CLINICAL PRACTICE GUIDELINES

JULY 2004 MOH/P/PAK/72.03(GU)

DIABETIC NEPHROPATHY

MINISTRY OF HEALTH MALAYSIA

MALAYSIAN SOCIETY OF NEPHROLOGY

ACADEMY OF MEDICINE

SUMMARY

Recommendations for Screening, Monitoring and Management of Diabetic Renal Disease

Stage	Definition	Screening/Monitoring	Management	Grade
Stage 1/2 Normoalbuminuria	• Normal renal function • Urine albumin concentration < 20 mg/l	• Annual urine protein dipstick • Recheck if positive • If negative test for microalbuminuria	• Optimise glycaemic control • Treat hypertensionn (target BP < 130/80)	A A
Stage 3 Microalbuminuria	• Normal renal function • Dipstick negative • Urine albumin concentration 20 – 200 mg/l • AER 30 – 300 mg/24h	• Recheck urine for microalbuminuria 2 – 4 times per year	• Optimise glycaemic control • Treat hypertension (target BP<130/80) • Use ACEI/ARB for hypertension and/or microalbuminuria reduction • Avoid excessive dietary protein and salt intake • Treat hyperlipidaemia	A A A C B
Stage 4 Overt proteinuria (Macroalbuminuria)	• Serum creatinine normal or raised • Dipstick positive • Urine albumin concentration > 200 mg/l • AER > 300 mg/24 h	• Quantitate proteinuria 2 – 4 times per year • Renal profile 2 – 4 times per year	• Target BP < 125/75 if proteinuria > 1 g/day • Use ACEI/ARB for hypertension and/or proteinuria reduction • Restrict protein • Restrict salt • Treat hyperlipidaemia • Consider referral to a nephrologist	B A B B B C
Stage 5 End stage kidney failure	• Serum creatinine > 500 µmol/L	• As dictated by individual circumstances	• Protect access sites • Dialysis / transplant	C

AER = Albumin excretion rate, BP = blood pressure
Adapted from SIGN Guidelines[1]

Statement of Intent

These guidelines are meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

These guidelines were issued in July 2004 and will be reviewed in July 2006 or sooner if new evidence becomes available.

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PREFACE

Diabetes mellitus is a major cause of end stage renal disease (ESRD) worldwide. In Malaysia the Dialysis and Transplant Registry 2002 reported that diabetic nephropathy was the predominant cause of ESRD accounting for 47% of new cases.[2] This places an enormous burden on clinical, public health and economic resources as such patients often have multiple co-morbid conditions such as coronary artery and peripheral vascular disease.

Thus the Malaysian Society of Nephrology council deemed it appropriate that a Clinical Practice Guideline on Diabetic Nephropathy be drawn up to guide healthcare professionals, with the major objectives being screening for diabetic nephropathy and instituting measures to prevent or retard its progression.

This task was given to the Penang nephrologists as it dawned on the council that the small island had a nephrologist in every corner! Apart from nephrologists, the panel included an endocrinologist, a family physician, an outpatient general practitioner, a cardiologist, and a physician with interest in diabetes mellitus. The committee has attempted to combine evidence based medicine with the practical strategies available locally to formulate these recommendations.

These fourteen recommendations are intended to assist primary health care doctors who manage diabetic patients in their day-to-day practice to intervene early and effectively so that the onset and the course of diabetic nephropathy can be ameliorated.

I would like to take this opportunity to thank the panel members for their hard work and commitment in preparing the guidelines. I would also like to thank the secretariat for services rendered, all those who contributed to the final draft presentation and finally to the Malaysian Society of Nephrology council for their infinite patience in waiting for the appearance of this guideline!

Dr. Rozina Ghazalli
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DEVELOPMENT OF THE GUIDELINE

- Relevant key words and terms were determined by the committee members. These were used to generate MEDLINE searches for scientific literature in the English language focusing on peer reviewed articles. The articles were retrieved for systematic review using a check list to assess the validity of the studies.

- A draft of the guideline was formulated based on the systematic review of the literature including existing guidelines. Some recommendations were modified taking into consideration local issues such as costs and available resources. The rationale for the modification was provided.

- The draft was subjected to peer review in stages. It was distributed to general practitioners, physicians, endocrinologists, nephrologists and Malaysian Society of Nephrology members and amended following their comments. A discussion of the recommendations was then made at the annual seminar of the Malaysian Society of Nephrology in May 2003 followed by an open forum for doctors in Penang.

- This guideline is structured for ease of reference. Each guideline is tabulated, numbered and titled. The evidence and rationale for the recommendation is provided to enable the reader to make an informed decision appropriate to the individual patient.

