The changing face of diabetic nephropathy

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When Dr David Kerr was a lad, diabetic nephropathy was diagnosed by the finding of proteinuria on an Albustix. One day, Tattersall's Tales will recall that about this time clinicians were unconvinced that treating blood pressure (BP) was either necessary or beneficial. Indeed, proteinuria was an indication that death from renal failure was not far off (50% in 10 years, I seem to remember). In the early 1980s, Mogensen and Parving demonstrated for the first time that treating hypertension slowed the progression of nephropathy, and soon afterwards microalbuminuria was identified as an earlier marker, and angiotensin-converting enzyme (ACE) inhibitors were found to have a renoprotective effect beyond BP lowering.

Several studies, particularly from Scandanavia, have subsequently shown both a falling incidence and mortality from nephropathy, but there are clearly a group of patients who develop microalbuminuria after a relatively short duration of diabetes. In the excellent review by Lane and colleagues, and the study by Lurbe et al, several options emerge to help identify these at-risk individuals. For example, an increase in systolic BP during sleep precedes the development of microalbuminuria. Neither casual BP measurements or daytime BP assessed by ambulatory BP monitoring changed significantly in subjects in whom microalbuminuria eventually developed.

Thus an increase in night-time systolic BP (or loss of dipping) appears to be the earliest detectable manifestation of diabetic nephropathy. Where resources permit, this may indicate a place for routine 24-hour BP measurement in young people with normoalbuminuria. This is unlikely to be possible, even in today's 'modern and dependable' NHS, so a more practical strategy may be to target those with a first-degree relative with hypertension. This clustering of risks suggests a genetic predisposition, which has been confirmed many times. One day, genetic mapping may be used to target susceptible individuals and hence facilitate even earlier treatment with ACE inhibitors or sartans.

Parving HH et al (1987) *British Medical Journal* **294**;1443-47

AMERICAN JOURNAL OF PHYSIOLOGY

Impact of puberty on diabetic renal disease

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

1 This article reviews the impact of puberty on diabetes, focusing on effects in the kidney.

2 Puberty accelerates microvascular complications of diabetes, including nephropathy.

3 Animal studies have shown that before and after puberty there is a different renal hypertrophic response to diabetes, owing to differences in the production of transforming growth factor-β (TGF-β).

4 Increased blood pressure, activation of the growth-hormone-insulin-like growth factor I axis and production of sex steroids all occur during puberty.

5 These factors may influence the effects of hyperglycaemia and ultimately several systems that control TGF-β production.

6 The same factors may also explain gender differences in kidney function and the incidence of end-stage renal disease.

7 Thus the normal changes of puberty, when coupled with diabetes and underlying genetic factors, might increase potentially pathogenic mechanisms of diabetic nephropathy, especially production and activity of TGF-β.

8 A better understanding of these processes might lead to new treatments to slow or prevent the progression of diabetic nephropathy.

Lane PH (2002) Diabetic kidney disease: impact of puberty. *American Journal of Physiology: Renal Physiology* **283** (4): F589–600

THE NEW ENGLAND JOURNAL OF MEDICINE

Raised nocturnal BP precedes microalbuminuria

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

1 This study set out to determine whether patients with type 1 diabetes and microalbuminuria develop elevated nocturnal blood pressure (BP) before or at the same time as developing microalbuminuria.

2 Seventy-five adolescents and young people who had had type 1 diabetes with normal urinary albumin excretion for more than 5 years were monitored for BP initially and again 2 years later. Subsequently, they were monitored for microalbuminuria.

3 Fourteen of the subjects developed microalbuminuria.

4 The mean nocturnal systolic BP in the subjects who developed microalbuminuria increased significantly from 109.9±11.3 to 114.9±11.7mmHg ($P=0.01$).

5 The ratio of systolic BP during sleep to systolic BP in the daytime was examined in relation to the risk of progression to microalbuminuria. A ratio of up to 0.9, which indicates a normal fall in nocturnal BP, had a negative predictive value of 91% for the development of microalbuminuria.

6 The risk of microalbuminuria was 70% lower (95% confidence interval, 44–110%) in subjects with a ratio of ≤0.9, than in those with a ratio >0.9 ($P=0.01$).

7 Thus for people with type 1 diabetes, an increase in systolic BP during sleep precedes the development of microalbuminuria.

Lurbe E, Redon J, Kesani A et al (2002) Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *The New England Journal of Medicine* **347** (11): 797–805

'This is the first confirmatory detection of diabetes-specific autoimmune markers in oral fluid.'

