The importance of vitamin D: a response to the article by Bolland and colleagues

Bolland et al (NZMJ 10 Feb 2012)\(^1\) have sounded a note of caution in rushing to over interpret the wave of epidemiological data linking vitamin D deficiency and insufficiency with a wide range of diseases, and appropriately pointed out that there is evidence that there may be harm in excessive supplementation. Further to their list of concerns it can now be added that vitamin D, whilst being anti inflammatory when supplemented in the context of a deficiency, appears to switch to be pro-inflammatory when given in excess.\(^2\) Bolland et al conclude “a policy of widespread use of vitamin D supplements should only be implemented in the context of rigorous evidence of the benefits and safety of vitamin D supplements in populations with vitamin D insufficiency.”

However an alternative view is that a policy of widespread neglect of a vitamin deficiency regarded by many as pandemic, associated with such a wide array of chronic diseases and in the context of an established Public Health policy of lifelong sun avoidance should also only be implemented in the context of rigorous evidence for its safety.

Vitamin D deserves a bit of respect. Although so many questions are unanswered, when I am confronted with an obese Maori patient with treatment resistant mental illness and type 2 diabetes who is doing very poorly, I have opted for assessment, treatment and follow up of her vitamin D levels along with the standard management of her conditions.

We should not really be surprised that vitamin D appears to have such pleiomorphic effects in health and disease. In an evolutionary sense it has been described as the oldest hormone associated with life on earth.\(^3\) Most cells in the body have a nuclear vitamin D receptor, and it regulates the expression of some 229 genes via 2776 different genomic positions,\(^4\) furthermore the expression of vitamin D-related genes are themselves influenced by DNA methylation.\(^5\) Many of these genes are involved in cell growth, proliferation, apoptosis, inflammation and immune system functioning. Vitamin D also modulates the activity of many transcription factors such as the potent mediator of inflammatory signalling, Nuclear Factor-kB (NF-kB).\(^6\) These factors all contribute to the plethora of associated disease and the individuality of possible clinical response to correction of deficiency.

All of this does not fit at all well with standard models of medical research that focus on a single determinant, or the dysregulation of a single molecular target in investigating the aetiology or the treatment of a specific disease process. Historically vitamin D adequacy was judged to be the dose required to prevent Rickets. This is akin to how much iodine might be required to prevent the birth of a cretin in the family, or how little vitamin C is required to prevent scurvy, but it may not tell us how much of any of these nutrients is required for optimum health. It also does not tell us about optimum doses for other target organs in the body, such as the central nervous system.\(^7\)
Vitamin D receptors are widely expressed in neurons and glial cells. Vitamin D induces Nerve Growth Factor (NGF) and Brain Derived Neurotrophic Factor (BDNF), inhibits Inducible Nitric Oxide Synthase (iNOS) and influences Glucocorticoid receptor function. Epidemiological studies link vitamin D insufficiency with mood disorders, Multiple Sclerosis, brain tumours and schizophrenia. The latter is a prenatal association, underscoring the importance of adequate vitamin D status in pregnancy and making vitamin D yet another piece of the fabric that determines the fetal origins of adult disease.

Bolland et al rightly point out the pitfalls of interpreting observational studies and confusing correlation with causality. However, the same epidemiological observations made between various diseases and vitamin D status have also been made in populations according to their distribution in latitude from the equator. In the case of cancer the observation that rates of cancer increased with distance from the equator was made nearly 100 years ago, long before vitamin D was considered to be the link. The point being that such data provides an additional cross check on disease associations with vitamin D levels that further controls for many of the confounding variables listed in Bolland et al’s discussion.

The patient in question had serum 25OHD levels of 12 nmol/L and required very significant amounts of vitamin D in order to correct her deficiency. Both her physical and mental health have improved substantially since then.

William Ferguson
General Practitioner
Kumeu

References: