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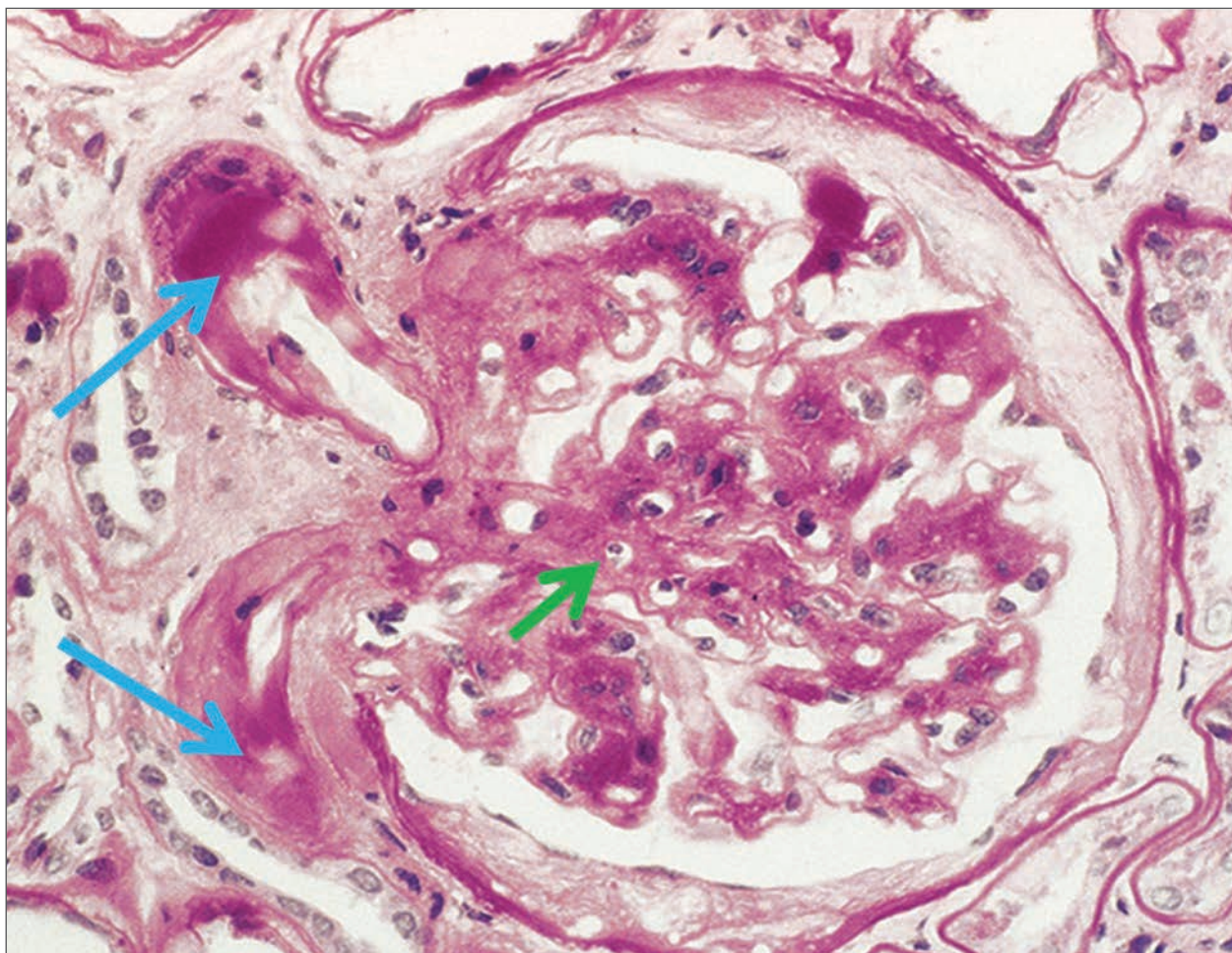
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FIGURE 1

Glomerular histological changes in diabetic nephropathy. Note that both afferent and efferent arterioles are extensively hyalinised or thickened due to the haemodynamic and toxic effects of the diabetic milieu (blue arrows). The supporting tissue or mesangium of the glomerulus is thickened (green arrow)



What are the causes of diabetic nephropathy?



