Chronic Renal Failure

Authors: Clinical Assoc Prof Mark Thomas; Dr Sophie Couzos

Reviewers: Dr Dan Ewald (ed); Dr Christine Connors; Dr Paul Lawton; Dr Paul Snelling

Note: Additional information can be sought from: Couzos S, Thomas M, 'Chronic Renal Failure', in Aboriginal Primary Health Care: An evidence-based approach, second edition, Oxford University Press, Melbourne, September 2003. This contains more information on the prevention and management of chronic renal failure, treatment goals and targets, case management, program implementation, data collection, and performance indicators.

Summary

Much is to be gained from optimal prevention and management of the increasing epidemic of chronic renal failure in Aboriginal people and conversely there is considerable avoidable illness and death where health care fails. Evidence shows that early recognition, early intervention and well-timed referral to specialist and tertiary care are all important. Renal failure is increasingly common in Aboriginal populations, especially those with diabetes, hypertension, obesity, or a family history of renal disease.

Social factors such as diet and exercise, combined with minimisation of smoking and alcohol use, are most important in the primary prevention of chronic renal disease. Environmental factors such as appropriate housing and community measures to reduce skin infections are likely to help reduce renal disease.

All Aboriginal adults should be encouraged to participate in screening for early renal disease with annual dipstick testing for proteinuria, and subsequent quantification if positive. People with diabetes should be tested for microalbuminuria with an ACR. The glomerular filtration rate (GFR) should be calculated for people with diabetes and microalbuminuria, and all others with overt proteinuria.

Control of hypertension is one of the major interventions for controlling the decline in renal function in those with renal impairment and blood pressure should be kept below 130/85, or even lower in the presence of proteinuria. The optimal choices of anti-hypertensive are the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (alone or in combination) as they have been shown to delay the progression of diabetic and non-diabetic-related renal disease by as much as twofold, and reduce proteinuria by 50%.

Patients with progressive renal failure should be referred to a nephrologist at or before reaching a calculated GFR of 30 ml/min (and preferably around 60 ml/min) for further management, including correction of anaemia, education on end-stage renal failure (ESRF) options and timely creation of vascular access for dialysis. Aboriginal patients should be

given the same opportunities for ESRF treatment as non-Aboriginal patients, and those in remote areas the same as those in urban settings.

Burden of suffering

For the most part, the progression from early through to advanced renal failure is asymptomatic. However, with the onset of end-stage disease, uraemia and renal replacement therapy, there is considerable physical and social disruption for most patients. Aboriginal Australians in particular face a significant and increasing burden of renal disease, mandating decisive action at all levels of health provision.[1] Current and future projections are of 'epidemic proportions' in the NT.[2] Maintenance haemodialysis is the leading cause of hospital admissions among Indigenous Australians (26% of all episodes of care, and 44% as principal procedure in 1998–99).[3] The population-adjusted incidence of new patients accepted on to ESRF programs in the year 2000 was 400 per million in the total Australian Aboriginal population. This compared to 300 in Pacific Islanders, 200 in Maoris and was five times the rate of the Australian Caucasian population (80 per million).[4,5] The racial disparity data from the ANZDATA Registry has been independently validated.[6] The rates of ESRF in Aboriginal populations vary greatly in different regions, but are generally increasing. The average annual incidence of ESRF in Northern Territory Aboriginal people was 440 per million in 1988–93 (approximately ten times the non-Aboriginal rate), while that in Tiwi people was 1636 per million.[7] In the last decade, the nation-wide incidence of ESRF has risen over twofold, from 170/million in 1991 to a peak of 430/million in 1997–99.[4] Despite likely differences in the difficulty in access to diagnostic services, the incidence is increased in remote versus urban centres, and in northern versus southern states.[8] Furthermore, ESRF incidence may be underestimated, as many remote area Aboriginal people decline treatment.[9] ESRF in Aboriginal people more often presents acutely and earlier (median age 48 versus 61 years in non-Indigenous patients), with a higher proportion of females (57% vs 41%).

Diabetes is a major contributing factor in renal failure in Aboriginal people with 47% of those with a biopsy-proven cause (20% of total) being attributed to diabetic nephropathy. In reality, the renal pathology is multifactorial, representing the cumulative insults of virtually every recognised risk factor for progressive renal failure[10] and indeed mortality.[11] These lifetime risk factors include:

- intra-uterine growth and nutrition, which may impair nephronogenesis[12]
- low birth weight[13]
- childhood post-streptococcal infection[14]
- adult obesity[15]
- diabetic control[16,17]
- hypertension[18]
- smoking[18]
- albuminuria/proteinuria (correlated with loss of GFR[19] as well as all-cause (predominantly cardiovascular) mortality[20]
- glomerulomegaly[21] (unclear if congenital or acquired secondary to hyperfiltration associated with focal glomerulosclerosis)[22]
- socioeconomic disadvantage[23]
- lack of access to health services[24]

Most Indigenous patients with renal disease have significant co-morbidities (alcohol dependency, smoking, frequent infections, poor nutrition,

diabetes, ischaemic heart disease), which contribute to a deterioration in renal function[20] as well as a 50% increased risk of cardiovascular or respiratory disease versus non-Indigenous patients.

As a result, survival of those with ESRF (i.e. haemodialysis (HD), peritoneal dialysis (PD) and transplant (Tx)) in 1991–2000 was worse in Indigenous patients, being 60% at five years, compared to 85% in non-Indigenous patients (p<.001). Similarly, Indigenous patients with renal transplant had worse five-year patient and graft survival (70% versus 82% in non-Indigenous patients).[4]

Approximately 40% of Aboriginal patients in ESRF programs were not known to have had renal disease before presenting with renal failure.[25] The late presentation is associated with a lower likelihood of acceptance of dialysis treatment.

Many Aboriginal people face additional social stress and disruption if they have to leave their home community for end-stage renal treatment. Because ESRF mainly affects older people, some remote communities lose contact with their community elders/leaders through this dislocation. This sometimes impacts on the choice of treatment, and hence survival and morbidity. About 90% of the Aboriginal people who received haemodialysis in Alice Springs were from bush communities, often more than 200 km away. The family disruption involved in a move to regional dialysis units is therefore significant. Often there is a failure to match these health needs with accommodation services. Only a minority of patients (18%) were able to get Housing Commission accommodation in Alice Springs in 1996.[26]

Despite the rapidly-expanding patient numbers, only a small number of satellite HD Units have been established in remote areas of Australia, limited by funding and staff retention.

Definitions

The definitions used to describe stages of chronic kidney disease are important in order to clarify optimal specialist referral times, and for data collection.[27,28,29]

Diabetic nephropathy

In the absence of a renal biopsy or an alternative explanatory cause a clinical diagnosis of overt diabetic nephropathy is defined by the presence of persistent or overt proteinuria (>300 mg/24 hr or >200 microgram/ min). It is usually accompanied by hypertension, little or no microscopic haematuria and normal-sized kidneys on renal ultrasound. The American Diabetes Association states that the diagnosis of diabetic nephropathy in NIDDM requires an elevated albumin excretion as well as evidence of diabetic retinopathy.[30]

Incipient nephropathy is defined by microalbuminuria without overt proteinuria (30–300 mg/24 hr or 20–200 microgram/min, or an albumin:creatinine ratio of 3.4–30 mg/mmol). This phase is often accompanied by glomerular hyperfiltration, with a serum creatinine lower than expected for age and weight, and GFR greater than normal.

Chronic renal failure

The sustained and irreversible reduction in the glomerular filtration rate (GFR), accompanied by a rise in serum creatinine, is the hallmark of chronic renal failure. A low GFR may occur with a normal serum creatinine

in older and smaller patients. The GFR (normally >100 ml/min adult and >50 ml/min child) can be calculated from the serum creatinine (see Diagnosis).

A generally accepted definition of significant chronic renal failure is a serum creatinine >200 micromol/L or calculated GFR <60 ml/min on two occasions at least a month apart in the absence of acute illness.

End-stage renal failure

ESRF is usually reached when less than 10% of normal renal function remains and regular dialysis or renal transplantation is required to maintain life.[31]

Diagnosis

The most appropriate screening test is an annual dipstick urinalysis on a spot urine for proteinuria followed (if positive one plus or more) by quantitation of albuminuria by albumin:creatinine ratio (ACR). If the ACR is more than 3.4 on two occasions in the absence of urinary tract infection or sexually transmitted infection, they should proceed to further assessment and investigation as per the protocol.

[Editor: The CARPA STM protocol only suggests calculating creatinine clearance/GFR if the person is hypertensive or diabetic or the ACR is confirmed to be >100. This difference is because this is the group with the strongest evidence of benefit of intervention, and less useful calculating of GFR may be a significant burden on health staff. Given that the protocol includes measuring EUC on everyone with ACR confirmed to be over 3:4, this compromise could be revised if, for example, electronic/computer/paper-based normograms or GFR calculators were widely available. Otherwise the EUC test is to detect grossly elevated creatinine, which will be less sensitive for detecting pre-existing renal failure – calculated GFR's are probably for the GP to do rather than the health worker. The CARI guidelines website has a nice sex-specific nomogram for those who can't do the rough calculation mentally or manually.]

Microalbuminuria

Microalbuminuria is a recognised early phase of diabetic nephropathy and indicates leakage of a small protein (albumin) from the kidney that is not detectable by conventional dipstick tests for proteinuria. Approximately 9% of diabetic patients with microalbuminuria progress to overt proteinuria per year.[28] It is now proven to be a predictor of the progression to renal failure in insulin-dependent diabetes mellitus (type 1 diabetes) and non-insulin–dependent diabetes mellitus (type 2 diabetes). The highest predictive value for progression to renal failure in diabetic nephropathy is an ACR two to three times the upper limit of normal.[32]

A timed urinary albumin excretion rate is generally agreed to be the most sensitive assay for microalbuminuria.[31] Because of the impractical nature of the required urine collection, an ACR is recommended as the test of choice. A first morning sample is preferred, but a randomly obtained specimen may also be used.[33] A review of the potential limitations of this assay for microalbuminuria estimation has been described.[32]

Making a diagnosis of microalbuminuria, according to the American Diabetes Association, requires two of three tests (performed over a three- to six-month period) with elevated results before the patient is considered to have microalbuminuria.[28] This is to reduce the number of false positives. However, a systematic review concluded that repeated testing is

onerous, unsubstantiated by studies and probably does not improve diagnostic certainty due to minimal improvements in specificity in low prevalence situations. This lack of adherence to even single annual screening tests raised questions of whether the screening strategy of repeated screening followed by treatment will effectively prevent diabetic nephropathy.[34]

> *[Editor: An unpublished study (Stephen P McDonald, Zhiqiang Wang, Wendy E Hoy. Menzies School of Health Research. Darwin NT) reports:*
> *Predictive value of dipstick results for subsequent ACR was examined in 3554 observations on 1366 people in a community screening and treatment program for renal disease. Reproducibility of ACR was examined for both same-day (n = 120) and same-month (n = 230) collections.*
> *In both groups, variability was less with ACR than with albumin concentration. It was, however, still substantial: 95% limits of agreement for a second test range from less than 1/3 to over 3 times the initial result. This figure is relatively robust to effects of glucose, blood pressure, gender and obesity. This variability may result in differences in diagnostic and treatment decisions if not recognised . . . Taking the mean of 2 repeated tests will reduce the width of the range by 40% (÷2).*
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> *We believe these findings are important as they are derived from a population with similar patterns of UTI and STI and other co-morbidities to the populations where this protocol is to be used. These factors may influence the reliability of the ACR test. The CARPA STM suggests that the best practical assessment will come from the average of two ACR measurements in the absence of STI and UTI. Though this involves a significant amount of work for the clinic, it does change treatment choices, and then does not have to be repeated once the person is known to be albuminuric / micro-albuminuric.]*

Testing with the DCA 2000 (Bayer) point-of-care instrument to assay ACR from spot urines enables immediate feedback to the patient (within seven minutes), thereby potentially enabling treatment changes.[35,36] This approach has been successfully used and validated in a number of Aboriginal community settings.[37,38] At present there is insufficient evidence and a lack of consensus on whether the non-diabetic population should be screened for microalbuminuria, and CARPA does not advocate it.

Overt proteinuria
The presence of dipstick-positive proteinuria (more than or equal to +1 for protein) usually indicates overt proteinuria (approximately equivalent to protein excretion rate of 300 mg in 24 hours, or a protein:creatinine ratio >30 mg/mmol, or an albumin:creatinine ratio >30). Commercially available dipsticks are sensitive to albumin in concentrations of 100–200 mg/L, but may produce a false-negative reading in the presence of a dilute urine sample. Urinary tract infections, physical exercise, congestive cardiac failure, menstrual loss and vaginal contamination can cause proteinuria on dipstick in the absence of renal disease (false-positive). If detected in the absence of infection, dipstick proteinuria can be quantified by a 24-hour collection or (much more practicably) by a spot albumin–creatinine ratio (ACR). There is evidence that an ACR estimate of proteinuria is more reliable as a predictor of renal decline than a 24-hour urine collection in non-diabetic patients with chronic renal failure.[39,19]

Proteinuria is often the first indication of renal disease. However, it may be present transiently in people without renal disease. A greater degree of proteinuria and progressively increasing proteinuria correlates strongly with the progression of renal failure.[28] It is now widely accepted that overt proteinuria is also an independent risk factor for cardiovascular disease.[30] In the Aboriginal population, proteinuria can predict all-cause natural death as well as non-renal death, and is considered a marker of general systemic and possibly vascular compromise.[20] Proteinuria has also been related to smoking[31] and malignancy, which suggests that it may be a general marker of chronic poor health as well as acute disease.[40]

Serum creatinine and calculated GFR

A reduction in glomerular filtration rate (GFR) is the hallmark of renal failure, and usually only occurs after longstanding structural changes have occurred in the kidney. Microalbuminuria, hypertension and overt proteinuria usually precede any fall in GFR by years.

For routine clinical practice, the GFR is most simply estimated from the serum creatinine, adjusted for the age, weight and sex of the patient, providing the serum creatinine is stable. The original Cockcroft and Gault formula for calculated GFR[41] has been shown to both over-estimate and under-estimate true (isotopic) GFR in various situations. These include: extremes of renal function, obesity, malnutrition, fluid overload, or use of cimetidine or trimethoprim (blocking tubular creatinine secretion). Several modifications have been proposed with varying degrees of additional complexity.[42-45] These formulae can be simplified to the approximation:

$$\text{Calculated GFR (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 1.23 \text{ (males only)}}{\text{serum creatinine (micromol/L)}}$$

This formula assumes the patient is close to ideal body weight. Using the actual weight of an obese patient will produce a falsely high, calculated GFR. To estimate upper limit of normal weight, replace actual weight with (height (metres)^2 x 25) or use a nomogram.

No systematic correlations of calculated and true GFR have been performed in the Aboriginal population, where muscle mass is frequently clinically greater than the non-Aboriginal population.

[Editor: The term 'calculated creatinine clearance' is interchangeable (for our purposes) with 'calculated glomerular filtration rate' (GFR). We have used the term creatinine clearance (CrCl) in the STM because several other resources in common use in the Northern Territory also use this term.

The STM protocol does not emphasise the importance of using lean body mass in the Cockroft calculation, as described above, as this will make it more difficult to use. The value of the calculated CrCl in the PHC setting is to monitor progress/deterioration and to trigger referral to specialist services at an appropriate stage.

The nephrologists reviewing this chapter point out that the stages of renal failure are fairly arbitrary, are based on expert and consensus opinion, and we have chosen to use the categorisation used in the American K/DOQI discussion document and guidelines. They expect future Australian guidelines to do likewise. There is little evidence to say that referral to a specialist should happen by a specific CrCl value. Further, the patient is not likely to be monitored so closely that this difference will be

detected, unless they are under specialist driven care already for some reason. The point of referral will be determined by the overall complexity of the case and the skills and confidence of the PHC team as well as the calculated creatine clearance.

We do not expect using gross weight rather than lean body mass will often have a negative impact on care except for very overweight people, in which case their weight if their BMI was 25 should be used.]

The GFR may be increased above normal (known as 'hyperfiltration'). Hyperfiltration can occur acutely following a high protein meal or raised glucose. A more sustained rise in GFR occurs in the presence of obesity or the inital phases of diabetic nephropathy. These are commonly seen clinical situations in Aboriginal patients, and can be identified by the recognition of a serum creatinine reading lower than expected. Hyperfiltration is believed to accelerate renal injury (the Brenner hypothesis). Hyperfiltration is reversed by the use of ACE inhibitors or angiotensin receptor blockers, accounting for the 20–30% increase in serum creatinine commonly seen after introduction of either of these two classes of antihypertensives. Provided the serum creatinine plateaus, this rise therefore represents the unmasking of the 'true' serum creatinine, once hyperfiltration is corrected.

Summary: Assessing renal function
An increasing serum creatinine concentration is a highly specific indicator of a decline in renal function and is often accompanied by hypertension. The presence of proteinuria is also a marker of renal disease, but non-specific. Overt proteinuria with diabetes can be regarded as clinically diagnosed diabetic nephropathy. Microalbuminuria is a lesser degree of renal protein leakage and is a precursor to overt proteinuria. An ACR is the test of choice for microalbuminuria. Expert groups recommend confirmation of positive results. Semi-quantitative microalbuminuria dipsticks have a use where laboratory access is difficult and have value as a screening tool, but positive results also need to be confirmed with an ACR. In the presence of a high prevalence of microalbuminuria (>20%), these dipsticks may not be cost-effective. Point-of-care ACR estimates are acceptable and valid for assessing microalbuminuria in those with diabetes.

Effect of interventions
The prevention of renal disease has been divided into approaches that describe the onset and stage of renal disease:
- Primary prevention strategies relate to interventions that may prevent the onset of renal disease.
- Secondary prevention strategies relate to interventions for screening or the early detection of existing disease, and optimal strategies to prevent further deterioration.
- Tertiary prevention strategies relate to the prevention and control of end-stage renal complications.

Primary prevention
In the prevention of renal disease in Aboriginal populations, the likely important influence of socioeconomic and environmental factors needs to be acknowledged. Much emphasis is placed on tertiary level interventions and the optimal treatment of ESRF, and early screening strategies for chronic

renal failure, when the greatest gains in preventability are likely to be found in the prevention of the socioeconomic and lifestyle related antecedents of renal disease in Aboriginal populations.

Intra-uterine growth and renal disease

Increasing ratios of current-weight to birth-weight in adults from a small Aboriginal community have been correlated with an increased risk for overt proteinuria. It was proposed that this might be due to impaired nephrogenesis from intra-uterine malnutrition, compounded by the subsequent development of a pre-diabetic syndrome (syndrome X) of metabolic dysfunction.[12,46] The prevention of intra-uterine growth retardation (IUGR) in Aboriginal pregnancies, and the prevention of malnutrition in infants, should continue to be important goals in primary health care. Whether the prevention of IUGR is often possible and prevents renal disease is still uncertain.

Adult obesity, smoking and ethanol excess

These factors are unfortunately often closely-linked, and their modification can offer great benefits. The calorie load of ethanol promotes obesity and subsequent diabetes. There is a quantitative relationship between alcohol intake and the level of blood pressure.[47] Smoking independently trebles the risk of kidney failure in several forms of kidney disease.[93]

Skin infections and renal disease

Skin infections with group A streptococci (GAS) can cause glomerulonephritis. A strong correlation was shown in the NT between past evidence of infection with GAS and the presence of albuminuria in adulthood.[48] There is a strong rationale that more effective control of GAS skin infections in childhood is required for the prevention of renal disease. Control of skin infections is described in CDC guidelines and in the skin infections chapter of this book.

Secondary prevention

Early detection

- Screening for chronic renal disease (proteinuria or microalbuminuria, followed by serum creatinine and calculated GFR)
- Screening for hypertension, discussed in the adult health check and hypertension chapters.

Preventing acute deterioration

- Avoidance of volume depletion, radiographic contrast media and NSAIDS

Managing progressive deterioration and late stages of chronic renal disease

- Monitoring and early referral to nephrology service
- Treatment of hypertension
- Avoidance of dietary protein excess
- Control of diabetes, smoking and dyslipidaemia
- Treatment of anaemia
- Maintenance of acceptable calcium and phosphate metabolism

Screening for proteinuria

The Australia and New Zealand Society of Nephrology consensus statement (1999) recommended urinalysis for proteinuria as part of the periodic examination of Aboriginal and Torres Strait Islander patients.[49] The Caring for Australians with Renal Impairment (CARI) Guidelines (2001) recommended screening for overt proteinuria in patients at increased risk of renal disease (Aboriginal and Torres Strait Islander population) in conjunction with access to referral services. There is currently no evidence to support the mass screening of the general population for renal disease by urine dipstick, blood sampling or other means, and this is consistent with Canadian, US and Scottish guidelines.[50-53]

Because proteinuria is considered an independent predictor of progressive renal disease in non-diabetic renal disease[54] and a predictor of cardiovascular disease, it has been suggested that proteinuria screening of the non-diabetic population may provide a mechanism for modifying the development and progression of cardiovascular disease. No study has yet explored this.

Aboriginal population-based screening for microalbuminuria has also been proposed in the Northern Territory.[55] Since it is recognised that those with diabetes should receive annual screening for microalbuminuria, and a urinalysis for overt proteinuria is recommended within the periodic health examination of all Aboriginal adults, the role of population-based microalbuminuria screening may be limited.

[Editor: The CARPA STM no longer recommends annual ACR measurement for anyone who is known to have albuminuria or, in the case of those with diabetes, microalbuminuria. We believe these people have an indication for aggressive BP control with ACEi and or ARB medication and need their creatinine/calculated CrCl monitored, not their ACR.

Authors' reply: As a personal view, rather than an evidence-based one, serial ACRs or PCRs are actually a very nice quantitative way of monitoring sequential improvements in the glomerular hyperfiltration – it's the 'renal sphygmo'. BPs are too 'bouncy' and creatinines are too late to really get a feel for how well someone is responding (?complying) with treatment.]

At present, there appears to be little evidence to support screening for microalbuminuria in the general Aboriginal population. However, as a marker of general vascular disease and early renal compromise, screening this population for microalbuminuria may complement other risk factor assessments (such as blood pressure, weight, diabetes, smoking, lipids etc.) but this has yet to be shown.

Screening for raised serum creatinine

The serum creatinine representing the referral threshold GFR of 30 ml/min can vary from 140 µmol/L in a 50 kg 60-year-old female up to 400 umol/L in a 90 kg 20-year-old male. A high serum creatinine is a late marker of renal failure. By the time a serum creatinine is elevated above the population normal range up to 50% of renal function may be lost, particularly in small elderly females. Screening for raised serum creatinine is not recommended, but calculation of GFR is critically important in those with any known renal disease and consistent with local and international guidelines.[56]

[Editor: Note that the CARPA STM protocol suggests initial referral to a renal physician earlier in the disease deterioration. This is because of added difficulties in patient education, logistics and ensuring a venous shunt is established and matured. In many instances referral to a renal

physician as soon as either a raised serum creatinine or low GFR is identified will be advisable.]

Preventing acute deterioration
Avoidance of volume depletion, radiographic contrast media and NSAIDS

Radiographic contrast media (such as in intravenous pyelograms) may provoke sudden and severe deterioration in damaged kidneys, and so caution is advised. The probability of acute renal failure occurring has been estimated at 5–10% (>25% increase in serum creatinine levels) and 1–2% (requiring dialysis).

Non-steroidal anti-inflammatory drugs (NSAIDS) (including the newer COX-2 inhibitors) can cause a significant decrease in GFR in patients with renal insufficiency (those with GFR 30–70 ml/min), particularly during episodes of intravascular volume depletion.[57,58,59] NSAIDs can also worsen hypertension (through sodium retention) and hyperkalaemia (through renin suppression). Paracetamol is the preferred analgesic for mild-to-moderate pain in patients with renal impairment.

Intravascular volume depletion (such as following recent inadequate fluid intake, gastrointestinal losses or inappropriate diuretic use) is another well-recognised cause of acute renal impairment. The degree of volume depletion required to cause a renal functional deterioration can be as little as 2% of body weight in the presence of three at-risk situations: i. pre-existing renal disease (including patients aged over 65 years); ii. chronic reduction in intravascular volume (cirrhosis, nephrosis, diuretic use); or iii. impaired renal compensatory mechanisms (ACE inhibitors blocking efferent arteriolar constriction by angiotensin II or NSAIDs preventing prostacyclin-induced afferent arteriolar dilatation). Patients with renal impairment should have intravenous saline provided in such at-risk situations.[60]

Managing progressive deterioration
Monitoring and early referral to nephrology service

Once chronic renal disease is diagnosed as the cause, rate of progression and co-morbidities must be determined. Earlier referral to nephrologists of patients with elevated creatinine levels is expected to lead to better health care outcomes and lower health care costs. Adequate preparation for dialysis or transplantation (or both) requires at least 12 months of relatively frequent contact with a renal care team.[61] Given the rapid progression of renal disease in many Aboriginal patients, the time between the onset of microalbuminuria and development of ESRF can be as short as 18–24 months. People with chronic renal failure need regular review, including calculated GFR and a care plan guided by specialists.

I recommend that the response to ACEi/ARB therapy in all those with chronic renal failure be monitored by ACR every three to six months. Whilst the prime target of monitoring is systemic blood pressure reduction to 120/70 if possible, a steady fall in serial ACR or protein:creatinine ratios may indicate successful intra-glomerular pressure reduction (a surrogate marker suggesting improved prognosis) as well as confirming medication compliance. Anecdotally, patients with proteinuria resistant to ACEi/ARB therapy appear more likely to have irreversible glomerular disease. Monitoring proteinuria in non-diabetic chronic renal failure may also assist with therapeutic adjustments. The degree of reduction in proteinuria with or without concurrent rise in serum creatinine following

ACEi/ARB therapy can be seen as an indication of the degree of hyperfiltration present prior to therapy.

[Editor: Though monitoring the albuminuria response to ACEi/ARB treatment has some theoretical appeal, it is yet to be shown to lead to better outcomes. The CARPA STM does not advocate monitoring the effectiveness of ACEi or ARB medication via the ACR. It is the blood pressure that counts, and 'full doses' should be used if tolerated, adding additional medications as needed to achieve the target BP as mentioned. The effect on the ACR will not generally change management.

This position is supported by anecdotal experience from the Top End, described here by Dr Christine Connors:

> *From auditing at Tiwi, and other communities, we know that the level of monitoring for diabetes and renal disease is actually very high; the bush staff are doing an extraordinary job of delivering a high level of monitoring services. However, the proportion of patients achieving target BP is suboptimal. My experience is that ACRs are variable and, as Paul Lawton pointed out, there are many factors that will cause this: time of day; 'inflammatory' process; UTI/STI etc. I know that many people, especially bush nurses, become confused about this variability, and basically all of us ignore the results. The evidence is very strong that achieving BP target is renoprotective, there is currently no evidence that reducing protein further after meeting target BP will affect outcome. Again, this is a pragmatic solution for PHC teams, not nephrologists, who will have greater interest and knowledge about variable ACR. We want PHC staff to save time (and money) by not doing multiple ACR, and use that time to make conscious decisions about BP results and take appropriate action (e.g. put chart in box for GP/chronic disease coordinator review, refer to GP etc.) or increase drug treatment if seen by GP/CD coordinaotr. Removing the ACR and focusing on BP is the message for improving renal outcomes. All remote staff I have discussed this with are very happy with this decision.]*

Treatment of hypertension, with diabetic nephropathy

Hypertension, diabetes and renal insufficiency/failure are very common and commonly coexist in the one person. All need to be managed as part of whole-person care. However, for protecting renal function the reduction of blood pressure to target levels is the most important of all interventions.

