

Editorial

Lithium and eGFR: a new routinely available tool for the prevention of chronic kidney disease

Richard Morriss and Benson Benjamin

**Summary**

The National Strategic Framework for Renal Services introduced the routine reporting of estimated glomerular filtration rates (eGFR) on serum urea and electrolyte tests. Estimated glomerular filtration rates might reduce renal failure induced by lithium and cardiovascular mortality but there are many false positives. We propose how eGFR might be used in lithium monitoring.

Declaration of interest

R.M. has received honoraria from various pharmaceutical companies for non-promotional lectures and consultancy work. He was also part of the National Institute for Health and Clinical Excellence (NICE) guideline group for bipolar disorder.

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The National Strategic Framework for Renal Services, part two, has recommended a change to the routine reporting of serum urea and electrolyte results with the introduction of reporting of estimated glomerular filtration rates (eGFR).¹ In many parts of the UK, eGFR is already reported routinely as part of urea and electrolyte results. Estimated glomerular filtration rate is calculated using the four-variable 'modification of diet in renal disease' equation:¹

$$\text{GFR} = 175 \times \frac{[\text{serum creatinine } (\mu\text{mol/l}) \times 0.011312]^{-1.154} \times [\text{age}]^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if female}]}{1.73 \text{ m}^2}$$

Sadly, the National Strategic Framework for Renal Services completely neglected consideration of lithium as a drug that could be toxic for the kidney, and did not develop any guidance in relation to lithium and eGFR. Psychiatrists who usually work in separately managed health organisations from renal physicians and chemical pathology laboratories have not been educated about the change in reporting of urea and electrolytes. Yet, a recent survey from France shows that 5% of patients taking lithium aged 40–69 years are in stage 4 of chronic kidney disease,² when patients become symptomatic from the disease and may require dialysis or transplantation, compared with 0.4% of the general population.³ Therefore, psychiatrists require education about eGFR now that changes have been made to the routine reporting of serum urea and electrolytes.

The benefits of reporting eGFR

The National Strategic Framework for Renal Services promotes the reporting of eGFR on routine serum urea and electrolytes because eGFR is a more sensitive indicator of grade 3 chronic kidney disease than elevated or rising urea and creatinine levels. Stage 3 chronic kidney disease is asymptomatic but it is associated with a 40% increase in cardiovascular mortality in the community when all other cardiovascular risk factors are controlled for.⁴

Improved detection of chronic kidney disease using eGFR will mean that more people will have the disease detected at an early stage. A Canadian study found that of 2781 out-patients referred by community physicians to an urban laboratory network for serum creatinine measurement, 182 (6.5%) had both abnormal serum creatinine levels and abnormal eGFR ($\leq 50 \text{ ml/min}^{-1}$), but a further 387 patients (14%) had normal serum creatinine and abnormal eGFR.⁵ Assuming that by 2014/2015, half of the 40% of late referrals could be avoided, this could lead to about 568 more renal patients per annum surviving at least 2 years longer.¹ Although only a small proportion of these will have end-stage disease induced by lithium, mortality from cardiovascular disease might be delayed or prevented in many more patients prescribed lithium.

Is lithium worth prescribing?

The first reaction to high rates of poor renal function in patients on long-term lithium medication might be to discontinue lithium therapy. However, alternative drugs with both antimanic and antidepressant properties may not be efficacious in a patient with bipolar disorder who has remained well on lithium; alternative drugs also have potential long-term undesirable effects. Furthermore, lithium has a demonstrated effect on reducing suicide, suicidality and cardiovascular mortality that may be superior to other antimanic and antidepressant drugs.^{6,7} The addition of lithium to antidepressants is one of the few evidence-based adjunctive strategies for the management of unipolar depression that has not responded to other first- and second-line treatments. A full discussion of benefits and adverse effects of lithium can be found in National Institute for Health and Clinical Excellence (NICE) guidelines for bipolar disorder and a recent paper in this Journal.^{8,9}

