Monitoring Kidney Function In Relation To Thalassaemia - A Nephrologist's View

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Summary
There is much monitoring of patients with thalassaemia in terms of the heart, endocrine organs (thyroid, testes, ovaries, pancreas) and the liver, but very little of the "forgotten organ", the kidneys. Although thalassaemia does not directly affect the kidneys, unlike sickle cell anaemia where kidney damage is common, one should be aware that although, renal disease has not been a large problem in thalassaemia, this will probably change in the future, for several reasons.

1) Chronic kidney disease is common.
2) Patients, including thalassaemia patients, are living longer.
3) Many patients go on to develop diabetes and hypertension (high blood pressure), 2 disorders which are closely related to kidney disease.
4) Many patients will develop diseases of the blood vessels – narrowing of the arteries as a result of lifestyle including obesity, smoking and the effects of high blood pressure.
5) Traditional measures of kidney function (the serum creatinine level in the blood) have been demonstrated to be a poor measure of actual function and a better measure called eGFR (estimated Glomerular Filtration Rate) which is calculated using a formula is of better value in identifying patients with kidney disease. Also proteinuria (the presence of protein in the urine) is known to be a strong risk factor for both cardiac and renal disease.
6) Finally and extremely important, with the explosion in medical therapies, many drugs may be nephrotoxic (damaging to the kidney) in some patients.

This short report will discuss the various factors listed above in more detail and how they might impact on the thalassaemia population in the future.

So what do the kidneys actually do?

Most people have 2 kidneys which function to keep the body composition on an even keel. Basically the kidneys act a large sieve retaining all the good materials in the blood while sieving out waste products including drugs. They also are vital in controlling fluid balance, and controlling the various salts in the body and in particular the acid in the body. The kidneys also secrete several hormones which are essential for blood pressure control, maintenance of bones (vitamin D) and very importantly in haemoglobin (blood) production.

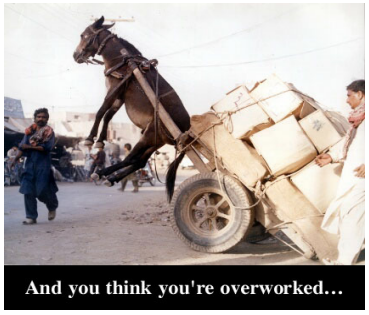
How do we measure kidney function/dysfunction?
It is crucial to examine how one actually measures kidney function accurately to allow one to make a diagnosis of kidney disease. In the past, people have used serum creatinine for its convenience as a measure, as this is easily measured from a blood sample. However this correlates poorly with the gold standard measurement of kidney function obtained using a radio-isotope method (a special dye test with x-rays to calculate function). This latter method is however inconvenient and, more recently, both in the UK and the USA, the MDRD

(modified diet in renal disease) equation has been used. This equation was developed more than 15 years ago to produce a measure called eGFR (see above), which is now automatically calculated from a blood sample. The equation requires input of the patient's age, sex, serum creatinine and race.

Why the change in measurement to estimate kidney function?

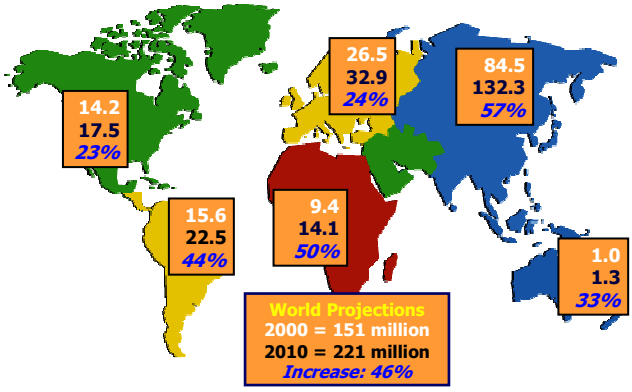
A better method has been an important change, because 50% of people, despite a normal measured serum creatinine on a routine blood test, have evidence of impaired kidney function. Indeed, we have previously shown that using the MDRD method of calculation (eGFR) it is more likely to pick up renal dysfunction in comparison to the serum creatinine. More importantly, after the age of 35 everyone will lose approximately 1% of kidney function per year. These changes are not reflected in the serum creatinine. Therefore, as the population ages, kidney function will naturally deteriorate. Hence, eternal life is virtually impossible without dialysis therapy, but in most cases, reassuringly the kidneys will outlive a person.

