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Abnormal Renal Function and Electrolyte Disturbances in Older People

Michael Hsieh, David A Power

ABSTRACT

The decline in renal and cardiac function with advancing age predisposes older people to abnormalities in renal function and electrolyte disturbances. The widespread availability of the estimated glomerular filtration rate has highlighted the high incidence of chronic kidney disease in the elderly, which is supported by data demonstrating that the elderly are the largest cohort undergoing kidney dialysis in the general population. Older people are also susceptible to electrolyte disturbances, especially if they have concomitant diseases, such as heart failure, and are receiving diuretics and blockers of the renin-angiotensin system. Management of these patients requires skill, as well as realistic objectives. In this article we discuss some of the issues pertaining to renal and electrolyte abnormalities experienced by older people.

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INTRODUCTION

The widespread reporting of estimated glomerular filtration rates (GFRs) in recent years has led to an awareness of renal function abnormalities in the elderly. Two factors support the aggressive treatment of abnormal renal function in older people. Firstly, the increasing number of elderly being accepted into kidney dialysis programs. Secondly, emerging data have revealed that patients with modest reductions in estimated GFRs have an increased incidence of cardiovascular disease.^{1,2} The retrospective analysis of the VALIANT trial of high-risk patients post myocardial infarction demonstrated a stepwise increase in mortality with reduction in estimated GFR to less than 75 mL/min/1.73 m².³

The treatments used to prevent renal function decline in young patients are mainly potent antihypertensives along with aggressive blood pressure targets. Adopting similar aggressive strategies in the elderly is associated with problems, mainly because of the changes in renal function that occur with advancing age, such as decrease in total body water; decrease in renal blood flow; decrease in GFR; decrease in urinary concentrating ability; increase in antidiuretic hormone secretion; increase in atrial natriuretic peptide; decrease in aldosterone secretion; decrease in the thirst mechanism; and decrease in free water clearance.⁴

DECLINE IN RENAL FUNCTION

Decline in renal function is a phenomenon of the ageing process. There are few published studies exploring GFRs in the elderly and most of these studies are small.^{4,5} An annual GFR decline of 0.8 to 1.4 mL/min/1.73 m² was reported in one study of subjects who did not have diabetes and were over 65 years of age.⁶ A GFR decline of 1 mL/min/year is consistent across numerous studies of GFR and creatinine clearance.⁷

Estimated Glomerular Filtration Rate

The loss of muscle mass with advancing age results in many older people experiencing a rise in serum creatinine despite the loss of renal function. Therefore, most assessments of renal function in the elderly are calculated by estimating equations, using serum creatinine and other parameters. Serum creatinine concentrations will not reflect renal function in the elderly in the same manner as in younger populations—especially in young people with impaired kidney function for whom the equations to calculate creatinine clearance were first derived. The estimated GFRs derived from the Modification of Diet in Renal Disease formula (reported by Australian laboratories) are relatively accurate in the elderly and more so than the Cockcroft-Gault formula.^{8,9} It has been suggested that the Modification of Diet in Renal Disease formula should be used to calculate changes in drug dosing but this is not widely accepted, and especially not for drugs where dosing is critical.⁸

The widespread availability of the estimated GFR has created practical problems of interpretation in the elderly. For example, when is a loss of estimated GFR compatible with age-related decline and when does it represent disease. There is no consensus approach but patients are screened for reversible renal disease when the estimated GFR reaches 60 mL/min/1.73 m² and attention is given to the rate of decline in estimated GFR over time. An estimated GFR decline of 2 mL/min/year and more is beyond what would be expected through non-renal age-related decline. Often, it is hard to be certain because of fluctuations in estimated GFRs, especially in patients receiving antihypertensives or diuretics and in patients with heart failure.

STRUCTURAL CORRELATES

Structural and functional changes in the kidneys have been associated with the ageing process. With advancing age the kidneys atrophy and the cortical thickness decreases by approximately 10% per decade after the age of 30 years.¹⁰ This is associated with histological changes of kidney scarring.¹¹

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CHRONIC KIDNEY DISEASE

The stages of chronic kidney disease are listed in Table 1. Generally, patients with an estimated GFR below 30 mL/min require specialist care, and require it prior to reaching this degree of renal impairment. Renal dialysis is required when the estimated GFR reaches 5 to 15 mL/min. Symptoms of renal failure, such as anorexia, nausea and vomiting, and tiredness, usually occur late in the disease process.

