53]. Reduction of GFR has as a result a reduction to exogenous insulin clearance and

its plasma accumulation [54–57]. For GFR levels between 50 and 10 ml/min insulin dosage should be reduced by half [19]. Even more, subjects on dialysis have less need for exogenous insulin [57]. Rapid-acting insulin analogs are preferred for subjects with CKD since their half-life time is almost unchanged in subjects with CKD because of the lower risk of hypoglycemia [58]. Long-acting insulin, glargine and detemir, are acceptable in CKD subjects [58].

Antihypertensive Treatment

Diuretics

Thiazide diuretics are used in CKD stage 1-4 while loop diuretics are used in CKD stage 4-5 [59]. Although a large dose of a thiazide diuretic will initiate a diuresis in subjects with mild renal insufficiency, the response in subjects with GFR < 50 ml/min is more limited. In subjects receiving fixed-dose combination antihypertensive therapy containing a thiazide diuretic, a loop diuretic should be considered when GFR values drop to below 50 ml/min and BP control is inadequate and/or edema is present [60]. Fixed-dose combination antihypertensive therapies with a thiazide diuretic component do not require change in the non edematous CKD subjects with good BP control.

Potassium-sparing diuretics are generally used cautiously in CKD subjects because of the risk of hyperkalemia. Dosage adjustment for aldosterone receptor antagonists is based on the level of renal function and by the possibility of hyperkalemia [61]. Spironolactone has a prolonged potassium- sparing effect, which should be accounted for when it is prescribed. Eplerenone has less significant effects in serum potassium [61].

Alpha adrenergic antagonists

Dose adjustment of alpha adrenergic antagonists in CKD subjects is not required. These compounds are used in the hypertensive CKD subjects as useful add-on compounds in the setting of resistant hypertension [62]. Adrenergic antagonists have a tendency to increase plasma volume in subjects with CKD, and therefore, these drugs should be used with diuretic therapy [63].

Central α-agonists

Central α-agonists are still used in the hypertensive CKD subjects. Clonidine undergoes modest renal clearance and its plasma half-life is somewhat prolonged in CKD subjects [64]. However, there are no specific recommendations for dosage adjustment in this population [64].

Beta blockers

Beta blockers are commonly utilized drugs in CKD subjects either for the treatment of hypertension and/or for their cardioprotective effects [65–67]. The BP-lowering effect of beta blockers is somewhat unpredictable in CKD subjects unless combined with a diuretic [65]. If side effects occur, one option is to continue the beta blocker with dose reduction and the other to convert to a hepatically-cleared beta blocker.

Calcium-channel blockers

Calcium-Channel Blockers (CCBs) are commonly used drugs in CKD subjects because of the consistency of their BP lowering response and the absence of dose adjustment in these subjects [68]. Dihydropyridine and non-dihydropyridine CCBs (Verapamil and Diltiazem), reduce BP similarly in CKD subjects. The addition of a CCB to other drug classes, including diuretics, produces a better result to BP control [69].

Greater reductions in proteinuria have been seen with non-dihydropyridine CCBs such as Verapamil and Diltiazem, despite BP reduction comparable to those seen with dihydropyridine CCBs [70]. When given in combination with either an ACE inhibitor or an Angiotensin Receptor Blocker (ARB), the treatment advantage of a non-dihydropyridine versus a dihydropyridine CCB becomes less important [71]. The side effects of CCB are more pronounced in CKD subjects. CKD subjects tend to be constipated, a process aggravated by Verapamil. In addition, CCBs can produce a vasodilatory peripheral edema, which is a type of edema without weight gain [72].

Angiotensin-converting enzyme inhibitors

Most ACE inhibitors are exclusively renally cleared with varying degrees of filtration and tubular secretion [73]. The BP-lowering effect of ACE inhibitors is generally less in volume expanded forms of hypertension, as in the case of CKD. In CKD subjects, the addition of a diuretic to an ACE inhibitor is frequently necessary to lower BP. The major adverse events of ACE inhibitor accumulation are prolonged BP reduction, an extended decrease in GFR, and/or an unacceptable increase in serum potassium concentration. These adverse events do not mandate permanent discontinuation of the ACE inhibitor and in most cases ACE inhibitor can be cautiously reintroduced [74]. If the ACE inhibitor effect, BP reduction, or the side effect, drop in GFR and/or hyperkalemia, occur, then the dose should be reduced if not temporarily discontinued. If hyperkalemia occurs with an ACE inhibitor, a reduced dose or use of a non-accumulating ACE inhibitor can be considered. If hyperkalemia persists and ACE inhibition remains vital (congestive heart failure), a potassium-binding resin can be used [74].

Angiotensin receptor blockers

Like ACE inhibitors, ARB monotherapy is generally less efficacious in the treatment of CKD-related hypertension and typically requires the addition of a diuretic to maximize its BP-lowering effect. These drugs undergo significant hepatic elimination with the exception of candesartan, olmesartan, and one metabolite of losartan, which are 40%, 60%, and 50% hepatically-cleared, respectively [75]. Like ACE inhibitors, the dose of an ARB given to a CKD subject should be adjusted to achieve a specific BP goal and thereafter empirically for any additional antiproteinuric effect [76].

Treatment of Dyslipidemia

Statins are generally well tolerated at moderate doses in subjects with CKD stages 1-2 [77]. Safety issues and dose adjustment become important in more advanced stages of CKD (stages 3-5), as adverse events are commonly dose related and due to increased blood concentration of the compound. Statins

with minimal renal excretion should be the drug of choice (Atorvastatin, Fluvastatin, and Pitavastatin) [77].

