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PROTEINURIA OR ALBUMINURIA – DOES IT MATTER?

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Proteinuria is a classic sign of kidney disease and its presence carries powerful prognostic information, identifying a sub-group of patients that are at increased risk of renal disease progression and cardiovascular morbidity. Endorsement of proteinuria testing in at-risk groups has been recommended by the English Renal National Service Framework and by other national and international guidelines. Although proteinuria testing is enshrined in clinical practice there is variation amongst published guidelines as to the definition of significant proteinuria and whether it should be defined in terms of albumin or total protein loss, with a different approach being used to stratify diabetic and non-diabetic nephropathy. Further, the role of reagent strip devices in the detection and assessment of proteinuria is unclear.

Both laboratory and reagent strip tests purporting to measure total protein appear particularly sensitive to albumin. Albumin is the predominant protein in the vast majority of proteinuric kidney diseases, including diabetes, hypertension and glomerular diseases. Albumin measurement offers greater sensitivity and improved precision for the detection of lower, but clinically significant, levels of proteinuria compared to total protein, and its measurement can be standardised. Overall, the use of urinary albumin measurement as the front-line test for proteinuria detection appears to offer the best chance of improving the sensitivity, quality and consistency of approach to the early detection and management of kidney disease.

The recent National Institute for Health and Clinical Excellence (NICE) guideline on chronic kidney disease favours urinary albumin rather than total protein measurement and recommends against the use of standard total protein reagent strip devices.[1] In a non-diabetic individual, NICE defines significant proteinuria as an albumin to creatinine ratio of >30 mg/mmol (equivalent to a total protein loss of approximately 0.5 g/24 h), with a ratio of >70 mg/mmol (equivalent to total protein loss of approximately 1.0 g/24 h) representing heavy proteinuria.

Reference

1 National Institute for Health and Clinical Excellence. *Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care*. London: NICE; 2008. Available from: http://www.nice.org.uk/Guidance/CG73

Declaration of interests The author was a member of the NICE CKD Guideline Development Group.

CARDIAC TROPONINS IN PATIENTS WITH CHRONIC KIDNEY DISEASE – INTERPRETATION AND SIGNIFICANCE

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The elevation of cardiac troponins in patients with renal failure has variously been described as being an analytical false-positive, an example as to why cardiac troponin I (cTnI) was a superior test, and being due to re-expression of cardiac troponin T (cTnT) within the skeletal muscle. However, patients with renal disease have a reduced lifespan compared to those without renal failure. Mortality rates are highest in those receiving haemodialysis as renal replacement therapy, closely followed by those with end-stage renal disease (ESRD). Cardiovascular mortality accounts for the majority of renal deaths.

Elevation of cTnT and cTnI is a common finding in patients with ESRD and is prognostic, although cTnT appears to be a better prognostic marker than cTnI. The advent of more sensitive cTnI assays has increased the number of patients with ESRD and a detectable cTnI.

The mechanism of elevation in patients with renal failure remains a matter of debate. Imaging studies have shown that troponin release is associated with a pattern of diffuse myocardial injury. The nature of troponin present in circulation remains controversial. Some authors have reported detection of low molecular weight fragments of the troponin molecule, implying degradation of the intact molecule. Others have not confirmed these findings. The possibility is that detectable troponin in the circulation is a combination of reduced clearance combined with myocardial injury. Unfortunately, there is poor correlation between troponin elevation and glomerular function. The advent of new and more sensitive troponin methods has allowed definition of a true reference interval, so the net contribution of clearance may be more clearly defined. It is more likely that the elevation of troponin seen represents myocardial injury secondary to renal failure rather than purely a clearance phenomenon.

The presence of troponin in patients with renal disease should not cause diagnostic confusion. An elevated troponin in the presence of an elevated creatinine should raise the possibility that the troponin elevation is secondary to renal dysfunction rather than an acute coronary syndrome. Further, the diagnosis of myocardial infarction requires demonstration of a changing troponin value in the presence of an appropriate clinical situation. A repeat measurement of troponin two to four hours following the initial value will soon confirm whether troponin is due to an acute myocardial injury. A rising value suggests an acute injury; a value which is not significantly changed excludes this.

Perhaps the real challenge now offered to renal physicians is to generate treatment strategies that will minimise or abolish cardiac troponin elevations in patients with ESRD.

Further reading

- Collinson PO, Gaze DC. Cardiac troponins in patients with renal failure: what are we measuring and when should we measure it? *Ann Clin Biochem* 2009; 46:269–70.
- Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007; 50:2173–95.

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HYPONATRAEMIA – AN ONGOING CLINICAL CONUNDRUM

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Hyponatraemia is probably the most common biochemical abnormality seen in a hospital setting and remains an enigma to most physicians, for whom the knee-jerk request for plasma and urine osmolality betrays a limited understanding of the mechanisms involved. All patients with hyponatraemia have an element of water retention (dilutional hyponatraemia), although some are also volume/sodium deplete. At the other end of the clinical spectrum the easiest conditions to recognise are those associated with volume expansion (congestive cardiac failure, cirrhosis with ascites or the nephrotic syndrome), but separating the apparently clinically euvolaemic group into those who would benefit from fluid restriction (most) and those who need saline infusion (some) remains difficult. For most practical purposes the term dilutional hyponatraemia should be regarded as being synonymous with syndrome of inappropriate antidiuretic hormone (SIADH).