Several meta-analyses and recent randomised controlled trials describe the beneficial activity of both ACEi and angiotensin receptor blockers (ARB), either alone or in combination, in reducing proteinuria in diabetic renal disease that is independent of the anti-hypertensive effect of the drug.[62-68] A recent systematic review confirmed the progression of microalbuminuria to overt proteinuria in those with diabetic nephropathy is delayed by ACEi.[69]

Reduced progression of proteinuria is protective against ESRF, but few studies have shown a reduction in ESRF incidence due to treatment with ACEi or ARB in those with type 2 diabetes. Over 2.6 years, a 20% reduction (p = 0.07) in the risk of nephropathy progression was reported with ARB Irbesartan in type 2 diabetics. This outcome was achieved with mean blood pressure approximating 140/80 in both treatment and placebo groups.[70]

People with type 2 diabetes and microalbuminuria or overt proteinuria should receive ACEi or angiotensin blockade therapy, regardless of the presence or absence of hypertension.[28] The evidence that this treatment can

prevent ESRF is still lacking[71], though it prevents increasing albumin excretion rates.[71]

Tight control of blood pressure reduces the rate of progression of chronic renal failure by about 50%, and some cases of prolonged stabilisation of impaired kidney function have been described.[72] Diabetic patients with chronic renal failure or overt nephropathy should aim for a target of less than 130/80 mmHg.[28]

Hypertension and non-diabetic renal disease

High blood pressure is a strong and independent risk factor for end-stage renal disease, as shown in a subgroup analysis of the large Multiple Risk Factor Intervention Trial.[73] The control of hypertension in those with chronic renal failure before the onset of ESRF is the single most potent intervention to reduce the progression of renal failure and prevent cardiovascular mortality in those on dialysis.[74]

The use of ACEi in those without diabetes who show overt proteinuria in the presence of hypertension has been shown in numerous systematic reviews and recent trials to be of benefit in reducing the progression to ESRF.[75-81] The protective effect of ACEi in chronic renal disease of non-diabetic origin is certainly due in large part to a substantial decrease in blood pressure, but ACEi have some independent effects.[81] A Cochrane review is re-examining the impact of antihypertensive agents other than ACEi on non-diabetic renal disease.[82]

Evidence supports counselling patients to incorporate regular physical activity into their daily routines and is recommended to prevent hypertension, coronary heart disease, obesity and diabetes.[83]

A lower-than-usual blood pressure goal has also been shown to be protective in those with proteinuria and non-diabetic renal disease. In two randomised controlled trials a low blood pressure goal (<130/80 mmHg) significantly reduced proteinuria during the first four months after randomisation. Some guidelines recommend a lower blood pressure goal (<125/75 mmHg) in non-diabetic chronic renal failure, often necessitating the use of three or more antihypertensive agents in addition to lifestyle modification.[50,84]

Limited dietary protein

Dietary protein restriction ('low' protein diet of approximately 0.6 g/kg body weight/day) slows the progression of both diabetic and non-diabetic renal diseases, according to meta-analysis. In non-diabetic renal disease, the risk of renal failure and death is reduced by protein restriction by about 40% as compared with higher or unrestricted protein intake.[85,86,87] However, there is potential for adverse consequences in protein restriction, so expert guidance should be sought in relation to nutritional intervention in patients with impending ESRF. Protein-restricting diets are notoriously difficult to implement and require resource-intensive health education strategies. The potential for health gain versus the opportunity costs of diversion from other health issues, and the potentially adverse consequences of an inadequate caloric intake need to be considered.

Control of diabetes, smoking and dyslipidaemia

Deaths due to cardiac disease and atherosclerosis are the most common cause of death in patients on dialysis, including Aboriginal patients.[88] Chronic renal failure is associated with lipid abnormalities as well as an

increased risk of cardiovascular events predicted by the presence of proteinuria.[31,89] A recent meta-analysis showed that lipid therapy can decrease proteinuria and preserve GFR in patients with chronic renal disease.[90]

Cigarette smoking was associated with an increased risk of end-stage renal disease in several large studies.[91,92] Cessation of smoking has also been shown to retard the progression of renal failure in those with diabetes, but this has not yet been shown in those with non-diabetic renal disease.[60]

Treatment of anaemia

Recombinant human erythropoietin (EPO) given intravenously or subcutaneously increases haemoglobin levels, improves quality of life and avoids blood transfusion in those with anaemia due to uraemia (generally late-stage renal disease). The major side effect is hypertension (in up to 30% of recipients). The benefits of subcutaneous EPO is that it can be self-administered and is more cost-effective than when given intravenously. However, it is an expensive treatment, costing $4000 to $10,000 per patient per year, and a rare but serious side effect of pure red-cell aplasia due to anti-EPO antibodies has recently been described.[93]

There has also been concern that the increased haemoglobin in the pre-dialysis period may accelerate renal failure. A systematic review concluded that treatment with EPO in pre-dialysis patients corrects anaemia, avoids blood transfusions, and increases quality of life and exercise capacity. Whilst hypertension may be increased, effects on renal progression could not be confirmed due to short-term studies.[94] The general consensus is that EPO therapy does not affect the rate of progression of renal failure.

Maintenance of acceptable calcium and phosphate metabolism

There is some evidence that control of calcium and phosphate metabolism (lowering phosphate levels) may prevent the progression of renal function loss, although most of the evidence arises from animal studies. Effects on the progression of chronic renal failure are still unclear.[95] However, the onset of severe renal osteodystrophy due to secondary hyperparathyroidism can be delayed,[96,97] particularly when phosphate binders are initiated at an early and reversible stage.

Summary of interventions

It is important to detect asymptomatic renal disease through screening for overt proteinuria and microalbuminuria in those with diabetes. Monitoring for progression to chronic renal failure with a serum creatinine and calculated GFR is recommended in those found to have overt proteinuria, diabetes with microalbuminuria and those with a family history of renal disease.

The treatment of hypertension to a target level below 130/85 is crucial to prevent progression. The optimal choice of anti-hypertensive is an ACE inhibitor, as they have been shown to delay the progression of non-diabetic-related renal disease in the presence of overt proteinuria.

The use of radiographic contrast media requires caution, and NSAIDS should be avoided in those with renal disease as acute renal failure can be precipitated.

Dyslipidaemia should be treated to prevent cardiovascular events in those with a high absolute risk. This treatment may also prevent renal disease deterioration. Calcium and phosphate monitoring and treatment are

advised to prevent renal osteodystrophy. Therapy for anaemia using erythropoietin and aggressive iron supplementation (usually parenteral) can enhance the quality of life.

Tertiary prevention
Early approaches to ESRF management
Failure to recognise impending ESRF is a major contributor to morbidity and mortality in patients with chronic renal disease. Delayed referral leads to emergency dialysis, which has a very high mortality (up to 25%) and prevents an optimal choice in modality of dialysis and psychological preparation of the patient for ESRF care. Early and coordinated approaches to the care of patients with impending ESRF may increase the expected duration and quality of life.

In Aboriginal populations, preparative processes may increase the acceptance of tertiary level interventions. A quarter of all Aboriginal people with ESRF in the Northern Territory withdraw from treatment.[88] All renal units in Australia are now encouraged to develop a pre-dialysis education program for all clients and to be monitored for the proportion of clients commencing dialysis who have completed an education program.[60]

Treatment of ESRF
Options for the treatment of ESRF include:
- Dialysis — peritoneal (continuous ambulatory peritoneal dialysis, CAPD, or automated overnight PD, APD) or haemodialysis (home/hospital/satellite)
- Transplantation — cadaveric or living/related/ non-related.

Treatment priorities are to maximise independence and rehabilitation by the most cost-effective option. This means offering transplantation when available; encouraging home dialysis (CAPD or home haemodialysis); siting satellite units for maximal access; and reserving medically supervised hospital haemodialysis for those patients unable to use other options.

[Editor: Timing of referral to kidney specialist:
Paul Lawton (a key contributor to the protocol) points out that the 'Stages' flow chart will indicate referral to kidney specialist at <30 ml/min. There is no evidence of benefit of referral earlier than this at this stage. This is even more pronounced with the knowledge that the majority will have 'the usual' glomerulomegaly with focal scarring and/or IgM deposition, for which we have no specific 'specialist' therapies. Those who require earlier specialist nephrologist involvement will be picked up with the other indications for referral —blood in the urine, nephrotic syndrome, renal artery stenosis, etc.

The whole point of this protocol in the STM is to reduce the numbers flying in from remote communities for appointments when they can be equally well managed in community, given the available evidence.]

References
1.   Thomas MA. Kidney disease in Australian aboriginals: time for decisive action. Med J Aust 1998 Jun 1; 168(11):532–3.
2.   Hoy W. Renal disease in Australian Aboriginals. Med J Aust 1996; 165:126–7.

3.   Commonwealth Department of Health and Aged Care and Australian Institute of Health and Welfare (1999). National Health Priority Areas Report: Diabetes Mellitus 1998. AIHW Cat. No. PHE 13.

4.   McDonald SP, Russ GR. Prevalence, treatment patterns and outcome of end-stage renal disease among indigenousIndigenous groups in Australia and New Zealand. Nephrology (in press).

5.   Interhospital Renal Dialysis and Transplant Service. A three year operational plan for nephrology services in Western Australia, 1996–1999. Health Dept of WA (HDWA), Perth, February 1996.

6.   Brameld K, Holman D, Thomas M, Bass J. Use of a state data bank to measure incidence and prevalence of a chronic disease: end-stage renal failure. Am J Kidney Dis 1999 Dec; 34(6):1033–9.

7.   Hoy WE, Mathews JD, Pugsley DJ. Treatment of Australian Aboriginals with end stage renal disease in the top end of the Northern Territory: 1978–93. Nephrol 1995; 1:307–13.

8.   Cass, A., Gillen, A.G. & Horvath, J.S. End-stage renal disease in Aboriginals in New South Wales: a very different picture to the Northern Territory. Med J Aust 1999; 171(8):407–10.

9.   Silva D, Pugsley D, Snelling P, Hoy W. End-stage renal disease (ESRD) in Aboriginal Australians in the 'top end' of the Northern Territory [abstract]. Conference papers 4th national rural health conference: rural and remote Australia: health for all by the year 2000, Perth, 9–12 February 1997. National Rural Health Alliance 1997; 658.

10.   Hoy WE, Mathews JD, Pugsley DJ, McCredie DA, Hayhurst BG, Rees M, Walker KA, Kile E, Wang Z. The multidimensional nature of renal disease: rates and associations of albuminuria in an Australian Aboriginal community. Kidney International 1998; 54:1296–304.

11.   McDonald SP, Wang Z, Hoy WE. Physical and biochemical predictors of death in an Australian aboriginal cohort. Clin Exp Pharmacol Physiol 1999 Aug; 26(8):618–21.

12.   Spencer J, Wang Z, Hoy W. Low birth weight and reduced renal volume in Aboriginal children. Am J Kidney Dis 2001 May; 37(5):915–20.

13.   Hoy WE, Rees M, Kile E, Mathews JD, Wang Z. A new dimension to the Barker hypothesis: low birthweight and susceptibility to renal disease. Kidney Int 1999 Sep; 56(3):1072–7.

14.   White AV, Hoy WE, McCredie DA. Childhood post-streptococcal glomerulonephritis as a risk factor for chronic renal disease in later life. Med J Aust 2001 May 21; 174(10):492–6.

15.   Wang Z, Hoy W, McDonald S. Body mass index in Aboriginal Australians in remote communities. Aust N Z J Public Health 2000 Dec; 24(6):570–5.

16.   Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in IDDM. N Eng J Med 1993; 329:977–86.

17.   UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837–53.

18.   Hoy W, Kelly A, Jacups S, McKendry K, Baker P, MacDonald S, Wang Z, Punguatji N, Kerinauia J, Tipiloura E, Tipiloura E, Harrison C. Stemming the tide: reducing cardiovascular disease and renal failure in Australian Aborigines. Aust N Z J Med 1999 Jun; 29(3):480–3.

19.   Hoy WE, Wang Z, Baker PRA, McDonald S, van Buynder PB, Mathews JD. The natural history of renal disease in Australian Aborigines, Part 1. Progression of albuminuria and loss of glomerular filtration rate over time. Kidney Int 2001; 60:243–8.

20. Hoy WE, Wang Z, VanBuynder P, Baker PR, McDonald SM, Mathews JD. The natural history of renal disease in Australian Aborigines. Part 2. Albuminuria predicts natural death and renal failure. Kidney Int 2001 Jul; 60(1):249–56.

21. Young RJ, Hoy WE, Kincaid-Smith P, Seymour AE, Bertram JF. Glomerular size and glomerulosclerosis in Australian aborigines. Am J Kidney Dis 2000 Sep; 36(3):481–9.

22. Hughson MD, Johnson K, Young RJ, Hoy WE, Bertram JF. Glomerular size and glomerulosclerosis: Relationships to disease categories, glomerular solidification, and ischemic obsolescence. Am J Kidney Dis 2002 Apr; 39(4):679–88.

