only a relatively small number of patients achieved this normalization. Nevertheless, treatment with pasireotide may be effective for active acromegaly in a proportion of patients resistant to current somatostatin analogues, and disease control might be further optimized by use of combination therapy with pegvisomant. Temozolomide is a well-tolerated and often effective chemotherapy for aggressive pituitary tumors when other therapeutic options have failed, but the duration of therapy needs to be established and long-term follow-up is necessary. The role of *MGMT* expression status as a prognostic biomarker of therapeutic response to temozolomide also requires further evaluation. We eagerly await what 2011 will bring to the field of pituitary tumors.

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A. B. Grossman declares an association with the following companies: Ipsen, Novartis. See the article online for full details of the relationships.
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1. Boscaro, M. *et al.* Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. *J. Clin. Endocrinol. Metab.* **94**, 115–122 (2009).
2. Colao, A. *et al.* Pasireotide (SOM230) provides clinical benefit in patients with Cushing's disease: results from a large, 12-month, randomized-dose, double-blind, phase III study [abstract]. 14th European NeuroEndocrine Association Congress (abstract OC-1.7) (2010).
3. Feelders, R. A. *et al.* Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. *N. Engl. J. Med.* **362**, 1846–1848 (2010).
4. Petersenn, S. *et al.* Pasireotide Acromegaly Study Group. Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, phase II trial. *J. Clin. Endocrinol. Metab.* **95**, 2781–2789 (2010).
5. Peverelli, E. *et al.* The dopamine-somatostatin chimeric compound BIM-23A760 exerts antiproliferative and cytotoxic effects in human non-functioning pituitary tumors by activating ERK1/2 and p38 pathways. *Cancer Lett.* **288**, 170–176 (2010).
6. Lesage, C. *et al.* A phase II exploratory study of BIM23A760 in acromegalic patients: Preliminary results of safety and efficacy after a single-dose administration [abstract P3–673]. The Endocrine Society's annual meeting (2009).
7. Raverot, G. *et al.* Temozolomide treatment in aggressive pituitary tumors and pituitary carcinomas: a French multicenter experience. *J. Clin. Endocrinol. Metab.* **95**, 4592–4599 (2010).
8. McCormack, A. I. *et al.* Low O_6-methylguanine-DNA methyltransferase (MGMT) expression and response to temozolomide in aggressive pituitary tumours. *Clin. Endocrinol. (Oxf.)* **71**, 226–233 (2009).
9. Kovacs, K. *et al.* MGMT immunoexpression predicts responsiveness of pituitary tumors to temozolomide therapy. *Acta Neuropathol.* **115**, 261–262 (2008).
10. Bush, Z. M. *et al.* Temozolomide treatment for aggressive pituitary tumors: correlation of clinical outcome with O_6-methylguanine methyltransferase (MGMT) promoter methylation and expression. *J. Clin. Endocrinol. Metab.* **95**, E280–E290 (2010).

VITAMIN D DEFICIENCY IN 2010

Health benefits of vitamin D and sunlight: a D-bate

Michael F. Holick

Vitamin D deficiency increases the risk of autoimmune, cardiovascular and infectious diseases, type 2 diabetes mellitus, as well as the risk of falls and fractures. Several prospective, randomized, controlled trials published in 2010 highlight the importance of improving vitamin D status in children and adults to reduce the risk of upper respiratory tract infections and cardiovascular disease, amongst other disorders.

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Vitamin D deficiency is one of the most common medical conditions worldwide with more than 1 billion children and adults at risk.[1] The major causes of vitamin D deficiency are lack of adequate vitamin D from dietary sources and avoidance of sensible sun exposure, amongst many others (Figure 1). Over the past decade, several thousand articles have been published about the health benefits of sunlight exposure and optimal vitamin D status via UV exposure, diet and supplements. Being born or living at lower latitudes reduces the risk of developing type 1 diabetes mellitus, multiple sclerosis, hypertension and deadly cancers.[1] These observations have been supported by retrospective studies that link low circulating levels of 25-hydroxyvitamin D, a measure of vitamin D status, with an increased risk of a vast array of detrimental conditions, including type 2 diabetes mellitus, infectious diseases, cancer, multiple sclerosis and neurocognitive dysfunction (Figure 1).[1] However, most of these reports were association studies, and there remains great skepticism as to whether enhancing vitamin D status in children and adults can reduce these and other health issues. In 2010, several prospective studies examined whether an increase in vitamin D status has direct health benefits for children and adults.