- This guideline complements the existing guideline on “Care of the Diabetic Patient (The Malaysian Consensus practice guideline : Second edition July 1999)”. The focus of this guideline is on the prevention, screening and management of diabetic nephropathy.

- Recommendations have been graded based on levels of evidence using the following system: -

GRADE A	Based on evidence from one or more randomised clinical trials and/or meta-analyses.
GRADE B	Based on evidence from high quality clinical trials but no randomised clinical trial data available.
GRADE C	Based on expert committee reports and/or clinical experience of respected authorities but lacking in directly applicable studies of good quality.

INTRODUCTION

- In recent years there has been an increase in the prevalence of diabetes worldwide. In Malaysia the prevalence of diabetes has increased from 6.3% in 1986 to 8.3% in 1996.[3]

- With improvement in the survival of patients with diabetes, nephropathy has now emerged as a major health problem.

- Nephropathy develops in about 20-40% of diabetics. Known risk factors for the development of diabetic nephropathy include genetic predisposition, poor glycaemic control, hypertension and smoking.

- Prevention, early detection and aggressive intervention are needed to retard the progression of diabetic nephropathy to end stage renal failure.

- Cardiovascular disease is the commonest cause of death in patients with diabetic nephropathy. Thus it is necessary to address the associated risk factors for this condition.

DIAGNOSIS OF DIABETIC NEPHROPATHY

- The diagnosis of diabetic nephropathy is usually made clinically. Other target organ involvement is often present. 90-95% of type 1 diabetics and about 70% of type 2 diabetics with nephropathy will have retinopathy as well. In the absence of retinopathy, non-diabetic renal disease may need to be excluded.

- Non-diabetic renal disease should also be considered when :-
  - significant haematuria or urinary red blood cell casts are present
  - renal failure occurs in the absence of proteinuria
  - there is evidence of other systemic disease e.g. systemic lupus erythematosus, myeloma, viral hepatitis

- Concomitant renal artery stenosis should be suspected :-
  - when rapid deterioration of renal function occurs with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)
  - in the presence of severe peripheral vascular disease, renal bruits, severe uncontrolled hypertension or unequal sized kidneys

NATURAL HISTORY OF DIABETIC NEPHROPATHY

- Diabetic nephropathy is a spectrum of progressive renal lesions secondary to diabetes mellitus ranging from renal hyperfiltration to end stage kidney disease.

- The earliest clinical evidence of nephropathy is the presence of microalbuminuria (Table 1). It occurs in 30% of type 1 diabetics, 5 to 15 years after diagnosis but may be present at diagnosis in type 2 diabetics as the time of onset of type 2 diabetes is often unknown.

- Microalbuminuria progresses to overt proteinuria over the next 7 to 10 years (Figure 1).

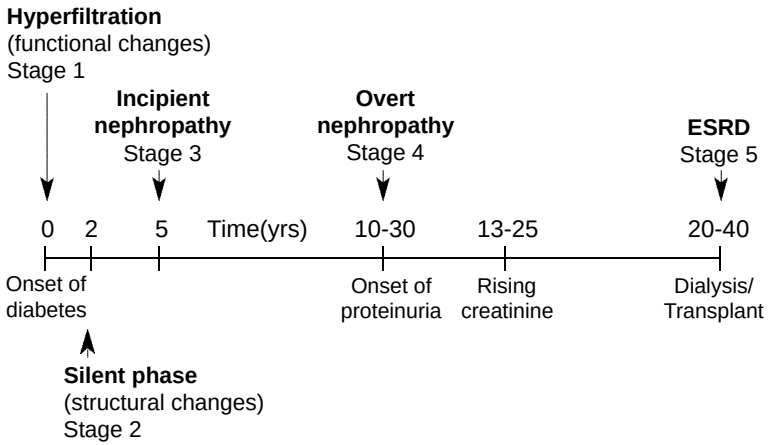
- Once overt proteinuria develops, renal function progressively declines and end stage renal failure is reached after about 10 years.

Table 1. Evolution of Diabetic Renal Disease

Stage 1	• Glomerular hypertension and hyperfiltration • Normal albuminuria: urinary albumin excretion rate (AER) <20 µg/min • Raised GFR, normal serum creatinine
Stage 2	• "Silent phase" (structural changes on biopsy but no clinical manifestations) • Normoalbuminuria
Stage 3	• Microalbuminuria: AER 20 – 200 µg/min • Normal serum creatinine • There may be increased blood pressure
Stage 4	• Overt "dipstick positive" proteinuria (macroalbuminuria) : AER > 200 µg/min • Hypertension • Serum creatinine may be normal • Increase in serum creatinine with progression of nephropathy
Stage 5	• End stage renal failure • Requiring dialysis or transplant to maintain life

Adapted from SIGN Guidelines[1]

Figure 1. Natural history of diabetic nephropathy[4]



PREVENTION OF DIABETIC NEPHROPATHY

- One of the most important aspects in the management of diabetes mellitus is to prevent macrovascular and microvascular complications including diabetic nephropathy and cardiovascular disease.

