



SILENT ASSASSIN

HUGE GAINS ARE BEING MADE IN OUR ABILITY TO DETECT EARLY SIGNS OF CHRONIC KIDNEY DISEASE – BUT AS MATT JOHNSON REPORTS, SPOTTING THOSE AT RISK REMAINS HALF THE BATTLE.

You would certainly notice if half your heart had become so diseased it couldn't function. And you wouldn't feel well with just one lung, or one side of your brain. But lose up to 50% of your kidney function and you won't notice much.

Such is their efficiency that your kidneys can actually cope with losing nearly half the nephrons they use to filter your blood.

By that stage though, the disease process could be so well entrenched that reversing it is next to impossible. Then, all that lies between you and catastrophic physiological collapse are two organs, each the size of your fist and weighing less than 2% of your body weight.

For decades, the appearance of symptoms marked almost the end for patients with chronic kidney disease (CKD), which can be caused by diabetes, obesity, hypertension or smoking.

But advances in pathology have shown that early detection is possible. We know that treatment can slow the disease – but ultimately, we may be able to prevent it developing at all.

Every day, fleets of mini-buses collect patients with CKD for their dialysis treatment. The bus trip precedes four or five hours of sitting tethered to a machine as it filters and cleans their blood. By the time they arrive home these patients have lost another day to simply surviving. Most of them have to repeat this process every second day. Forever.

But what is most disturbing is that until 90 days before they required dialysis,

more than a quarter of these patients had never seen a kidney specialist. For years they had unknowingly been developing a condition that would not clinically declare itself until it was too late.

Appalling costs

The economic costs of CKD are, quite simply, appalling. This year it will directly cost \$700 million. That will rise by \$1 million per week next year and continue to do so until 2010, when conservative estimates of the total health sector cost lie between \$4.26 and \$4.52 billion annually.

Every day during that time will have seen five more Australians added to the list of patients requiring dialysis or a transplant.

But these figures pale against the human cost. The burden of regular dialysis and the general disability associated with CKD are so severe and interminable that many – such as Australia's then richest man, Kerry Packer – chose to decline the treatment and succumb to the disease.

The million or so nephrons that lie near the outer edge of your kidneys receive 25% of the blood pumped by your heart every minute. It's a totally disproportionate amount for organs their size, but as the blood flows through the capillary beds, it's not just supplying the kidney with oxygen and nutrients.

Those delicate glomerular capillary beds are much more porous than normal capillaries and they act like sieves, allowing the passage of plasma and

nearly all solutes out through the capillary wall and into a series of tubules that run parallel to the capillaries.

In an energy-sapping process, the kidneys then pump 99% of the filtrate and its dissolved components back into the bloodstream, leaving wastes, drugs and a small amount of water in the tubules to be excreted as urine.