In most patients the finding of hyponatraemia is synonymous with the presence of hypo-osmolar plasma, and the condition of pseudo-hyponatraemia is less of an issue with most modern electrolyte assays. The relevant clinical question relates to the assessment of volume status in hyponatraemic patients and in the absence of overt volume expansion, such as in heart failure or obvious fluid loss, clinical judgement may be correct in only 50% of cases. Measurement of urine osmolality does not separate dilutional from depletional hyponatraemia, but the measurement of urinary sodium is often discriminatory with values above 30 mmol/l suggesting dilution while below 30 mmol/l indicating depletion. It is important to understand the effect of the anti-diuretic hormone (vasopressin) on both water and sodium excretion in explaining why patients with a dilutional hyponatraemia have 'normal' amounts of sodium in their urine.

It is worth reflecting that we probably do more harm by attempting to correct hyponatraemia than would be done if it were left alone, and that urgent therapeutic intervention is rarely necessary. Hypertonic saline will raise plasma sodium acutely, but in the presence of dilutional hyponatraemia the benefits will not be sustained. All patients with clinical evidence of volume depletion should be given normal saline. The most difficult and controversial area arises in the context of acute central nervous system disease (classically a sub-arachnoid haemorrhage), where there remains debate as to what constitutes cerebral salt wasting and what is SIADH.

The standard management of dilutional hyponatraemia involves fluid restriction, which is notoriously difficult to maintain either as an inpatient or indeed in the free-living setting. If the primary cause cannot be alleviated, demeclocycline has long been used to induce a state of partial nephrogenic diabetes insipidus in patients with SIADH where long-term therapy is indicated. The advent of specific V2 vasopressin receptor antagonists offers a more precise way of treating SIADH (dilutional hyponatraemia), but these agents are extremely expensive and will probably have a limited part to play in clinical management.

Further reading

- Chung HM, Kluge R, Schrier RW et al. Clinical assessment of extracellular fluid volume in hyponatraemia. *Amer J Med* 1987; 83:905–8.
- Leaf A, Bartter FC, Santos RF et al. Evidence in man that urinary electrolyte loss induced by Pitressin is a function of water retention. *J Clin Invest* 1953; 32: 868–78.
- Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; 356:2064–72.
- Decaux G, Soupart A, Vassart G et al. Non-peptide arginine vasopressin antagonists – the vaptans. *Lancet* 2008; 371:1624–32.
- Sterns RH, Silver SM Cerebral salt wasting versus SIADH: what difference? *J Am Soc Nephrol* 2008; 19:194–6.

Declaration of interests None declared.

THE PREGNANT PATIENT WITH RENAL DISEASE

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The kidneys undergo marked haemodynamic, renal tubular and endocrine changes during pregnancy. A failure of these adaptations in women with renal disease creates a sub-optimal environment for fetal development and increases the risk of obstetric complications such as pre-eclampsia, pre-term labour and fetal growth restriction (FGR). In turn, the diseased maternal kidneys are exposed to the damaging consequences of a prothrombotic state, ascending urinary infections, gestational hypertension and altered haemodynamics that exacerbate proteinuria. Women with a pre-conception glomerular filtration rate (GFR) of less than 25 mlmin-1, (serum creatinine >177 mmolL-1; 2.0 mg/dL) have a 1:3 chance of a pregnancy-related decline to end-stage renal failure and are likely to have pre-term, growth-restricted babies. Pre-existing hypertension, proteinuria, recurrent urinary tract infections and, in women with diabetic nephropathy, poor glycaemic control are all independently but cumulatively detrimental to maternal and fetal outcome. Women with end-stage renal failure are far more likely to have a successful pregnancy following a kidney transplant compared with those on dialysis. Pregnancy itself can cause acute renal disease, or uncover a previously sub-clinical renal condition.

Further reading

- Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ* 2008; 336:211–5.
- Williams DJ. Pregnancy with pre-existing renal disease. In: Feehally J, Floege J, Johnson R. *Comprehensive clinical nephrology*. 3rd ed. Philadelphia: Mosby; 2007. p. 495–504.
- Williams DJ. Renal disorders in pregnancy. In: James DK, Steer PJ, Weiner CP et al, editors. *High-risk pregnancy*. 3rd ed. Philadelphia: Elsevier Saunders; 2006. p. 1098–124.

Declaration of interests None declared.

THE PATIENT WITH RENAL TRACT STONES

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Renal tract stones form a common part of everyday urological practice. Recurrence rates are high, with up to 50% of patients experiencing recurrence within 10 years.

