Nephropathy

The jury is out: Encouraging results for paricalcitol in the treatment of diabetic nephropathy, but at what cost?

Colin Close, Consultant Physician, Division of Medicine, Taunton and Somerset Hospital, Taunton

Vitamin D is critical to bone health and overt deficiency has major skeletal effects. A whole new literature is emerging around the apparent association between low levels of vitamin D ("insufficiency") and other non-skeletal health effects. Observational studies have shown associations between low levels of vitamin D and an increased risk of both types 1 and 2 diabetes, cancer and cardiovascular disease mortality (Thacher and Clarke, 2011). Alongside this come suggestions of a role for the vitamin D receptor in the development of kidney injury and albuminuria in both animal and human studies (Mizobuchi et al, 2007; Zhang et al, 2008).

The VITAL (Vitamin D and Omega-3 Trial; de Zeeuw et al, 2010; summarised alongside) formally tests the hypothesis that activation of the vitamin D receptor reduces albuminuria in diabetic nephropathy. de Zeeuw and colleagues randomly assigned 281 people with type 2 diabetes and nephropathy to placebo, 1 µg or 2 µg of the synthetic vitamin D analogue paricalcitol and the effect on albuminuria was studied over 24 weeks of treatment. All participants were receiving an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (although only 40% received the maximum dose); however, renin–angiotensin–aldosterone system (RAAS) blockade remained unaltered for the study's duration.

The primary analysis demonstrated a 15% reduction in albuminuria in the combined paricalcitol groups versus placebo, although this was not statistically significant. Secondary analysis showed that there was little difference in albuminuria (–2%) between the placebo and 1 µg paricalcitol groups, but a highly significant 28% reduction in albuminuria in the 2 µg paricalcitol group. Albuminuria lowering seemed to be independent of whether RAAS inhibition was full or sub-maximal and, although the 2 µg dose was associated with a small reduction in both systolic blood pressure and glomerular filtration rate, the majority of its effect on albuminuria seemed to be independent of blood pressure changes. The effects on blood pressure and glomerular filtration rate were reversible on cessation of treatment.

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Whether treatment with paricalcitol will have a meaningful role in slowing the progression of diabetic nephropathy through a demonstrable improvement in hard renal outcomes remains to be seen. Although de Zeeuw et al judged that none of the three deaths that occurred during the study period – all of which occurred in the 2 µg paricalcitol group – were attributable to the study drug. It is interesting that all ten of the cardiovascular complications seen during the study were limited to the two paricalcitol groups alone. Watch this space.

Mizobuchi M, Morrissey J, Finch JL et al (2007) Combination therapy with an angiotensin-converting enzyme inhibitor and a vitamin D analog suppresses the progression of renal insufficiency in uremic rats. *J Am Soc Nephrol* **18**: 1796–806

Thacher TD, Clarke BL (2011) Vitamin D insufficiency. *Mayo Clin Proc* **86**: 50–60

Zhang Z, Sun L, Wang Y et al (2008) Renoprotective role of the vitamin D receptor in diabetic nephropathy. *Kidney Int* **73**: 163–71

LANCET

Paricalcitol reduces albuminuria in diabetic nephropathy

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓✓

1 People with diabetes have an increased cardiovascular and renal risk, correlated with albuminuria.

2 This study aimed to determine whether paricalcitol, a selective activator of the vitamin D receptor, reduces albuminuria in people with diabetic nephropathy.

3 In a placebo-controlled, double-blind trial, 281 people with T2D and albuminuria on angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers were randomised to placebo (n=93), paricalcitol 1 µg/day (n=93) or paricalcitol 2 µg/day (n=95) for 24 weeks.

4 The main outcome measurement was the percentage change in geometric mean urinary albumin-to-creatinine ratio (UACR) from baseline to last measurement during treatment.

5 Change in geometric mean UACR was higher in the combined paricalcitol groups than in the placebo group, with a between-group difference of –15% (95% confidence interval [CI], –28 to 1; P=0.071).

6 The between-group difference versus placebo was –11% (95% CI, –27 to 8; P=0.23) in the paricalcitol 1 µg/day group and –18% (95% CI, –32 to 0; P=0.053) in the paricalcitol 2 µg/day group.

7 People in the paricalcitol 2 µg/day group showed an early and sustained reduction in UACR, ranging from –18% to –28% (P=0.014 vs placebo).

8 Addition of paricalcitol 2 µg/day was found to safely reduce albuminuria in people with diabetic nephropathy.

de Zeeuw D, Agarwal R, Amdahl M et al (2010) Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 (VITAL study): a randomised, controlled trial. *Lancet* **376**: 1543–51

DIABETOLOGIA

Physical activity reduces CVD events in people with T2D without proteinuria

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 People with T2D are at increased risk of cardiovascular disease (CVD).

2 Although physical activity reduces CVD and total mortality in people with T2D, the presence of proteinuria strongly predicts CVD and total mortality rates in this at-risk group.

3 The authors investigated the association between physical activity and both CVD and total mortality rates in people with T2D with and without proteinuria.

4 In total, 577 people with T2D (aged 45–64 years) and free from CVD at baseline were stratified according to the presence of proteinuria and extent of physical activity.

5 During a follow-up of 18 years, 356 people died; 217 following CVD events.

6 The group with proteinuria who were more physically active had significantly increased total and CVD mortality rates.

7 The group without proteinuria who were more physically active had significantly reduced total, CVD and coronary heart disease mortality rates.

8 In the group without proteinuria, the beneficial effects of physical activity on mortality rates was independent of conventional CVD risk factors, glycaemic control, diabetes duration and treatment.

9 The authors concluded that increased CVD and total mortality rates in those with proteinuria may make physical activity harmful in this group.

Vepsäläinen T, Soinio M, Lehto S et al (2010) Proteinuria modifies the effects of physical activity on total and cardiovascular disease mortality rates in patients with type 2 diabetes. *Diabetologia* **53**: 1886–9

DIABETES

Maternal T1D reduces offspring renal reserve

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 The effect of maternal diabetes on fetal kidney development is uncertain.

2 This study comprised 19 offspring of mothers with T1D and 18 offspring of fathers with T1D (control group); the offspring were similar in terms of age, sex, BMI and birth weight.

3 Tests included glomerular filtration rate, effective renal plasma flow, mean arterial pressure and renal vascular resistances measured at baseline and during amino acid infusion, which mobilises renal functional reserve.

4 Effective renal plasma flow increased less in the offspring of mothers with T1D (from 509±58 to 536±80 mL/min, 5±9%) compared with the control group (from 536±114 to 620±140 mL/min, 16±11%; P=0.0035).

5 Results showed that fetal exposure to maternal T1D was associated with a reduced renal reserve in offspring; thus offspring of mothers with T1D may be predisposed to glomerular and vascular disease.

Khalil CA, Travert F, Fetita S et al (2010) Foetal exposure to maternal type 1 diabetes is associated with renal dysfunction at adult age. *Diabetes* **59**: 2631–6

NEJM

Target-based ESA dosing increases risk of death

Readability	✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 This study sought to determine the relationship between responsiveness to erythropoiesis-stimulating agents (ESAs), achieved haemoglobin levels and outcomes in 1872 anaemic people with T2D and chronic kidney disease (CKD) not on dialysis.

2 In this double-blind, placebo-controlled trial, participants were randomised to receive two weight-based doses of either darbepoetin alfa or placebo; haemoglobin levels were measured at 4 weeks and subsequent darbepoetin alfa doses administered to maintain target levels.

3 Participants who had a poor initial response to darbepoetin alfa (n=471) had a lower mean haemoglobin level throughout the study than those with a better initial response. This group also had higher rates of all-cause mortality than those with a good initial response.

4 The authors suggest that their findings raise concern about current target-based strategies for treating anaemia in people with CKD.

Solomon SD, Uno H, Lewis EF et al (2010) Erythropoietic response and outcomes in kidney disease and type 2 diabetes. *N Engl J Med* **363**: 1146–55

JOURNAL OF MATERNAL–FETAL AND NEONATAL MEDICINE

Overweight affects T1D pregnancies with diabetic nephropathy

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Women (n=46) with T1D and diabetic nephropathy were followed from pre-conception to delivery for pregnancy complications (i.e. pre-eclampsia, pre-term delivery, small- or large-for-gestational age infant, macrosomia, admission to the neonate intensive care unit, fetal loss).

2 Thirty-one women (67%) had at least one complication during pregnancy during the study.

3 Maternal BMI was found to be the only parameter to have a significant effect on pregnancy complication.

Yogev Y, Chen R, Ben-Haroush A et al (2010) Maternal overweight and pregnancy outcome in women with type 1 diabetes mellitus and different degrees of nephropathy. *J Matern Fetal Neonatal Med* **23**: 999–1003

"Maternal BMI was found to be the only parameter to have a significant effect on pregnancy complication."