Management of type 1 diabetes

Vitamin D and diabetes: Hype or hope?

Daniel Flanagan, Consultant Physician, Derriford Hospital, Plymouth

Vitamin D appears to be rapidly becoming the nutrient of choice for health stories relating to a wide variety of disease processes. Lack of vitamin D has been associated with a number of cancers, osteoporosis, fracture risk, heart disease and, of course, diabetes.

The "Sunshine Vitamin", as those selling the product like to refer to it, may possibly provide a weapon in the prevention of diabetes. Vitamin D is produced in the skin in response to exposure to ultraviolet light as vitamin D2, and is also present in our diets as vitamin D3.

The study by Kayaniyil et al (2011; summarised alongside) compares a measure of total 25-hydroxyvitamin D (the combined total of vitamin D2 and vitamin D3) with the results of an oral glucose tolerance test at baseline and 3 years later. The homeostasis model analysis calculation was used to give a measure of insulin resistance and insulin secretion. The conclusion was that those with higher levels of vitamin D showed higher insulin secretion and a suggestion of improved glucose tolerance. This observation is supported by a number of previous articles, but there are two important caveats.

First, an association between low vitamin D and diabetes risk does not prove causality. We need a plausible mechanism for the link and the exclusion of potential confounding factors. Vitamin D is a fat-soluble vitamin. The proportion of vitamin D sequestered in fat and, therefore, not available for measurement is likely to be proportional to fat mass. Low vitamin D may simply be a surrogate for increased adiposity. It has been suggested that vitamin D may suppress chronic inflammation or increase expression of the insulin receptor or proteins involved in the insulin signalling cascade. For the moment there are few data to support these ideas. Where measures have been attempted, such as looking at C-reactive protein, no association has been found.

Second, having shown that low vitamin D is associated with progression towards diabetes, we need to know if supplementing vitamin D reverses this. Again, the studies performed so far have shown mixed results. We have some evidence for improvements in insulin resistance with vitamin D supplementation (von Hurst et al, 2010) but also evidence for no improvement in insulin secretion or resistance in people who were vitamin D deficient but otherwise healthy (Grimnes et al, 2011). To distil this down, there may be something there but we are a long way from recommending vitamin D supplementation for people with diabetes.

Grimnes G, Figenschau Y, Almås B, Jorde R (2011) Vitamin D, insulin secretion, sensitivity, and lipids: results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique. *Diabetes* **60**: 2748–57

von Hurst PR, Stonehouse W, Coad J (2010) Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomised, placebo-controlled trial. *Br J Nutr* **103**: 549–55

BMJ

T1D mortality trends in Finland

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

1 This Finnish study examined mortality trends among people diagnosed with early-onset (age 0–14 years) and late-onset (15–29 years) T1D between 1970 and 1999.

2 There were 1338 deaths during 370 733 person-years of follow-up, giving an all-cause mortality rate of 361/100 000 person-years.

3 The standardised mortality ratio (SMR) was 3.6 in the early-onset (EO) cohort and 2.8 in the late-onset (LO) cohort, and women had higher SMRs than men in both cohorts.

4 The SMR at 20 years' diabetes duration in the EO cohort decreased from 3.5 to 1.9 in those diagnosed in 1970–4 and 1985–9, respectively; in the LO cohort the SMR increased from 1.4 to 2.9.

5 Mortality due to complications decreased with time in the EO cohort but not in the LO cohort.

6 It was concluded that survival in LO T1D has deteriorated since the 1980s, but has improved over time in EO T1D. Furthermore, the proportion of deaths caused by acute complications of diabetes has increased in people with LO T1D.

Harjutsalo V, Forsblom C, Groop PH (2011) Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. *BMJ* **343**:d5364

DIABETES

A role for vitamin D in beta-cell function and glycaemia?

