Sleep-disordered breathing: a pervasive problem in CKD

Summary:
Sleep apnoea is a modifiable CV risk factor for the general population, including patients with CKD and dialysis patients. Although renal transplant patients have a similar prevalence of sleep apnoea to the general population, it is their main determinant of nocturnal hypertension. Renal transplantation is associated with an early improvement in sleep-disordered breathing, but stabilisation is not seen and re-emergence occurs over longitudinal observations. BMI appears to be an important determinant of the re-emergence of sleep-disordered breathing after renal transplantation.

Comment:
Sleep apnoea has been recognised for two decades and is associated with increased activation of the sympathetic nervous system, including during the day. Studies comparing GFR and the incidence of sleep apnoea have not demonstrated an increased frequency of overall sleep apnoea as renal function declines (Canales et al. NDT 2008; stage 3 CKD versus higher GFR levels). Fleshman (NDT 2010) showed that whilst obstructive sleep apnoea was not increased in incidence, central sleep apnoea was increased in patients with lower GFRs. Other studies showed that sleep apnoea increases in severity as patients approach end-stage renal failure (Markou et al. Lung 2006).

Mallamaci reported she has a publication in preparation showing a direct relationship between hypertension and nocturnal hypoxaemia, and also a correlation between SaO$_2$ and arterial intimal medial thickness. Unselected dialysis patients had a 15% incidence of sleep apnoea but there was a 75% incidence in patients with symptoms of sleep disturbance. Zoccali et al. found (J Am Soc Nephrol 2002) that lower oxygen saturations are associated with an increase in vascular events in association with sleep apnoea and a poorer survival.

Renal transplantation results in improved sleep apnoea, but on return to dialysis, apnoea/hypopnoea worsens. Post-renal transplant polysomnography has shown in 221 transplant patients that apnoea/hypopnoea was increased in association with oxygen desaturations, and whilst it improves initially following renal transplant, it worsens with time. BMI, male gender, increased C-reactive protein level, phosphate level, CV comorbidities, age and diabetes were all linked to an increased risk of sleep apnoea. Sleep apnoea is the most powerful functional correlate of nocturnal hypertension in renal transplant patients. Sleep apnoea improves post-transplant, but later emerges. In essence, central sleep apnoea is an issue in patients with renal disease.

Symposium 04

Independent commentary by Paul Champion de Crespiigny, who is a nephrologist at The Royal Melbourne Hospital and obstetric physician at the Royal Women’s hospital. He has a longstanding interest in general nephrology, dialysis, renal transplantation and clinical trials in nephrology. He has an interest in women’s health and in particular the effect of renal disease on women’s reproductive function and pregnancy outcomes.
Outcomes of SGLT2i in diabetic kidney disease: is it all diabetes?

Presenter: Agarwal R, Indianapolis, IN, USA

Summary: Previous trials investigating the use of SGLT-2 inhibitors to reduce CKD progression in type 2 diabetes have not prespecified renal protection as a primary endpoint. The CREDENCE trial has reported that canagliflozin reduced the relative risk of CKD progression to end-stage renal disease by around one third in patients with an estimated GFR down to 30 mL/min/1.73m². The effect of canagliflozin on glycemic control and the reduction in systolic BP were both small and the study suggested that the renal protection was greater than would be explained by the glycemic control and the reduction in BP.

Comment: The CREDENCE study was terminated early because the interim analysis suggested the superiority of canagliflozin compared with placebo. Other studies have also suggested a reduction in progression to end-stage renal failure in patients with renal impairment treated with SGLT-2 inhibitors, but the studies did not have renal protection as a prespecified primary endpoint.

Industry Sponsored Symposium

The clinical landscape of managing patients with CKD: where are we now and what can we expect?

Presenter: Herrington W, Oxford, UK

Summary: Several large ongoing placebo-controlled trials in patients with renal and heart failure are expected to provide data on the effects of SGLT-2 inhibitor use on kidney disease progression, CV disease and safety outcomes across a wide range of different, as-yet unstudied patient types. Two such trials (DAPA-CKD and EMPA·KIDNEY), are particularly relevant to nephrology practice. This presentation on these ongoing trials covered some of the rationale for their designs and how they will add to the currently available data.

