di-methylarginine (ADMA)—a predictor of accelerated decline in glomerular filtration rate and increased cardiovascular disease events in diabetic nephropathy.[6] Studies in patients requiring hemodialysis, however, suggest that cosupplementation with folate and methylcobalamin (a vitamin B_{12} vitamer) tends to decrease both levels of plasma homocysteine and ADMA.[7]

A further factor underlying the association of high-dose vitamin B_6, B_9 and B_{12} supplements and metabolic dysfunction in diabetic nephropathy could be the effect of high-dose folic acid on metabolite transport via the folate transporter 1 (RFC-1). In addition to facilitating transport of folate, RFC-1 is also a transporter of thiamine monophosphate (TMP) and thiamine pyrophosphate (TPP).[8] Diabetic nephropathy occurs within a background of thiamine (vitamin B_1) deficiency owing to impaired renal reuptake of thiamine. Plasma thiamine concentrations were inversely linked to plasma soluble vascular cell adhesion protein 1 (sVCAM-1)—a risk marker of cardiovascular disease.[9] Folate binds to and is transported into cells by the RFC-1 transporter.[8] High-dose folic acid supplementation might exacerbate thiamine deficiency at susceptible sites, such as the kidney and vascular cells in diabetic nephropathy, by competing with TMP and TPP and impairing their uptake into tissues, thereby inhibiting sharing of thiamine metabolites between tissues rich in thiamine and those deficient in it.[9] This mechanism could be a further factor underlying the accelerated decline in glomerular filtration rate and increased vascular disease reported in the DIVINe study. Preclinical investigations are now required to test this and other plausible mechanisms underlying adverse effects of high dose vitamin B_6, B_9 and B_{12} supplementation.

Finally, clear discrimination of treatment with vitamin B_6, B_9 and B_{12} from other B-vitamins in titles, headlines, presentations and press releases, as well as in text of scientific reports, is required for clarity. 'B-vitamin therapy' is a catch-all, convenient phrase for a report title but can be misleading and lead to unnecessary concern in patients taking other B-vitamin supplements and in their carers. Of course, not all B-vitamins are the same. In a pilot–scale, placebo-controlled intervention trial, high-dose thiamine supplementation of patients with type 2 diabetes mellitus and early-stage diabetic nephropathy (micro-albuminuria) improved renal function in all patients treated and produced regression

of microalbuminuria for some individuals.[10] High-dose thiamine therapy holds promise as a novel additional treatment for early-stage diabetic nephropathy.

In summary, the recent DIVINe study provided evidence of adverse effects of high-dose vitamin B_6, B_9 and B_{12} supplementation in advanced stage diabetic nephropathy. Following this, supplementation at high therapeutic doses with this particular vitamin combination should preferably be avoided in advanced stage diabetic nephropathy, whereas research on the biochemical basis for the adverse effects needs to be initiated and alternative interventions to decrease plasma homocysteine levels must be explored.

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1. House, A. A. *et al.* Effect of B-Vitamin therapy on progression of diabetic nephropathy: A randomized controlled trial. *JAMA* **303**, 1603–1609 (2010).
2. Lonn, E. *et al.* Homocysteine lowering with folic acid and B vitamins in vascular disease. *N. Engl. J. Med.* **354**, 1567–1577 (2006).
3. Jamison, R. L. *et al.* Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: A randomized controlled trial. *JAMA* **298**, 1163–1170 (2007).
4. Ebbing, M. *et al.* Cancer incidence and mortality after treatment with folic acid and vitamin B12. *JAMA* **302**, 2119–2126 (2009).
5. Williams, M. E. *et al.* Effects of pyridoxamine in combined phase 2 studies of patients with type 1 and type 2 diabetes and overt nephropathy. *Am. J. Nephrol.* **27**, 605–614 (2007).
6. Lajer, M. *et al.* Plasma concentration of asymmetric climethylarginine (ADMA) predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care* **31**, 747–752 (2008).
7. Koyama, K. *et al.* Randomized controlled trial of the effect of short-term coadministration of methylcobalamin and folate on serum ADMA concentration in patients receiving long-term hemodialysis. *Am. J. Kidney Dis.* **55**, 1069–1078 (2010).
8. Zhao, R., Gao, F. & Goldman, I. D. Reduced folate carrier transports thiamine monophosphate: an alternative route for thiamine delivery into mammalian cells. *Am. J. Physiol. Cell Physiol.* **282**, C1512–C1517 (2002).
9. Thornalley, P. J. The potential role of thiamine (vitamin B1) in diabetic complications. *Curr. Diabetes Rev.* **1**, 287–298 (2005).
10. Rabbani, N. *et al.* High dose thiamine therapy for patients with type 2 diabetes and microalbuminuria: a pilot randomised, double-blind, placebo-controlled study. *Diabetologia* **52**, 208–212 (2009).