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

1 The authors sought to explore the possible associations of baseline vitamin D [25-hydroxyvitamin D; 25(OH)D] with insulin resistance (IR), beta-cell function, and glucose homeostasis in people at risk of T2D.

2 Study participants (n=489; aged 50±10 years) were followed for 3 years. All received a 75-g oral glucose tolerance test (OGTT) at baseline and follow-up.

3 IR was measured using the Matsuda index (IS_{OGTT}) and the homeostasis model assessment of IR (HOMA-IR); beta-cell function was determined using both the insulinogenic index divided by HOMA-IR (IGI/IR) and the insulin secretion sensitivity index-2 (ISSI-2), and glycemia by using the area under the glucose curve ($AUC_{glucose}$).

4 After adjusting for a number of variables, no significant association of baseline 25(OH)D with follow-up IS_{OGTT} or HOMA-IR was observed; however, there were positive associations of baseline 25(OH)D and follow-up IGI/IR (beta, 0.005; P=0.015) and ISSI-2 (beta, 0.002; P=0.023), and a significant inverse association of baseline 25(OH)D and follow-up $AUC_{glucose}$ (beta, 20.001; P=0.007).

5 Some 116 participants progressed to dysglycaemia; higher baseline 25(OH)D was associated with a reduced risk of progression.

6 The authors concluded that higher baseline 25(OH)D independently predicted better beta-cell function and lower blood glucose levels.

Kayaniyil S, Retnakaran R, Harris SB et al (2011) Prospective associations of vitamin D with ß-cell function and glycemia: the PROspective Metabolism and ISlet cell Evaluation (PROMISE) cohort study. *Diabetes* **60**: 2947–53

NEW ENGLAND JOURNAL OF MEDICINE

Intensive diabetes therapy and GFR in people with T1D

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

1 The DCCT (Diabetes Control and Complications Trial) randomised 1441 people with T1D to 6.5 years of either intensive or conventional diabetes therapy; 1375 were then followed-up in the EDIC (Epidemiology of Diabetes Interventions and Complications) study.

2 The authors analysed data from both trials to determine the long-term effects of intensive diabetes therapy on the risk of glomerular filtration rate (GFR) impairment (defined as an estimated GFR of <60 mL/min/1.73 m^2).

3 Over a median follow-up of 22 years, GFR impairment developed in 24 participants in the intensive therapy group and 46 in the conventional therapy group, giving a risk reduction with intensive therapy of 50% (95% confidence interval, 18–69; P=0.006).

4 Of those with GFR impairment, end-stage renal disease (ESRD) developed in eight from the intensive therapy group and 16 from the conventional therapy group.

5 In comparison with conventional therapy, intensive therapy was associated with a reduced mean estimated GFR (eGFR) of 1.7 mL/min/1.73 m^2 during the DCCT study, but during the EDIC study was associated with a slower rate of GFR reduction and an increase in the mean eGFR of 2.5 mL/min/1.73 m^2 (P<0.001 for both).

6 It was concluded that the long-term risk of GFR impairment was significantly lower among people treated with early and intensive diabetes therapy than those treated with conventional therapy.

DCCT/EDIC Research Group, de Boer IH, Sun W et al (2011) Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* **365**: 2366–76

AMERICAN JOURNAL OF KIDNEY DISEASE

Sex differences in the development of ESRD in T1D

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

1 This study aimed to determine whether the historical male excesses in the incidence of end-stage renal disease (ESRD) in people with T1D persist.

2 Follow-up data (18 years) from the Pittsburgh Epidemiology of Diabetes Complications Study were analysed (n=788; baseline mean age, 27 years; diabetes duration, 19 years) using the sex and diagnosis intervals of 1950–64 and 1965–80).

3 A significant association was observed between sex and time of diagnosis for ESRD incidence by 25 and 30 years' duration (P=0.002 and P<0.001, respectively).

4 In the 1950–64 cohort, ESRD incidence was higher in men than women by 25 years' (30.6% vs 18.0%, respectively) and 30 years' (43.4% vs 24.6%, respectively) T1D duration.