23. Cass A, Cunningham J, Wang Z, Hoy W. Social disadvantage and variation in the incidence of end-stage renal disease in Australian capital cities. Aust N Z J Public Health 2001 Aug; 25(4):322–6.

24. Cass A, Cunningham J, Wang Z, Hoy W. Regional variation in the incidence of end-stage renal disease in Indigenous Australians. Med J Aust 2001 Jul 2; 175(1):24–7.

25. Van Buynder P, Gaggin J, Mathews J. Renal disease patterns in Aboriginal Australians. Med J Aust 1993; 159:82–7.

26. Devitt J, McMasters A. Living on medicine: social and cultural dimensions of ESRD among Aboriginal people in Central Australia [draft]. Congress Aboriginal Medical Service, Alice Springs, 1996.

27. WHO Study Group. Prevention of diabetes mellitus. WHO Technical Series 844. WHO, Geneva, 1994; 55.

28. American Diabetes Association. Diabetic nephropathy. Diabetes Care 2002; 25(Supp 1):S85–S89.

29. Smith MBH. Chapter 21. Screening for urinary infection in asymptomatic infants and children. In: Canadian Task Force on the Periodic Health Examination (CTFPHE). The Canadian guide to clinical preventive health care. Health Canada, Ottawa, 1994; 222.

30. Alzaid AA. Microalbuminuria in patients with NIDDM: an overview. Diabetes Care 1996; 19:1:79–89.

31. Bennett P, Haffner S, Kasiske B, Keane W, Mogensen C, Parving H, Steffes M, Striker G. Diabetic renal disease recommendations: screening and management of microalbuminuria in patients with diabetes mellitus. Recommendations to scientific advisory board of National Kidney Foundation from ad hoc committee of Council on Diabetes Mellitus of National Kidney Foundation. Am J Kidney Dis 1995; 25:1:107–12.

32. Rowe DJF, Dawnay A, Watts GF. Microalbuminuria in diabetes mellitus: review and recommendations for the measurement of albumin in urine. Ann Clin Biochem 1990; 27:297–312.

33. Mogensen CE, Keane WF, Bennett P, Jerums G, et al. Prevention of diabetic renal disease with special reference to microalbuminuria. Lancet 1995; 346:1080–4.

34. Scheid DC, McCarthy LH, Lawler FH, Hamm RM, Reilly KE.Screening for Microalbuminuria to Prevent Nephropathy in Patients with Diabetes: A Systematic Review of the Evidence. J Fam Pract 2001 Aug; 50(8):661–8. http://www.jfponline.com/content/2001/08/jfp_0801_06610.asp [accessed 4 June 2002].

35. Croal BL, Mutch WJ, Clark BM, Dickie A, Church J, Noble D, Ross IS. The clinical application of a urine albumin: creatinine ratio point-of-care device. Clin Chim Acta 2001 May; 307(1–2):15–21.

36. Shephard MD, Barratt LJ, Simpson-Lyttle W. Is the Bayer DCA 2000 acceptable as a screening instrument for the early detection of renal disease? Ann Clin Biochem 1999 May; 36(Pt 3):393–4.

37. Hoy WE, Baker PR, Kelly AM & Wang Z. Reducing premature death and renal failure in Australian Aboriginals: a community-based cardiovascular and renal protective program. Medical Journal of Australia 2000; 172:473–8.

38.   Shephard M, Brown M, Hudson M, Riessen C, Braun J. The Umoona Kidney Project. Aboriginal and Islander Health Worker Journal 2000; 24:2:12-15.

39.   Ruggenenti P, Gaspari F, Perna A, Remuzzi G. Cross sectional longitudinal study of spot morning urine protein:creatinine ratio, 24 hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. BMJ 1998; 316:504-9.

40.   Stephenson JM, Kenny S, Stevens LK, Fuller JH, Lee E, and WHO Multinational Study Group. Proteinuria and mortality in diabetes: the WHO multinational study of vascular disease in diabetics. Diabet Med 1995; 12:149-55.

41.   Cockcroft DW, Gault MH: prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.

42.   Hillbrands LB, Artz MA, Wetzels JF, Koene RA: Cimetidine improves the reliability of creatinine as a marker of glomerular filtration. Kidney Int 1991; 40:1171-6.

43.   Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR. Predicting glomerular filtration rate after kidney transplantation. Transplantation 1995 Jun 27; 59(12):1683-9.

44.   Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999; 130:461-70.

45.   Timing of referral of chronic renal failure patients to nephrology services. The   CARI   Guidelines,   2001.   At: [http://www.cari.kidney.org.au/drafts/a1medical.html]

46.   Hoy WE, Pugsley DJ, Norman R, Rees M, Kile E, Hayhurst BG, Mathews JD. Birth weight and risk for renal disease: findings in an Australian Aboriginal community [abstract]. ASN 29 Annual Meeting, 3-6 November, 1996.

47.   Puddey IB, Rakic V, Dimmitt SB, Burke V, Beilin LJ, Van Bocksmeer F. Apolipoprotein E genotype and the blood pressure raising effect of alcohol. Am J Hypertens 1999; 12(9):946-7.

48.   Goodfellow AM, Hoy WE, Sriprakash KS, Daly MJ, Reeve MP, Mathews JD. Proteinuria is associated with persistence of antibody to streptococcal M protein in Aboriginal Australians. Epidemiol Infect 1999 Feb; 122(1):67-75.

49.   Thomas M, Australia and New Zealand Society of Nephrology consensus statement Delivery of Nephrology Services to Remote Areas of Australia, 1999.

50.   The CARI Guidelines. Caring for Australians with Renal Impairment. Prevention of   progression   of   renal   disease.   2001. http://www.cari.kidney.org.au/drafts/drafts.html [Accessed 4th June 2002].

51.   Nagai R, Wang EEL, Feldman W. Chapter 38. Dipstick proteinuria screening of asymptomatic adults to prevent progressive renal disease. In: CTFPHE. Canadian guide to clinical preventive health care. Health Canada, Ottawa, 1994; 436.

52.   Hayward RSA, Steinberg EP, Ford DE, Roizen MF, Riach KW. Preventive care guidelines: 1991. Ann Intern Med 1991; 114:758-83.

53.   Scottish Intercollegiate Guidelines Network. Investigation of asymptomatic proteinuria in adults: A national clinical guideline recommended for use in Scotland. SIGN, Edinburgh, August 1997.

54.   Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. 'Gruppo Italiano di Studi Epidemiologici in Nefrologia' (GISEN). Kidney Int May 1998; 53(5):1209-16.

55.   Territory Health Service to act on renal disease. The Chronicle (Bulletin of the Chronic Diseases Network of the North) July 1997; vols 1, 2.

56.   Manjunath G, Sarnak MJ, Levey AS. Estimating the glomerular filtraion rate. Dos and don'ts for asessing kideny function. Postgrad Med 2001; 110:55-62.