- This may require a multidisciplinary team approach which includes general practitioners, physicians, endocrinologists, dietitians and trained diabetic nurses.

- The focus of management should be on good glycaemic control which includes patient education, lifestyle modification, diet, exercise, attainment of ideal body weight and frequent self-monitoring of blood glucose.

- The strongest evidence in the prevention of diabetic nephropathy and other microvascular complications has been with tight glycaemic control. The Diabetes Control and Complications Trial (DCCT) in type 1 diabetics[5,6] and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetics[7] have shown that intensive blood glucose control reduces the risk of developing nephropathy, retinopathy and neuropathy.

- Strategies to prevent diabetic nephropathy also include monitoring and tight control of blood pressure.

SCREENING FOR MICROALBUMINURIA AND OVERT PROTEINURIA

- Microalbuminuria refers to the presence of a small amount of albumin in the urine, which cannot be detected with the usual urine dipstick. The definition depends on the method of urine collection (Table 2).

Table 2. Definition of abnormal urinary albumin excretion[1]

	SPECIMEN COLLECTED			
			First voided morning specimen	
Albumin Excretion	24 hr collection (mg/24h)	Timed collection (µg/min)	Urine Albumin concentration* (mg/l)	Urine Albumin: Creatinine ratio** (mg/mmol)
Normoalbuminuria	<30	<20	<20	<3.5 women <2.5 men
Microalbuminuria	30-300	20-200	20-200	3.5 to 35 women 2.5 to 25 men
Overt proteinuria	>300	>200	>200	>35 women >25 men

* *urine albumin of 200mg/l is equivalent to 300mg/l of protein*
** *3.5 as lower limit in females because of lower creatinine excretion*

Recommendation 1 : Screening for proteinuria

Screening for proteinuria should be performed yearly in the following patients*:

(a) Type 1 diabetes mellitus: 5 years after diagnosis of diabetes, or earlier in the presence of other cardiovascular risk factors
(b) Type 2 diabetes mellitus: at the time of diagnosis of diabetes

Grade C

* *Other factors affecting urinary albumin excretion should be excluded when screening for microalbuminuria and proteinuria (Appendix 1).*

Recommendation 2 : Method of screening for proteinuria

Urine should be screened for proteinuria with conventional dipstick on an early morning urine specimen*

Grade C

* *Other factors affecting urinary albumin excretion should be excluded when screening for microalbuminuria and proteinuria (Appendix 1).*

Recommendation 3 : Screening for microalbuminuria

(a) If urine dipstick for proteinuria is negative, screening for microalbuminuria should be performed on an early morning urine specimen
(b) Urine dipstick for microalbuminuria is an acceptable screening test
(c) If microalbuminuria is detected, confirmation should be made with two further tests within a 3 to 6 month period (see Algorithm)
(d) If microalbuminuria is not detected, re-screening should be performed annually