DIABETIC NEPHROPATHY OCCURS IN UP TO 40% OF THOSE WITH DIABETES¹ AND HAS BECOME THE

most common cause of end-stage renal disease in most countries including the UK.²

Diabetic nephropathy is also associated with substantially higher cardiovascular risk and the severity of chronic kidney disease (CKD) is correlated with premature mortality in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).³

How should diagnosis be made?

Nevertheless, < 5% of patients with CKD stage 3 will progress to renal replacement therapy over a ten-year period.⁴

Diabetic nephropathy results from the combined effects of various genetic and environmental factors, see figure 1, above. Prolonged duration of diabetes, poor glycaemic control and hypertension are major risk factors for both diabetic nephropathy and cardiovascular disease.^{5–7}

Clinical trials have confirmed that optimising blood sugar control

How should patients be managed?

together with excellent control of blood pressure can reduce the risk of developing diabetic nephropathy.^{5,6,8}

Several pathological mechanisms are responsible for the clustering of diabetic microvascular and macrovascular complications. These include formation of advanced glycation end products, increased oxidative stress, endothelial dysfunction, growth factor pathway disruption and accelerated atherosclerosis.⁹

Of note, elevated serum levels of angiotensin II are observed prior

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SYMPOSIUM RENAL MEDICINE

DIABETIC NEPHROPATHY

to the onset of overt diabetic nephropathy.⁴ Persistently elevated angiotensin II activity results in a chronic rise in intraglomerular pressure with eventual pathological kidney injury and development of clinical diabetic nephropathy, see figure 2, below.

DIAGNOSIS

Diabetic nephropathy should be considered in any patient with diabetes when persistent albuminuria develops. The amount of urinary albumin excretion is defined by the urinary albumin:creatinine ratio (ACR) and the risk of diabetic nephropathy is

directly related to the absolute amount of albumin excretion. Microalbuminuria, defined by a urinary ACR of 3–30 mg/mmol on two occasions three months apart, see table 1, p15, is the earliest clinically detectable indicator of diabetic nephropathy risk.

FIGURE 2a
Glomerular haemodynamic changes in diabetic nephropathy. Normal glomerular capillary pressure and glomerular filtration

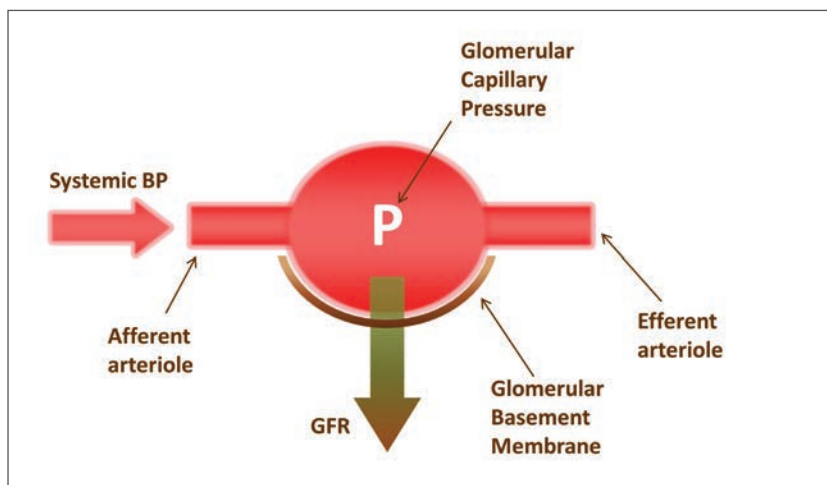


FIGURE 2b
Glomerular capillary hypertension, glomerular hypertrophy and hyperfiltration associated with angiotensin II mediated efferent arteriolar vasoconstriction

