

# Predialytic treatment of chronic kidney disease

**Predialytic treatment of chronic kidney disease is an important part of management.**

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The predialytic treatment of chronic kidney disease (CKD) begins at the time of the diagnosis of the kidney disease. Once this diagnosis is made, the advance towards end-stage kidney failure, with consequent death or dialysis therapy, is virtually inexorable in the majority of cases. In a study from Norway, 73% of 3 047 patients in stage 3 (see staging below) had a decline in the glomerular filtration rate over a 44-month period.<sup>1</sup> The decline in females is slower (the weaker sex?).

The length of time of this progression to end-stage kidney failure is dependent on the underlying kidney disease and the therapeutic intervention. One attempts to slow the progression for as long as possible. Some improve, as seen in the MDRD study<sup>2</sup> and above,<sup>1</sup> and many patients die with kidney disease rather than from it.

It must also be apparent that a glomerulonephritis, which is secondary to systemic disease, has its course, to a large extent, determined by the culprit disease. A good example of this is syphilis. Luetic disease classically produces a membranous nephropathy, which in some cases is curable within 24 hours but in all cases is curable within approximately 2 weeks with antibiotic treatment. Systemic lupus erythematosus (SLE), which has no characteristic histological type, may have a rapidly deteriorating course, depending on the presence of crescent and necrosis. The NIH studies on long-term SLE therapy showed that the course can be favourably influenced by utilising cyclophosphamide. However, at present there is no satisfactory treatment for lupus nephritis. More recently, the use of mycophenolate mofetil (MMF) has raised hopes of an enduring, successful form of less toxic therapy for SLE. Diabetic nephropathy is a condition where tight control of blood sugar slows the progression of the nephropathy to end-stage kidney failure.<sup>3</sup>

There are many causes of CKD and the approach outlined below can be applied to all of them.

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An idiopathic glomerulonephritis is used as an example below to illustrate an approach to the predialytic treatment of CKD. The indisputable fact is that there is no definitive therapy *per se* for most of the idiopathic glomerulonephritides. Immunosuppression may or may not have a positive effect. In a percentage of cases of idiopathic membranous glomerulonephritis, spontaneous remission occurs.

In Fig. 1, the diagnosis of glomerulonephritis (GN) is made at a time when the creatinine clearance is normal. The patient may present for an insurance examination and is then coincidentally noted to have proteinuria and haematuria with a renal biopsy confirming the clinical impression of an idiopathic GN. The renal function will invariably deteriorate over the ensuing years – in the hypothetical case under discussion the number of years shown is 20 (this would hold true for many of the nephritides).

In my original description, published 10 years ago,<sup>4</sup> I had divided the progression into the stages A, B, C, D, E, and F. Each stage merged into the next and represented a continuum in the progressive deterioration of the renal function of the index case. I pointed out that each doctor must utilise various treatment options

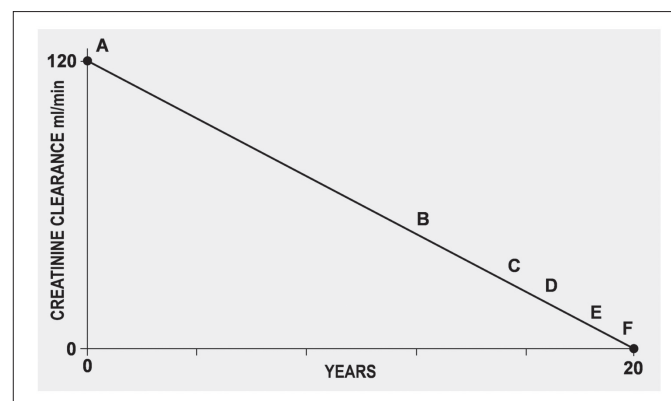


Fig. 1. A hypothetical case showing stages in the progression to end-stage kidney disease. Treatment options are proposed at each stage.

**Table I. Stages of chronic kidney disease<sup>5</sup>**

Stage	Description	GFR (ml/min/1.73m <sup>2</sup> )	Accompanying clinical stage
1	Kidney damage + normal or ↑ GFR	≥ 90	A
2	Mild ↓ GFR	60 - 89	A
3	Moderate ↓ GFR	30 - 59	B & C
4	Severe ↓ GFR	15 - 29	C, D & E
5	Kidney failure	< 15 or dialysis	F

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at each stage in an effort to ensure that the progression to end-stage renal failure is as slow and as symptom free as possible. Recently the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines were published and incorporated a staging system for glomerular filtration rate (GFR).<sup>5</sup> I have attempted to match these stages of GFR with the clinical stages first described in the article of 1997 (Table I).

*Clinical stage A*

At this early stage, the serum creatinine may be normal and the patient may be asymptomatic and, unfortunately in many instances, unaware of the disease lurking in the kidneys. Important aspects during this stage that will require attention are obesity, hypertension and smoking habits. An important first-step consideration in the management of any glomerulonephritis is to reduce weight in the obese patient. In patients with renal disease, obesity *per se* has been shown to aggravate hypertension and proteinuria.<sup>6,7</sup> Reduction of weight in obese patients significantly reduces proteinuria.<sup>6</sup> Exercise will aid in weight reduction, but there are no convincing studies that exercise *per se* is beneficial in slowing the progression of deteriorating renal function.<sup>8</sup> It has been shown without a satisfactory explanation that, paradoxically, being overweight confers an advantage for all-cause mortality in patients on dialysis. The exact mechanisms giving this advantage are uncertain, but Malnick and Knobler have derived a list of clinical characteristics in the obese patients who are at risk.<sup>9</sup> The risk factors include all features of the metabolic syndrome.

During these early years, clinically classified as stage A, maintenance of a normal blood pressure must be the main objective for the attendant doctor. CKD is a risk factor for

cardiovascular disease. Early treatment of blood pressure and lifestyle changes may reduce the incidence of this complication. Various studies have shown the important benefits to be gained by good blood pressure control. This is also the single most important factor in slowing the progression to end-stage failure for non-diabetic kidney disease.<sup>10</sup> Angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin II receptor blockade (ARB) agents must be first-line therapy in any patient with kidney disease.

The realisation that there exists an ACE-I 'escape' phenomenon whereby peripheral conversion of angiotensinogen and angiotensin I takes place, despite ACE-I use, is well recognised. It has, however, been found that combining an ACE-I with an ARB is of synergistic value and overcomes the 'escape'. The use of these combinations has succeeded in reducing the amount of protein lost, particularly in diabetics, more than with an ACE-I alone. The ARB studies, particularly in type 2 diabetics, make it almost mandatory to use an ARB as first-line treatment in these patients.

More recently a total blockade of the renin-angiotensin-aldosterone system (RAAS) has been suggested whereby an aldosterone antagonist is also prescribed. It was shown that spironolactone may reduce proteinuria and slow progression in patients with CKD.<sup>11</sup> Be watchful for the development

of hyperkalaemia. I have not used an aldosterone antagonist in my practice and will await positive results from bigger efficacy and safety studies before I follow.

The diseased kidney retains salt and water and any patient with nephritis should be educated to reduce salt intake. Therefore, if the patient is hypertensive, part of the antihypertensive therapy must be a diuretic. Do not wait for signs of fluid overload before prescribing a diuretic; the retained fluid may not be clinically detectable early in the disease process.

Various hypertension guidelines have been promulgated; the KDOQI guidelines of 2002 are generally followed and these suggest that the blood pressure be maintained below 130/80. He and Whelton have shown that the reduction of systolic blood pressure is more important than the reduction in diastolic blood pressure in preventing end-stage kidney failure.<sup>12</sup>

Since hypertension may be the early sign of an underlying glomerulonephritis, it is surprising to learn that clinicians fail to recognise early renal disease among patients with hypertension.<sup>13</sup> Any patient with hypertension must be worked-up to exclude or prove an underlying glomerulonephritis.

It is also important to recognise that smoking is an independent risk factor for the development of end-stage kidney disease in hypertensive patients.<sup>14</sup> There is evidence that smoking increases the prevalence of microalbuminuria (a marker for the development of nephropathy) in insulin-dependent diabetes.<sup>15</sup>

*Clinical stage B*

Clinical stage B starts at a time when half of the renal function is lost. The management started in stage A continues (as it will through to stage F), but perhaps slightly more aggressively, with greater attention to antihypertensive therapy and ensuring compliance with salt restriction.