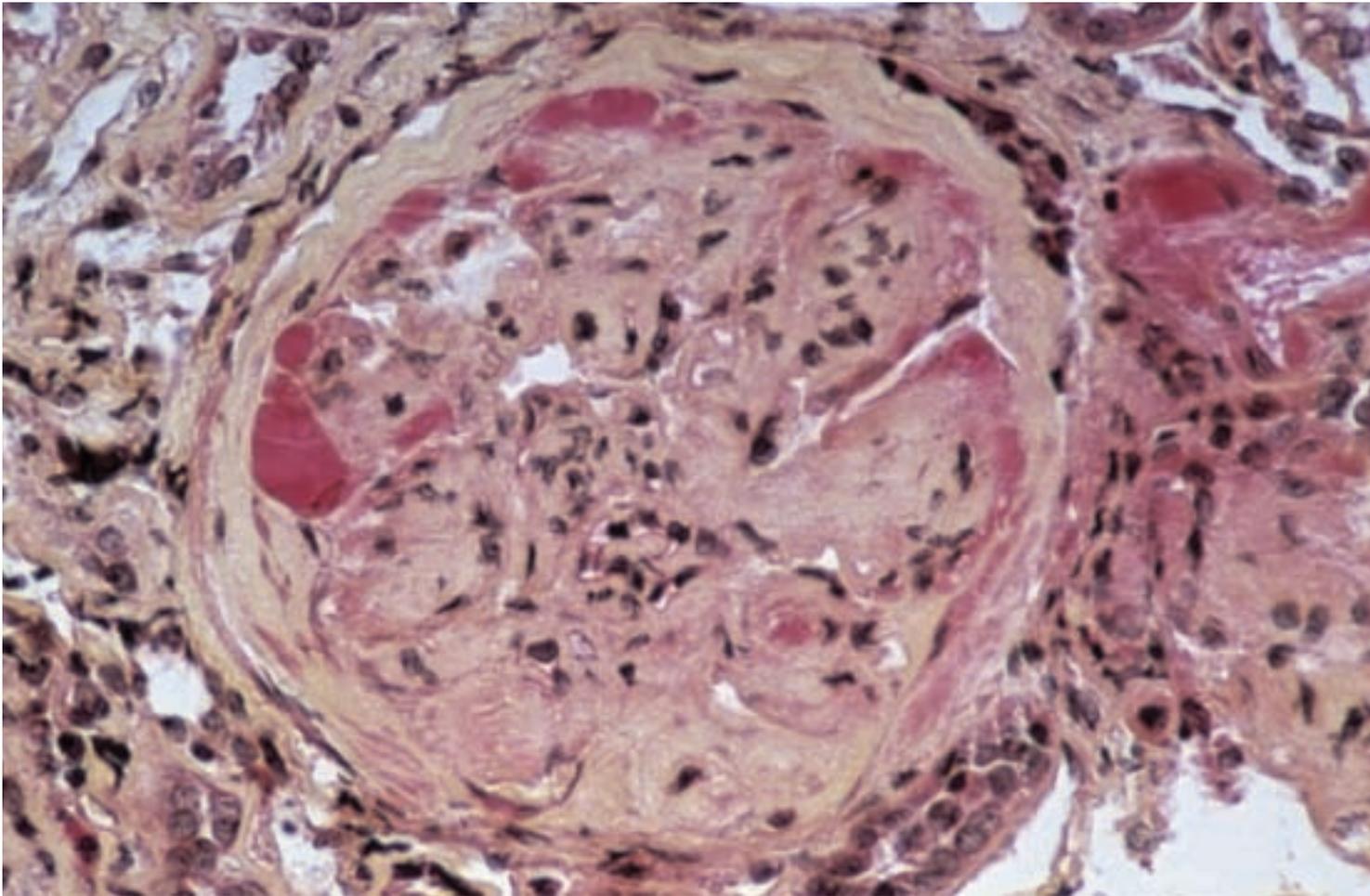
The glomerular filtration rate (GFR) for a healthy kidney is about 100 mL/minute, which means nearly 200 litres of filtrate is collected every day in the tubules: all from a blood volume of just six litres.

The effort of returning nearly all this filtrate requires almost as much energy as the heart, and about twice as much as the brain.

But the process of filtration and reabsorption allows the kidney tubules to delicately control blood volume and pressure, nitrogenous wastes, pH (acidity/alkalinity), haematocrit (percentage of red blood cells) and even bone density.

Nephrons severely damaged by disease or trauma cannot be replaced – but the surviving nephrons can, to a point, take on an increased workload. Patients who have a kidney removed effectively lose half their nephrons, resulting in a 50% reduction in GFR at the time of surgery, but within several months their total GFR will have risen to 80% of the pre-operative value.

But beyond a 50% nephron loss, the remaining nephrons are forced past their capacity, become irreversibly damaged,



Light micrograph of a section through kidney tissue in a case of diabetes.

and the symptoms of uraemia (literally, urea in the blood) begin to emerge. The increased workload itself causes the relentless destruction of the remaining nephron pool – and at this point, even if the original disease process is halted, the degeneration can continue.

Raising awareness

Alerting GPs and the public to this long asymptomatic development period of CKD has become the focus for groups such as Kidney Health Australia.

“The emphasis in the past five years in CKD has swung to early detection of damage and impaired function rather than on diagnosis of explicit disease that is causing the damage,” explains Kidney Health Australia Medical Director Dr Tim Mathew.

“A number of large studies across the world have led to the realisation the kidney function is significantly reduced in greater numbers in the community than we have previously realised.