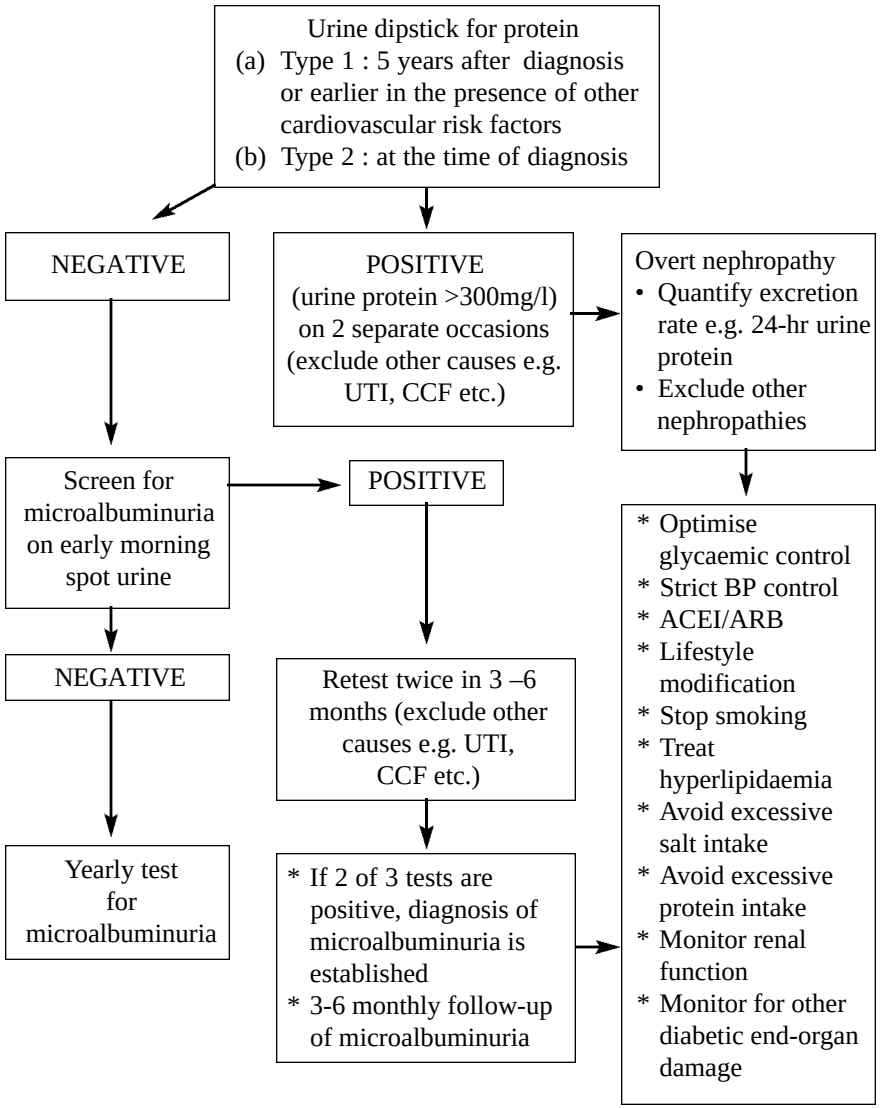
Grade C

- Timed urine collection is the gold standard for screening and quantification of urinary albumin excretion. However this is expensive, impractical and collection is often incomplete. Refer to Appendix 2.

- Urine dipstick testing for albumin concentration or albumin/creatinine ratio are quick, convenient tests that can give rapid on-site results. Both tests have reasonable sensitivity and specificity[8].

- Early morning urine should be used to minimise fluctuations in urinary concentration and changes in AER related to posture and physical activity. Currently available methods for screening of microalbuminuria are listed in Appendix 3.

Algorithm : Screening for Proteinuria



Adapted from Practice Guidelines for Diabetes Mellitus type 2. The Malaysian consensus : Second Edition (July 1999)

MANAGEMENT OF DIABETIC NEPHROPATHY

- The development of diabetic nephropathy has a devastating impact on morbidity and mortality of patients with diabetes mellitus. Microalbuminuria is a powerful and independent predictor of cardiovascular death.[9,10]

- Therapeutic intervention should include strategies to prevent or retard the progression of diabetic renal disease as well as to reduce cardiovascular complications.

- The management of these patients includes good glycaemic control, tight control of blood pressure, reduction of proteinuria with ACEIs or ARBs, cessation of smoking, lipid control and salt and protein restriction.

Glycaemic Control

Recommendation 4 : Glycaemic control

Glycaemic control should be optimised, with FBS ≤ 6 mmol/l and/or HbA1c ≤ 7%

Grade A

FBS = fasting blood glucose, HbA1c = glycosylated haemoglobin

- In type 1 diabetes mellitus, intensive treatment usually with multiple insulin injections, coupled with self-management education and self monitoring of blood glucose can achieve near ideal glucose and HbA1c goals. The risk of getting microalbuminuria and albuminuria is reduced with intensive treatment.[5]

- Maintaining the HbA1c target long term can sustain the benefits.[6]

- In type 2 diabetes, intensive blood glucose control can reduce the risk of microvascular endpoints including albuminuria irrespective of the drugs used,[7] except in overweight diabetics where metformin was shown to have a significantly greater effect on any diabetic related endpoints.[11]

- Any reduction of HbA1c can reduce the risk of diabetic complications.[12]

- In the presence of renal failure the dose of hypoglycaemic agents should be adjusted to avoid hypoglycaemia. Refer to Appendix 4.

Blood Pressure Control

In type 1 diabetics, blood pressure rises with the development of microalbuminuria. With the onset of overt proteinuria, hypertension is usually present and worsens as the nephropathy progresses. However in type 2 diabetics, hypertension may precede the onset of diabetic nephropathy and is often associated with the metabolic syndrome of obesity, insulin resistance and hyperlipidaemia.