In a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, Urashima *et al.*[2] investigated the effect of a vitamin D supplement on the incidence of seasonal influenza A infection in school children aged 6–15 years. Of 167 children who received 1,200 IU of vitamin D per day for 4 months, 18 (10.8%) were documented to be infected with influenza A compared with 31 of 167 children (18.6%) who received placebo—a relative risk reduction of 42%. Furthermore, children previously diagnosed as having asthma who took the vitamin D supplement had a relative risk reduction of having an asthma attack of

Key advances

- Vitamin D deficiency and insufficiency are common medical problems with insidious health consequences, including increased risk of upper respiratory track infections and diabetes mellitus
- Children with a history of mild-to-moderate persistent asthma and vitamin D insufficiency have higher odds of hospitalization or emergency department visit than children with normal levels of 25-hydroxyvitamin D[3]
- Vitamin D supplementation reduces the relative risk of seasonal influenza A infection by 42% and of having an asthma attack by 93% in children aged 6–15 years compared with placebo[2]
- Healthy adults with a 25-hydroxyvitamin D concentration ≥95 nmol/l have a twofold reduced risk of acute viral respiratory tract infections[4]
- Increased vitamin D intake significantly decreases arterial wall stiffness, a known precursor of hypertension and atherosclerotic plaque formation[6]
- Active sun exposure lowers the risk of developing type 2 diabetes mellitus by 30%[8]

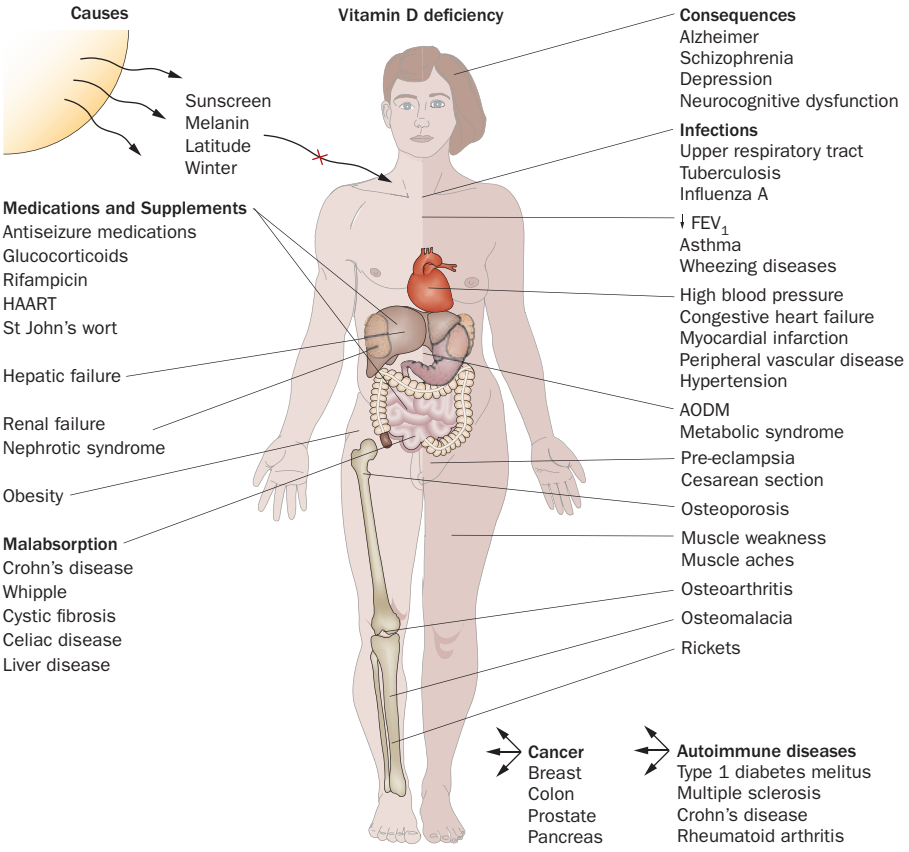

Figure 1 | The major causes of vitamin D deficiency and potential health consequences. Abbreviations: AODM, adult onset diabetes mellitus; FEV_1, forced expiratory volume in 1 s; HAART, highly active antiretroviral therapy.

93% compared with children on placebo. This observation is supported by a study of 1,024 children with a history of mild-to-moderate persistent asthma and vitamin D insufficiency (<75 nmol/l). This study population was found to have higher odds of any hospitalization or emergency department visit than children with normal levels of 25-hydroxyvitamin D (odds ratio 1.5).[3] A prospective cohort study that measured serial concentrations of 25-hydroxyvitamin D in 198 healthy adults observed that individuals with a 25-hydroxyvitamin D concentration ≥95 nmol/l had a twofold reduced risk of acute viral respiratory tract infections and a marked reduction in the percentage of sickness days.[4]

Vitamin D deficiency has been associated with a 50% increased risk of having a myocardial infarction and a 100% increased risk of death.[1] In the US, an estimated 50 million teenagers are vitamin D deficient or insufficient, which has been associated with a 2.4-fold, 2.5-fold and 4.0-fold increased risk of high blood pressure, high blood glucose levels and the metabolic syndrome, respectively.[5] Dong *et al.*[6] conducted a 16-week randomized, blinded, clinical trial in 49 normotensive black boys and girls aged 16.3 ± 1.4 years to evaluate the effect of enhancing vitamin D intake from 400 IU to 2,000 IU daily on arterial stiffness, determined by measuring carotid–radial pulse wave velocity. They confirmed that body fat mass was significantly and inversely associated with 25-hydroxyvitamin D levels, and the group of teenagers who received 2,000 IU vitamin D per day had a significant decrease in arterial wall stiffness,[6] a prelude to hypertension and atherosclerotic deposition. This observation is supported by an *in vitro* study in macrophages isolated from 76 obese, diabetic, hypertensive patients with vitamin D deficiency, which showed that culture media supplemented with 1,25-dihydroxyvitamin D modified LDL cholesterol and suppressed foam-cell formation by reducing acetylated or oxidized LDL cholesterol uptake.[7]