The unreliability of a single eGFR estimation

Unfortunately a single estimation of eGFR is not a reliable estimate of stage 3 chronic kidney disease and this may be especially true in patients taking lithium. The percentages of patients taking lithium with eGFR results below the usual stated normal level ($\leq 59 \text{ ml/min}^{-1}$) in age groups 20–39, 40–59, 60–69 and ≥ 70 years were 36%, 53%, 73% and 77% respectively.²

A single abnormal eGFR is clearly not sufficient to establish chronic kidney disease. The eGFR estimate may be inaccurate in people over 70 years of age, people less than 18 years old, pregnancy, amputees, malnourishment and dehydration states, and also in people of African–Caribbean origin. However, people from African–Caribbean backgrounds are at increased risk of renal failure because of their increased risk of hypertension.¹ Laboratories will modify their estimation on eGFR according to an agreed formula if they are supplied information on ethnicity. Even a recent fall, muscle injury or an injection may lead to a substantially increased eGFR, which is exquisitely sensitive to changes in creatinine level for any reason.

Recommendations for the correct use of eGFR

How can we detect progressive deterioration in renal function in patients taking lithium using eGFR? Any approach should be compatible with current guidelines for lithium testing so that large increases of unnecessary investigation are avoided. As part of routine safety and monitoring procedures that psychiatrists should follow, patients on lithium receive 3-monthly checks on lithium levels, 6-monthly checks on urea and electrolyte levels, and thyroid function tests, together with regular but unspecified checks on weight.⁸ More frequent tests are required if there is evidence of clinical deterioration, abnormal results, a change in sodium intake, other risk factors such as starting medication known to affect renal function (e.g. non-steroidal anti-inflammatory drugs, diuretics and angiotensin-converting enzyme inhibitors) or symptoms (such as thirst) indicating abnormal renal or thyroid function.⁸ In addition, a recent review encouraged yearly assessment of urine production (below 4 litres in 24 h) in patients taking lithium.⁹ Therefore recommendations for serial eGFRs over 6 months if the first eGFR is ≤ 59 ml/min are compatible with existing NICE guidelines on lithium monitoring. However, some clinicians are concerned that the use of even serial eGFR levels generates a ‘disease’ that may merely be age-related kidney function decline.¹⁰

We recommend an approach to eGFR advocated by the UK Consensus Conference on Early Chronic Kidney Disease,¹⁰ organised by the Royal College of Physicians of Edinburgh with the UK and Scottish Renal Associations. We have adapted their recommendations for patients taking lithium, although none of these bodies specifically considered patients prescribed lithium in drawing up their recommendations.

- (a) Whether or not the eGFR is less than 60 ml/min, a rise in creatinine on three or more occasions will require further investigation, including urinalysis for proteinuria, haematuria, glucose, review of medical history (including urological history and medication) and blood pressure. If a urine dipstick test suggests there is protein in urine, then the laboratory should be requested to perform a protein:creatinine ratio test on a sample of urine.
- (b) In all patients with eGFR of 30–59 ml/min, repeat eGFR and other urea and electrolyte measurements every 3 months unless there is a clinical indicator for even more frequent estimation. Every patient should have urinalysis for proteinuria, haematuria, glucose, review of medical history (including urological history and medication) and blood pressure measurement. All risk factors for cardiovascular disease should be actively treated and monitored according to national guidelines developed for primary care.
- (c) Referral for specialist renal opinion should occur in any patient where:
 - (i) the eGFR is decreasing by more than 4 ml/min per year as shown by a progressive fall on three or more serial tests without evidence of acute renal failure or dehydration;
 - (ii) there is a progressive rise in serum creatinine level on three or more serial tests;
 - (iii) there is proteinuria (plasma:creatinine ratio ≥ 1);
 - (iv) there is haematuria;
 - (v) there are symptoms of chronic renal failure; symptoms such as tiredness due to anaemia from renal disease are unlikely unless renal function falls below 45 ml/min;
 - (vi) eGFR is below 30 ml/min.
- (d) In patients with a glomerular filtration rate of 30–59 ml/min who do not require specialist renal referral, 3-monthly urea and electrolyte monitoring should be accompanied by measures to decrease other risk factors for renal impairment and cardiovascular disease such as obesity, hypertension, diabetes mellitus, smoking, high alcohol consumption, adverse lipid profiles, urological problems and the prescription of drugs with adverse renal effects such as non-steroidal anti-inflammatory drugs, diuretics and angiotensin inhibitors.
- (e) Among patients with slowly progressive renal disease diagnosed by a renal physician, the adverse effects of lithium on the kidney might be reduced by lowering the therapeutic dose, having drug holidays through periods of prolonged remission, or using alternative antimanic or antidepressant treatments.