Recommendation 5 : Target blood pressure
Target blood pressure in diabetics should be less than 130/80mmHg Grade A

- Tight blood pressure control is the primary goal in the management of hypertension in diabetics. This may be achieved with any antihypertensive agent.

- Hypertension aggravates microvascular and macrovascular complications of diabetes including diabetic nephropathy.[13]

- Diabetics benefit more from aggressive blood pressure lowering compared to non-diabetics in the reduction of cardiovascular events.[14-16]

- Tight blood pressure control is also important to slow the progression of nephropathy and deterioration of renal function.[17,18]

- Target blood pressure should be less than 130/80mmHg if this can be safely achieved. Although the target is relatively arbitrary, the

Hypertension Optimal Treatment (HOT) study has demonstrated the value of aiming for a diastolic pressure of less than 80mmHg to reduce cardiovascular and other diabetic complications.[14] However this can be difficult to achieve and multiple (2 or more) drugs may be necessary.[19]

- The choice of antihypertensive agent(s) should be individualised, tailored to patients' co-morbidities. Diuretics, beta-blockers, calcium channel blockers, ACEIs or ARBs may be used to achieve the target blood pressure.

- ACEIs or ARBs may be considered as first line therapy for treatment of hypertension in diabetics in the absence of contraindications. Several studies have suggested that ACEIs[20-24] and ARBs[25] may confer cardioprotective benefits beyond their blood pressure effect in diabetics although other studies did not show specific advantages.[26,27]

Microalbuminuria

Recommendation 6 : Treatment of microalbuminuria
ACEIs or ARBs should be initiated for the reduction of microalbuminuria unless contraindicated ACEIs in type 1 & type 2 diabetics : Grade A ARBs in type 2 diabetics : Grade A

Refer to Appendix 5 for dosage of commonly used ACEIs and ARBs

- ACEIs[24] and ARBs have been shown to reduce microalbuminuria in diabetic patients independent of their effect on blood pressure.

- In type 1 diabetic patients with or without hypertension, ACEIs have been shown to reduce microalbuminuria.[28-31] In type 2 diabetics, ACEIs[32-38] and more recently ARBs[39-41] have been shown to reduce microalbuminuria.

Overt Proteinuria

This is the stage when urine is positive for protein by conventional dipstick. Treatment at this stage should be aimed at aggressive lowering of blood pressure and reduction of proteinuria.

Recommendation 7 : Target blood pressure in overt nephropathy
In patients with proteinuria > 1 g/day, target blood pressure should be lowered to < 125/75mmHg Grade B

The target is extrapolated from the Modification of Diet in Renal Disease (MDRD) study where 3% of subjects were diabetics. In the subset of patients with proteinuria of more than 1 g/day, lowering of blood pressure to below 125/75mmHg was associated with reduction in deterioration of renal function.[17]

Recommendation 8 : Treatment of overt proteinuria
(a) In Type 1 diabetics with overt proteinuria, ACEIs should be initiated unless contraindicated Grade A
(b) In Type 2 diabetics with overt proteinuria, ARBs or ACEIs should be initiated unless contraindicated ARBs : Grade A ACEIs : Grade B

Refer to Appendix 5 for dosage of commonly used ACEIs and ARBs.

- Early studies on type 1 diabetic nephropathy have demonstrated the effectiveness of blood pressure control with conventional antihypertensive agents in reducing proteinuria and deterioration of renal function.[18]

- The most compelling evidence supporting drug specific advantages beyond blood pressure control has been with ACEIs and ARBs.

Landmark studies of ACEIs in type 1[42] and ARBs in type 2 diabetics[43,44] have shown the effectiveness of these agents to retard the progression of overt diabetic nephropathy. In these trials, there were significant reductions in the risk of doubling of plasma creatinine and developing renal failure. These benefits were independent of blood pressure lowering.

- The role of ACEIs in type 2 diabetics with overt nephropathy is less clear. As yet, large long-term studies on hard renal endpoints have not been performed. Small scale studies have shown beneficial effect on proteinuria but data on retardation of progression of renal failure is limited.[36,45-49] Despite the lack of direct evidence, an ACEI is a reasonable alternative to an ARB as it is cheaper and more widely available.

- Current data suggests that ACEI/ARB should be instituted even in patients with moderately severe renal failure.[43,44] However renal function should be monitored closely. Refer to Appendix 5.

- Several small studies have indicated that the combination of ACEI and ARB may have additive effect in lowering blood pressure and proteinuria in diabetic patients with microalbuminuria[50,51] and overt nephropathy.[52,53] Data on long term renoprotective benefits is required.