“Surveys of otherwise healthy people show up to 8% have reduced function –

and there’s another 6.5% on top of that figure who show some signs of significant damage. That’s one in seven.”

Standard tests

There are several tests commonly used to assess kidney disease. A urine sample can be analysed for red and white blood cells or proteins that get into the urine through damaged nephrons. Or a blood sample can be analysed for waste products such as urea and electrolytes that start to accumulate in the blood as kidney function fails.

An ESR (erythrocyte sedimentation rate) test used to measure inflammation can also be indicative of kidney disease, but most of these tests are non-specific, and it’s the presence of creatinine in the blood and its relationship to GFR that is considered the most reliable test.

Pathologists and clinicians have known for decades that the onset of CKD symptoms would be preceded by a long period of steadily falling GFR, but the lack of an accurate test made it difficult to predict if a person was indeed on the path

to CKD, or how far they had to go before the point of no return and becoming permanently dependent upon dialysis or transplantation. Under these conditions it was difficult to determine treatments and how aggressively they should be administered.

The standard test was to use the link between GFR and creatinine – a product of muscle metabolism that is freely filtered at the nephrons but never reabsorbed in the tubules, so high creatinine levels in the blood reflect low GFR. However, the creatinine figure gained in testing could be affected by diet, weight loss, ethnicity, sex or age, making its clinical significance difficult to interpret.

“There’s been more than 50 equations over the past 30 years that have tried to estimate GFR from a creatinine result,” explains Dr Graham Jones, SydPath’s staff specialist in chemical pathology at St Vincent’s Hospital in Sydney.

“But for previous equations to be accurate they need detailed information about the patient, such as weight and body composition.”

A new formula – the MDRD equation – has changed that and given pathologists the ability to accurately quantify renal function on lab tests alone.

“The MDRD equation is robust and at least as accurate as any alternative. It’s been widely validated and doesn’t need any measurement of the patient – just age and sex,” Dr Jones says.

The new formula has also been easy to integrate into the existing testing process.

“It’s much easier to add a calculation to existing samples than if you were to bring [in] a new test, where there’s not only the cost of the test, but also the cost of educating GPs and pathologists about the test and what the results mean.

“The cost of the new formula to Medicare has been zero.”

Significantly, Kidney Health Australia has persuaded every lab to report the new eGFR value created by the MDRD equation with every creatinine test.

Technically the eGFR test is quite simple: a chemical reaction changes light absorbency, depending on the volume of creatinine in the sample, but even with the new MDRD equation, problems remained with standardisation between laboratories and the testing products they used.

“There were a number of companies supplying assays for creatinine, but they were all slightly different,” Dr Jones explains.

“We weren’t able to compare the results gained with one assay with the same person tested by another assay. Lab to lab there would be differences.”

Synergy and standardisation

But unprecedented cooperation between clinicians, pathologists and the companies that develop the assays led to a breakthrough.

“Most diagnostic companies have a very high level of expertise, but their ability to cooperate has not been great,” Dr Jones says.

“In this case the doctors and scientists provided the diagnostic companies with what they needed to align their assays, and the companies agreed. It has been expensive for companies in the short term, but doctors and patients have benefited enormously.”

The significance of uniform lab reporting cannot be overstated as it now allows expert groups to review the evidence and know if a treatment is effective, regardless of which lab the patient has attended. From there clinical

guidelines and policies can be implemented.

This standardisation has ultimately extended beyond the researchers, clinicians, laboratories and diagnostic companies, to include a standardisation between countries.

“The work on serum creatinine is hopefully the forerunner of many other tests that could become aligned.

“It’s one of the most dramatic examples of cooperation between pathologists and clinicians – and it’s a paradigm for future collaboration, and the way healthcare should be coordinated and then delivered,” says Dr Jones, who sees this degree of accuracy as integral to pathology.

“We should aim to deliver a message to the doctor with every result. We should be able to provide every doctor, every time, with information to assist with the diagnosis or management of the patient. This way pathology can essentially be an ‘effector organ’ for the guidelines.”

The eGFR test has proved successful not only for its accuracy, but because it has made the test easy to understand. Normal GFR is 100, so any eGFR result is effectively a percentage which doctors say is simple for patients to understand. And long-term studies have accurately established the values at which treatments need to be implemented.