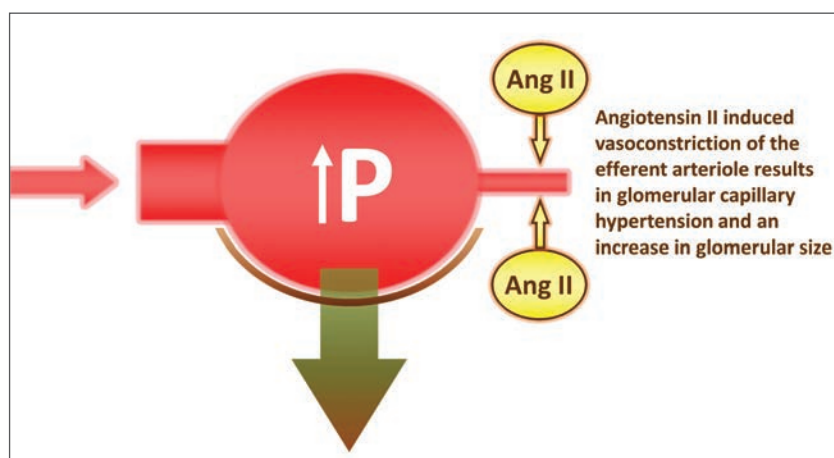
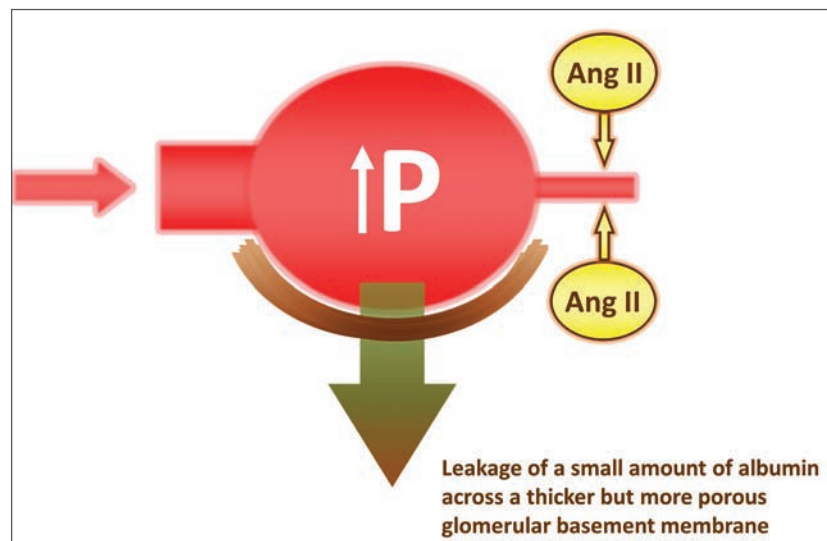


FIGURE 2c
Development of microalbuminuria associated with thickened but leaky glomerular basement membrane



‘Diabetic nephropathy should be considered in any patient with diabetes when persistent albuminuria develops’

Initially, albuminuria may or may not be accompanied by a rise in serum creatinine and corresponding fall in estimated glomerular filtration rate (eGFR). Retinopathy typically accompanies diabetic nephropathy (90% T1DM; 70% T2DM).

A renal biopsy, see figure 1, p13 and figure 3, p15, is usually not necessary for confirmation of diabetic nephropathy and the majority of patients with diabetic nephropathy are appropriately diagnosed based on elevated urinary albumin excretion and/or reduced renal function. Individuals with T2DM should have annual urinary ACR measurements from the time of diabetes diagnosis while those with T1DM should commence five years after diagnosis.

A recent UK study reported that annual ACR measurements were performed in only 73.7% of T2DM patients and 54.4% of T1DM patients which is a cause for concern.¹⁰ There are substantial numbers of at-risk individuals in whom the earliest stages of diabetic nephropathy could be missed.

REFERRAL

In accordance with NICE (2008)¹¹ and KDIGO (2012)¹² guidelines patients with known or suspected diabetic nephropathy should be referred to a nephrologist in the following situations:

- eGFR < 30 ml/min/1.73m²
- eGFR fall > 5 ml/min/1.73m² per year or otherwise rapidly deteriorating

Table 1**Comparison of methods used to measure proteinuria**

	Urine dipstick	ACR (mg/mmol)	PCR (mg/mmol)	24 hr collection
Normal	Nil	< 3	< 5	< 0.15 g
Microalbuminuria	Nil or trace	3-30	5-50	< 0.5 g
Proteinuria	+ or ++ 0.3 g/L to 1 g/L ++ or +++ 1 g/L to 3 g/L	70 70-200	100 100-350	1 g 1-3.5 g
Nephrotic range proteinuria	+++ or ++++ 3 g/L to 20 g/L	> 300	> 350	> 3.5 g
Comments	Qualitative: Easy to use, can detect blood, glucose, nitrites. Cannot detect microalbuminuria	Quantitative: Measures albumin excretion. Total proteinuria underestimated if proteins other than albumin present	Quantitative: Measures all urinary proteins. Divide PCR by 100 to derive proteinuria in grams	Gold standard: However, it is cumbersome and relies on appropriate collection techniques

- ACR > 100 mg/mmol despite maximum tolerated ACEI or ARB therapy
- Presentation with nephrotic range proteinuria (ACR > 300 mg/mmol)
- Dipstick-positive or frank haematuria on two occasions
- Uncontrolled hypertension on four agents
- Suspicion of alternative diagnosis (family history, renal structural or stone disease)

If uncertainty still exists a telephone call or email to a local nephrologist may be helpful.