- Calcium channel blockers (CCBs) have class specific effect on proteinuria. Non-dihydropyridine CCBs (e.g. verapamil, diltiazem) have consistently been shown to reduce proteinuria but dihydropyridine CCBs (e.g. nifedipine, amlodipine) have variable effect.[54-57]

- There is currently insufficient evidence to support a specific recommendation on the use of sulodexide, a glycosaminoglycan, in the treatment of diabetic nephropathy. Small scale studies with short-term follow-up have suggested that sulodexide may be useful to reduce urinary albumin excretion rate in type 1 and type 2 diabetics with microalbuminuria or overt proteinuria.[58,59] The data on its effect on renal function is limited.

Smoking

Recommendation 9 : Cessation of smoking

Cigarette smoking should be actively discouraged

Grade B

There is clear epidemiological evidence to link smoking to increased risk of cardiovascular events. Smoking has also been shown to accelerate progression of diabetic and non-diabetic renal disease and cessation of smoking ameliorates the decline of renal function.[60-62] Thus patients with diabetic nephropathy should be strongly advised against smoking.

Lipids

- Diabetics often have abnormal lipid profiles with raised serum triglycerides, cholesterol and decreased HDL cholesterol level.

- While dyslipidaemia may aggravate renal disease,[63] the evidence that correction of lipid abnormality slows progression of renal failure is still lacking.[64-68]

Recommendation 10 : Monitoring of serum lipids

Full lipid profile should be performed at least annually in adult diabetics

Grade C

- Lipid profile should be performed at least annually. However more frequent monitoring may be required particularly after commencement of treatment to achieve target levels.[69]

- In diabetic children lipid monitoring every 5 years may be sufficient.[69]

- In type 1 diabetics, tight glycaemic control is associated with normal lipoprotein level. Thus, good glycaemic control in type 1 diabetics may be more important than in type 2 diabetics to reduce cardiovascular risk.[70]

Recommendation 11 : Correction of dyslipidaemia

In diabetics :

(a) therapeutic lifestyle changes should be instituted if LDL-cholesterol is > 2.6 mmol/l

(b) drug therapy should be considered if LDL-cholesterol is > 3.4 mmol/l

Grade B*

* *recommendations are graded on evidence from trials on diabetics in general as data in diabetic nephropathy is limited*

- Dyslipidaemia in diabetics should be identified and aggressively treated.

- All diabetics should be encouraged to go on a therapeutic lifestyle change comprising increased physical activity, reduction in intake of saturated fat and cholesterol, as well as achievement of ideal body weight.[69]

- Therapy with lipid lowering drugs, especially with statins, has been shown to reduce cardiovascular morbidity and mortality in diabetics and in other patients at high risk of clinical atherosclerotic disease.[70-72]

- There have been no large randomised placebo-controlled trials to show the effects of lipid lowering in patients with diabetic nephropathy. Nevertheless the beneficial outcome of lipid lowering in the diabetic population in general supports aggressive on-going therapy when nephropathy develops.

- In diabetics with LDL-cholesterol above 3.4 mmol/l, drug therapy should be considered to achieve an ideal LDL-cholesterol level of under 2.6 mmol/l (or to achieve non- HDL-cholesterol of under 3.4 mmol/l). Statins are drugs of first choice, with fibrates as an alternative especially in those with low HDL-cholesterol and high triglycerides.[73,74]

- As patients with renal failure are at a higher risk of myositis with lipid lowering drugs lower doses should be used when commencing therapy and increased cautiously. Combination of statins and fibrates should be avoided in renal failure. Refer to Appendix 4.

Diet

Recommendation 12 : Protein restriction
Moderate protein restriction of 0.6 – 0.8 g/kg/day* may be considered in patients with overt nephropathy and/or renal impairment Grade B

** one matchbox sized cooked protein source is equivalent to 7g of protein*

- With the onset of overt nephropathy, protein restriction of 0.8g/kg/body weight or less may be useful in slowing the decline of GFR.[75-78] More severe protein restriction of < 0.6g/kg/body weight may further retard the progression of diabetic nephropathy. However, this should be supervised by an experienced dietitian to prevent malnutrition.[79]

Recommendation 13 : Sodium restriction
Sodium intake should be restricted to < 80mmol/day (or 5g sodium chloride)* in patients with hypertension and/or proteinuria Grade B

** equivalent to 1 teaspoon of salt*

- High sodium intake should be avoided.