Table 1. Stages of chronic kidney disease

Stages	Estimated glomerular filtration rate
Stage 1	> 90 mL/min/1.73 m ² with abnormal urine, structural kidney abnormality or genetic disease likely to affect the kidney
Stage 2	60 to 89 mL/min/1.73 m ²
Stage 3	30 to 59 mL/min/1.73 m ²
Stage 4	15 to 29 mL/min/1.73 m ²
Stage 5	15 mL/min/1.73 m ²

Blood Pressure

The increasing number of elderly being accepted into kidney dialysis programs, along with widespread reporting of estimated GFRs, has increased the number of older people receiving aggressive antihypertensive therapy to reduce progression to end-stage renal disease. Antihypertensive targets are aggressive in patients with reduced estimated GFRs, especially if they are diabetic, and a target blood pressure of 130/80 mmHg or less is widely reported. Most guidelines do not distinguish blood pressure targets based on age but there are risks associated with low blood pressure targets in elderly patients with vascular disease and comorbidities. Hypotension is common in the elderly when they are treated to low blood pressure targets.¹² When the blood pressure is lowered aggressively, a precipitous decline in renal function with an attendant increase in serum potassium can occur.

Renin-Angiotensin System

The angiotensin II receptor blockers and angiotensin converting enzyme inhibitors were used together because of their ability to reduce proteinuria. In the ONTARGET study their use was associated with a significant increase in adverse renal outcomes.^{13,14} Therefore, it has been

recommended that patients should not receive this combination (it is less clear whether patients already receiving this combination should continue).

The range of drugs available for younger patients can mostly be used in the elderly. In elderly patients with chronic kidney disease, calcium channel blockers, thiazide diuretics and beta-blockers (lesser extent) were well tolerated and reduced complications.¹⁵ The angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are widely used first-line in young patients with chronic kidney disease. They can also be used first-line in the elderly with chronic kidney disease and should be started at low doses and gradually increased (there is little evidence to support their superiority over other therapies). It is useful to check the serum potassium and creatinine within a week of starting, as they can sometimes cause a precipitous decline in renal function or a rise in serum potassium.

END-STAGE RENAL FAILURE

Increasing numbers of older people are reaching end-stage renal failure and are being accepted into dialysis programs (Figure 1). There are regional variations in the acceptance of the elderly into dialysis programs.^{1,16} Many of these patients are very frail and find the imposition of fluid restriction and a demanding treatment regimen extremely challenging. Renal dialysis offers these patients several years of additional life. Although transplantation is less common in the elderly, their treatment is similar to younger people.

Calcium Carbonate

In elderly patients not needing dialysis, the drug most widely used to reduce serum phosphate is calcium carbonate (usually 1250 mg or 1500 mg with each meal). The target phosphate level is around 1.6 mmol/L or less, a serum calcium level in the lower normal range and parathyroid hormone level less than 35 pmol/L.

Vitamin D

Calcitriol is needed if the parathyroid hormone level is high or the serum calcium level is low despite calcium carbonate supplementation. As patients with renal failure are sensitive to calcitriol it is administered as 0.25 mg on alternate days or 0.75 to 1 mg once weekly. 25-Hydroxy vitamin D3 (Ostelin) is safe in patients with renal failure as they do not metabolise it to the active form.

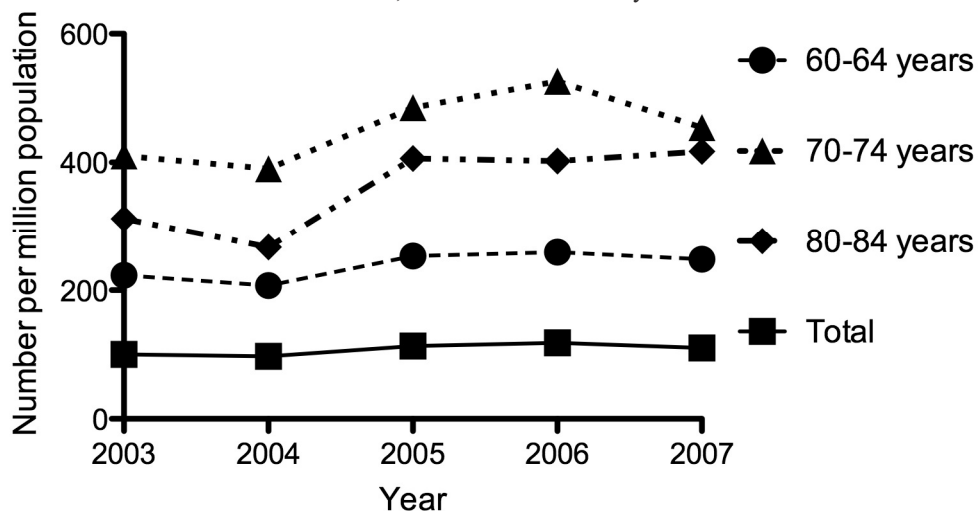


Figure 1. Incidence of new elderly patients entering dialysis in Australia for end-stage kidney failure 2003 to 2007 (data redrawn from ANZDATA Annual Report 2008. Not all of the age ranges have been included for the sake of clarity).

