Vitamin D deficiency as a cause of diabetes? A critique of the current evidence base

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Vitamin D research is hot! The vitamin D deficiency hypothesis as a cause for several diseases is very much in vogue, albeit predominantly based on findings from observational studies.

Kayaniyil et al (2010; summarised alongside) provides yet another such study and reports a significant association between 25-hydroxyvitamin D levels (the best blood measure of vitamin D status) and measures of both insulin resistance and beta-cell dysfunction in a cross-sectional study of 712 people at risk of diabetes. The authors suggest their analysis, which is adjusted for several potential confounders, supports the role of vitamin D deficiency in the pathogenesis of type 2 diabetes.

While Kayaniyil et al's, and others', findings on the vitamin D–type 2 diabetes link are of interest, there is a need for caution before widespread supplementation is recommended. First, adjusting for potential confounding factors in this context can be difficult. For example, take sunlight exposure, a major stimulus for vitamin D levels. To assess sun exposure most studies have attempted to adjust for physical activity but, to date, none have directly measured sunlight exposure (clearly, difficult to do), leaving the potential for residual confounding. Equally, few studies have considered socioeconomic status, yet emerging data suggest vitamin D levels may vary by this measure (perhaps linked to different diets, activity levels, smoking status, etc.; Hyppönen et al, 2010).

Concern over confounders undermining research findings is not a new phenomenon in the world of vitamin epidemiology; socioeconomic status and a range of lifestyle factors influence circulating levels of vitamins C and E, and carotenoids (Talwar et al, 2010) are likely to confound associations between circulating vitamin levels and cardiovascular endpoints (Lawlor et al, 2004).

Currently, no clear conclusions can be drawn with regard to type 2 diabetes and vitamin D. Observational studies in isolation cannot prove a causal role for vitamin D in type 2 diabetes, or any other condition. Furthermore, recent short-term studies in type 2 diabetes do not report benefits of routine (Patel et al, 2010) or high-dose (Witham et al, 2010) vitamin D supplementation on insulin resistance or glycaemia. Only longer, larger, well-conducted, randomised trials, with appropriate clinical endpoints, will demonstrate whether vitamin D represents a potential "magic bullet" for diabetes, or perhaps another false dawn.

> "Currently, no clear conclusions can be drawn with regard to type 2 diabetes and vitamin D. Observational studies in isolation cannot prove a causal role for vitamin D in type 2 diabetes, or any other condition."

Hyppönen E, Berry D, Cortina-Borja M, Power C (2010) 25-Hydroxyvitamin D and pre-clinical alterations in inflammatory and hemostatic markers: a cross sectional analysis in the 1958 British Birth Cohort. *PLoS One* **5**: e10801

Lawlor DA, Davey Smith G, Kundu D et al (2004) Those confounded vitamins: what can we learn from the differences between observational versus randomised trial evidence? *Lancet* **363**: 1724–7

Patel P, Poretsky L, Liao E (2010) Lack of effect of subtherapeutic vitamin D treatment on glycemic and lipid parameters in type 2 diabetes: a pilot prospective randomized trial. *J Diabetes* **2**: 36–40

Talwar D, McConnachie A, Welsh P et al (2010) Which circulating antioxidant vitamins are confounded by socioeconomic deprivation? The MIDSPAN family study. *PLoS One* **5**: e11312

Witham MD, Dove FJ, Dryburgh M et al (2010) The effect of different doses of vitamin D(3) on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia* **53**: 2112–9

DIABETES CARE

Vitamin D may play a role in the aetiology of T2D

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

1 Although some evidence suggests vitamin D plays a role in the aetiology of T2D, the association of vitamin D with insulin resistance (IR) and beta-cell dysfunction remains uncertain.

2 The objective of this study was to examine the association of serum vitamin D concentration with IR and beta-cell dysfunction in a cohort from the PROMISE (Prospective Metabolism and Islet Cell Evaluation) trial.

3 People (n=712; aged ≥30 years) at high risk of T2D participated.

4 Insulin sensitivity was measured using the Matsuda insulin sensitivity index for oral glucose tolerance tests (IS_{OGTT}), IR was measured using the homeostasis model assessment of IR index (HOMA-IR) and beta-cell dysfunction was determined by dividing the insulinogenic index (IGI) by HOMA-IR (IGI/IR) and calculating the insulin secretion sensitivity index-2 (ISSI-2).

5 Univariate analyses showed a positive association between vitamin D and IS_{OGTT} (P<0.0001), a negative association between vitamin D and HOMA-IR (P<0.0001) and positive associations between vitamin D and IGI/IR and ISSI-2 (P=0.0002).

6 Multivariate regression analyses showed that vitamin D status was a significant independent predictor of insulin sensitivity (IS_{OGTT} and HOMA-IR) and beta-cell function (IGI/IR and ISSI-2) in this multi-ethnic cohort of people at risk of T2D.