- Moderate sodium restriction can potentiate the hypotensive effect of many antihypertensives.[80-83]

- A low sodium diet enhances the antiproteinuric effects of some antihypertensives e.g. ARBs, ACEIs.[84,85]

Referral

Recommendation 14 : Referral to nephrologist
Referral to a nephrologist should be made if the serum creatinine exceeds 200 umol/L Grade C

- Several studies have shown that late referral leads to increased morbidity, prolonged hospital stay and early mortality on dialysis.[86-94] Uraemic symptoms and complications often occur earlier in diabetics compared to non-diabetics and dialysis may be required once GFR falls to 10 to 15mls/min.[95-97]

- Pre-dialysis evaluation should be considered once the serum creatinine exceeds 200 umol/l. Measures that would need to be instituted include :-
  - optimisation of blood pressure control and proteinuria reduction to retard further progression of renal failure
  - correction of anaemia
  - correction of calcium and phosphate abnormalities
  - nutritional management
  - counselling and assessment for dialysis
  - early preparation of access for dialysis

- Earlier referral to a nephrologist may be indicated if :-
  - the diagnosis of diabetic nephropathy is in doubt e.g. proteinuria occurs in the absence of retinopathy, renal failure occurs without proteinuria
  - nephrotic syndrome or unexplained haematuria occurs
  - a sudden worsening of renal function occurs
  - blood pressure is difficult to control
  - hyperkalaemia arises
  - renal artery stenosis is suspected

- Diabetic patients on renal replacement therapy (i.e. dialysis or transplant) have a 2 to 4 times higher mortality risk than non-diabetic patients, mainly from cardiovascular disease. Coronary artery revascularisation may reduce this complication especially in type 1 diabetics.[98,99]

Appendix 1

Factors affecting urinary albumin excretion[100,101]

Increases AER	Decreases AER
• Strenuous exercise • Poorly controlled diabetes mellitus • Heart failure • Urinary tract infection • Acute febrile illness • Uncontrolled hypertension • Haematuria • Menstruation • Pregnancy	• NSAIDs • ACE inhibitors

AER = Albumin excretion rate

Appendix 2

Methods of urine collection

<u>24-hour urine collection</u>

- 24-hour urine collection minimises fluctuations in urinary albumin excretion (UAE) due to diurnal variation.
- Patients should receive clear instructions on how to collect the urine sample to avoid incomplete collection.
- Patients should be instructed to pass urine completely at a specified time. The first urine voided is NOT collected.
- Subsequently ALL urine passed should be collected into a urine bottle until the next day when the last sample of urine is collected at precisely the same time as the first voided urine.
- Patients should be instructed to void completely at first and last void particularly in patients with incomplete evacuation of the bladder e.g. patients with diabetic cystopathy, prostatic hypertrophy or other bladder outlet obstruction.

<u>Timed overnight urine collection</u>

- Patients should be instructed to pass urine completely before retiring to bed and to record the exact time. The urine voided is NOT collected.
- Subsequently any urine passed during the night should be collected into a bottle.
- Upon waking the next morning, the patient should pass urine completely into the bottle. The exact time of this collection should be recorded.

Appendix 2

- The urine should be sent to the laboratory for quantification of urinary albumin on the same day.

- UAE (µg/min) = $\frac{\text{urine albumin concentration (µg/l) x urine volume (l)}}{\text{duration of urine collection (min)}}$

Early morning spot urine

- An early morning urine sample is more reliable than a random sample. The urine of an early morning sample is more concentrated and less liable to be affected by fluid intake during daytime. Early morning collection also minimises variation in albumin excretion rate due to changes in posture and physical activity.

- Patients should be instructed to pass urine before retiring to bed.

- The next morning, the first urine voided should be collected and brought to the clinic for testing as early as possible.

Appendix 3

Methods of measurement of microalbuminuria

Methods	Tests	Sensitivity	Specificity	Advantages	Disadvantages
24h urine albumin measurement	1. Radio-immunoassay 2. ELISA 3.Immuno-nephelometric method e. g. Assay® analyser (from Beckman)			Quantitative, can also measure creatinine clearance simultaneously	Expensive, inconvenient, impractical, incomplete collection common
Timed overnight urine albumin measurement				Quantitative, not affected by physical activity	Expensive
Urine albumin: creatinine ratio (ACR)*	Clinitek 50® Microalbumin Reagent Strip for ACR	89%	91%	Cheap, simple, corrects for changes in urine concentration	
	DCA2000 Microalbumin/ creatinine Assay System	91.1%	98.3%	Immediate (7 mins), quantitative determination	Expensive
Urine albumin concentration*	Micral Test II® (Co.)	96.7%	71%	Cheap, simple, reliable, rapid on-site test	Semi-quantitative Subject to errors from alteration in urine concentration
	Clinitek 50 Albumin test pad (Co.)	92%	93%		

