Therapeutic Considerations in the Management of Diabetes among Patients with Chronic Kidney Failure

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ABSTRACT

Introduction: The chronic kidney disease (CKD) secondary to diabetes mellitus required extensive treatment plan for several clinical parameters. Clinical factors including, hyperglycemia, hypertension, fluid overload/restriction, nutritional assessment, electrolyte balance and others.

Methods: A clinical literature search was conducted in multiple databases using keywords like chronic kidney disease, diabetes type2 and oral diabetic medications and identified guideline, articles, reports and clinical trial. All the screened studies were reviewed and considered for inclusion in the review.

Review Findings: Patient related factors mainly focused on age, concurrent clinical comorbidities, compliance and adherence play vital role in the selection and dose optimization of antidiabetic medications. The literature is lacking with primary prevention strategies of CKD associated with diabetes and hypertension. Therapeutic planning should be optimize individually depending on drug-related efficacy profile and therapeutic goals of the patients. Several novel therapeutic drugs showed promising results in the treatment of CKD but currently none of them have reached successful phase-3 clinical trials. It is recommended to have pharmacokinetic safety-toxicity profiling of antidiabetic drugs so that the dose-related adverse drug reactions can be identified, and therapeutic considerations will be optimized to achieve optimum care.

Conclusion: The management of insulin resistance will be better managed with the quantitative understanding of drug effect. Therefore, the rational selection of antidiabetic drugs should be based on drug-efficacy profile rather than patient-specific factors.

KEY WORDS
chronic kidney disease, insulin, antidiabetic, adverse drug reactions, A1c

INTRODUCTION

Chronic kidney disease/failure (CKD) is a condition required multi-interventions including, glucose tolerance, blood pressure management, intensive control to lipids/cholesters, fluid management (either resuscitation or restriction) dietary & calorie management and other life-style modifications life smoking cessations etc. Each treatment intervention needs secondary monitoring like; risk of hypoglycemia, risk of hyperkalemia, malnutrition, electrolyte disbalance, alkalosis/acidosis and others. Clinical decision to selection of appropriate therapy based on these specific patient characteristics. Secondary patient related factors are; special population, significant comorbidity, known hypersensitivity, adherence and physical or mental disability. The drug selection and treatment plan should consider all the mentioned factor to achieve optimal therapeutic cure.

METHOD OF LITERATURE SEARCH

A clinical literature search was conducted in SCOPUS, PUBMED/ MEDline, therapeutic guidelines, society reports for primary literature identification. Secondary search was made in cochrane Library and PROSPERO for systematic review and meta-analysis articles. The guidelines and reports were then screened and reviewed to be considered for inclusion. The search was limited to last 7-10 years of research documents.

REVIEW FINDINGS AND DISCUSSION

The American diabetes association (ADA)³ provided therapeutic goals for the management of diabetic kidney disease. It summarizes that both glucose control and blood pressure required intensive and optimize treatment to reduce the risk of onset and/or slow the progression of dia-
betic kidney disease. Other highlights included the recommended use of Angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin II receptor blockers (ARBs) for patients with urinary albumin-creatinine ratio (ACR) > 300 mg/g with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m². Daily protein requirement to prevent malnutrition increased for patients with hemodialysis (1.2-1.5 g/kg) than nonhemodialysis patients (0.8 g/kg). Intensive monitoring required for serum creatinine and potassium levels during treatment with ACEIs, ARBs or diuretics in CKD. Nutritional formulas should be fluid restricted and high protein in case of fluid overload and polymeric for patients with dehydration. The clinical practice is lack with the recommendation of primary prevention of diabetic kidney disease in patients with diabetes mellitus.

The national kidney foundation-kidney disease outcome quality initiative and the kidney disease improving global outcomes (KIDGO) guideline recommend target HbA1c of about 7.0% to prevent or delay progression of the microvascular complications of diabetes. However, patients at risk for hypoglycemia, such as those with diabetes and CKD, should not be treated to an HbA1c target of < 7.0%. The only reason for "relaxed" control in CKD is risk of hypoglycemia. This is only an issue in subjects on a sulphonylurea and/or insulin. If other agents are used, then tighter targets can be agreed with the patient. Figure 1 shows the micro and macrovascular development pattern among diabetes patients over time.

Table 1: Antidiabetic drug characteristics for the management of CKD [1-10,14].