*Clinical stage C*

The beginning of this stage is marked by a serum creatinine of 200 µmol/l (which translates into a creatinine clearance of approximately 30 ml/min). It was generally

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thought that the patient must now be put on a reduced protein intake. The protein restriction approach is still being debated. Those in favour<sup>16</sup> of restriction are balanced against those who do not believe that protein restriction has an influence in halting the decline of kidney function.<sup>17</sup> The opinion among the 'non-believers' is that a protein-restricted diet serves only to alleviate symptoms (and the patients should rather be on dialysis) and relieve the pruritus (via inorganic phosphate depletion). The work of Giovannetti using vegetable protein with essential amino-acid supplements has not been generally popular. This supplemental approach requires total compliance with good financial resources. We<sup>18</sup> and others have shown that not much is to be gained by using the very-low-protein diet supplemented with essential amino acids.

**In patients with type 1 diabetes, there is evidence that a low-protein diet positively limits the progression of diabetic nephropathy.**

In my opinion the majority of our patients are undernourished and are financially forced to be on a 'natural' protein restriction. In South Africa, we have no reports of benefit derived from protein restriction alone. Perhaps in the more affluent patients a compromise could be the use of 0.8 g/kg of protein per day, of which approximately 85% is animal in origin and the rest is made up of vegetable protein.

In patients with type 1 diabetes, there is evidence that a low-protein diet positively limits the progression of diabetic nephropathy.<sup>19</sup> The evidence of benefit in type 2 diabetic nephropathy is contradictory. This may be as a consequence of the associated vascular disease morbidity, which is such a predominant feature in type 2 diabetics.

At this fairly advanced clinical stage of renal failure, the renal preserve depends on the maintenance of perfusion and any disruption of its regulation will cause the filtration pressure, and consequently the creatinine clearance, to drop. Therefore the use of certain drugs, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), and excessive

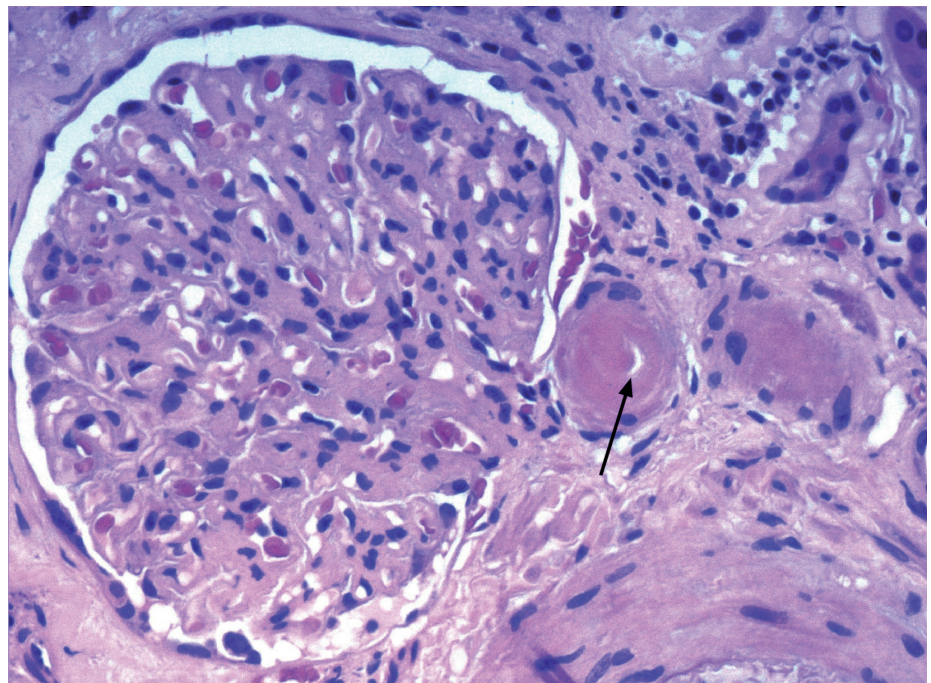


Fig. 2. An afferent arteriole in the kidney of a diabetic patient. The arrow points to an almost absent lumen which has been obliterated by extensive hyalinosis.

use of diuretics must be monitored carefully. The use of an ACE-I or ARBs in patients with severe peripheral vascular disease (and therefore, by extrapolation, main and/or smaller renal artery atherosclerosis) will cause an already compromised glomerular perfusion to fall further.

I show Fig. 2 out of interest. It demonstrates the hyalinosis found in the afferent arteriole of a patient with diabetes. Note the marked narrowing of the lumen. If this degree of hyalinosis extended throughout the kidney, as is possible in advanced diabetic nephropathy, then it may give rise to a situation similar to that of renal artery stenosis.