DIABETES

Shining a light: the role of vitamin D in diabetes mellitus

Joanna Mitri and Anastassios G. Pittas

A new study shows that serum vitamin D concentration is inversely associated with HbA$_{1c}$ levels among adults in the US aged 35–74 years, in line with results from other observational studies. Should adults with diabetes mellitus or at risk of developing this disease take vitamin D to improve glycemia or reduce this risk?

Vitamin D status is known to influence bone and mineral homeostasis but research over the past 5 years has identified potential roles for this vitamin in several nonskeletal disorders, including diabetes mellitus. In a study published in *Diabetes Care*, Kositsawat and colleagues[1] showed that serum vitamin D concentration is inversely associated with HbA$_{1c}$ levels among adults in the US aged 35–74 years, but not among adults 18–34 years or those aged >75 years.

Vitamin D insufficiency has long been suspected to be a risk factor for type 1 diabetes mellitus. In the past few years, accumulating evidence has suggested that altered vitamin D homeostasis might also have a role in the development of type 2 diabetes mellitus. In patients with type 2 diabetes mellitus, impaired pancreatic β-cell function, insulin resistance and systemic inflammation are often present in varying degrees and the evidence suggests that vitamin D modulates all

these characteristics.[2] Vitamin D might exert these effects directly via the binding of its circulating active form, 1,25-hydroxyvitamin D, to the vitamin D receptor in β-cells and insulin-responsive tissues or indirectly through its well-recognized role in regulating extracellular calcium concentration and flux through cell membranes.

Kositsawat et al. conducted cross-sectional analyses of data from 9,773 adults (age ≥18 years) who participated in the 2003–2006 National Health and Nutrition Survey (NHANES), a large survey conducted at regular intervals to assess the health and nutritional status of adults and children in the USA. Participants' vitamin D status was assessed with an assay that measured both serum 25-hydroxyvitamin D_3 and serum 25-hydroxyvitamin D_2 concentration. Data on BMI, HbA_{1c}, serum 25-hydroxyvitamin D and parathyroid hormone were measured directly, whereas ethnicity, sex, physical activity and any vitamin supplement use were self-reported. Participants were defined as having diabetes mellitus (both type 1 and type 2) based on self-report or current use of any diabetes mellitus medication.

In the entire cohort, 25-hydroxyvitamin D concentration was not associated with HbA_{1c} level after adjustment for ethnicity, sex, BMI, history of diabetes mellitus, parathyroid hormone levels, physical activity and any dietary supplement use. However, the researchers found that the association between 25-hydroxyvitamin D and HbA_{1c} was affected by age ($P = 0.026$). The researchers then divided the cohort into three age-groups (18–34, 35–74 and ≥75 years) and repeated the analyses. Serum 25-hydroxyvitamin D concentration was inversely associated with HbA_{1c} level in individuals 35–74 years old, but not among the younger or older adults. The investigators also reported an inverse association between 25-hydroxyvitamin D and HbA_{1c} among all adults without diabetes mellitus, but not among those with diabetes mellitus.

These findings are consistent with observations from other cross-sectional studies that have also reported inverse associations between 25-hydroxyvitamin D concentration and HbA_{1c} level, both in NHANES participants[3] and in cohorts from outside the USA.[4–6] Vitamin D status—measured by vitamin D intake or 25-hydroxyvitamin D concentration—also seems to be associated with the presence of diabetes mellitus or the metabolic syndrome. Kositsawat and colleagues report that the association between 25-hydroxyvitamin D and HbA_{1c} was not present in the younger and older age groups. This interesting finding might be explained by lack of statistical power, especially in the younger group, of whom only 1.5% had hyperglycemia. In the older group, the lack of association might be explained by vitamin D insufficiency being a lesser contributor to hyperglycemia than other age-related risk factors for diabetes mellitus. Similarly, the lack of this association among adults with diabetes mellitus might be owing to vitamin D having a prominent role only among those without established diabetes mellitus or to a confounding effect of active diabetes mellitus therapy. These observations provide important guidance for the design of future clinical trials with vitamin D supplementation.

