

Global Guideline for Type 2 Diabetes

Chapter 14: Kidney damage

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These guidelines are concerned with preventative *diabetes* care. No advice is given on further investigation of kidney disease by a renal specialist, or subsequent tertiary care.

Recommendations

■ Standard care

KD1 Check annually for proteinuria in an early morning urine sample (or a random sample otherwise) using a dipstick.

- if dipstick test positive,
 - check for urinary tract infection
 - obtain a laboratory urine protein:creatinine ratio (PCR)
- if dipstick test negative, check urine albumin using:
 - laboratory or site-of-care urine albumin:creatinine ratio (ACR), or
 - a semi-quantitative reagent strip if ACR test is unavailable.

Measure serum creatinine annually, and calculate GFR ('eGFR').

KD2 If PCR or ACR is raised (microalbuminuria ACR >2.5 mg/mmol in men, >3.5 mg/mmol in women; or 30 mg/g), repeat twice over the following 4 months.

- confirm as positive if proteinuria or raised urine albumin on two of three occasions
- if both repeat tests are not raised, check again annually.

KD3 Manage those with raised urine albumin or proteinuria or reduced eGFR (<90 ml/min/1.73 m² and falling) as follows:

- use ACE-inhibitor or A2RB titrated to maximum tolerated dose
- intensify management of blood pressure (actively target <130/80 mmHg) using drugs and dietary modification (low salt intake)
- intensify management of blood glucose (target DCCT-aligned HbA_{1c} <6.5 %)
- monitor progression by ACR or PCR, serum creatinine and potassium; calculate eGFR; discuss results
- advise limiting protein intake to 0.8 g/kg daily if proteinuric
- intensify other renal and cardiovascular protection measures (not smoking, aspirin therapy, lipid-lowering therapy).

KD4 Measure Hb/ferritin every 6 months if eGFR <90 ml/min/1.73 m², give iron or other haematinics if indicated, and refer to nephrologist if still anaemic despite supplements (Hb <11 g/dl in pre-menopausal women, <12 g/dl in others).

KD5 Refer to a nephrologist when eGFR <60 ml/min/1.73 m², or earlier if symptomatic or biochemical or fluid retention problems occur.

■ Comprehensive care

KD_c1 This is in general as for *Standard care*, but assessment of albuminuria would always be by a laboratory quantitative method (ACR).

KD_c2 Investigations to exclude other possible causes of renal disease for all with raised ACR or PCR might include auto-antibodies, ultrasound, biopsy.

■ Minimal care

KD_M1 Check annually for proteinuria in an early morning urine sample (or a random sample otherwise) using dipstick or sulfosalicylic acid method.

- if test positive,
 - exclude urinary tract infection by microscopy (and culture if possible)
 - if possible, obtain a laboratory protein:creatinine ratio (PCR) and repeat on two occasions over the following 6 months (proteinuria confirmed if positive on two of three occasions)
- if test negative, check again annually.

If available measure serum creatinine (or urea) annually.

KD_M2 Manage those with proteinuria as follows:

- advise to avoid risk factors (analgesic use, alcohol consumption, illicit drug use), to limit protein intake (to 0.8 g/kg daily), and not to smoke
- aim for blood pressure <130/80 mmHg using any anti-hypertensive drug and control of salt intake
- consider use of ACE-inhibitors if available
- aim to achieve targets for blood glucose control
- aim to improve lipid profile using available drugs
- check proteinuric status/progression annually
- measure serum creatinine or urea every 6 months.

Rationale

Diabetic renal disease has only received less attention in people with Type 2 diabetes in the past because their life expectancy was limited by cardiovascular disease. However, because of the higher incidence of Type 2 than Type 1 diabetes, renal failure in the former group has always been a significant cause of morbidity and mortality. With increasing numbers of people with Type 2 diabetes, younger age of onset, and better cardiovascular protection measures, the health impact of renal impairment in this population and in individuals is growing. While the major effort of management must go to primary prevention (good blood glucose and blood pressure control from early diagnosis), the success of interventions at a later stage (see below) suggests that detection of developing kidney damage would be useful.

