High dose cholecalciferol blunts rise in PTH in short term study

High doses of cholecalciferol alleviate the progression of hyperparathyroidism in patients with CKD Stages 3–4: results of a 12-week double-blind, randomized, controlled study


Debate continues as to the potential pleotropic benefits of cholecalciferol in CKD. Westerberg, et al. aimed to determine if high doses of cholecalciferol could improve secondary hyperparathyroidism, muscle weakness and fatigue in 25-OH vitamin D deficient CKD patients with secondary hyperparathyroidism. Ninety-seven participants with stage 3-4 CKD were randomised to 8000IU per day of cholecalciferol or placebo for 12 weeks, resulting in a rise in mean 25-OH vitamin D from 57.5nmol/L to 161.6 nmol/L in the treatment group. The PTH level in the treatment group did not change (10.9±5 to 10.5±5 pmol/L), whereas it rose significantly in the placebo group (13.1±9 to 15.2±11) (mean difference in change: p<0.01). There were no differences in grip strength, fatigue, phosphate or fibroblast growth factor 23. While this study shows that high doses of cholecalciferol are safe in the short-term for patients with CKD, the importance of the small (albeit statistically significant) change in PTH is not clear. Moreover, in the absence of any improvement in patient-reported outcomes, any move to routinely supplement CKD patients with supratherapeutic doses of cholecalciferol must await larger and longer term studies.

Targeting ghrelin receptors activates growth hormone pathway in hemodialysis patients

Oral ghrelin receptor agonist MK-0677 increases serum insulin-like growth factor 1 in hemodialysis patients: a randomized blinded study


Ghrelin, an endogenous hormone, increases secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) which may result in reduced inflammation and increased appetite. Campbell, et al. performed a double blind randomized cross-over trial to test the ability of the oral ghrelin receptor agonist, MK-0677, to trigger the GH/IGF-1 pathway in hemodialysis patients. Twenty-six participants were recruited from three sites and completed one month of MK-0677, a one-month washout period and one month of placebo (or vice versa). In the 22 who completed the study, IGF-1 levels increased by 1.65 times (relative to placebo) (95% CI 1.33-2.04; p<0.001) during the treatment period. Body weight increased by 1.6kg, although this was not significantly different from placebo (0.5kg; p=0.159). Although it is too early to say what, if any, role this approach will have in the management of dialysis-related protein-energy wasting, this study demonstrates that activation of the GH/IGF-1 axis via ghrelin receptors agonists is feasible in hemodialysis patients.
**Tauroldine-heparin with weekly urokinase reduces catheter infection and dysfunction**

Tauroldine-based catheter lock regimen significantly reduces overall costs, infection, and dysfunction rates of tunneled hemodialysis catheters


Dialysis catheter-related bloodstream infections (CRI) and dysfunction are a significant cause of morbidity and cost. The optimal method for reducing their incidence is still not clear. Winnicki, et al. sought to test the combination of tauroldine-heparin (twice weekly) and tauroldine-urokinase (once weekly) locking solutions on CRI and catheter dysfunction (defined as blood flow rate <200mL/hr or >30% less than previously). One hundred and six participants from three centres who were receiving a tunneled dialysis catheter were randomized 1:1 to the treatment regime or a control regime of 4% citrate thrice weekly. Over 15690 observed catheter days there were 6 infections in tauroldine group and 18 in the citrate group, equating to a rate of 0.67 vs 2.7 per 1000 catheter days (p=0.003). Catheter dysfunction was less common (18.7 vs 44.3 per 1000 catheter days, P=0.001), as was need for catheter removal (0.2 vs 1.2 per 1000 catheter days, p=0.034). The costs including complications were 43% lower in the tauroldine/urokinase group. Although small (with only 24 primary endpoints) this promising study suggests the combination of tauroldine-heparin and tauroldine-urokinase may have a role in preventing catheter infections. Larger and more generalised studies are required to determine if this therapy, from among the many available, is the right choice for an overall CRI reduction package.

**Patient blood pressure self-monitoring is an effective aid to achieving treatment targets**

Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial


The reliability and effectiveness of patient self-monitoring of blood pressure for the long-term management of hypertension and the role of tele-monitoring has been unclear. McManus et al. randomized 1182 patients with hypertension not controlled to below 140/90mmHg to self-monitoring alone, tele-monitoring and standard care in general practice patients with. The tele-monitoring group performed self-monitoring of their BP but also transmitted the results to the GP via SMS. Compared to standard care, clinic BP at 12 months was significantly lower in the self-monitoring (−3·5 [−5·8 to −1·2]; p=0·0029) and tele-monitoring groups (−4·7 [−7·0 to −2·4]; p<0·0001). There was no difference between the two treatment groups (−1·2 mm Hg [95% CI −3·5 to 1·2]; p=0·3219) and both achieved target BP below 140/90mmHg on average (137·0±16.7 and 136.0±16.1, respectively). Follow up was 85% complete and did not significantly differ between groups. The main limitation of this trial is the unblinded outcome assessment (although an automated BP device was used). This trial helps to reassure clinicians that patient self-monitoring, with or without simple tele-monitoring, can be a simple and safe way to help patients achieve their BP goals.

**Self-management coaching of hemodialysis patients leads to small improvements in treatment adherence**

Hemodialysis Self-management Intervention Randomized Trial (HED-SMART): A Practical Low-Intensity Intervention to Improve Adherence and Clinical Markers in Patients Receiving Hemodialysis


Behavioural interventions to improve adherence to medication and dietary regimens in hemodialysis patients have generally shown limited effectiveness. Griva, et al. tested the effect of four 2-hour group education sessions over a two month period on clinical and biochemical markers of treatment adherence. Sessions were interactive and emphasised problem solving, peer support and self-management. They recruited 235 hemodialysis participants using cluster randomisation of dialysis shifts at 14 centres, of whom 88% completed at least 3 of the four sessions. The control group received standard care only. Significant reductions from baseline in mean inter-dialytic weight gain (2.32±0.60kg from 2.49±0.71kg; P<0.001) and serum potassium (4.82±0.65mmol/L from 5.00±0.64mmol/L; P<0.001) were maintained at 9 months, but the improvement in phosphate at 3 months was not sustained. Despite this, there
were no significant differences between the intervention and control groups at 9 months. Per-protocol analysis did not materially affect these results. While significant improvements from baseline were maintained at 9 months, these benefits were small and did not result in significant differences from the control group. This study emphasises the continued challenge of making and sustaining meaningful behavioural change in patients with chronic disease.

**Dosing cyclosporine to gene-expression may improve outcomes in renal transplantation**

**Improved Pulse Wave Velocity and Renal Function in Individualized Calcineurin Inhibitor Treatment by Immunomonitoring:**

**The Randomized Controlled Calcineurin Inhibitor-Sparing Trial**


Targeting the ‘right’ level of immunosuppression is a key challenges in transplant medicine. Cyclosporine acts by increasing the activity of a gene regulator called nuclear factor of activated T cells (NFAT), activity of which is only loosely correlated to blood cyclosporine levels. This single-blind trial randomized 55 stable renal transplant recipients to 6 months of cyclosporine dosing guided by direct measurement of NFAT-regulated gene expression versus standard pharmacokinetic monitoring. The primary endpoint was arterial pulse wave velocity (PWV), a measure of cardiovascular risk thought to correlate with cyclosporine toxicity. After six months, mean cyclosporine dose and levels (both C₀ and C₁) were lower in the investigational group. In addition, PWV and systolic blood pressure had reduced significantly in the investigational group (-1.7±2.0m/s vs 0.4±1.4m/s, P<0.001; 133±11mmHg vs 127±13mmHg, P=0.026) and eGFR was non-significantly higher. At 12 months (both groups received standard pharmacokinetic monitoring after 6 months) significant differences were seen in both systolic BP and eGFR (132±13mmHg vs 124±8mmHg, P=0.013; 57.2±19.0ml/min/1.73m² vs 68.5±17.4ml/min/1.73m², P=0.009). The investigational group had fewer non-urinary tract infections (9/27 vs 2/26, P=0.021) and no episodes of biopsy-proven rejection were identified in either group. In short, this study demonstrated the feasibility of cyclosporine monitoring by gene-expression and suggests it may lead to lower cyclosporine exposure and reduced renal and cardiovascular side effects. Multi-centre studies are required to validate this finding.

**Twin studies tackle the balanced fluid debate**

**Balanced Crystalloids versus Saline in Noncritically Ill Adults / Balanced Crystalloids versus Saline in Critically Ill Adults**


The physiological benefits of balanced crystalloids are well described, but whether this translates into clinical benefit is still debated. Two recent studies (published simultaneously) present results from different arms of a large single-centre cross-over study comparing balanced crystalloid (lactated Ringer’s solution or Plasmalyte-A) to 0.9% saline. The emergency department and intensive care units of one large US hospital alternated monthly between balanced crystalloid and 0.9% saline as their default intravenous fluid for 16 months. Self, et al. present the results in the 13,347 patients presenting to the emergency department during the study period who received at least 500mL of intravenous fluid and who were admitted to a non-ICU ward (non-critically ill adults). While their primary outcome of hospital-free days to day 28 did not differ between groups (OR 0.98, 95% CI 0.92-1.04; P=0.41), they did observe a reduction in the composite of death, dialysis and persistent doubling of creatinine (4.7 vs 5.6%, OR 0.82, 95% CI 0.70-0.95; P=0.01). No significant reduction in mortality was observed (OR 0.88 0.66-1.16; P=0.36). Selmer, et al. present the results in the 7942 patients admitted to the hospital ICUs during the same period (critically ill adults). The primary outcome in this arm (the same composite of death, dialysis and persistent doubling of creatinine) was also reduced (14.3 vs 15.4%, OR 0.91, 95%CI 0.82-0.99; P=0.04). Although, as with the study in non-critically ill adults, components of the composite were reduced without achieving statistical significance: mortality 10.3 vs 11.1% (P=0.06), RRT 2.5 vs 2.9% (P=0.08), persistent doubling of serum creatinine 6.4 vs 6.6% (P=0.60).

While only a single centre study and the primary result of the non-critically ill arm was negative, these results are likely to shift the debate towards the broader use of balanced crystalloid in both emergency department and ICU settings.