How common is renal impairment?


And you think you're overworked…

In the UK this has become overwhelming; indeed approximately 10% of the UK population (which equates to approximately 6 million people) have evidence of chronic kidney disease, which presents a potentially huge burden for society to manage. This is because people are getting older, diabetes and high blood pressure are becoming more common and overall body weight of individuals is increasing. Also the medical fraternity are increasingly becoming more aware of kidney dysfunction as a major medical problem which needs proactive measures to prevent future problems.

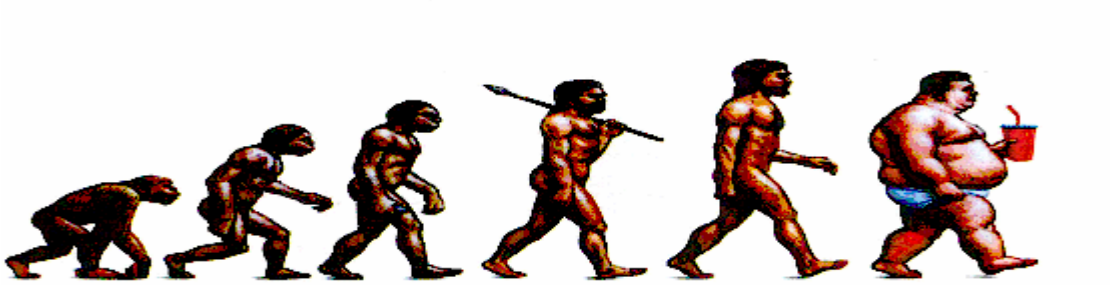
Factors implicated in the increase in kidney disease?



If one first looks at the epidemic of diabetes. At the last world estimates in 2000 there were 151 million cases of diabetes. This figure is projected to increase by 46% by 2010, to 221 million and will affect all countries world wide. Diabetes represents the commonest cause of renal failure and the need for dialysis in this country, and therefore presents a huge problem, both in the normal population and potentially in those with thalassaemia.

Again, high blood pressure (hypertension) is becoming more common. If this is untreated, a person will lose up to 12% of kidney function a year. Therefore, within a matter of 5 or 6 years a patient can progress to needing kidney dialysis therapy. However, by treating the blood pressure to an optimal level, one can reduce the rate at which kidney function deteriorates to 1 or 2% a year; just above what would be expected for age.

Another significant factor to consider is the change from our ancestral active hunter/gatherer lifestyle to the new sedentary fast food freak, and the effects this has had on obesity and hence kidney disease.



Finally, as previously alluded to, we as clinicians are becoming more aware of chronic kidney disease. Many people would be surprised to know about some of the people who have kidney disease. For example Jonah Lomu, the famous New Zealand rugby player, has had kidney failure, dialysis treatment and subsequently been transplanted. Despite this he still manages to have an excellent quality of life and continues to play rugby.

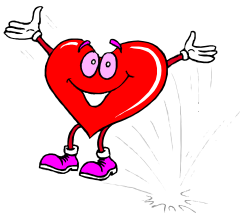
What about the use of medications and their effects on the kidney?

There has been an exponential increase in new available medications over the last decade. It is important to realise that medications are used more and more frequently; not just prescribed medications but herbal remedies. One should remember that **all drugs are potentially toxic**. Indeed, certain herbal remedies could cause kidney failure. Also many herbs from the ancient continents have been grown in soils contaminated with heavy metals such as arsenic and cadmium, which can be detrimental and therefore caution should be taken with these agents.

