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EDITORIAL

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Vitamin D – has the new dawn for dietary recommendations arrived?

Since the beginning of our new millennium, vitamin D has been the absolute focus of attention: there can be no doubt about that! Whether it be the scientific, clinical or academic communities, government/regulatory organisations, industry, media or indeed the public, everyone has 'woken up' to the reality that the functions of this nutrient go far wider than that of the skeletal system. Concomitant with that, there is universal acceptance that we have a high prevalence of people with vitamin D levels lower than is good for their health.

Vitamin D is a most unique nutrient – the term 'vitamin' is a misnomer since vitamin D is not a 'vital-amine' in the true sense of the word but rather it is a pro-hormone – with the main source not being diet but rather ultraviolet B-rays (UVB) from sunlight. This makes vitamin D such a challenging (but exciting!) nutrient to study as in areas of northern latitude, vitamin D can be made from UVB only during the months of April to September. Hence, randomised, controlled trials (RCTs) involving vitamin D should strictly be confined to the winter months when vitamin D is not made endogenously via the act of sunlight on skin, and all dietary vitamin D studies (cross-sectional and longitudinal) need to adjust for sunlight exposure in their analyses (Lanham-New *et al.* 2011).

Vitamin D_3 is formed as the direct effect of UV irradiation of the skin. The action of UVB converts 7-dehydrocholesterol to pre-vitamin D, which is then metabolised to vitamin D by a temperature-dependent isomerisation. We know that 7-dehydrocholesterol is a zoosterol, which functions in the serum as a cholesterol precursor, and is converted to vitamin D_3 in the skin, therefore operating as pro-vitamin D_3. This is particularly important since there is a growing recognition that people who take cholesterol-lowering statin drugs have a problem with vitamin D deficiency, although to date this has attracted relatively little focus. Cholesterol is required by the body to synthesise vitamin D and statin drugs are responsible for reducing cholesterol production and eliminating it, leading many to speculate that statin drug users do not have enough cholesterol to process vitamin D efficiently. Studies, albeit observational in nature, are beginning to show convincingly that statin users have a greater prevalence of vitamin D deficiency, with muscle pain being a common characteristic. This is an area that the clinical field must take forward as a genuine concern in their clinical practice and is a research area that warrants urgent attention.

Once vitamin D is metabolised from pre-vitamin D to vitamin D, it is transported via the general circulation and, following enzymatic activity in the liver (by 25-hydroxylase), it is converted to 25-hydroxy vitamin D (25OHD), which is considered to be the best clinical indicator of vitamin D status. The concentration of 25OHD in the blood reflects the vitamin D supply from both the skin and the diet, and with a decent half-life (approximately 3 weeks), it is a good integrated marker of recent vitamin D supply and can thus be used to assess vitamin D adequacy. Using the vitamin D-binding protein, 25OHD is transported to the kidney where it undergoes a final hydroxylation step via the enzyme 1-alpha-hydroxylase to become 1-alpha, 25-dihydroxyvitamin D, also known as calcitriol, which is the active form of vitamin D.

What has held the field back is the lack of standardised measurements of 25OHD status, with laboratories worldwide showing alarmingly poor consistency of measurement. Indeed, in the well-publicised paper by Binkley *et al.* (2004), remarkably different results were yielded from samples, which had been spiked with 20 ng/ml and processed by a number of top vitamin D measuring laboratories using their specific methodologies. This has had ramifications for the field of vitamin D research and is one clear reason why there are such inconsistencies and controversies, nationally and internationally, as to what level of 25OHD status defines

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vitamin D 'deficiency', 'insufficiency' and 'optimum' and which method should be used (Spiro & Buttriss 2014). However, what is very positive is that a gold standard reference vitamin D method (liquid chromatography-mass spectrometry; LC-MS) has been introduced in recent years and is now being actively used by a number of key organisations, including (but not limited to) the US Centres for Disease Control and Prevention (CDC) and the UK National Laboratories. Five years ago, the US National Institutes for Health (NIH) established the *Vitamin D Standardization Program* (*VDSP*) in an attempt to standardise the laboratory measurement of vitamin D across the globe, with key bodies signing up to it, including laboratories in the UK. In addition to this, there is now greater prominence than ever for the *Vitamin D External Quality Assessment Scheme* (*DEQAS*), which has been led by the UK. The *DEQAS* Advisory Panel performance targets call for 75% or more of the results falling within ± 25% of the Target Value [the National Institute of Standards and Technology (NIST) LC-MS/MS assigned value]. The international *DEQAS* has been monitoring the performance of 25OHD assays since 1989 and now has >1000 registered participants worldwide. In essence, *DEQAS* is an ongoing multicentre trial of the methods used by its participants and provides a unique opportunity to assess the accuracy and specificity of 25OHD methods, as well as the analytical performance of a large number of their users. These initiatives are extremely important and can only serve to be beneficial to the vitamin D field in the long-term.

Low vitamin D status has been reported throughout the world – and there is, at last, recognition that this is a real problem in the 21st century. In the recent report by the International Osteoporosis Foundation (Mitchell *et al.* 2015), vitamin D insufficiency (25OHD status <50 nmol/l) has been identified as being prevalent in women of child-bearing age, pregnant women (see Toher *et al.* 2013), children and adolescents, as well as adults in general. Adults who are at particular risk of having low vitamin D status include individuals living at higher latitudes, such as in the UK and many parts of mainland Europe, with minimal exposure to sunlight; those who are overweight and obese; individuals with a darker skin tone; those who cannot expose their skin to the sun for medical or cultural reasons and populations who are institutionalised and spend very little time outdoors. Furthermore, individuals with diseases that reduce the uptake of vitamin D from the intestine are at an increased risk of low vitamin D status and require a special focus.