'Where cerebral oedema occurs, it is important to recognise the possibility of hypothalamo-pituitary dysfunction in survivors.'

DIABETES RESEARCH AND CLINICAL PRACTICE

Diabetes-specific autoantibodies found in oral fluid

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

1 To assess a different sampling technique and new assay for detecting circulating antibodies to glutamic acid decarboxylase (GADab) in oral fluid, 32 subjects with type 1 diabetes (mean age ± SD: 13.9 ± 3.7 years) provided oral fluid and venous blood samples.

2 The oral fluid samples were assayed for total immunoglobulin G (IgG), then concentrated to a tenth of their volume using mini-centrifugal protein concentrators. Samples were assayed by a GAD65 antibody radio-immunoprecipitation method.

3 Oral fluid antibodies were detected in 10 of 16 seropositive subjects. Percentage counts per minute (%cpm) were significantly higher for seropositive subjects than for seronegative subjects ($P<0.001$).

4 A highly significant correlation (Spearman's rho: 0.85, $P<0.001$) was found between %cpm of concentrates and respective serum titres for seropositive subjects.

5 GADab recovery from oral fluid collections was estimated at 90%.

6 This is the first confirmatory detection of diabetes-specific autoimmune markers in oral fluid.

7 Further studies could lead to an alternative non-invasive screening method for preclinical autoimmune diabetes.

Todd AL, Ng WY, Lee YS et al (2002) Evidence of autoantibodies to glutamic acid decarboxylase in oral fluid of type 1 diabetic patients. *Diabetes Research and Clinical Practice* **57**: 171–7

ARCHIVES OF DISEASE IN CHILDHOOD

Long-term outcome of cerebral odema in ketoacidosis

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

1 Clinical evidence of cerebral oedema occurs in approximately 1% of diabetic ketoacidosis episodes.

2 Mortality from this complication is decreasing, but little is known about the long-term outcome.

3 This article describes a case of hypopituitarism and executive dysfunction developing 2 years after cerebral oedema in a 12-year-old boy.

4 The subject was diagnosed with type 1 diabetes at 2 years of age.

Transient left facial palsy and hemiparesis followed a hypoglycaemic episode at 7 years.

5 At 12.9 years he was admitted to hospital with diabetic ketoacidosis. Later he developed unequal and dilated pupils, which responded to treatment; a CT scan of the brain was normal.

6 Neuropsychological assessment revealed signs of dysexecutive syndrome, the subject's height velocity fell over the next 2 years and he had low growth hormone concentration following hypoglycaemic stimulation.

7 Human growth hormone therapy was commenced at 15.4 years and led to an acceleration in height velocity.

8 Where cerebral oedema occurs, it is important to recognise the possibility of hypothalamopituitary dysfunction in survivors.

Dunlop KA, Woodman D, Carson DJ (2002) Hypopituitarism following cerebral oedema with diabetic ketoacidosis. *Archives of Disease in Childhood* **87**: 337–8

DIABETES

Nitrosative stress impairs peripheral nerve function

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

1 The aim of this study was to determine whether nitric oxide overproduction is associated with deterioration in peripheral nerve function in type 1 diabetes.

2 Peripheral nerve function and biochemical indicators of nitrosative stress were measured annually for 3 years in 37 subjects with type 1 diabetes.

3 Plasma nitrite and nitrate (collectively NO(x)) was 34.0 ± 4.9 µmol/l in control subjects, compared with 52.4 ± 5.1, 50.0 ± 5.1 and 49.0 ± 5.2 in subjects with diabetes at 1, 2 and 3 years respectively ($P<0.01$).

4 Nitrotyrosine (NTY) was 13.3±2.0 µmol/l in control subjects and 26.8±4.4, 26.1±4.3 and 32.7±4.3 in subjects with diabetes at 1, 2 and 3 years respectively ($P<0.01$).

5 Uric acid was suppressed by 20% in the subjects with diabetes.

6 Composite motor nerve conduction velocity for the median, ulnar and peroneal nerves was reduced in subjects with higher NTY levels.

7 Decreased sweating was found in subjects with high NO(x).

8 Decreased autonomic function was found in subjects with suppressed uric acid.

9 In early diabetes, therefore, nitrosative stress is associated with suppressed uric acid and reduced peripheral nerve function.

Hoeldtke RD, Bryner KD, McNeill DR et al (2002) Nitrosative stress, uric acid, and peripheral nerve function in early type 1 diabetes. *Diabetes* **51**: 2817–25