I suggest that whenever an ACE-I or ARB is used (and they must be used whenever possible) with advanced diabetic nephropathy, the serum creatinine be measured 3 - 5 days after starting treatment (as well as the potassium). Any unexplained increase in the serum creatinine level must compel one to stop the ACE-I or ARB. Similarly, if a diabetic patient with advanced CKD has been on treatment with either an ACE-I and/or an ARB and there is an unexplained deterioration in renal function, consider that decreased glomerular perfusion may be one of the causes. One may wish to stop the ACE-I or ARB temporarily and repeat the creatinine measurement. Obviously renal artery stenosis must always be excluded in these situations.

An important point is that NSAIDs, by inhibiting prostaglandin synthesis, produce a state of diuretic resistance.

### Clinical stage D

According to the KDOQI staging of kidney disease, this is still stage 4. My original reason for splitting the creatinine clearance between 20 - 30 ml/min into 2 was because I believe this period is extremely important. It requires much attention to detail. This clinical stage D is at a creatinine clearance of approximately 20 - 25 ml/min and has important implications for the practitioner. The treatment begun in clinical stages A, B and C continues. In stage D, the functioning renal mass has been reduced considerably and it is unable to maintain the successful excretion of inorganic phosphate, with the consequent development of hyperphosphataemia. In addition, the kidney's ability to further hydroxylate hydroxy25-D<sub>3</sub> is impaired. Both the hyperphosphataemia and the diminished production of vitamin D<sub>3</sub> result in hypocalcaemia and the excessive secretion of parathyroid hormone (PTH).

The abnormal blood biochemistry, elevated inorganic phosphate and PTH levels may occur at earlier stages. The approach to the treatment of these abnormalities at an earlier stage is uncertain. There are cost implications, as well as exposure to excessive calcium, in designing the treatment strategy. Which CKD patient would wish to take calcium carbonate for many years and risk the exposure to excessive calcium with the possibility of vascular calcification a looming threat? The decision to treat this biochemical abnormality at an earlier stage must be individualised. The treatment programme must include one of the newer

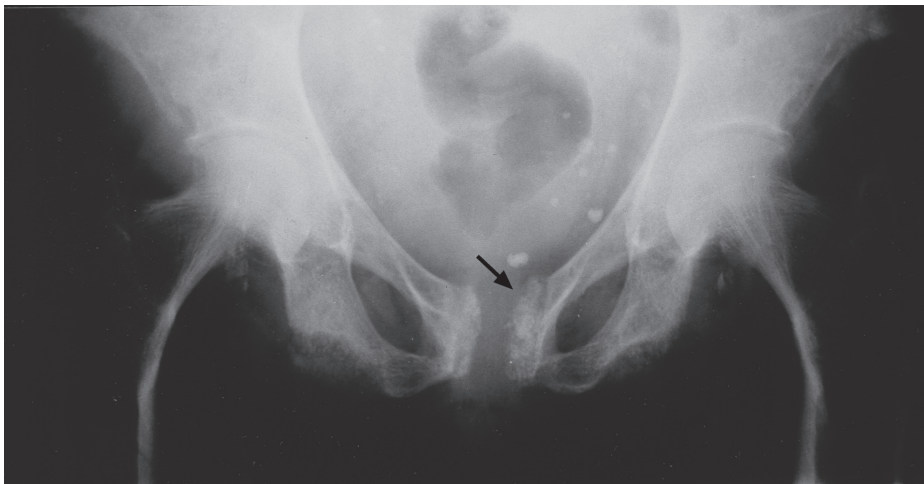


Fig. 3. X-ray of the pelvis in a patient with CKD. The arrow points to periosteal resorption as occurs in high turnover bone disease. Note the poor outline of the femurs.

calcium-free phosphate binders mentioned below.

The effect of this abnormal physiology results in a bone mineral disorder. The 'new' terminology is chronic kidney disease-bone mineral disorder (CKD-BMD). Only when a bone specimen is examined by histomorphometry, is the term renal osteodystrophy used.

Renal osteodystrophy is further classified into states of T (turnover), M (mineralisation) and V (volume). Clinically it is easy to recognise a high turnover state, i.e. osteitis fibrosa cystica, diagnosed by the classic X-ray appearances (Fig. 3) as well as the low turnover bone state, i.e. osteomalacia and adynamic bone disease. With the TMV classification, the old histological terminology, e.g. osteitis fibrosa cystica, will disappear from use.