The major strengths of the study by Kositsawat et al. are the inclusion of a large representative sample of the US adult population and the multivariate adjustment for important confounding variables that can influence levels of both the biomarker (25-hydroxyvitamin D) and the variable of interest (HbA_{1c}). The major weakness is the cross-sectional study design that does not establish whether impaired vitamin D status is a cause or consequence of hyperglycemia. Importantly, the potential for residual confounding by unmeasured or unmeasurable variables can never be excluded with certainty in observational studies. Confounding is especially of concern in studies that assess vitamin D because a high vitamin D status is an excellent marker of good health, as it is associated with young age, normal body weight and a healthy lifestyle, including good dietary and exercise behaviors. Furthermore, impaired vitamin D status could reflect chronic nonspecific illness, which might prevent individuals from participating in outdoor activities and receiving sufficient sun exposure. Inverse associations between vitamin D status and diabetes mellitus reported in cross-sectional studies are, therefore, likely to be explained by reverse causation—diabetes mellitus is causing low vitamin D status rather than low vitamin D status causing diabetes mellitus.

Six longitudinal observational studies have reported an association between baseline vitamin D status (measured as vitamin D intake or 25-hydroxyvitamin D concentration) and incident type 2 diabetes mellitus.[7] Three of the six analyses (from four different cohorts) showed a lower incidence of type 2 diabetes mellitus in participants with the highest vitamin D status compared with those with the lowest vitamin D status. Eight trials have reported that vitamin D supplementation was not associated with changes in glycemia-related variables or the incidence of type 2 diabetes mellitus.[7] However, several of these studies had nonglycemic primary end points and were, therefore, underpowered to detect any association between vitamin D supplementation and glycemia-related variables. In a post hoc subgroup analysis of one of these trials, which was designed to assess the effects of combined calcium and vitamin D supplementation on osteoporosis, treatment with vitamin D_3 (17.5 μg per day) and calcium carbonate (500 mg per day) supplementation improved glycemia among adults with impaired glucose tolerance at baseline.[8] These findings suggest that taking vitamin D supplements might benefit individuals at risk of developing type 2 diabetes mellitus.

The optimal blood 25-hydroxyvitamin D concentration is hotly debated and is currently under review by the US Institute of Medicine. A consensus has emerged that blood 25-hydroxyvitamin D concentration <25 mmol/l defines vitamin D deficiency, whereas levels >75 mmol/l are required to improve several outcomes, for example, osteopenia and osteoporosis.[9] Currently, the recommended intake of vitamin D in the US is 5 μg per day for adults <50 years,

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Practice points

- In observational studies, vitamin D status is inversely associated with HbA_{1c} level, especially among participants without a diagnosis of diabetes mellitus

- This association might be confounded by many unmeasured and unaccounted-for variables

- Intervention studies will be required to provide convincing evidence that vitamin D supplementation will reduce the risk of incident diabetes mellitus or improve glycemia among those with established diabetes mellitus

- Vitamin D supplementation at levels proven to improve skeletal outcomes (for example, 20–25 μg daily) should be recommended for adults

10 µg per day for those aged 51–70 years and 15 µg per day for those aged >70 years. In Europe, the recommended daily intake for adults is 5 µg per day. The US recommendations will be revised by the Institute of Medicine when it concludes its review in the fall of 2010 to reflect the growing consensus that vitamin D intakes above the current recommendations might be associated with improved health outcomes.

Definitive conclusions cannot yet be drawn with regard to the apparent link between vitamin D status and diabetes mellitus, as this association might be confounded by a variety of factors and no trials have specifically been designed to test the effects of vitamin D levels on diabetes mellitus risk. The role of vitamin D supplementation in diabetes mellitus prevention and/or therapy needs to be proven in randomized controlled trials specifically designed to test the hypothesis that such supplementation reduces the risk of developing diabetes mellitus in high-risk populations or improves glycemia among those with established diabetes mellitus.