5 In the 1965–80 cohort, ESRD incidence was higher in women than in men by 25 years' (7.6% vs 13.8%, respectively; P=0.04) and 30 years' (13.7% vs 21.0%, respectively; P=0.09) T1D duration.

6 The authors concluded that the excess in ESRD in men with T1D in the earlier cohort had been eliminated in the younger cohort.

Costacou T, Fried L, Ellis D, Orchard TJ (2011) Sex differences in the development of kidney disease in individuals with type 1 diabetes mellitus: a contemporary analysis. *Am J Kidney* **58**: 565–73

COCHRANE REVIEW

Insulin therapy preferable to SU in people with LADA

Readability	✓
Applicability to practice	✓
WOW! factor	✓✓

1 Latent autoimmune diabetes in adults (LADA) is a slowly developing form of T1D.

2 In this study the authors aimed to compare interventions used for people with LADA by reviewing studies obtained from electronic databases, hand-searches, conferences proceedings and consultations with experts.

3 Studies were selected if they were randomised controlled trials and controlled clinical trials evaluating interventions for LADA or T2D with antibodies.

4 A total of 13 306 citations were identified, of which 15 publications comprising 10 studies were included. These involved a total of 1019 participants who were followed for between 3 months and 10 years (1060 randomised).

5 In two studies it was shown that sulphonylurea (SU) therapy led to earlier insulin dependence.

6 A meta-analysis of four studies showed poorer glycaemic control with SUs compared with insulin: SU plus insulin did not improve glycaemic control significantly more than insulin alone at 3 and 12 months of treatment and follow-up, and SU (mono or in combination with metformin) gave poorer glycaemic control compared with insulin alone, with a mean HbA_{1c} difference from baseline to study end, for insulin compared with oral therapy, of –1.3% (P=0.03).

7 In one study it was shown that using vitamin D plus insulin may have a protective effect on pancreatic beta-cells in people with LADA.

8 The authors concluded that novel treatments such as GAD65 (glutamic acid decarboxylase formulated with aluminium hydroxide) in certain doses (20 µg) may have the potential to maintain fasting and stimulated C-peptide levels. However, they point out that there is no significant evidence for or against other lines of treatment of LADA.

Brophy S, Davies H, Mannan S et al (2011) Interventions for latent autoimmune diabetes (LADA) in adults. *Cochrane Database Syst Rev* **9**: CD006165

> *"The long-term risk of glomerular filtration rate impairment was significantly lower among people treated with early and intensive diabetes therapy than those treated with conventional therapy."*

"... the presence of islet antibodies, especially islet antigen-2, makes the diagnosis of MODY very unlikely; genetic testing should therefore only be performed if other clinical characteristics strongly suggest MODY rather than T1D."

DIABETOLOGIA

Hypoglycaemia may lower K+ levels in people with T1D

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

1 Although it is well known that diabetes causes disturbances in electrolyte levels, little is known regarding the cumulative effects of glycaemia excursions on ionic profiles of people with T1D.

2 The authors of this study therefore explored the electrolyte profiles of people with T1D during consecutive hyper- and hypoglycaemic events using a glucose clamp.

3 Participants (n=15) had a mean (±SD) age of 27±6 years, diabetes duration of 10.2±7.2 years, BMI of 23.2±2.1 kg/m^2, and HbA_{1c} level of 52.0±6.9 mmol/mol (6.9±0.8%).

4 Two successive hyperglycaemic excursions to 18 mmol/L were induced (protocol 1); then hypoglycaemia was induced to 2.5 mmol/L, followed by hyperglycaemia to 12 mmol/L, and then again to hypoglycaemia (3.0 mmol/L).