Evidence-base

The evidence-based diabetes guidelines which address the subject of nephropathy describe the early stages of kidney damage in terms of albumin excretion rate (AER) increasing through 'microalbuminuria' to 'macroalbuminuria' (at which point it equates with proteinuria, 'overt nephropathy') [1-6]. There is general agreement on annual screening, and on the albumin:creatinine ratio (which corrects for urine concentration) as the preferred method of detection, but cut-off values differ somewhat, microalbuminuria being defined as 30 mg/g in the USA [1], 2.0/2.8 mg/mmol (men/women) in Canada [2], and 2.5/3.5 mg/mmol in Europe [3-6], and macroalbuminuria as 300 mg/g, 20/28 mg/mmol, and 30 mg/mmol respectively. Issues surrounding screening tests are reviewed in detail by the NICE Type 2 guideline [4],

with attention drawn to the day-to-day variation in albumin excretion which underlines the need for confirmatory testing. Monitoring of changes in glomerular filtration rate (which are not necessarily in line with changes in albumin excretion) is emphasized in all the guidelines, which recommend serum creatinine measurement, and more recently emphasize the need for calculation of estimated GFR [1,2].

UKPDS provided clear evidence for the benefits of blood glucose control and blood pressure control in delaying the development of kidney disease [7,8]. Other evidence for the importance of blood pressure control in prevention comes from trials of various anti-hypertensive drugs, and evidence continues to emerge in this area (although there will be no more placebo-controlled trials). Choice of agent stems from evidence on the additional benefits of agents which target the renin-angiotensin system in offering renal and cardiovascular (see *Cardiovascular risk protection*) protection, over and above the blood pressure-lowering effect. Both ACE-inhibitors and the newer A2RBs delay progression from micro- to macro-albuminuria in people with Type 2 diabetes and hypertension [1,2,9]. A2RBs have been shown to delay progression of nephropathy in those who have macroalbuminuria and renal insufficiency (serum creatinine >1.5 mg/dl (>130 µmol/l)) [1]. Of the other anti-hypertensive agents which might be used, the ADA cites evidence that dihydropyridine CCBs do not slow progression of nephropathy so should not be used as first-line therapy in nephropathy [1].

Targets for blood pressure have been tightening in diabetes care generally and the advice to treat to tighter targets for those with albuminuria, 130/75 mmHg as against 140/80 mmHg in people with Type 2 diabetes [4], is perhaps now a minority view, with general advice converging towards 130/80 mmHg for all irrespective of AER [1,2,5]. NICE found that reduction of blood pressure to less than 135/75 mmHg reduced the rate of progression of renal disease, with lowest achieved mean blood pressure being 134/75 mmHg in studies showing benefit in people with Type 2 diabetes and albuminuria [4].

The recommendation on treatment of anaemia once GFR starts to decline is supported by the finding in the RENAAL study that mild anaemia is associated with risk of renal disease progression [10].

Cardiovascular risk is increased in people with microalbuminuria, and further increased in those with proteinuria and/or reduced GFR. The issue of cardiovascular risk is addressed elsewhere in this guideline (see *Cardiovascular risk protection*).

Consideration

Although it is possible to treat kidney failure by dialysis or transplantation, availability of these very expensive treatments is severely limited in a global context. This makes efforts at prevention all the more important. It has been estimated that, once a dipstick test is positive, time to kidney failure is about 9 years, but that this time-interval can be doubled through appropriate treatment of blood pressure. The issue of targets can be a particular problem in people with Type 2 diabetes who are often more elderly, and in whom attainment of 140/80 mmHg or less can seem impossible even with multiple drugs and reasonable lifestyle intervention. Nevertheless control around this level has been achieved in a number of studies, implying that around half the population can get to (and thus benefit from) lower levels.

Implementation

Management of blood pressure overlaps with the advice given in *Blood pressure control*. Recurrent measurement and drug dose titration need good access for people with evidence of renal damage, where repeated measurements of potassium and creatinine are particularly important. Additionally the current section requires access to laboratory microalbumin estimation (or availability of semi-quantitative reagent strips), and availability of multiple blood-pressure-lowering drugs and in particular renin-angiotensin system blockers.

Evaluation

The percentage of people with appropriate urine albumin and serum creatinine measurements should be ascertained. Where abnormalities are detected, evidence of action to ensure tight blood pressure control is required, together with achieved blood pressure. Level of eGFR at which referral to nephrologists occurred may also be determined.

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