Understanding Diabetic Nephropathy

Renal involvement in diabetes is heralded by an increase in albumin excretion (microalbuminuria). Microalbuminuria is defined as a urinary albumin creatinine ratio (ACR) between 30-300 mg/g and macroalbuminuria is defined as an ACR > 300 mg/g.¹

Diabetic nephropathy is defined by the presence of proteinuria (macroalbuminuria).

Proteinuria in diabetes mellitus is occasionally due to a glomerular disease other than diabetic nephropathy. The major clinical clues suggesting non diabetic glomerular disease are onset of proteinuria less than five years from the documented onset of diabetes in type 1 diabetes, acute onset of renal disease, presence of an active urine sediment containing red cell and cellular casts, and in type 1 diabetes, the absence of diabetic retinopathy or neuropathy.²

Risk factors for developing diabetic nephropathy include family history of diabetes, race/ancestry, higher systemic blood pressures, poor glycaemic control, smoking and possibly the use of oral contraceptives. Obesity and older age may also be risk factors.

Management of Diabetic Nephropathy

- Low salt diet
- BP control
- Exercise
- Weight loss
- Smoking Cessation

Protein excretion will decrease with BP control and low salt diet. Aim to decrease protein excretion to less than 500 to 1000 mg/day or to 60% of their baseline.³
BP control:

- Aim for a reduction in blood pressure to less than 130/80 mmHg
  Do not lower the diastolic pressure to below 75 mmHg in patients with active coronary disease, and the systolic blood pressure should not be lowered to below 110 mmHg in any patient.  

Stepwise Management of Hypertension in Diabetic Nephropathy.  

1. Start an ACE inhibitor or ARB. It is advisable not to use both together.

2. Add in a Diuretic. Diuretics will also help to attain “Dry weight” in renal patients. Dry weight is defined as the weight at which further fluid loss will lead to symptoms (fatigue or postural hypotension) or decreased tissue perfusion (unexplained rise in urea/creatinine).

3. If BP still not controlled consider adding a nondihydropyridine calcium channel blocker (diltiazem or verapamil should not be given with a beta blocker)

Salt intake:

- Salt restrict to ≤100 meq/day. Salt restriction has a role in reducing proteinuria in these patients.

What effect does CKD have on a patient’s diabetic control?

Key points to note:

- In advanced CKD, there is decreased insulin metabolism. This leads to decreased insulin requirements in these patients. Dialysis can reverse some of these changes.

- Uraemia can affect methods used to assess glycaemic control, and the metabolism of most oral diabetes agents is prolonged, making them more difficult to use.

- HbA1c is used to monitor longer term glycaemic control. However HbA1c can be affected by reduced red blood cell life span, transfusions, iron deficiency, accelerated erythropoiesis due to administration of erythropoietin, and metabolic acidosis.
Diabetic Drugs in CKD

Although many patients end up on insulin therapy because it is more effective, oral agents can be used.

**Nondialysis CKD patients:**

1) Short-acting sulphonylureas (e.g., gliclazide) are first line in patients who have an estimated glomerular filtration rate (eGFR) <30 mL/min.  
2) Long-acting sulphonylureas are not recommended because of the risk of hypoglycaemia.  
3) Meglitinide, repaglinide are also safe since these agents are not renally cleared.

4) **Metformin Rules:**  
eGFR <30 mL/min - Do not use because of an increased risk of lactic acidosis.  
eGFR between 30 and 44 ml/min – clinical decision.  
eGFR >45 ml/min/1.73 - Metformin may be used.  
Also use metformin with caution in any patient whose renal function is rapidly deteriorating.

As mentioned earlier, insulin metabolism can be decreased in advanced CKD. Therefore the dose may need adjustment according to GFR. A rough outline is given in the table below.

<table>
<thead>
<tr>
<th>GFR</th>
<th>Insulin Dose Adjustment Required</th>
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<tbody>
<tr>
<td>&gt;50mL/min</td>
<td>Nil</td>
</tr>
<tr>
<td>10 – 50 mL/min</td>
<td>Reduce dose to 75%</td>
</tr>
<tr>
<td>&lt;10mL/min</td>
<td>Reduce dose to 50%</td>
</tr>
</tbody>
</table>

The best way to be safe with insulin management in these patients is to closely monitor blood sugars in the induction period and after any changes are made.

**Haemodialysis patients**

Most haemodialysis patients use insulin rather than oral agents. Most patients will require their insulin dose to be titrated up after they start haemodialysis.

The use of long-acting insulin preparations remains controversial.
Some clinicians prefer to use oral agents rather than insulin, especially among patients who are already on these agents and have achieved acceptable glycaemic control. Gliclazide or Repaglinide are the preferred agents since they are primarily metabolized by the liver and the risk of hypoglycaemia is lower than with other oral agents. Repaglinide may be the drug of choice in ESRD as dose reductions are not necessary.

**Peritoneal dialysis (PD) patients**

Remember there is glucose in peritoneal dialysate which can increase blood sugars and the need for therapy.

Oral agents can be used in PD patients, however over time, the majority will require insulin. Gliclazide and Repaglinide remain good choices of oral agents. Metformin should not be used in these patients because of an increased risk of lactic acidosis.

With PD patients, there is the option of intraperitoneal insulin. However, it is not very popular; reasons include inadequate control of blood sugars, complex insulin regimens, an increased risk of bacterial contamination of dialysate during injection of insulin into the bags and an associated risk of peritoneal fibroblastic proliferation. Therefore subcutaneous insulin remains the commonly used route.

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**Hyper and Hypoglycaemia in CKD patients**

**Hyperglycaemia:**

Check medication compliance and doses.

**Severe hyperglycaemia and ketoacidosis:**

An important point to note is that hypovolaemia and marked hypernatraemia may not occur in these patients as there is no glucosuria in anuric patients. Patients may therefore experience minimal or no symptoms, even with very high sugars.

Marked hyperkalaemia is often seen due to the efflux of potassium ions in response to the extracellular fluid hypertonicity, hyponatraemia and acute intravascular volume expansion.

Patients with type 1 diabetes may develop diabetic ketoacidosis. Instead of fluid replacement, management is mainly the administration of low doses of intravenous insulin (commonly beginning at a dose of 2 units/hour). Serum glucose and potassium concentrations must be closely monitored.
Hypoglycaemia:

When assessing hypoglycaemia in diabetic dialysis patients, causes to consider include: severe underdialysis, poor calorie intake, or occult disease, such as infection or malignancy. Management centres around identifying and correcting these causes as well as frequent blood sugar monitoring with insulin dose adjustment. Drugs that interfere with the counterregulatory response to hypoglycaemia (such as beta blockers) and long-acting insulin and oral agents should be discontinued until the bloods sugars stabilise.

References


Dr. Legate Philip, CT2
Dr. Adam Kirk, Consultant Nephrologist
Queen Alexandra hospital, Portsmouth