As advantageous as the new eGFR test has proven, it remains only a screening test – and once it identifies kidney damage, doctors and pathologists must then try to identify what disease is causing the damage by a range of other blood and urine tests and interpretation of biopsy samples.

But with the emphasis on early detection, are there other ways of identifying these patients?

The presence of protein or albumin in urine may actually be an earlier marker than creatinine, but before it can be used as a screening test it too needs to be standardised.

Reaching those at risk

There also needs, according to Dr Tim Mathew, to be a shift towards conducting more urine tests on high-risk individuals.

“We’ve already identified the high-risk groups for CKD: it’s those over the age of 50 years, with diabetes, hypertension,

TREATMENT APPROACHES

Treating CKD involves firstly treating the underlying causes, and secondly, slowing the progression.

The optimal time for treating the underlying cause is usually well before CKD is established, and effective control of blood pressure and blood glucose levels is often enough to stop the progression of the disease. Once the disease is established these remain just as important, but additional treatments such as restricting protein intake can help slow progression.

Ultimately, most patients will require renal replacement therapy: either peritoneal or haemodialysis. Unfortunately, even optimal dialysis therapy is not a panacea, with some of the symptoms unlikely to respond fully, while others will continue to progress and some new problems may even arise.

Haemodialysis currently costs the community \$72,000 per person per annum, and has a significant impact on the lifestyle of those restricted to attending a dialysis centre every second day. Technological advances are allowing more patients to dialyse at home – and if taken to the optimum level this would, according to Kidney Health Australia, produce an annual saving of \$88.2 million, as well as improving the freedom and lifestyle of these patients. Simply increasing the rate of peritoneal dialysis to an optimal level would produce a saving of \$135.4 million.

Virtually all abnormalities associated with CKD are completely reversed by successful renal transplantation, and increasing the number of kidney transplants by 10% to 50% would save \$5.8 million to \$25.9 million a year.

“It’s one of the most dramatic examples of cooperation between pathologists and clinicians.” – Dr Graham Jones



PHOTO CREDIT: ELIZABETH ADAMS

obesity, malnutrition, family history and those who smoke, and Aboriginal and Torres St Islander people,” he says.

“And we know that early detection reduces the impact of the disease, but we have to take the message out to both doctors and patients that this is a silent condition, and unless you get a regular kidney check – that’s blood pressure, eGFR, and urine protein and blood sugar – you won’t know until it’s probably too late.”

Dr Mathew has been encouraged by large cost-effectiveness studies that applied best care to high-risk groups and found the process more cost effective than the current screening processes for breast, cervical or bowel cancer.

But he is dismayed by other studies that found of 1600 diabetics, 30% had not had a proteinuria test in the preceding year, despite their cycle of care requiring it annually.

“Chronic kidney disease is simply not being thought about enough at a GP level – and if it’s not considered it can’t be diagnosed,” he says.

“Once diagnosed, treatment is remarkably effective.” 🔥

GPs NOTE: This article is available for patients at <http://pathway.rcpa.edu.au>

CHRONIC KIDNEY DISEASE: risk factors, stages and complications

Risk factors are hypertension, obesity, diabetes, family history, smoking, and Aboriginal or Torres Strait Islander descent.

CKD has been divided into five stages based on GFR.

Stages 1–2

Patients usually remain symptom free, other than those symptoms associated with the original disease causing the damage.

Stage 3

Anaemia; loss of energy and appetite.

Abnormalities in sodium and water balance can lead to generalised oedema, congestive cardiac failure and shortness of breath.

Stage 4

Cardiovascular and gastrointestinal disturbances continue.

Possibility of uriferous odour to the breath (associated with metallic taste).

Gastritis, peptic disease and mucosal ulcerations can lead to abdominal pain, nausea, vomiting, blood loss.

Skin affected with anaemia, bruising and yellow discolouration from the deposition of pigmented metabolites, or even urea itself forming in a ‘frost’ on the skin.

Stage 5

Severe disturbance in activities of daily living, sense of well-being, nutritional status and electrolyte balance.

Survival without renal replacement therapy impossible.