MANAGEMENT

The patient should be at the centre of any treatment strategy. Patient education and engagement are key steps to successfully implementing measures known to improve prognosis.¹³ The potential for fragmentary care is

high and it is of the utmost importance that members of the multidisciplinary team check and confirm the patient's understanding and expectations at clinic visits. This paves the way to deliver effective multifactorial interventions that optimise blood pressure, proteinuria and cardiovascular risk with demonstrable reductions in morbidity and mortality.⁶

The role of good glycaemic control in delaying the onset of microalbuminuria is well established.^{5,7,14} The current target is to achieve an HbA_{1c} of 7% (53 mmol/mol) provided hypoglycaemic episodes are minimised.

Blood pressure lowering to 130/80 mmHg and reduction of proteinuria to < 1 g/day retards progression of diabetic nephropathy and reduces the number of cardiovascular events.¹⁵ If proteinuria exceeds 1 g/day then the target BP is 125/75 mmHg.

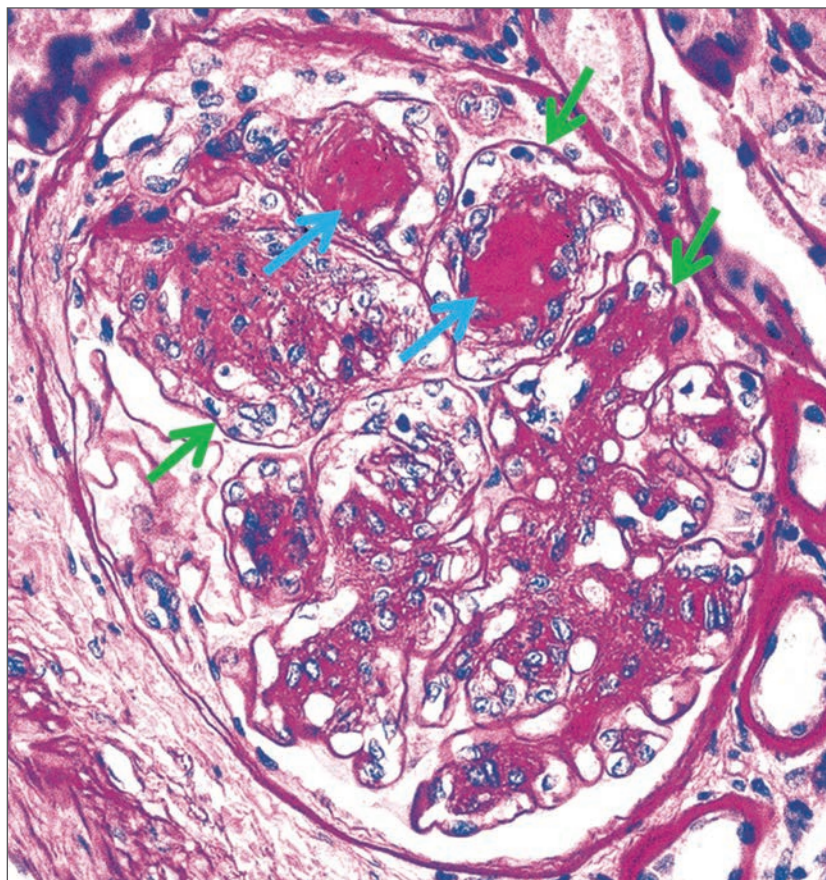
Drugs that block the renin-angiotensin-aldosterone system (RAAS) are effective in reducing proteinuria, managing hypertension and reducing cardiovascular risk. Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are felt to be equivalent in terms of efficacy.¹⁶

Many individuals will start with an ACEI and only switch to an ARB if symptoms such as cough are troublesome. Unless there are clear contraindications or intolerance all patients with diabetic nephropathy should be prescribed an ACEI or ARB.