Growing evidence indicates that fibrates increase serum creatinine and homocysteine, both being established cardiovascular risk factors [77]. Effects of fenofibrate are more pronounced than those of gemfibrozil [77]. As fibrates have no effect on creatinine excretion into urine, the estimation of GFR is hampered by the rise of creatinine [77]. Fenofibrate is also non-dialyzable and should not be used in subjects with GFR < 50 ml/min. The dose of gemfibrozil is recommended to be reduced to 600 mg/day if GFR is < 60 ml/min and avoided if GFR is < 15 ml/min [77].

Recently the availability of prescription brand n-3 fatty acids provides an option to lower triglycerides in subjects with mixed dyslipidemia [77].

Statins in Subjects with CKD

Some dosage modifications for some of the statins need to be carried out as GFR levels fall. Atorvastatin and its metabolites are excreted mostly in bile, and urinary excretion is low, so dosages do not have to be modified as GFR levels fall [78]. Atorvastatin can be given in dosages up to 80 mg per day in subjects who are on both hemodialysis and Chronic Ambulatory Peritoneal Dialysis (CAPD) [78]. In subjects who are on hemodialysis, the dosage can be given before or after dialysis [78].

Fluvastatin is almost completely metabolized by the liver with 5% excreted in the urine [78]. Therefore, it also can be given in dosages up to 80 mg per day even in subjects who are on hemodialysis and CAPD [78].

Data on pravastatin are less certain with respect to declining GFR levels, and pravastatin and its active metabolites may accumulate [78]. Therefore, it has been recommended that dosages of pravastatin start at 10 mg per day and higher doses be used cautiously when the GFR is < 50 ml/min [78]. However, as noted in the Pravastatin Pooling Project, 40 mg was used down to 30 ml/min, and there were no adverse effects from this [79].

Simvastatin is almost completely metabolized by the liver [78]. In the First United Kingdom Heart and Renal Protection (UK-HARP-I) study, 448 subjects with CKD (242 predialysis subjects with serum creatinine level > 1.7 mg/dl, 73 on hemodialysis and 133 with a transplant) were randomly assigned to simvastatin 20 mg or placebo for 1 year. Low Density Lipoprotein (LDL)-cholesterol levels were lowered by 27, 20, and 20 mg/dl in these three groups without any significant increase in the adverse effects of muscle pain, muscle weakness, rhabdomyolysis, or elevation of creatinine phosphokinase or alanine aminotransferase [80]. In the HPS study, subjects were treated with 40 mg per day in many subjects with CKD stage 3 without an excess risk for rhabdomyolysis [81].

Rosuvastatin is 90% excreted unchanged in the feces and only 10% in urine [79]. When the GFR is < 30 ml/min, it has been found to accumulate, so it should not be given at a dosage of > 10 mg with this degree of CKD [79].

Ezetimibe is being used with increasing frequency in many patients to augment the LDL-cholesterol lowering effects of statins [82]. The recent Second United Kingdom Heart and Renal Protection (UK-HARP-II) study found in a randomized, controlled study that 10 mg of ezetimibe added to 20 mg of simvastatin in 203 subjects with CKD (152 predialysis subjects with serum creatinine > 1.7 mg/dl, 18 on peritoneal dialysis and 33 on hemodialysis) resulted in an incremental 21% reduction of LDL-cholesterol levels over simvastatin alone without an excess risk for abnormal liver or muscle function tests or other adverse events [83]. Therefore, no dosage adjustment of ezetimibe is needed in subjects with renal insufficiency [82,83].

Bile acid sequestrants, such as cholestyramine, also can be used, and the dosage does not have to be altered with decreases in GFR [84]. When the GFR falls to < 30 ml/min, it seems that atorvastatin and fluvastatin are preferred because no dosage adjustments need to be made.

Gemfibrozil dosing does not have to be adjusted even for CKD stage 4 [85]; in CAPD subjects, dosages of > 600 mg per day have been associated with an increased frequency of CPK elevations [86]. However, fenofibrate dosages should be reduced by one third in CKD stage 2, by an additional one third in CKD stages 3 and 4, and avoided in CKD stage 5 [84]. Combination of fibrates and statins probably best are avoided in subjects with CKD to avoid the complication of rhabdomyolysis [84,87]. Nicotinic acid dosages do not have to be adjusted until CKD stage 5, when the dose should be reduced by 50% [84].

In conclusion, diabetic subjects with CKD are a high cardiovascular risk population that needs intensive treatment aiming at diabetes, BP and lipids control. However, presence of diabetic nephropathy influences therapeutic choices leading either to dose adjustment or to contradiction of agents used for the treatment of diabetes, hypertension and lipids disorders.

Recommendations

In view of above mentioned facts, it is recommended that tight glycemic control is essential to prevent diabetes complications. Hypertension and dyslipidemia management is essential as well while managing diabetes. In case of renal impairment or rising creatinine levels above 1.5 mg/dl (CKD), it is highly recommended to discontinue metformin, sulfonylureas, or any anti-diabetic agents to avoid further complications or hypoglycemia. In such cases, replacement of oral agents with insulin therapy is advised. Similarly, patients already on insulin and who recently demonstrated renal impairment (CKD), insulin dosages should be reduced according to the results of Self-Monitoring Blood Glucose (SMBG) to prevent hypoglycemia.

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