Future directions

More research is required on the clinical significance and optimal use of eGFR in patients taking lithium, and the stage at which more active intervention is required to prevent end-stage chronic kidney disease due to lithium. Such research may be particularly required in the elderly, where the false-positive rate for eGFR may be especially high. From a clinical perspective, mental health services are employing nurses to help with the physical health monitoring of patients with serious mental illness, particularly those who may not attend primary care services. A fresh challenge to our clinical services and health purchasers is the integration of monitoring and proactive physical healthcare with the rest of clinical care for patients with serious mental illness across primary and secondary care services.

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References

- 1 Department of Health. *National Strategic Framework for Renal Services, Part Two. Chronic Kidney Disease, Acute Renal Failure and End of Life Care*. Department of Health, 2007.
- 2 Bassilios N, Martel P, Godard V, Froissart M, Grunfeld JP, Stengel B, on behalf of the Reseau Nephropar. Monitoring of glomerular filtration rate in lithium-treated outpatients: an ambulatory laboratory database surveillance. *Nephrol Dial Transplant* 2008; **23**: 562–5.

- 3 Coresh J, Slevin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038–47.
- 4 Di Angelantonio E, Danesh J, Eriksdottir G, Gudnason V. Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review. *PLoS Med* 2007; **4**: e270.
- 5 Duncan L, Heathcote J, Djurdjev O, Levin A. Screening for renal disease using serum creatinine: who are we missing? *Nephrol Dial Transplant* 2001; **16**: 1042–6.
- 6 Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behaviour and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry* 2005; **162**: 1805–19.
- 7 Angst J, Angst F, Gerber-Werder R, Gamma A. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. *Arch Suicide Res* 2005; **9**: 279–300.
- 8 National Collaborating Centre for Mental Health. *Bipolar Disorder: The Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care*. British Psychological Society & Gaskell, 2006.
- 9 Young AH, Hammond JM. Lithium in mood disorders: increasing evidence base, declining use? *Br J Psychiatry* 2007; **191**: 474–6.
- 10 Royal College of Physicians of Edinburgh. *UK Consensus Conference on Early Chronic Kidney Disease*. Royal College of Physicians of Edinburgh, 2007 (http://www.rcpe.ac.uk/Whats_New/consensus-statements/final-early-chronic-kidney-disease.pdf).

psychiatry
in pictures



Diego Velazquez (1599–1660). Portrait of Juan Calabazas (Calabacillas) (1637–9)

Picture selection and text by Dr Miriam Barrett

This portrait by Velazquez is of Juan Calabazas, also called 'The Fool from Coria' and nicknamed Calabacillas or 'pumpkin-head'. He was court jester first to Prince Don Fernando and then to the naturally melancholic King Philip IV. Some claim he had autism but it is probable that he had infantile hypothyroidism, resulting in growth retardation and intellectual disability. Velazquez as court painter and royal servant shared the life of these so-called 'dwarfs', 'fools' and 'jesters' (or *truhanes* in Spanish) and was able to show them with empathy and respect in his paintings. Velazquez's choice of subject for this portrait provides a historical perspective of how people with intellectual disability, and/or short stature, were regarded 400 years ago. They were present in large numbers at the Spanish court of Philip IV, as at other European courts. They were maintained in accordance with a charitable tradition extending back to the Middle Ages. Although this often resulted in the creation of a kind of human menagerie for the amusement of the court, some individuals came to be appreciated for their wit, arousing affection and at times achieving considerable fame and privileges. Under cover of jest they would often tell their lords and masters home truths, suppressed within the strictures of the court, and were free to parody the rigid etiquette by which the courtiers and courtesans were bound.

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