The major source of vitamin D for most humans continues to be exposure to sunlight. The circulating levels of 25-hydroxyvitamin D are at their highest at the end of the summer and at their nadir at the end of the winter, irrespective of where you live on this globe. The association of sensible sun exposure with health has been recognized by most civilizations for thousands of years. However, over the past 40 years, the suggestion that any sun exposure is hazardous to your health and should, therefore, be avoided without adequate sun protection has remained unchallenged.

Vitamin D has been produced by organisms being exposed to sunlight for more than 500 million years. Most tissues and cells in the body have a vitamin D receptor, and an estimated 200 to 2,000 genes may be directly or indirectly controlled by 1,25-dihydroxyvitamin D. These genes include those that regulate cell growth and prevent malignancy; enhance killing activity of macrophages; modulate the immune system by altering the ratio of T-helper-1 and T-helper-2 lymphocytes, which may be important in reducing the risk of autoimmune diseases; enhance insulin production and improve insulin sensitivity, cardiomyocyte contractility and skeletal muscle function; and maximize bone health.[1] It is conceivable that, throughout evolution, vitamin D was so important for not only vertebrate skeletal evolution but also overall health and that the need to obtain vitamin D from the diet did not exist. This theory would explain the lack of natural sources of dietary vitamin D. Findings of a recent study that habits of active sun exposure lower the risk of developing type 2 diabetes mellitus by 30%[8] are consistent with the earlier observation that increased intake of vitamin D and calcium reduced the relative risk of type 2 diabetes mellitus by 33%.[9]

In light of all of the revelations about the health benefits of vitamin D, a re-examination of recommendations on the vitamin D status of children and adults by the WHO, health-care regulators and providers is vital. The Institute of Medicine (IOM) recently recognized that the vitamin D intake for children and adults needs to be tripled from 200 IU to 600 IU of vitamin D daily. It was also acknowledged that vitamin D is not as toxic as once thought, and the upper limit was doubled to 4,000 IU per day. These recommendations are most welcome but still short of what many experts believe is necessary to maximize the health benefits of vitamin D, including those noted in this review.[10]

An increased vitamin D status can easily be accomplished by encouraging food fortification with higher amounts of vitamin D,

taking a vitamin D supplement and discouraging abstinence of direct sun exposure. The goal should be to achieve and maintain a blood level of 25-hydroxyvitamin D >75 nmol/l by ingesting foods that naturally contain vitamin D, including oily fish and mushrooms exposed to UV radiation, foods fortified with vitamin D in combination with a vitamin D supplement and from sensible sun exposure. For every 100 IU of vitamin D ingested, the blood level of 25-hydroxyvitamin D increases by approximately 1.5–2.5 nmol/l, which is why children should receive at least 600 IU (as recommended by the IOM) and preferably 1,000 IU of vitamin D daily and teenagers and adults at least 2,000 IU of vitamin D per day. This simple and cost-effective approach to enhance the vitamin D status of the world's population could substantially reduce the burden of disease and potentially reduce health-care costs across the board by 25%.

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The author declares no competing interests.

1. Holick, M. F. Vitamin D deficiency. *N. Eng. J. Med.* **357**, 266–281 (2007).
2. Urashima, M. *et al.* Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am. J. Clin. Nutr.* **91**, 1255–1260 (2010).
3. Brehm, J. M. *et al.* Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J. Allergy Clin. Immunol.* **126**, 52.E5–58.E5 (2010).
4. Sabetta, J. R. *et al.* Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS ONE* **14**, E11088 (2010).
5. Reis, J. P., von Mühlen, D., Miller, E. R. 3rd, Michos, E. D. & Appel, L. J. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. *Pediatrics* **124**, E371–E379 (2009).
6. Dong, Y. *et al.* A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. *J. Clin. Endocrinol. Metab.* **95**, 4584–4591 (2010).
7. Oh, J. *et al.* 1,25(OH)2 vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. *Circulation* **120**, 687–698 (2009).
8. Lindqvist, P. G., Olsson, H. & Landin-Olsson, M. Are active sun exposure habits related to lowering risk of type 2 diabetes mellitus in women, a prospective cohort study? *Diabetes Res. Clin. Pract.* **90**, 109–114 (2010).
9. 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).
10. Ross, A. C., Taylor, C. L., Yaktine, A. L. & Del Valle, H. B. (Eds) *Dietary Reference Intakes for Calcium and Vitamin D.* (The National Academies Press, Washington DC, 2011).