The high turnover states have high bone volumes and the low turnover states low volumes. A proportion of patients may have a mixed picture. Earlier studies showed that adynamic bone disease (a very low turnover state) occurs commonly in predialysis patients and diabetics.<sup>20</sup> It is important to realise that at the early stages the bone disease is unusually asymptomatic.

The treatment is to decrease the phosphate level in the blood and supply calcium. This is achievable by using calcium carbonate or calcium acetate, taken a few minutes before each meal.<sup>21</sup> The fall in the phosphate level and the supply of calcium will suppress PTH secretion and prevent the development of renal osteodystrophy. However, if the PTH level is suppressed too vigorously, then low turnover bone disease will develop. This is because the PTH receptors, in this predialysis period, are less responsive to parathyroid hormone. Therefore it is not advisable to lower the PTH levels within the normal range. Conversely, very high PTH levels are associated with high turnover disease. The recommendation is to keep the

PTH levels approximately 2 - 3 times above the normal level.

There have been recent concerns about the assay used to measure PTH. Currently the intact assay is used; it includes in the measurement those 'bits' of PTH that are inactive and inhibitory. So, a very high PTH level, as measured by the intact method, may not represent an active hormone and consequently not a high turnover bone state. It is for this reason that the examination of bone histology becomes important.

Aluminium hydroxide is the most effective phosphate binder in use.<sup>21</sup> The deleterious effects of aluminium deposited in body tissues and the calcification front in the bones is well known. Therefore if aluminium hydroxide is required (e.g. in those who are particularly unresponsive to calcium carbonate, i.e. hyperphosphataemia persists) then it should be used for short periods only. Aluminium deposition, at the calcification

front, results in the development of low turnover bone disease.

There are newer agents on the market that are not calcium based. They are lanthanum carbonate (Fosrenol) and sevelamer (Renagel). The cost of these is extravagant and prohibits their use in the state sector. In a comparative study, the CARE study, calcium acetate was superior to sevelamer in reducing phosphate levels.<sup>22</sup> Any calcium-containing phosphate binder is contraindicated in the presence of hypercalcaemia.

Vitamin D<sub>3</sub> plays an important role in the remodelling process of the bone. If the serum calcium does not recover with calcium carbonate use, then, provided the phosphate level has been controlled, vitamin D<sub>3</sub> must be prescribed. Excessive doses of vitamin D<sub>3</sub> may result in excessive suppression of PTH secretion, hypercalcaemia and the development of the low turnover bone diseases. An important consideration is to maintain the product of calcium and inorganic phosphate below 4.0 mmol/l. Above a value of 4.0, the calcium phosphate may no longer be held in solution and it will deposit out into various tissues, i.e. metastatic calcification occurs. A form of metastatic calcification, where calcium is deposited in the walls of small arterioles, called calciphylaxis, may also occur in a milieu of secondary/autonomous hyperparathyroidism. It is far more common in those patients on dialysis and in the post-transplant period but may have its 'beginnings' in the predialysis period. The patient presents with skin infarcts or, as a prelude to the skin infarcts, with livedo reticularis (Fig. 4). The progression of the disease may be halted by parathyroidectomy or may continue relentlessly with massive



Fig. 4. Severe calciphylaxis in a patient with CKD. Note the extensive skin and subcutaneous infarction with underlying muscle clearly visible.

## If haemodialysis is the best choice for a patient, then early creation of an arteriovenous fistula must be undertaken for access to the dialysis machine.

skin necrosis and ultimate death from sepsis (as occurred with the patient in the photograph).

A fall in haemoglobin usually occurs at the end of this stage, but with the advent of recombinant human erythropoietin (EPO), this can easily be treated. The EPO does not have a negative or positive influence on the progression to end-stage kidney disease. It does improve the quality of life.

### Clinical stage E

Treatment begun in the earlier stages continues. Urine output begins to fall and far more aggressive diuretic and antihypertensive therapy may be required. Electrolyte disorders on a normal diet may occur. The most lethal electrolyte disorder is that of hyperkalaemia (usually when urine output falls to less than 1 litre per day) and the patient must be advised on the appropriate diet. The main culprit foods are citrus fruits, tomatoes, bananas and avocado pears.

### Clinical stage F

This is end-stage renal failure and the form of the future maintenance dialysis therapy needs to be planned, i.e. haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A Tenckhoff catheter for CAPD can be inserted a week before use, although laparoscopic techniques allow for earlier (almost immediate) use. If haemodialysis is the best choice for a patient, then early creation of an arteriovenous fistula must be undertaken for access to the dialysis machine. Such early preparation is vital since it takes approximately 6 weeks for the fistula to 'mature' before being used.

Sepsis is a major problem with emergency push-in dialysis catheters (either internal jugular vein, which is preferred, or femoral vein). The advent of more permanent tunnelled access, inserted by a surgeon, has to a large extent circumvented the sepsis problem. The application of mupirocin (Bactroban) ointment to the exit site is now mandatory and has reduced serious exit-

site sepsis. The ointment is applied in the dialysis centres after each dialysis session. Unfortunately, costs have consequently increased, since the catheters, theatre-time, surgeon and anaesthetist are expensive.

Early referral to a registered nephrologist is therefore very important. A group of investigators has shown that in those patients who died within 1 year of starting dialysis, when compared with those who survived longer than 1 year, the interval between first presentation and dialysis was shorter in the death group. Plasma urea and creatinine were also greater at presentation in the group that died.<sup>23</sup> So share the management of these complex patients with your friendly nephrologist.

### The dyslipidaemia of CKD

The results of investigations on the influence of the abnormal lipid metabolism on progression in CKD have to date been unhelpful. There are many short-term studies, with few patients, which have shown variable results. The outcome of a clinical study in our unit showed that, by using a HMGCoA reductase inhibitor in a group with idiopathic membranous nephropathy, proteinuria was markedly decreased. In this small study, no influence on the creatinine clearance was shown.<sup>24</sup> However, until bigger studies are available and there are no contra-indications to the use of lipid-lowering agents, I recommended their use, not only to attempt to slow progression, but also to treat the dyslipidaemia. This is particularly relevant in the nephrotic syndrome where there is a major lipid abnormality.

### Urinary tract infections

Clearly another self-explanatory step in the slowing of progression relates to the treatment and prevention of urinary tract infections. Long-term prophylaxis must also be employed in those with surgically uncorrectable ureteric reflux and renal calculi as well as those with repeated infections from bladder diverticulae or

indwelling catheters (long-term use in those with spinal injuries).

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## Predialytic treatment of CKD

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### *In a nutshell*

- Progression of renal function deterioration occurs in the majority of patients with CKD.
- The progression can be slowed by paying particular attention to blood pressure control and, additionally in diabetic nephropathy, tight control of blood sugar.
- Obesity and smoking are deleterious factors in progression and must be handled from the outset.
- Salt retention is always a problem with the diseased kidney and therefore salt restriction and a diuretic are useful in alleviating fluid retention and controlling the blood pressure.
- ACE-I and/or ARB treatment is essential in any patient with CKD with proteinuria and/or hypertension. They have a positive influence in slowing renal function deterioration.
- NSAIDs inhibit diuretic action.
- Spironolactone is being suggested for use in patients with CKD accomplishing total RAAS block. The evidence of efficacy in slowing progression and reducing proteinuria is encouraging but not substantial. Judgement on the safe use of this agent is still awaited.
- Reduction of phosphate levels is essential for the bone well-being of the patient with CKD. The only way we in SA can achieve this is with the use of calcium carbonate given before meals.
- The new osteodystrophy classification relies on states of bone turnover together with mineralisation status and bone volume.
- Lipid-lowering agents should be prescribed in patients with CKD (insulin-resistant state) although the efficacy in slowing progression has not yet been established. This is particularly pertinent in patients with the nephrotic syndrome.

## *single suture*

### *Superwater strikes down bugs*

The developers of a form of 'super-oxidised' water claim that their discovery can kill harmful bacteria, fungi and viruses in wounds. The new water may be more effective than bleach and not harm human tissue.

The product, called Microcyn, was presented recently at a biomedical business conference in Monaco. The developers said that the wounds of diabetic patients treated with the product and an antibiotic healed within 43 days on average, compared with 55 days for patients given the standard treatment of iodine plus an antibiotic.

The key ingredients are oxchlorine ions. These ions rapidly pierce the walls of free-living micro-organisms and so kill them. Human cells are not affected because they are tightly bound together in a matrix. Microcyn only kills cells that it can completely surround, according to researchers.

*New Scientist*, 26 May 2007.