Comment: SGLT-2 studies have demonstrated beneficial effects in slowing the decline in renal function in patients with progressive declines in renal function and in treating heart failure. Long-term follow-up has not been undertaken. The CANVAS and DECLARE-TIMI58 trials showed reductions in disease progression. Aggregating previous studies suggests an approximate 25% reduction in acute kidney injury in patients taking SGLT-2 inhibitors. It should be noted that the studies have looked at specific subgroups of patients, but the benefits have been shown across multiple studies with differing populations studied. Studies will hopefully be undertaken in patients with lower levels of proteinuria and lower levels of renal function. It is likely that the use of SGLT-2 inhibitors will become the ‘standard of care’, probably in combination with renin-angiotensin inhibition in proteinuric diabetic disease. Investigation in nondiabetic renal disease needs to be undertaken. The beneficial effects demonstrated appear greater than the benefits of renin-angiotensin blockade alone.

Industry Sponsored Symposium

Intradialytic hypoxia

Presenter: Kotanko P, New York, NY, USA

Summary: Patients undergoing haemodialysis have impaired oxygen supply to their tissues and organs. Tissue hypoxia is the terminal pathway of several pathologies, and the heart, gut and brain are particularly susceptible organs. Fluid management and ways of increasing intradialytic haemodynamic stability are important for improving oxygen supply to organs and tissues. There are a number of interventions that can be ‘tissue protective’, but noninvasive and continuous means of assessing tissue oxygen content are urgently needed.

Comment: This presentation discussed issues related to tissue oxygen delivery and fluid status. Peter Kotanko discussed that oxygen is delivered to tissues and the rate is defined by the cardiac output × haemoglobin + an adjustment for the dissolved oxygen. Oxygen transfer has both diffusive and convective components with a diffusion pattern dependent on the distance between the tissue and the capillaries. Increased lung water is associated with impaired pulmonary oxygen uptake and in particular impaired oxygen diffusion with interstitial fluid overload. Pulmonary ultrasound images can identify B lines as described by Zoccali C et al. in J Am Soc Nephrol in 2013; pulmonary congestion is associated with an increased all-cause mortality and cardiac events. Convective oxygen transport is affected by cardiac dysfunction, anaemia and reduced arterial oxygen saturations. Patients with average nocturnal oxygen saturations <95% have worse outcomes compared with those with average nocturnal oxygen saturations >95%. Intradialytic oxygen saturations can be measured 150 times per second or 9000 times per minute.

Oxygen saturations have been shown to be variable during dialysis and there were noted to be improved oxygen saturations in association with fluid removal during dialysis. It was noted that one patient’s oxygen saturation fell to 63.7% on dialysis who was noted by the caring nurse to be ‘sleeping’.

A study over 3 years (Meyring-Wösten A et al. Clin J Am Soc Nephrol 2016) found a link between the more time a patient has oxygen <90% and all-cause mortality. The concept of hypoxaemic burden was discussed and 10% of patients who had an oxygen concentration <90% for one third of dialysis were shown to have an increased rate of hospitalisation and a doubling of mortality rate. Mt Sinai hospital is identifying patients with nocturnal hypoxia and oxygen administration versus air (given as placebo) alters outcomes in dialysis patients. Intestinal oedema is described in the heart, gut and brain in association with fluid overload. Appropriate management of fluids is essential to ensure adequate tissue oxygenation.

Symposium 04

Chronic interstitial nephritis of unknown etiology is a toxic tubular nephropathy

Presenter: de Broe M, Antwerp, Belgium

Summary/comment: Regional increases in incidence of interstitial nephritis of unknown aetiology were noted in growing areas of Europe for renal disease. It has been noted in a patchy distribution in multiple countries including Sri Lanka, El Salvador, Peru, Egypt, Cameroon, France, Portugal and other countries. A hypothesis has been raised that the interstitial nephritis could be related to heat and dehydration; however, there are soft data to suggest it is related to chemicals and mechanisation. Interstitial nephritis is common in Cuba where similar climate and crops are found, but in Cuba where similar climates and crops are found, but Cuba has banned the introduction of chemicals/herbicides. In Sri Lanka there appears to be a correlation between interstitial nephritis and shallow wells and absent where the water supply is plentiful. The possibility of herbicide contamination of shallow water supplies was proposed as a possible cause.

There are studies that suggest the death rate in Nicaragua and El Salvador relate to pesticide and end-stage renal failure, with the suggestion that the source of the problem is contaminated water. A US study by Sandor et al. in Occup Environ Med 2016 suggested an association between the use of agricultural chemicals and the incidence of end-stage renal disease. There is certainly no evidence that heat and volume depletion is associated with chronic interstitial nephritis. Histological studies in Sri Lanka and El Salvador have suggested the interstitial nephritis is associated with tubular basement membrane thickening and the presence of irregular shaped structures on electron microscopy measuring 4–5 microns in the proximal tubular cells, which stain with Jones stain. The structures in the proximal convoluted tubules have positive staining for γ-glutamyl transpeptidases with lysosomes positive for cathepsin B and the distal tubules were found to be full of PCNA (proliferating cell nuclear antigen) activity, whereas there is usually none. It is unclear what the Jones positive staining structures are but they are not autophagosomes or lipids. There are also high concentrations of chronic interstitial nephritis of unknown aetiology in wine growing areas in Europe, where it is known there is extensive use of herbicides. Dr de Broe’s group intend to survey the wine growing areas of Europe for renal disease.

Interstitial nephritis of unknown aetiology is associated with a reduction in renal size and tubular proteinuria without macroproteinuria.
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Effects of linagliptin on kidney outcomes in patients with nephrotic range proteinuria: insights from CARMELINA

Presenter: Warner C, Würzburg, Germany

Summary: This presentation reported on one of the largest cohorts of patients with type 2 diabetes and proteinuria in the nephrotic range treated with linagliptin. Over a median of 2.2 years of follow-up, linagliptin treatment did not impact the risk of CV events, heart failure events, all-cause hospitalisations, all-cause mortality or a series of composite renal outcomes. There was a modest reduction in the burden of albuminuria, and HbA1c levels were reduced without affecting the risk of hypoglycaemia.

Comment: This was a review of the CARMELINA study, which investigated the role of the dipeptidyl peptidase-4 inhibitor, linagliptin, versus placebo. Linagliptin or placebo was added to ‘standard of care’. CV risk factors were treated according to local guidelines. Inclusion criteria were documented type 2 diabetes on stable glucose-lowering drugs, >18 years of age, HbA1c level 6.5–13.0%, BMI <45 kg/m², at least one confirmed history of ischaemic heart disease, stroke or peripheral vascular disease, and an estimated GFR of 15–<45 mL/min/1.73m² or estimated GFR ≥45–75 mL/min/1.73m² with an albumin-creatinine ratio of >200 mg/mmol. Primary outcomes were 3P-MACE, being CV-related death, nonfatal myocardial infarction and nonfatal stroke, and secondary outcomes were end-stage kidney disease, estimated GFR decrease >40% from baseline or death due to kidney disease. There were no differences in adverse events. The results showed that there was a modest reduction in albuminuria but no effect on CV or renal endpoint outcomes.

Symposium 05: Late Breaking Clinical Trials

Pregnancy outcomes in patients enrolled in the global aHUS registry

Authors: Cummings L et al.

Summary: Patient characteristic and outcome data from the Global aHUS Registry on 37 patients with aHUS (atypical haemolytic uraemic syndrome) who had 40 pregnancies recorded were presented. Outcomes were not reported for seven cases and there were two ongoing pregnancies at data cutoff. For the 31 pregnancies with known outcomes, 22 included eculizumab exposure. Compared with eculizumab-nonexposure, pregnancies with eculizumab exposure resulted in fewer live births (55% vs. 78%) and more elective terminations (36% vs. 11%) but a lower relapse rate (5% vs. 22%). There were no neonatal malformations reported. Among tested patients, 55% had complement mutations detected.

Comment: This poster is of interest in that the registry documents significant numbers of patients exposed to eculizumab in pregnancy. Whilst not showing that eculizumab is safe in pregnancy, it does support other publications that have supported that there is no current evidence of adverse outcomes related to the use of eculizumab in pregnancy when clinically indicated. As is frequently the case with the use of pharmacological agents in pregnancy, there are no totally convincing data to support safety from a pharmacological perspective in terms of foetal exposure to eculizumab; however, it is thought to be safe. Proof of safety is unlikely to be possible in the foreseeable future given such a trial would be difficult to undertake. The risk-benefit ratio needs to be considered in all patients. This registry will continue to provide valuable data relating to this uncommon condition in which there are relatively few reported pregnancies. In the future, given the greater awareness of aHUS, increasing numbers of women with aHUS are likely to embark on pregnancies whilst undergoing therapy with eculizumab.

Clinical nephrology 2: Poster SP075

Abstract

When to start dialysis: the final answer?

Presenter: Maizel J, Amiens, France

Summary/comment: Disappointingly, Dr Maizel presented data and a review of trials showing that the appropriate time to commence renal replacement therapy with dialysis in acute renal failure has not been established for either patient or renal survival. Dialysis is typically commenced for life-threatening complications, but the trials have failed to elucidate clear indications for the initiation of renal replacement therapy. In patients with slowly declining renal function, clinicians typically consider both results of laboratory tests including urea, potassium, acidosis and fluids, and the progression/decline in tests.

Symposium 18: Treatment of AKI: next generations therapies and renal replacement therapy in the Future Care Unit

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