Phosphate Binder

A number of new drugs have become available on the Pharmaceutical Benefits Scheme for management of calcium, phosphate and parathyroid hormone metabolism. The phosphate binders, sevelamer (Renagel) and lanthanum carbonate (Fosrenol) are taken with meals to reduce serum phosphate levels.^{17,18}

Cinacalcet

Cinacalcet (Sensipar) mimics calcium binding at the calcium receptor on parathyroid glands and reduces parathyroid hormone levels.¹³ Cinacalcet can severely reduce serum calcium levels giving rise to symptomatic hypocalcaemia. Monitoring calcium and parathyroid hormone levels in patients taking cinacalcet is vital.

Erythropoiesis Stimulating Agents

The erythropoiesis stimulating agents available in Australia, darbepoetin alfa (Aranesp), epoetin alfa (Eprex) and epoetin beta (NeoRecormon) are not interchangeable because of differences in pharmacokinetic parameters. They are available on the Pharmaceutical Benefits Schemes for patients with haemoglobin levels below 100 g/L and intrinsic renal disease. The target haemoglobin level is 100 to 120 g/L, as there is evidence that higher haemoglobin levels are detrimental.¹⁹ Iron stores need to be replaced at regular intervals by iron infusion. Rarely, patients can develop pure red cell aplasia.

ELECTROLYTE ABNORMALITIES

The changes in renal function, especially in handling of salt and water excretion, are important in the genesis of electrolyte abnormalities in the elderly. Although the elderly can develop any electrolyte abnormality, hyponatraemia, hypernatraemia, hyperkalaemia and hypokalaemia are common.

Hyponatraemia

The serum sodium falls by around 1 mmol/L each decade.⁴ Hyponatraemia has many causes and some of the more common ones are listed in Table 2. Hyponatraemia is prevalent in hospitalised elderly patients and is associated with increased mortality.²⁰ In the study by Sunderam et al., an iatrogenic origin was thought to explain the low sodium levels in 73% of inpatients and was attributed mainly to intravenous fluids and diuretic use.²⁰ Hyponatraemia is also common in the community, especially in patients with heart failure. In a recent study from Denmark, 2.1% of people aged 55 to 75 years with no apparent heart disease had a serum sodium of 134 mEq/L or less.²¹ They had a poorer prognosis than individuals with normal sodium levels, especially when it was not associated with diuretic use. When hyponatraemia becomes severe (serum sodium below 125 mmol/L), patients are more likely to develop symptoms, such as confusion and somnolence.

The patient's volume status should be first assessed and then the diagnosis made (Table 2). Diagnosing the cause of the hyponatraemia is the cornerstone of therapy. Most oedematous patients have heart failure and there is often confusion as to the role of diuretics in the treatment of heart failure and their contribution to hyponatraemia. Most patients with heart failure have an excess of salt and water and diuretics are indicated. When serum sodium falls to dangerous levels (below 125 mmol/L), it is useful to restrict water intake to less than one litre

Table 2. Causes of hyponatraemia

Diagnosis	Causes
Hypovolaemia	Gastrointestinal losses Diuretics Adrenal insufficiency
Oedema	Heart failure Cirrhosis with portal hypertension Nephrotic syndrome
Normal salt and water	Hypothyroidism Drugs Syndrome of inappropriate antidiuretic hormone (cytotoxics, antidepressants, antipsychotics)

per day. Diuretics should be ceased and reinstated when the serum sodium begins to climb, while maintaining water restriction.

Rarely is it necessary to administer hypertonic saline. Normal saline is never administered to hyponatraemic patients with oedema as it will make matters worse. If hyponatraemia needs correction with intravenous hypertonic saline, the rate of correction should not be excessive, as there is a risk of demyelination in the central nervous system (central pontine myelinolysis).

Hypovolaemia

Excessive use of diuretics is a common problem in hypovolaemic patients. Hypovolaemia is diagnosed by the absence of oedema, and the presence of tachycardia and hypotension. Treatment is withdrawal of the causative drug and increased fluids, if required.