5 An increase in blood osmolarity was observed during hyperglycaemia but not hypoglycaemia.

6 Hyperglycaemia induced an increase in K^+ levels and a decrease in plasma Na^+, Ca^{2+} and Cl^- levels.

7 While hypoglycaemia induced rapid and rapidly reversible increases in Na^+, Ca^{2+} and Cl^-, the same glycaemic excursion induced a rapid and substantial decrease in K^+ levels, which failed to recover even 2 hours after euglycaemia was restored.

8 The results were concluded to suggest that recurring episodes of hypoglycaemia in people with T1D may lead to progressively lower K+ levels despite rapid re-establishment of euglycaemia.

Caduff A, Lutz HU, Heinemann L et al (2011) Dynamics of blood electrolytes in repeated hyper- and/or hypoglycaemic events in patients with type 1 diabetes. *Diabetologia* **54**: 2678–89

EUR J GASTROENTEROL HEPATOL

Early appearance of EGG abnormalities in children with T1D

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

1 This study sought to assess gastric myoelectrical activity using electrogastrography (EGG) in children with T1D and to correlate it with metabolic control (HbA_{1c} and fasting blood glucose levels, and fructosamine) and BMI.

2 Forty-nine children with T1D aged were age-matched with 17 healthy controls. EGG was performed after measuring HbA_{1c}, fasting blood glucose and fructosamine levels.

3 An increase in bradygastria was observed in the T1D group when compared with controls (7.9±8.8 vs 2.1±1.0 cpm; P=0.011), with an associated decrease in preprandial normogastria (72.2±14.5 vs 82.7±14.7 cpm; P=0.013).

4 A significant increase in normogastric power ratio (postprandial/preprandial power) was observed in the T1D group compared with controls (mean, 6.67 vs 3.14; P=0.034).

5 Longer T1D duration was associated with increased risk of EGG abnormalities (P=0.036). Hyperglycaemia was associated with bradygastria (P=0.01) and power ratio bradygastria (P=0.042). EGG parameters were not affected by HbA_{1c}, fructosamine or BMI.

6 EGG abnormalities are associated with acute hyperglycaemia, and are not related to HbA_{1c} and fructosamine levels. The authors concluded that diabetic autonomic neuropathy is therefore an unlikely pathogenic factor for EGG abnormalities in children with T1D.

Posfay-Barbe KM, Lindley KJ, Schwitzgebel VM et al (2011) Electrogastrography abnormalities appear early in children with diabetes type 1. *Eur J Gastroenterol Hepatol* **23**: 881–5

DIABETIC MEDICINE

Islet autoantibodies can discriminate MODY from T1D

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

1 Maturity-onset diabetes of the young (MODY) is often misdiagnosed as T1D and inappropriately treated with insulin. T1D is characterised by the presence of islet autoantibodies, including glutamate decarboxylase (GAD) and islet antigen-2 (IA-2) antibodies. However, the presence of islet autoantibodies in MODY is currently unknown.

2 This study assessed the prevalence of GAD and IA-2 antibodies in people with MODY and T1D to determine the potential to differentiate between the two conditions.

3 Plasma GAD and IA-2 antibodies were measured in 508 people with MODY and 98 people with newly-diagnosed T1D (<6 months). Autoantibodies were considered positive if in the ≥99th centile of 500 adult controls.

4 GAD or IA-2 antibodies were present in 82% (80/98) of people with T1D and <1% (5/508) of people with MODY.

5 Both GAD And IA-2 antibodies were detected in 37.8% of people with T1D – GAD-only in 24.5% and IA-2-only in 19.4%.

6 In the five people with MODY with detectable antibodies, all were GAD antibodies, with no detectable IA-2 antibodies.

7 It was concluded that the presence of islet antibodies, especially IA-2, makes the diagnosis of MODY very unlikely; genetic testing should therefore only be performed if other clinical characteristics strongly suggest MODY rather than T1D.

McDonald TJ, Colclough K, Brown R et al (2011) Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from type 1 diabetes. *Diabet Med* **28**: 1028–33