For the UK, vitamin D deficiency (as defined as a 25OHD status <25 nmol/l) is a major public health problem, particularly in older people (>65 years) and in the UK South Asian population (including children). In the largest longitudinal study available in South Asian women, funded by the Food Standards Agency, 25OHD status was below 25 nmol/l for the entirety of the year in both pre-menopausal and post-menopausal groups (Macdonald *et al.* 2011; Darling *et al.* 2013). The UK *National Diet and Nutrition Survey* (*NDNS*) shows there to be a high prevalence of low vitamin D status in adolescents, particularly boys (see Prentice 2013). Data from the *NDNS* in older children show that 19.7% of boys and 24.4% of girls aged 11–18 years had a vitamin D status below 25 nmol/l (Bates *et al.* 2014). It is of course well established that vitamin D deficiency is an issue in the growing child, particularly with respect to impairment of bone development and a reduced peak bone mass attainment. Severe vitamin D deficiency results in rickets in children (osteomalacia in adults) and must be avoided at all costs. In 2012, the Chief Medical Officer (CMO) for England, Professor Dame Sally Davies, called for a review of cost-effectiveness of making the *Healthy Start* programme universal and offering free vitamins to all children under the age of 5 years and this is currently under review by the National Institute for Health and Care Excellence (NICE) (Alderton 2014). Vitamin D deficiency in our ageing population is undeniably a huge problem and one which must be the target of focused public health attention in the future (Buttriss 2015).

Vitamin D has many functions in addition to its key role in the regulation of calcium and phosphorus homoeostasis. The active hormone, 1,25-dihydroxyvitamin D, binds to the vitamin D receptor (VDR) in a large number of cells to promote/suppress gene transcription and thus regulate cell function. The VDR is not just present in bone but in muscle, adipose tissue, immune systems, the central nervous and endocrine systems, and some cancer cells.

The evidence for the role of vitamin D in skeletal health is robust but what we lack are strong RCTs or prospective studies to establish whether there is a role for vitamin D in relation to other health outcomes. Certainly, vitamin D plays a key role in muscle health, particularly in older adults. By helping to maintain muscle function and prevent falling and reducing the risk of falling, this will undoubtedly be of benefit to our (growing) ageing population (McCarthy & Kiely 2015). There are important RCT studies underway for other health outcomes, and we await their completion and publication with anticipa-

tion. One key project currently running is the European Commission-funded *ODIN* project (food-based solutions for optimal vitamin D nutrition and health throughout the life cycle), which commenced in November 2013 and is a multidisciplinary consortium of 31 partners from a total of 19 countries, and incorporates a 48-month programme of work. Further details of this exciting project, which will publish its final report in 2017, can be found at www.odin-vit-d.edu (see Kiely *et al.* 2015).

Dietary vitamin D intake varies considerably worldwide and is directly associated with the extent of vitamin D fortification specific to the country. Vitamin D as cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2) is legally permitted to be added to foods [only in cholecalciferol and ergocalciferol form as stated in Annex 1 of Regulation (EC) No 1925/2006, amended by the Commission Regulation (EC) No. 1170/2009]. In the UK, dietary intakes of vitamin D are low, typically varying between 100 and 200 IU (2.5–5 μg) per day across different population groups. The recent update of the vitamin D content of fortified foods and supplements in the UK *NDNS Nutrient Databank* is very important and will ensure that dietary intake estimates of vitamin D in the UK are accurate and informative (Allen *et al.* 2014).

Vitamin D is naturally present in foods in two forms, with vitamin D_2 being present in plants and fungi whereas vitamin D_3 is found in fish, meat and eggs. There has been controversy for many years as to whether it matters if vitamin D_2 or vitamin D_3 is used as the source for raising vitamin D status (either as supplements or through food fortification) (see Tripkovic 2013). Results from the D_2-D_3 study, which has been funded by the Biotechnology and Biological Sciences Research Council (BBSRC) – Diet and Health Research Industry Club (DRINC) programme and is the largest RCT to directly compare vitamin D_2 with vitamin D_3, has shown some exciting results in both Caucasian and South Asian populations (Wilson *et al.* 2015) and there are intriguing new leads on mechanisms of action (Professor C. P. Smith & L. R. Wilson, personal communication 2015).

It is important to note that there are currently very few foods in the UK providing a valuable contribution to vitamin D intake, suggesting that food fortification with vitamin D could be an effective way of improving vitamin D status. This is a topic that requires urgent consideration from the consumer perspective – which foods would be most effective; and from a food industry perspective – to which foods can vitamin D be added in appropriate amounts.

The setting of dietary requirements for vitamin D has proved just as controversial as defining the level of 25OHD status to signify vitamin D 'sufficiency' (see Cashman & Kiely 2014). The Scientific Advisory Committee on Nutrition's *Vitamin D and Health* draft report released for consultation in July 2015 is a landmark for the vitamin D field in the UK (see Buttriss 2015). Whilst there are more questions than answers (as is the case for so many nutrients), a new era of vitamin D exploration is upon us – the future will be exciting, challenging and revealing!

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