Management of hypovolaemia is more difficult in the elderly because of changes in physiological responses. When healthy elderly men were compared to younger controls, the elderly more commonly exhibited hyporeninaemic hypoaldosteronism, relative serum arginine-vasopressin unresponsiveness and high levels of plasma atrial natriuretic peptide.⁵ Older people require nearly twice as long to attain the same degree of sodium conservation when sodium is restricted, and they excrete less sodium with salt loading compared to younger subjects.²² The ability to concentrate or dilute urine in the face of dehydration or water loading is also impaired in the elderly.²³ Furthermore, as well as a decline in GFR, there is an increased incidence of renal disease, which may contribute to impaired ability to conserve water. As the total body water decreases with age, equal volume of fluid loss in young and old patients may represent more severe dehydration in the elderly. This is further exaggerated by age-related changes in the cardiovascular system with reduced diastolic relaxation of the myocardium and blunting of the heart rate response to exercise or volume depletion, resulting in an increased risk of hypotension.²⁴ The thirst mechanism is also reduced in the elderly.²⁵

Euvolaemia

The possibility of the syndrome of inappropriate antidiuretic hormone secretion should be considered in euvolaemic patients. In euvolaemia, antidiuretic hormone is secreted by the hypothalamus in the presence of low serum osmolality (normally this would be a strong signal to reduce secretion). A variety of conditions, such as head injuries, stroke, pneumonia and various cancers, may be responsible. The most useful screening test is direct measurement of urine and plasma osmolality.

Hypernatraemia

The serum sodium concentration represents a balance between water and sodium in extracellular fluid. Hypernatraemia can develop with either normal or low total body sodium and rarely with increased total body sodium (usually iatrogenic). Symptoms of hypernatraemia include changes in conscious state, seizures and death.

Hypernatraemic patients with low total body sodium display symptoms of hypovolaemia with hypotension, tachycardia and dry mucous membranes. The usual cause of hypernatraemia is loss of fluids containing less sodium than is present in serum. The elderly are susceptible to hypernatraemia for a number of reasons, including their reduced thirst mechanism and the aggressive use of diuretics. Therapy is directed to correction over 48 hours, with normal saline to correct volume depletion followed by hypotonic fluids.

Hypernatraemic patients with normal total body sodium have lost water without sodium and do not have hypovolaemia. Common causes include diabetes insipidus, head injury or subarachnoid haemorrhage.

Potassium

Although potassium is the most abundant cation within cells, the level of potassium in the serum is an important determinant of its biological effects. Hyperkalaemia or hypokalaemia can arise from true excess or deficiency, or an imbalance in the distribution between the potassium inside and outside of cells.

Hyperkalaemia

Hyperkalaemia is common in diabetic patients, partly due to the presence of a type of renal tubular acidosis (hyporeninaemic hypoaldosteronism) and the use of drugs that increase serum potassium, such as the angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, potassium-sparing diuretics and spironolactone. Clinical manifestations include muscle weakness and fatal cardiac arrhythmias. Fatalities are more likely to occur when the serum potassium level is 7 mmol/L and above.

Drugs that increase serum potassium levels are often used together and are frequently associated with hyperkalaemia. This was noted as a significant concern in the ONTARGET study where telmisartan and ramipril were used in combination.²⁶ Using these drugs alone can also cause hyperkalaemia, especially in elderly diabetic patients. These drugs have beneficial effects in slowing or preventing cardiovascular and renal disease, but some patients are unable to tolerate them because of a rise in serum potassium.

A number of strategies have emerged to deal with this issue. The simplest is to monitor the serum potassium and ignore it until it reaches a near-dangerous level with some physicians accepting levels in the 5.5 to 6.5 mmol/L range. This strategy entails risk and patients need to be aware of not modifying their diet by significantly increasing potassium intake (e.g. fruits, coffee, chocolate) or commencing drugs that influence serum potassium. Other strategies involve restriction of dietary potassium and use of diuretics such as frusemide that tend to reduce serum potassium. The potassium binder Resonium is limited to short-term use because it is unpalatable and expensive. Mineralocorticosteroids (e.g. fludrocortisone) can be used, as they promote potassium excretion in the renal distal tubule and collecting ducts but at the expense of increased sodium and water retention.

Hypokalaemia

The major causes of hypokalaemia are gastrointestinal and renal losses of potassium. The clinical effects are mainly muscle weakness, cardiac arrhythmias and impaired kidney function. Hypokalaemia can be corrected with oral potassium-sparing diuretics. Oral potassium chloride is less effective and the number of tablets required is large. For example, each 600 mg tablet contains 8 mmol of potassium and replacement requires 40 to 60 mmol of potassium per day. It is difficult to administer sufficient potassium through diet alone, e.g. 2.5 cm of banana contains 1 mmol of potassium. Potassium is largely an intracellular cation and a 1 mmol/L reduction in serum potassium indicates a total body deficit of approximately 350 mmol.

Diet can be effective in preventing hypokalaemia if a deficit has not been allowed to occur. A more common approach is to check the serum potassium regularly and treat when a deficit occurs.

CONCLUSION

Changes in renal and cardiac function in the elderly make them prone to chronic kidney disease and electrolyte abnormalities. Management is often complex, especially in view of the numerous drugs and comorbidities often present in this patient group. A realistic approach to treatment and careful monitoring are required to optimise outcomes and avoid complications of therapy.

Competing interests: None declared

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