Normal bone metabolism clearly requires vitamin D, it is undisputed for its classic role in bone metabolism, calcium and phosphorus homeostasis. Recently, a worldwide focus has been directed on the extra-skeletal effects of this vitamin. The New York Times even called it the “wonder drug”. Vitamin D is obtained by synthesis in the skin after ultraviolet B exposure or through food consumption. A shortage of vitamin D may cause osteomalacia, with muscle weakness and fatigue in children (rickets) as well as in adults. It is often an underestimated problem, especially in people with dark skin and in those lacking sun exposure. It is one of the causes of osteoporosis.

But vitamin D plays a role in many other disorders. Studies have shown associations between low 25-hydroxyvitamin D (25-[OH]D) levels and risk for fractures, falls, cardiovascular disease, colorectal cancer, diabetes, depressed mood, cognitive decline and even death. The potential extra-skeletal wonderful effects of vitamin D have revived further interest into particularly cardiovascular effects, antitumor properties, and last but not least, effects on the immune system.

In many rheumatic diseases a low level of vitamin D appears to be associated with disease severity, including systemic lupus erythematosus, fibromyalgia syndrome, especially in those with anxiety and depression, but also in osteoarthritis, rheumatoid arthritis (RA) and systemic sclerosis.

Vitamin D deficiency is determined by measuring total serum 25-(OH)D concentrations. Measuring 25-(OH)D levels is complicated by the presence of multiple assays, evidence of inter-method and inter-laboratory variability in measurement and the lack of an internationally recognized, commutable vitamin D reference standard. Efforts to increase standardization are in progress.

There is also no consensus on optimal 25-(OH)D concentrations. Although experts generally agree that levels lower than 50 nmol/L (20 ng/mL) are associated with worse bone health, disagreement exists about the optimal 25-(OH)D levels and exact thresholds. According to NHANES (National Health and Nutrition Examination Survey) data from 2001 to 2006, 33% of the US population was at risk for 25-(OH)D levels below 50 nmol/L (20 ng/mL) and 77% had 25-(OH)D levels below 75 nmol/L (30 ng/mL). Risk factors for low vitamin D levels include: darker skin pigmentation, low vitamin D intake, little or no ultraviolet B exposure and obesity. Older age, female sex, low physical activity, low education attainment and low health status were factors also associated with vitamin D deficiency in some studies.

**AN ANTIPROLIFERATIVE VITAMIN**

1,25-dihydroxyvitamin D is the biologically active form of vitamin D that has antiproliferative effects in various cell types by influencing cell differentiation and decreasing cell proliferation, growth, invasion, angiogenesis and metastasis. Several meta-analyses showed that low serum levels of 25(OH)D are associated with colorectal cancer and overall mortality, whereas the specific association with cancer mortality is less consistent. The vitamin D receptor (VDR) is a crucial mediator for cellular effects of vitamin D but conflicting data have been reported for VDR in most malignancies. Beyond VDR, the biological effects of vitamin D are modified via the vitamin D-binding protein (DBP). The group-specific component gene, encoding DBP, is polymorphic and several polymorphisms have been investigated in association with cancer development with controversial results.

Supplementation of vitamin D has been found to be associated with a reduced risk of overall mortality, reviewing all published trials on healthy subjects, whereas the evidence of a direct effect on cancer risk and mortality is less clear. Furthermore, long-term health effects of high doses of vitamin D, extended duration of supplementation, and the association with different baseline vitamin D levels, remain to be investigated. In summary, epidemiological and preclinical studies support the development of vitamin D as a preventative and therapeutic anticancer agent, with significant associations especially found for low vitamin D
status with overall mortality and cancer outcome, but not so much in cancer incidence.²

A VASCULAR VITAMIN

There is inconsistent evidence to suggest that vitamin D supplementation improves arterial stiffness. These inconsistencies may well be attributable to heterogeneity in study design. Therefore, adequately powered, well-designed randomized studies are required to determine causal relationships between vitamin D and diseased bone metabolism in chronic arthritis, relationships between vitamin D and cardiovascular risk and parameters reflecting arterial stiffness.³

A ROLE IN AUTOIMMUNE DISEASES SUCH AS RA

Additional to the classic role, vitamin D modulates the innate and adaptive immune responses: it is important within the immune system, which can be deduced from VDR being expressed on immune cells, that is, B/T-cells and antigen-presenting cells, and the activation of vitamin D within these cells.⁴ Next to these translational investigations there is increasing epidemiologic data linking vitamin D with multiple sclerosis, diabetes mellitus, inflammatory bowel disease, systemic lupus erythematosus (SLE), and rheumatoid arthritis.⁵ The etiology of RA is still largely unknown, although a combination of environmental and genetic factors is needed for its development. As vitamin D plays a role in immunopathology and osteopathology, it may be an intriguing factor for RA. In Thai patients with 7 years disease duration, Pakchotanon et al. found no association between serum 25(OH)D and disease activity or functional status; but factors associated with vitamin D insufficiency were: living in Bangkok, being non-farmers, obesity and not taking vitamin D supplementation.⁶

In a series of patients from Iran who had not been on disease-modifying antirheumatic drugs (DMARDs) or corticosteroids, an inverse correlation was found by Zakeri et al. between disease activity and vitamin D levels, the number of tender and swollen joints, patient global and duration of morning stiffness, but not with erythrocyte sedimentation rate and C-reactive protein.⁷ There may be a role for vitamin D shortage in new-onset RA, but so far data are not supporting a role for vitamin D in long-standing RA. In a study performed by Quraishi et al. in RA patients from Dubai, mainly originating from the Indian subcontinent and of Arab origin, no association was found between disease activity and vitamin D levels; this finding may be explained by the fact that the disease was well controlled with DMARDs, mainly methotrexate.⁸

In systemic lupus erythematosus it was found that a 20 ng/mL increase in 25(OH)D levels was associated with a 21% decrease in the odds of having a high disease activity score and a 15% decrease in the odds of having clinically important proteinuria, but the clinical importance is relatively modest.⁹ Should this lead us to prescribe vitamin D to all patients regardless of vitamin D status, without measuring the vitamin D level?

When should we prescribe vitamin D? In cases of proven shortage one has to provide monthly high-dose vitamin D supplementation in order to reach the 30 ng/mL 25-OH-D threshold, even though recent data did not show better lower extremity functioning.¹⁰ In a recent Cochrane review no consistent pattern was found proving vitamin D treatment was better than placebo for any chronic painful condition, but the studies had methodological shortcomings (low quality evidence).¹¹ Despite the fact that no proven benefit was shown in patients with rheumatic conditions, it may be important to supply patients who are vitamin D deficient as one has to realize the other benefits vitamin D is supposed to have.

Tim L. JANSEN¹,² and Johannes J. RASKER³

¹Department of Rheumatology, VieCuri Medical Centre, Venlo, ²Scientific IQ HealthCare RadboudUMC, Nijmegen, and ³Department of Psychology, Health and Technology, Faculty of Behavioural Sciences, University of Twente, Enschede, The Netherlands

Email: J.J.Rasker@utwente.nl

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