57.   Pugliese F, Cinotti GA. Non-steroidal anti inflammatory drugs and the kidney [editorial]. Nephrol Dial Transplant 1997; 12:3:386–8.

58.   Eknoyan G. Current status of chronic analgesic and NSAID nephropathy. Curr Opin Nephrol Hypertens 1994; 3:2:182–8.

59.   Murray MD, Black PK, Kuzmick DD, Haag KM, Manatunga AK, Mullin MA, Hall SD, Brater DC. Acute and chronic effects of NSAIDS on GFR in elderly patients. Am J Med Sci 1995; 310:188–97.

60.   The CARI Guidelines: Caring for Australians with Renal Impairment, 2001. At: [http://www.cari.kidney.org.au]

61.   Mendelssohn DC, Barrett BJ, Brownscombe LM, Ethier J, Greenberg DE, Kanani SD, Levin A, Toffelmire EB. Elevated levels of serum creatinine: recommendations for management and referral. CMAJ 1999 Aug 24; 161(4):413–7.

62.   Gansevoort RT, Sluiter WJ, Hemmelder MH, de Zeeuw D, Dejong PE. Anti-proteinuric effect of blood-pressure lowering agents: a meta-analysis of comparative trials. Nephrol Dial Transplant 1995; 10:11:1963–74.

63.   Mogensen CE, Keane WF, Bennett P, Jerums G, et al. Prevention of diabetic renal disease with special reference to microalbuminuria. Lancet 1995; 346:1080–4.

64.   Kasiske BL, Kalial RSN, Ma JZ, et al. Effect of hypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. Ann Intern Med 1993; 118:129–38.

65.   Bohlen L, de Courten M, Weidmann P. Comparative study of the effect of ACE-Inhibitors and other anti-hypertensive agents on proteinuria in diabetic patients. Am J Hypertension 1994; 7:9:Part2:84S–92S.

66.   Brenner BM, Cooper ME, De Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Eng J Med 2001; 345:861–69.

67.   Parving HH, Lehnert H, Brochner-Mortensen J et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Eng J Med 2001; 345:870–8.

68.   Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, Cooper ME. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000 Dec 9; 321(7274):1440–4.

69.   Kshirsagar A V, Joy M S, Hogan S L, Falk R J, Colindres R E. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. American Journal of Kidney Diseases 2000; 35(4):695–707.

70.   Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Eng J Med 2001; 345:51–60.

71.   Lovell HG. Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software, 2002.

72.   Hovind P, Rossing P, Tarnow L, Smidt UM, Parving HH. Remission and regression in the nephropathy of type 1 diabetes when blood pressure is controlled aggressively. Kidney Int 2001 Jul; 60(1):277–83.

73.   Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J. Blood pressure and end-stage renal disease in men. N Engl J Med 1996 Jan 4; 334(1):13–8.

74.   Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G. The effect of dietary protein restriction and blood pressure control on the progression of renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 1994; 330:877–94.

75.   Maschio G, Albert D, Janin G, Locatelli F, Mann J, et al., of the ACE Inhibition in Progressive Renal Insufficiency Study Group. Effect of the ACE inhibitor benazepril on the progression of chronic renal insufficiency. N Eng J Med 1996; 334:939–45.

76.   Giatras I, Lau J, Levey AS, for ACE Inhibition and Progressive Renal Disease Study Group. Effect of ACE inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomised trials. Ann Intern Med 1997; 127:337–45.

77.   Kshirsagar A V, Joy M S, Hogan S L, Falk R J, Colindres R E. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. American Journal of Kidney Diseases 2000; 35(4):695–707.

78.   The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, nondiabetic nephropathy. Lancet 1997; 349:1857–63.

79.   Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F, Schena FP, Remuzzi G. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999 Jul 31; 354(9176):359–64

80.   Jafar TH, Schmid CH, Landa M, et al. Angiotensin-Converting Enzyme Inhibitors and Progression of Nondiabetic Renal Disease A Meta-Analysis of Patient-Level Data. Ann Int Med 2001; 135:73–87.

81.   Maki DD, Ma JZ, Louis TA, Kasiske BL. Long-term effects of antihypertensive agents on proteinuria and renal function. Arch Intern Med 1995 May 22; 155(10):1073–80.

82.   Guidi E, Minetti E. Antihypertensive treatment for non-diabetic kidney disease (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software, 2002.

83.   US Preventive Services Task Force (USPSTF). Chapter 55. Counselling to promote physical activity. In: Guide to clinical preventive services. 2nd edn. Williams & Wilkins, Baltimore, 1996; 611.

84.   Curtis B, Barrett BJ, Levin A. Identifying and slowing progressive chronic renal failure. Can Fam Physician 2001 Dec; 47:2512–8.

85.   Pedrini MT, Levey AS, Lay JL, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and non-diabetic renal diseases: a meta-analysis. Ann Intern Med 1996; 124:627–32.

86.   Fouque D, Laville M, Boissel JP, Chifflet R, Labeeuw M, Zech PY. Controlled low protein diets in chronic renal insufficiency: meta-analysis. BMJ 1992; 304:6821:216–20.

87.   Fouque D, Wang P, Laville M, Boissel JP. Low protein diets for chronic renal failure in non diabetic adults (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software, 2002.

88.   Spencer JL, Silva DT, Snelling P, Hoy WE. An epidemic of renal failure among Australian Aboriginals. Med J Aust 1998; 168:537–41.

89.   Hoy WE, Mathews JD, McCredie DA, Pugsley DJ, Hayhurst BG, Rees M, Kile E, Walker KA, Wang Z. The multidimensional nature of renal disease: rates and associations of albuminuria in an Australian Aboriginal community. Kidney Int 1998 Oct; 54(4):1296–304.

90.   Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. Kidney Int 2001 Jan; 59(1):260–9.

91.   Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J. Blood pressure and end-stage renal disease in men. N Engl J Med 1996 Jan 4; 334(1):13–8.

92.   Orth SR. Smoking: a renal risk factor. Nephron 2000 Sep; 86(1):12–26.

93.   Casadevall N, Nataf J, Viron B, Kolta A et al. Pure red-cell aplasia and anti-erthyropoeitin antibodies in patients treated with recombinant erythropoeitin. N Engl J Med 2002; 346(7):469–75.

94.   Cody J, Daly C, Campbell M, Donaldson C, Grant A, Khan I, Pennington S, Vale L, Wallace S, MacLeod A. Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software, 2002.

95.   De Zeeuw D, Apperloo AJ, de Jong P. Management of chronic renal failure. Curr Opin Nephrol Hypertens 1992; 1:116–23.

96.   Gonzalez EA, Martin KJ. Renal osteodystrophy: pathogenesis and management. Nephrol Dial Transplant 1995; 10:suppl 3:13–21.

97.   Brookhyser J, Pahre SN. Dietary and pharmacotherapeutic considerations in the management of renal osteodystrophy. Adv Ren Replace Ther 1995; 2:1:5–13.