Biochemical abnormalities can be identified in more than 90% of patients, using a combination of serum and urine testing, as well as analysis of the stone itself. In order to help minimise recurrence, all patients should receive general advice regarding fluid intake and diet after the first stone episode. Recurrent stone formers may require more tailored dietary advice, and a small number of patients can benefit from pharmacological therapy. However, side effects are common, and compliance is disappointing.

The mainstay of imaging for calculi is now non-contrast computed tomography scanning, but more traditional methods such as ultrasound and plain films still have a role. Plain kidney, ureter and bladder X-rays remain important for treatment planning and follow-up. Computed tomography can also provide additional information in relation to treatment selection and outcomes.

Size is the most important factor in choosing the most appropriate treatment modality, all of which in the modern era are almost exclusively minimally invasive. Additionally, the site of the stone and various patient factors will determine which intervention is used in each case.

Modern management of stone disease uses a full range of technologies for both diagnosis and treatment, with generally high success rates. The prevention of recurrence remains an important goal, but is not universally achieved.

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ENCAPSULATING PERITONEAL SCLEROSIS

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Encapsulating peritoneal sclerosis (EPS) is a devastating and frequently fatal complication of peritoneal dialysis (PD), characterised by bowel obstruction and encapsulation due to severe sclerotic thickening of the peritoneal membrane. The aetiology is not known, but it is thought that EPS results from chronic intra-abdominal inflammation which is multi-factorial in origin. There has been concern that EPS is becoming less uncommon, but its incidence is not established.

All patients in Scotland who started PD from 1 January 2000 to 31 December 2007 were studied (n=1238). Patient records were examined to ensure that all cases met the diagnostic criteria of the International Society of Peritoneal Dialysis.

The incidence rate during the eight-year study period was 1.5%. The incidence increased with PD duration with rates of 0, 0.6, 2.0, 3.5, 8.1 and 8.8 at <1, 1–2, >2–3, >3–4, >4–5 and >5–6 years' PD exposure respectively. The median PD duration of EPS cases was 5.1 years. At diagnosis only 26% were still on PD and 72% were diagnosed within two years of stopping PD. The mortality rate was 42% at one year post-diagnosis, with a median survival of 149 days.

The incidence reported in this study may be used to inform patients of their minimum risk of developing EPS if they choose to start PD, as well as their incremental risk of developing EPS after increasing periods of time on PD.

Further reading

- Brown MC, Simpson K, Kerssens J et al. Encapsulating peritoneal sclerosis in the new millennium: a national cohort study. *Clin J Am Soc Nephrol* 2009; 4:1222–9.
- Kawaguchi Y, Saito A, Kawanishi H et al. Recommendations on the management of encapsulating peritoneal sclerosis in Japan 2005: Diagnosis, predictive markers, treatment, and preventative measures. *Perit Dial Int* 2005; 25 (Suppl 4): S83–S95.

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NEW BIOLOGICAL AGENTS

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Immune-mediated renal disease, which comprises primary disorders limited to the kidney and multi-system disorders, contributes to the burden of end-stage renal failure. There is an important unmet need for newer therapy due to the inefficacy or toxicity of current agents. Targeted biologic drugs, often licensed for oncology or rheumatic disorders, are now available which offer potential advances for the care of patients with these renal diseases.

Agents studied to date have targeted circulating or tissue-bound reactants, such as tumour necrosis factor α (e.g. infliximab), or cell surface receptors with the aim of blocking immune signalling, such as CTLA4Ig (abatacept), or depleting immune cells such as anti-CD20 (rituximab). Most experience has been in patients with disease refractory to standard therapies, but randomised controlled trials (RCTs) of induction therapy are under way with several agents and the first results are starting to appear.

Most experience has been in systemic lupus erythematosus (SLE) and lupus nephritis, and anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV).[1,2] Uncontrolled data have reported response rates with rituximab in relapsing or refractory SLE of approximately 75%, but two RCTs have failed to detect a significant benefit when rituximab was given in addition to standard therapy for routine remission induction. Preliminary experience in AAV has shown response rates up to 90%, with two RCTs demonstrating at least as good responses with rituximab when compared to cyclophosphamide for remission induction. Three uncontrolled studies of rituximab in membranous glomerulonephritis have reported improvements in proteinuria.[3]

An increasing number of renal indications are now being studied with rituximab, while an expanding number of other biologics are either in trials or in earlier development phases.

B cell depletion with rituximab is now an alternative treatment for AAV, but the current data in SLE and primary glomerulonephritis is more controversial. Many alternative biologic agents in development offer the potential for newer, safer therapies for immune-mediated renal disease in the future.

References

1 Jones RB, Ferraro AJ, Chaudhry AN et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2009; 60:2156–68.
2 Lu TY, Ng KP, Cambridge G et al. A retrospective seven-year analysis of the use of B cell depletion therapy in systemic lupus erythematosus at University College London Hospital: the first fifty patients. *Arthritis Rheum* 2009; 61:482–7.
3 Bomback AS, Derebail VK, McGregor JG et al. Rituximab therapy for membranous nephropathy: a systematic review. *Clin J Am Soc Nephrol* 2009; 4:734–44.

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