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1. Kositsawat, J., Freeman, V. L., Gerber, B. S. & Geraci, S. Association of A1c levels with vitamin D status in US adults: data from the National Health and Nutrition Examination Survey. *Diabetes Care* **33**, 1236–1238 (2010).
2. Pittas, A. G., Lau, J., Hu, F. B. & Dawson-Hughes, B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* **92**, 2017–2029 (2007).
3. Zhao, G., Ford, E. S. & Li, C. Associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with surrogate markers of insulin resistance among US adults without physician-diagnosed diabetes: NHANES, 2003–2006. *Diabetes Care* **33**, 344–347 (2010).
4. Hyppönen, E. & Power, C. Vitamin D status and glucose homeostasis in the 1958 British birth cohort: the role of obesity. *Diabetes Care* **29**, 2244–2246 (2006).
5. Lu, L. *et al.* Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. *Diabetes Care* **32**, 1278–1283 (2009).
6. McGill, A. T., Stewart, J. M., Lithander, F. E., Strik, C. M. & Poppitt, S. D. Relationships of low serum vitamin D_3 with anthropometry and markers of the metabolic syndrome and diabetes in overweight and obesity. *Nutr. J.* **7**, 4 (2008).
7. Pittas, A. G. *et al.* Systematic review: vitamin D and cardiometabolic outcomes. *Ann. Intern. Med.* **152**, 307–314 (2010).
8. Pittas, A. G., Harris, S. S., Stark, P. C. & Dawson-Hughes, B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. *Diabetes Care* **30**, 980–986 (2007).
9. Bischoff-Ferrari, H. A., Giovannucci, E., Willett, W. C., Dietrich, T. & Dawson-Hughes, B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am. J. Clin. Nutr.* **84**, 18–28 (2006).

PITUITARY GLAND

New consensus in acromegaly: criteria for cure and control

Nienke Biermasz

Developments in treatment modalities and assays over the past 10 years warranted a new consensus on the criteria for cure of acromegaly, which was reached at a meeting of the Acromegaly Consensus Group, in April 2009. The novel consensus statement highlights current analytical pitfalls and the need to optimize disease control in acromegaly.

Acromegaly is a serious endocrine disease associated with increased mortality and comorbidity.[1] The main therapeutic goal in patients with acromegaly is, therefore, to eliminate (progression of) morbidity, to normalize mortality risk and to control tumor mass with safe treatments.[2] Most will agree that these goals are probably achieved best by normalizing secretion of growth hormone and insulin-like growth factor 1 (IGF-1) and that the sequelae of acromegaly are serious enough to justify the currently available expensive treatments. However, the definition of 'normal concentrations' is not straightforward. In clinical practice, measurements of serum growth hormone and IGF-1 levels are subject to analytical pitfalls and interpretative difficulties.

Over the past decade, important progress in the treatment options for acromegaly has been made, which required an update of the 'Cortina criteria for cure' described in a consensus statement of 2000.[2] The new statement[3] is a result of a meeting of the Acromegaly Consensus Group, held in April 2009 in Paris, France, at which 74 leading experts in the field of acromegaly discussed and updated the Cortina consensus statement on criteria for cure of acromegaly.

The Acromegaly Consensus Group considered many of the advances that have occurred in the management of acromegaly over the past 10 years. First, the growth hormone receptor antagonist pegvisomant was introduced.[4] This compound has changed the clinical perspective of treatment outcome, as the disease of virtually all patients can now be biochemically controlled. Furthermore, effective combination treatment with somatostatin analogs plus pegvisomant was introduced.[5] New long-term follow-up data from uncontrolled studies of long-term treatment with somatostatin analogs, radiotherapy and surgery were published.[6] A (nearly) normalized mortality risk following 'modern' treatment (mainly primary transsphenoidal surgery), with the use of new criteria for cure (that is, a normal serum IGF-1 level and a growth hormone concentration <2.5 µg/l) was recorded by several groups.[7] On the other hand, increasing evidence suggests late, irreversible clinical effects can occur as a result of a period of growth hormone oversecretion. National registries of patients with acromegaly have been created, enabling future study of disease outcome and testing of new treatments.[8,9] In addition, highly sensitive and specific growth hormone assays are now readily available and IGF-1 assays have been improved. Thus, the lower threshold for the glucose tolerance test (0.4 µg/l) and a growth hormone concentration of 1 µg/l, as a reflection of normalized growth hormone suppression—already mentioned in the 2000 statement[2]—are currently feasible.

Given the low incidence of acromegaly, statements cannot be based on large, randomized controlled trials,[10] which compromises the strength of recommendations. Methodological issues, such as study design, patient selection bias and heterogeneity of biochemical measurements, are potential drawbacks of nearly all studies in acromegaly. Case series, mostly based on retrospective