<table>
<thead>
<tr>
<th>Drug list</th>
<th>Glycemic Effect</th>
<th>A1c effect</th>
<th>DKD indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Fasting and prandial</td>
<td>1-2% ↓</td>
<td>discontinue or not initiate if CrCl is less than 30 mL/minute.</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Fasting and prandial</td>
<td>1-2% ↓</td>
<td>Glipizide may be a better option than glyburide or glimepiride in older adults</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Prandial</td>
<td>0.5-1.5% ↓</td>
<td>No documented effect.</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Fasting and prandial</td>
<td>0.5-1.4% ↓</td>
<td>Fluid retention-precautions in renal impairment.</td>
</tr>
<tr>
<td>α-Glucosidase inhibitor</td>
<td>Prandial</td>
<td>0.5-0.8% ↓</td>
<td>No documented effect.</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>Prandial</td>
<td>0.5-0.8% ↓</td>
<td>CrCl: 30-50ml/min: 50% dose reduction (all sub-drugs except: Linagliptin)</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>OD/BD: Prandial</td>
<td>0.5-1.5% ↓</td>
<td>CrCl less than 30 mL/minute for either exenatide formulation; less than 15 mL/minute for albigratide, less specific for liragluride.</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Prandial</td>
<td>0.3-0.5% ↓</td>
<td>No documented effect.</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Fasting and prandial</td>
<td>0.1-0.6% ↓</td>
<td>No documented effect.</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Fasting and prandial</td>
<td>0.3-1% ↓</td>
<td>CrCL:15-59ml/min: reduce Canagliflozin max 100mg/day</td>
</tr>
<tr>
<td>Amylin agonist</td>
<td>Prandial</td>
<td>0.5-0.1% ↓</td>
<td>No documented effect. Black box warning for severe hypoglycemia.</td>
</tr>
<tr>
<td>Insulin</td>
<td>Basal: Fasting</td>
<td>varies</td>
<td>Use insulin: A1c &gt; 10%, Glucose &gt; 300-350 mg/dL, Urine ketones</td>
</tr>
<tr>
<td>Insulin</td>
<td>Bolus: Prandial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: literature reported adverse drug reactions

<table>
<thead>
<tr>
<th>Drug list</th>
<th>Hypoglycemia</th>
<th>Gl side effects</th>
<th>Renal impairment</th>
<th>Weight gain</th>
<th>Fluid overload &amp; Edema</th>
<th>GU infection &amp; Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>SU</td>
<td>GLP-1</td>
<td>DPP4</td>
<td>TZDs</td>
<td>SGLT2I</td>
<td>Acarbose</td>
</tr>
</tbody>
</table>
Chronic Kidney Disease and Therapeutic Management

The UK literature reporting recent trends in CKD²; as pattern of albuminuria and reduced glomerular filtration rate (GFR) is changing, and reduced GFR without albuminuria is becoming more common. Such patients usually have a better renal prognosis than those with overt albuminuria. Therefore, treatment should be based on intensive management to hyperglycemia and hypertension rather than protein-wasting calorie management (as primary prevention strategy). However, monitoring should be planned for malnutrition as it has a significant role in progression to ESRD and required dialysis eventually.

Recent recommendations from American college of cardiology for the management of diabetes in CKD reported the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonist (GLP-1RAs) for people with type 2 diabetes and CKD³,⁴. These drugs may reduce the risk of CDK progression, cardiovascular events, or both. The safety and efficacy profile are well-developed over couple of years, but evidence is limited with the therapeutic recommendation for Type 1 diabetes mellitus. Indeed, insulin is probably safer to use than sulphonylureas because of problems of build-up (reduced clearance through the kidneys) of the latter and also breakdown to still active products.

The selection and optimization of antidiabetic drugs based on several factors like; glycemic effect, extend on A1c effect, dosing impact in CKD⁵. The rational use of oral antidiabetic drug and insulin dosing (basal bolus) is critical step in the care plan of CKD with diabetes. Patient specific characteristics and therapeutic goals must align with the drug — efficacy. Table 1 showed details of clinical parameters considered for the care planning of diabetes among CKD patients. In fact, that renal impairment is associated with a massively increased risk of hyperglycemia and indeed a 10-fold increased risk of severe hypoglycemia compared with subjects with normal renal function. This risk is further magnified in older people. For these reasons one might argue that sulphonylureas should not be used at all in subjects with CKD.

The adverse drug reactions/side effects of antidiabetic medication and/or insulin are a considerable factor in the treatment success and patient compliance. In the clinical practice understanding of risk/benefit ratio is applied to achieve optimal therapeutic outcomes. However, each patient presents with different clinical characteristics and therapeutic goals. Therefore, the rational adaptation of these medications showed based on safety and efficacy profiling. Table 2 presenting the reported adverse effects of antidiabetic drugs.

Literature is limited with pharmacokinetic dose profiling of antidiabetic medications⁶,⁷. Consideration should be given to the probability of dose-related side-effects of antidiabetic drugs. It is highly recommended to investigate the dose-effect response of diabetic medications to achieve better clinical outcome with least toxicities.

Recent novel drug development focused on the diabetes kidney disease with different approach but till date inconclusive animal-based results available for further phase 3 trials. Some of the agents that have shown promising results are:

- Ruboxistaurin, a protein kinase C-β inhibitor⁸;
- Baricitinib, a selective Janus kinase 1 and Janus kinase 2 inhibitor⁹;
- Pentoxifylline, an anti-inflammatory and antifibrotic agent¹⁰;
- Atrasentan, a selective endothelin A receptor antagonist¹¹,¹²;
- Finerenone, a highly selective nonsteroidal mineralocorticoid receptor antagonist¹³.

Novel agents targeting mechanisms, such as glomerular hyperfiltration, inflammation, and fibrosis, have been a major focus for development of new treatments. In contrast, recently released data from clinical trials of SEMAGLUTIDE and DULAGLUTIDE consistently show reduced risk of albuminuria onset and progression¹⁴.

**CONCLUSION**

The management to CKD secondary to diabetes mellitus required extensive and multi-factorial intervention. Patient characteristics and drug-related clinical efficacies should be reviewed for the rational selection of antidiabetic medication in the therapeutic planning. Treatment monitoring should be drug-specific rather than disease-oriented. Also, it is recommended to explore the pharmacokinetic profiling of antidiabetic drugs and determine dose-related adverse drug reactions for better understanding of efficacious drug effect.

**REFERENCES**

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