Uptitrating to the highest tolerated dose will maximise both antihypertensive and antiproteinuric effects.¹² Data from meta-analyses of recent trials suggests that RAAS inhibition in normoalbuminaemic patients with

FIGURE 3

Glomerular histological changes in diabetic nephropathy. The classic nodules seen in advanced nephropathy are well demonstrated (blue arrows). Also noteworthy is the prominence of the glomerular basement membrane (green arrows) due to its thickening as a result of the increased glomerular pressure over time



key points

SELECTED BY

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Prolonged duration of diabetes, poor glycaemic control and hypertension are major risk factors for both diabetic nephropathy and cardiovascular disease. Optimising blood sugar control together with excellent control of blood pressure can reduce the risk of developing diabetic nephropathy.

Diabetic nephropathy should be considered in any patient with diabetes when persistent albuminuria develops. Microalbuminuria is the earliest clinically detectable indicator of diabetic nephropathy risk. The majority of patients with diabetic nephropathy are appropriately diagnosed based on elevated urinary albumin excretion and/or reduced renal function. Patients with type 2 diabetes should have annual urinary ACR measurements from the time of diabetes diagnosis while those with type 1 diabetes should commence five years after diagnosis.

Blood pressure lowering to 130/80 mmHg and reduction of proteinuria to < 1 g/day retards progression of diabetic nephropathy and reduces the number of cardiovascular events. Drugs that block the renin-angiotensin-aldosterone system (RAAS) are effective in reducing proteinuria, managing hypertension and reducing cardiovascular risk. Unless there are clear contraindications or intolerance all patients with diabetic nephropathy should be prescribed an ACEI or ARB.

Stopping an ACEI or ARB during intercurrent illness or during times of volume depletion is critically important. Co-prescription of an NSAID causes further reduction in glomerular pressure by inhibiting the beneficial prostaglandin-mediated afferent arteriolar vasodilation. A daily sodium chloride intake of 5 g or less is recommended and caution should be exercised in using salt substitutes containing potassium chloride as individuals taking RAAS inhibitors may develop dangerous hyperkalaemia.

Metformin should be stopped in the setting of illnesses such as sepsis, volume depletion or acute cardiac events as there is a small but important risk of lactic acidosis. All patients with diabetic nephropathy should have at least yearly measurements of blood pressure, renal function and urinary ACR. If possible, pregnant women should be switched to more 'pregnancy-friendly' antihypertensives such as methyldopa, labetalol or nifedipine.

T2DM retards time to development of microalbuminuria.¹⁷ The evidence is less clear cut in those with T1DM and normoalbuminaemia.

After commencing a RAAS blocker some patients will experience an initial rise in serum creatinine. Provided this is not > 25% of baseline creatinine and potassium levels remain < 6 mmol/L, RAAS blockade can be safely continued. Paradoxically, it has been observed that an initial fall in eGFR after RAAS blockade is predictive of a slower long-term decline in renal function.¹⁸ This reflects the effect of reduced intraglomerular pressure, secondary to inhibition of the RAAS, with fall in angiotensin II mediated vasoconstriction of the efferent arteriole.

The critical importance of stopping an ACEI or ARB during intercurrent illness or during times of volume depletion (vomiting, diarrhoea, surgery) is thus appreciated. Too great a reduction in intraglomerular pressure leads to a rapid fall in GFR and acute kidney injury.

Co-prescription of an NSAID causes further reduction in glomerular pressure by inhibiting the beneficial prostaglandin-mediated afferent arteriolar vasodilation.

Patients with diabetic nephropathy and proteinuria > 1 g/day may require additional antihypertensive agents to achieve targets. Despite this, blood pressure and proteinuria may still be poorly controlled. In this case it is always worth exploring any barriers to concordance as well as ensuring that dietary sodium restriction is maximised.

The effects of RAAS blockade can be entirely negated if sodium intake is too high.¹⁹ A daily sodium chloride intake of 5 g or less is recommended.¹¹ Great caution should be exercised in using salt substitutes, e.g. LoSalt containing potassium chloride, as individuals with diabetic nephropathy taking RAAS inhibitors may develop dangerous hyperkalaemia.

Addition of a diuretic to aid sodium excretion can be considered particularly for oedematous patients. Dual therapy with an ACEI and ARB, while effective in reducing BP and proteinuria, is associated with much greater risks of renal dysfunction and hyperkalaemia and should be avoided.²⁰ The most recent trial of dual therapy was terminated early because of these safety concerns.²¹

Investigations into the safety and longer-term benefits of supramaximal doses of individual RAAS inhibitors as

well as other new agents are currently underway.²²

To reduce cardiovascular risk, aspirin and statin therapy should be strongly considered for those with diabetic nephropathy.²³ Advice on smoking cessation, weight control and physical activity should be provided to all patients and their medication list reviewed. As GFR falls dose reduction is required for some drugs.²⁴

Metformin can be safely continued until an eGFR of 30 ml/min and possibly lower, but should be stopped in the setting of illnesses such as sepsis, volume depletion or acute cardiac events as there is a small but important risk of lactic acidosis.

‘In one report almost 70% of patients studied had been prescribed NSAIDs at some point with potential for adverse renal outcomes’

Insulin, as it is metabolised by the kidney, may accumulate as GFR falls and so dosing requirements may need to be reduced.

The sulfonylureas glipizide and glimepiride are relatively safe and thus preferred in those with CKD over longer-acting analogs. Meglitinide, nateglinide and the DPP-4 inhibitor, linagliptin are the agents of choice in their class for those with CKD.

Thiazolidinediones are probably safe in CKD but fluid retention and increased cardiovascular risk make other oral hypoglycaemic classes more attractive. GLP-1 receptor agonists such as exenatide are contraindicated with an eGFR < 60 ml/min.

If NSAIDs are required for short-term management of pain it is wise to discontinue ACEI or ARB therapy temporarily. Consultation with a pharmacist and the BNF is helpful in determining which drugs need to be altered or stopped as GFR declines.

MONITORING AND FOLLOW-UP

As the vast majority of patients with diabetic nephropathy and stage 3 CKD will have either stable or very slowly progressive renal dysfunction their care can best be concentrated in primary care with input from diabetologists and nephrologists on an ad hoc basis when required.^{13,25} All patients with diabetic nephropathy should have at least yearly measurements of blood pressure, renal function (serum creatinine; eGFR) and urinary ACR.

In the general population GFR declines at an average of 1 ml/min/year. With meticulous control of risk factors the GFR decline in those with diabetic nephropathy can approximate this population decline.²⁶

Patients of South Asian or Black ethnicity may have more rapid diabetic nephropathy progression and therefore require closer follow-up.

Alarming, in one report, almost 70% of patients studied had been prescribed NSAIDs at some point with potential for adverse renal outcomes.²⁶ For those patients observed to have stable renal function they can be safely referred back to their GP for ongoing CKD management.²⁷

Two-thirds of patients with diabetic nephropathy and stage 3 CKD who are under the care of nephrologists will remain within that stage and require minimal intervention.²⁸

PREGNANCY

Special mention should be made of women with diabetic nephropathy who are considering pregnancy.

RAAS blockade in the second and third trimester is definitely teratogenic but exposure up to the first trimester is more controversial.

In such cases, the risks and benefits should be discussed with the patients and, if possible they should be switched to more 'pregnancy-friendly' antihypertensives such as methyldopa, labetalol or nifedipine.

Some women may elect to continue ACEI or ARB up until pregnancy is confirmed because of suboptimal blood pressure or proteinuria control.²⁹

Careful coordination between primary care, nephrology, diabetology and obstetrics is essential so that rigorous control of blood pressure, glycaemic indices and proteinuria is achieved to ensure delivery of a healthy child to a healthy mother.³⁰

Acknowledgement

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Useful information

NICE clinical guidelines

Type 2 diabetes (CG66 and CG87)
Chronic kidney disease (CG73)
www.nice.org.uk

KDIGO

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease
See especially the Summary of Recommendation Statements, pp 5-14
www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf

Edinburgh Renal Unit

Very clear practical guidance for GPs
www.edren.org/pages/gpinfo.php

Concise information for patients
www.edren.org/pages/edreninfo/diabetic-kidney-disease.php

Diabetes UK: Kidneys (nephropathy)
www.diabetes.org.uk/Guide-to-diabetes/Complications/Kidneys_Nephropathy

Patient Plus: Diabetic nephropathy
www.patient.co.uk/doctor/diabetic-nephropathy

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