** dipstick test on spot urine sample for detection of urine microalbumin*

Dosage of hypoglycaemic agents in renal failure

Generic name	Usual dose	Dose adjustment in renal failure*		
		Mild (GFR 60-90ml/min)	**Moderate** (GFR 30-60ml/min)	**Severe** (GFR < 30ml/min)
Sulphonylureas				
Glibenclamide	5mg od - 10mg bd	25-50%	Avoid	Avoid
Gliclazide	80mg od - 160mg bd	50-100%	25-50%	Avoid
Glipizide	2.5mg od - 15mg od	100%	50%	Avoid
Chlorpropamide	250mg od - 500mg od	Avoid	Avoid	Avoid
Glimepiride	1mg od - 4mg od	100%	50%	Avoid
Others				
Insulin	Variable	100%	75%	50%
Metformin	500mg bd - 1g bd	50%	25%	Avoid
Rosiglitazone	4 - 8mg od	100%	100%	50-100%
Acarbose	25mg tds - 100mg tds	50-100%	50-100%	Avoid
Repaglinide	0.5mg tds - 4mg tds	100%	100%	50-100%
Nateglinide	120mg tds	100%	100%	50-100%

od = once daily, bd = twice daily, tds = three times daily
**Refer to Appendix 6 for Cockcroft-Gault formula to estimate renal function*

Insulin

- In renal failure the dose of insulin should be reduced to avoid hypoglycaemia as insulin is degraded by the kidney.
- Conversion to short acting insulin may be required.

Biguanides

- Metformin should be avoided if the serum creatinine is above 150 - 200umol/L as it can rarely cause lactic acidosis in renal failure.

Sulphonylureas

- Chlorpropamide is contraindicated in renal failure as it has a long half-life and its metabolites retain some hypoglycaemic effects.
- Glibenclamide should be avoided in renal failure as it has a long biologic effect despite its short plasma half-life.

- Gliclazide, glipizide and glimepiride (completely metabolised to inactive products) are safer alternatives. Lower starting doses should be used.

Meglitinides

- Repaglinide and nateglinide have short half-lives and duration of action with lower risk of hypoglycaemia.

Thiazolidinediones

- Rosiglitazone can be used in mild to moderate renal failure but can cause fluid retention.

Appendix 5

Dosage of commonly used ACEIs and ARBs

ACEI	Starting dose	Maximum dose
Captopril	6.25mg tds	50mg tds
Enalapril	2.5mg bd	20mg bd
Ramipril	2.5mg od	10mg od
Lisinopril	5mg od	40mg od
Perindopril	2mg od	8mg od
Fosinopril	10mg od	40mg od
Quinapril	5mg od	40mg od

ARB	Starting dose	Maximum dose
Losartan	50mg od	100mg od
Irbesartan	150mg od	300mg od
Valsartan	80mg od	160mg bd
Candesartan	8mg od	16mg bd
Telmisartan	40mg od	80mg od

od = once daily, bd = twice daily, tds = three times daily

- ACEIs/ARBs should be used with caution in patients with bilateral renal artery stenosis or renal artery stenosis of a single functioning kidney.
- ACEIs/ARBs should be started at lower doses in renal failure and titrated gradually to maximal tolerable dose to achieve anti-proteinuric effect.
- Serum potassium and creatinine should be checked prior to and within one to two weeks after initiating an ACEI or ARB as they can occasionally cause worsening of renal function.
- If serum creatinine increases acutely by more than 35%[102] or severe hyperkalaemia occurs, the drug may need to be reduced or withdrawn. Renal artery stenosis may need to be excluded.
- Diuretics may potentiate the hypotensive and anti-proteinuric effect of ACEIs/ARBs.
- Potassium sparing diuretics may worsen hyperkalaemia when combined with ACEI/ARB in the presence of renal failure. Careful monitoring of serum potassium is advisable.

Appendix 6

Estimation of renal function

Cockcroft-Gault formula[103]
Creatinine clearance (ml/min) $= \frac{(140 - \text{age}) \times \text{weight}}{0.814 \times \text{plasma creatinine}} \times 0.85$ (for females)

Age in years, Weight in kg, Creatinine in umol/l

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GLOSSARY OF TERMS

ACEI	Angiotensin converting enzyme inhibitor
ACR	Albumin creatinine ratio
AER	Albumin excretion rate
ARB	Angiotensin receptor blocker
BP	Blood pressure
CCB	Calcium channel blocker
CCF	Congestive cardiac failure
ESRD	End stage renal disease
GFR	Glomerular filtration rate
HDL	High density lipoprotein
LDL	Low density lipoprotein
NSAID	Non-steroidal anti-inflammatory drug
RCT	Randomised controlled trial
UTI	Urinary tract infection

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