

Evidence of gene-environment interaction in development of tuberculosis

Lancet 2000; 355: 588 – 589

The possibility that vitamin D may be important in immunity to tuberculosis has been suspected for some time. Before the availability of antituberculous chemotherapy, vitamin D was used to treat patients with cutaneous tuberculosis, with striking effects in many patients. In the 1800s cod-liver oil and sunlight exposure were popular treatments for tuberculosis patients. Interest in vitamin D declined with the development of specific antimycobacterial drugs, but in recent years further evidence has accumulated that this vitamin influences immunity to tuberculosis. Although best known for its role in regulating calcium metabolism, vitamin D is also an important immunomodulatory hormone. The active metabolite, 1,25(OH)₂ vitamin D₃, activates monocytes, and suppresses lymphocyte proliferation, immunoglobulin production, and cytokine synthesis. In-vitro studies have shown that vitamin-D metabolites can enhance the ability of human monocytes to restrict the growth of intracellular Mycobacterium tuberculosis, which suggests a mechanism by which vitamin D might stimulate immunity to this pathogen. Alveolar macrophages in the lungs of tuberculosis patients can produce large quantities of 1,25(OH)₂ vitamin D₃ so the local concentration of this metabolite within granulomas may be sufficient to prevent mycobacterial growth. Epidemiological evidence suggests a link between vitamin-D deficiency and tuberculosis. Tuberculosis is common among Asian immigrants in the UK, and the prevalence of vitamin-D deficiency among this population is high. A vegetarian diet, which can predispose to vitamin-D deficiency, is a strong risk factor for tuberculosis in immigrant south London Asians. Antituberculous chemotherapy affects vitamin-D metabolism, which complicates studies on vitamin D status in tuberculosis. However, serum 25(OH) vitamin D₃ has been found to be lower in untreated tuberculosis patients than in healthy controls in the UK and to be associated with disease severity in Indonesians. These studies could not differentiate whether vitamin-D deficiency is a risk factor for tuberculosis or whether tuberculosis-induced nutritional deficiency causes low concentrations of 25(OH) vitamin D₃. A prospective study to find out whether vitamin-D deficiency precedes the development of tuberculosis would be difficult and expensive because a large number of tuberculosis contacts would have to be followed up for a long time. Researchers have therefore used alternative approaches to examine whether the link between vitamin-D deficiency and tuberculosis is causal. Clinical disease develops in only one in ten individuals infected with M tuberculosis. There is substantial evidence from twin and adoption studies that host genetic factors strongly influence the outcome of an infection. Vitamin D exerts its effects via the vitamin-D receptor (VDR) that is present on activated T and B lymphocytes. Genetic variation in the VDR has been associated with circulating concentrations of 25(OH) vitamin D₃ and bone-mineral density, although the strength of the original association was probably overestimated. If vitamin-D deficiency is a risk factor for tuberculosis, then VDR gene variants might be associated with tuberculosis. In a large

Gambian case-control study of over 800 people, those with the genotype associated with high circulating concentrations of 25(OH) vitamin D3 were under-represented among the tuberculosis patients. However, this study recruited tuberculosis patients who had recently started therapy, so their serum vitamin-D metabolites were not measured. In today's Lancet Robert Wilkinson and colleagues report that the association between VDR gene polymorphism and tuberculosis is mediated via vitamin-D status. They investigated 126 tuberculosis patients and 116 healthy tuberculosis contacts who were positive for the purified-protein-derivative skin-test from the Gujarati Hindu immigrant population in London. Among the tuberculosis patients, 71 underwent VDR genotyping and measurement of serum 25(OH) vitamin D3 concentrations, 32 subjects only the serum measurements, 20 only the genotyping, and three neither test.

Among the 116 tuberculosis contacts, 42 underwent both tests and 74 only the genotyping. The investigators do not give the reason for this distribution of tests or whether any selection criteria were applied. Low and undetectable 25(OH) vitamin D3 concentrations were commoner among the patients than among the contacts (67% vs 26%). This study did not have the power to confirm the association between the tt genotype and lower risk of tuberculosis identified in a previous study, although there was a consistent trend (6% vs 11%). However, 33/38 (87%) of the patients, but only 10/42 (24%) of the contacts, had the high-risk VDR genotypes (Tt and TT) and vitamin-D deficiency. Interestingly a similar interaction was found for the Fok1 polymorphism, which has not previously been investigated in tuberculosis patients. Wilkinson and colleagues' finding of a specific gene-environment interaction in tuberculosis is novel but requires confirmation because of the small size of the study. Wilkinson and colleagues found a very high prevalence of vitamin-D deficiency. They also found questioning of dietary habits to be of limited value in identifying the deficiency. They therefore concluded that 25(OH) vitamin D3 supplements should be offered to all tuberculosis contacts of Gujarati origin. Since serum 25(OH) vitamin D3 concentrations were also low in non-Gujarati patients, vitamin-D supplements might benefit tuberculosis contacts from other population groups. However, there is insufficient evidence to recommend routine vitamin-D supplements for tuberculosis contacts. A placebo-controlled trial should be started because the results of such a study could be of great public-health importance. Richard Bellamy Department of Infectious Diseases, University Hospital of Wales, Cardiff CF14 4XW, UK