7 The authors concluded that vitamin D defiency may play a role in the pathogenesis of T2D.

Kayaniyil S, Vieth R, Retnakaran R et al (2010) Association of vitamin D with insulin resistance and beta-cell dysfunction in subjects at risk for type 2 diabetes. *Diabetes Care* **33**: 1379–81

DIABETES CARE

Diabetes a risk factor for oral leukoplakia

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

1 Leukoplakia is a premalignant lesion in the oral mucosa; between <1% and 18% of lesions will progress to oral cancer.

2 Known risk factors include smoking and drinking alcohol; diabetes may also be a risk factor, although the causal mechanism is unknown.

3 This study comprised 4310 adults from the Study of Health in Pomerania, of whom 4210 were screened for oral mucosal lesions; 123 cases of oral leukoplakia were identified.

4 Cases were matched 1:2 with controls without leukoplakia, and lifestyle factors, LDL-cholesterol, HDL-cholesterol and HbA_{1c} were assessed.

5 The risk of leukoplakia was increased in never-smokers with an HbA_{1c} level ≥6.5% (48 mmol/mol), which was comparable to the risk in smokers with normal glycaemia.

6 HbA_{1c} was significantly associated with leukoplakia; there was a continuously increasing risk with increasing levels of HbA_{1c} or LDL-cholesterol, related to quantitative metabolic disturbances.

7 People with oral leukoplakia had higher levels of diabetes-related metabolites, a higher LDL : HDL-cholesterol ratio, higher HbA_{1c} levels and were more frequently smokers.

8 The link between leukoplakia and increasing LDL : HDL-cholesterol ratios could be caused by abnormal lipid metabolism in people with diabetes.

9 Metabolic disturbances in diabetes with interactions between systemic and local factors (e.g. smoking) increased the risk of oral leukoplakia.

10 The authors found diabetes to be a risk factor for oral leukoplakia.

Meisel P, Dau M, Sümnig W et al (2010) Association between glycaemia, serum lipoproteins and the risk of oral leukoplakia. *Diabetes Care* **33**: 1230–2

DIABETES CARE

Exenatide reduces weight in obese people at risk of T2D

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

1 The authors looked at the effects of exenatide, in addition to lifestyle intervention, on body weight and glucose tolerance in obese people without T2D.

2 Obese people without diabetes (n=152) were randomised to receive exenatide (n=73) or placebo (n=79) with lifestyle intervention for 24 weeks.

3 By study end, people in the exenatide group had lost 5.1±0.5 kg and people in the placebo group had lost 1.6±0.5 kg (P<0.001).

4 More people in the exenatide group (77%) had impaired glucose tolerance or impaired fasting glucose normalised by the end of the study than those in the placebo group (56%).

5 The authors concluded that exenatide with lifestyle modification reduces weight and T2D risk among people with impaired glucose tolerance or impaired fasting glucose.

Rosenstock J, Klaff LJ, Schwartz S et al (2010) Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes. *Diabetes Care* **33**: 1173–5

DIABETES CARE

Educational disparities affect mortality in diabetes

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

1 Educational disparities in mortality were examined in 5007 adults with either T1D or T2D compared with 80 860 adults without diabetes.

2 Data were collected from the National Health Interview Survey; the people with and without diabetes at baseline were followed-up for mortality for a median of 10.5 years.

3 During follow-up, 15 351 people died (2188 with diabetes); cardiovascular disease (CVD) was the cause of death in 46.6% of people with diabetes and in 40.2% of those without diabetes.

4 People with diabetes had a 28% higher risk of all-cause mortality in the lowest versus the highest position on the educational scale.

5 The inverse relationship between education and mortality was statistically significant for people with diabetes, although this disparity was smaller than in the general population.

6 Low educational status in adults with diabetes was found to have a major impact on mortality, especially CVD mortality.

Dray-Spira R, Gary-Webb TL, Brancati FL (2010) Educational disparities in mortality among adults with diabetes in the U.S. *Diabetes Care* **33**: 1200–5

DIABETOLOGIA

BMI and T2D share minor fraction of genetic variance

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

1 The authors of this study aimed to determine whether BMI predicts the onset of T2D.

2 Data were obtained from the Finnish Twin Cohort Study; 4076 monozygotic and 9109 dizygotic adult twin pairs without T2D had their BMI assessed at baseline in 1975.

3 Incident cases of T2D were obtained until 2005; 1332 twins developed T2D.

4 The hazard ratio for T2D was 1.22 per BMI unit and 1.97 per standard deviation of BMI.

5 Only a fraction of covariation in BMI and incident T2D was of genetic origin despite high trait heritability estimates.

Lehtovirta M, Pietiläinen KH, Levälahti E et al (2010) Evidence that BMI and type 2 diabetes share only a minor fraction of genetic variance. *Diabetologia* **53**: 1314–21

> *"Metabolic disturbances in diabetes with interactions between systemic and local factors (e.g. smoking) increased the risk of oral leukoplakia."*