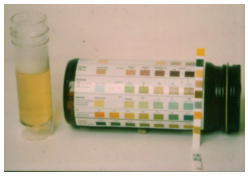
For prescribed medications there is the inherent toxicity of the molecule from which the drug is constructed. Unfortunately, in the Health Service prescribing, dispensing and administration errors remain a major concern and the direct toxicity of the drug on the kidneys warrants consideration as this is a potential hazard. Indeed, up to 20% of cases of acute kidney failure can be directly attributed to drugs and chemicals.

Why are drugs potentially hazardous to the kidney in particular?
Many drugs are excreted by the kidneys. The vast array of drugs can have numerous effects at various levels in the kidney, from affecting the blood flow to the kidney to directly damaging the cells of the kidney. Therefore it is extremely important that clinicians are aware of kidney function in all patients as many drug doses need to be adjusted to account for this to prevent/reduce the risks of such toxicity. Indeed one should perhaps **avoid potential nephrotoxic medications** in patients with known significant kidney dysfunction.

But why all the fuss about kidney dysfunction?

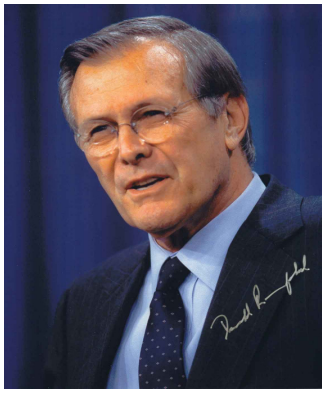


Finally, and most importantly, the presence of kidney dysfunction has been shown to increase the risk of strokes, heart failure and heart attacks. Indeed, somebody with less than 45% kidney function compared to somebody with greater than 75% kidney function has an almost 5 fold increased risk of having a heart attack or stroke or even death.



Also very important is the presence of protein in the urine. This can lead to a 4 fold increased risk of having a cardiovascular event (heart attack or stroke) or developing future kidney dysfunction. These 2 factors, the presence of kidney dysfunction and the presence of protein in the urine are synergistic, causing a multiple increased risk on life.

However, the main reason why this has become such a huge issue for nephrologists is that there are currently treatments available which can reduce the progression of kidney disease; and therefore the requirement for dialysis which on average costs around £28,000.00 a year per patient. By intervening we can hopefully reduce the risk of death (mortality) and the incidence of heart attacks and strokes. By delaying/slowing the progression of kidney dysfunction and reducing the leak of protein from the kidneys one can reduce the risks of death from cardiac causes.



So to try and sum up what I have said, I would like to use some "poetry" from Donald Rumsfeld (United States Secretary of Defence 2001-2006) who, back in February 2002 in a news briefing stated the following:-

The Unknown
As we know,
There are known knowns,
There are things we know we know.
We also know there are known unknowns,
That is to say,
We know there are some things we do not know.
But there are also unknown unknowns,
The ones we don't know we don't know.

So what do we know we know?
Hopefully one can see that:

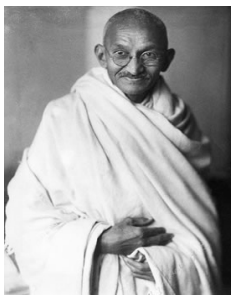
- Chronic kidney disease is common
- Serum creatinine is a poor measure of kidney function
- Drugs are a common cause of renal dysfunction and should be used with caution in any patient with evidence of kidney dysfunction.
- Chronic kidney disease progression can be delayed and the risk to the cardiovascular system reduced.
- Proteinuria is a very important marker of cardiac and kidney risk.

So what do we know we don't know?

- Although eGFR appears to be a better measure of kidney function, we really don't know the most reliable measure at present but hopefully in the future we can sort this out.
- We also don't know whether all treatments for iron overload, a common problem in thalassaemia, are the same and can be used safely.

For those unknown unknowns

- That remains an enigma.



Ghandi once said after being asked;

'What do you think about Western civilisation?'

He replied, 'I think it would be a very good idea'.

Certainly I think that monitoring renal function in patients with thalassaemia would be a very good idea in this day and age to ensure we adequately identify those patients at risk and treat them appropriately to prevent the need for renal replacement therapy.