Vitamin D in Musculoskeletal Health and Beyond

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It is 100 years since Mellanby first hypothesised that a fat soluble *antirachitic factor* cured rickets in puppies [1] and, in this edition of *Calcified Tissue International*, the effects of this steroid nutrient/pro-hormone, later named vitamin D, on many systems of the body are reviewed. Vitamin D is important in calcium homeostasis and deficiency states are associated with rickets, osteomalacia and myopathy, while other effects (some contested) on immunomodulation and non-musculoskeletal organ function are also considered.

Fraser et al. move us from the tentative characterisation of Mellanby's antirachitic factor in the early twentieth century to the identification of a number of biomarkers of vitamin D status, with serum (or plasma) 25 hydroxyvitamin D (25(OH)D) as our *go-to* marker of vitamin D status. Although the harmonisation of mass spectrometry with immunoassays for its measurement remains a challenge, using LC–MS/MS methods, a range of vitamin D metabolites can be measured, including 1,25 dihydroxyvitamin D (1,25(OH)₂D) and 24,25 dihydroxyvitamin (24,25(OH)₂D). The clinical role of new assays is not clear, although the ratio of 25(OH)D to 24,25(OH)₂D presents an example, where 24-hydroxylase deficiency is indicated in infantile hypercalcaemia [2]. Professor Cashman's agrees that 25(OH)D is the best biomarker defining vitamin D status [3]. However, the development of public health policy on vitamin D nutrition is a challenge. The National Academy of Medicine (NAM, formally the Institute of Medicine (IOM)) and the UK Scientific Advisory Committee on Nutrition (SACN) use threshold for circulating 25(OH)D predicting osteomalacia risk [4, 5], while alternative strategies lead to recommended daily

vitamin D intakes ranging from 400 IU [4, 5] to 2000 IU [6]. How can dietary change influence vitamin D status? Should we take vitamin D supplements or can foodstuffs by routinely supplemented and should we promote sun exposure for cutaneous synthesis of vitamin D? These questions are public health matters which may need to be addressed politically!

Vitamin D deficiency rickets appears to be increasing in the Americas, Europe and parts of the Middle East [7] and Moon et al. present an excellent overview of the consequences of maternal and childhood vitamin D deficiency [8]. They highlight significant physiological changes in pregnancy in vitamin D binding protein (DBP) and circulating levels of 1,25(OH)₂D as well as the impact of maternal vitamin D deficiency on obstetric outcomes, such as gestational blood pressure and glucose homeostasis. In addition to rickets, they consider the impact of vitamin D status on bone mineral density (BMD), neonatal hypocalcaemia, and wider health concerns including birthweight and skeletal development in infancy and childhood.

Girgis reminds us that vitamin D is not just about bone, as he reviews its effects on the morphology and function of muscle [9]. Thresholds for 25(OH)D may be as low as 20 nmol/L for optimal calcium homeostasis, which is critically important to avoid muscle dysfunction. The effects of vitamin D on muscle strength, accelerated muscle ageing and impairment of muscle repair are reviewed, particularly in animal studies. However, mechanisms of action remain controversial, as the vitamin D receptor (VDR) is only found in very small amounts in muscle tissue, although Girgis and colleagues recently showed that myocyte-specific vitamin D receptor (mVDR) null mice, with no myocyte VDR whatsoever, still had altered muscle size and decreased strength [10]. There is also some complementary human research, including functional MRI studies showing evidence of improved mitochondrial function with vitamin D supplementation [11].

The potential immunomodulatory effects of vitamin D in vitro are well recognised and Harrison et al. describe their potential impact in vivo, particularly in rheumatoid arthritis

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[12]. They present a delightfully clear figure reminding the reader of the immune mechanisms under consideration. Vitamin D metabolites cause immune modulation as seen in diseases such as type 1 diabetes, Crohn's disease and rheumatoid arthritis. However, the clinical evidence is inconsistent and they recommend work on the *metabolome* should include circulating vitamin D analytes including the inflamed joint. The therapeutic questions remain whether vitamin D could and should be used to treat inflammatory arthritis, how it might work and who might benefit most? Complementing the theme of inflammation, Maes et al. look at the impact of vitamin D on infection in pulmonary disease [13]. They present epidemiological evidence of vitamin D deficiency in chronic lung disease and the therapeutic effects of vitamin D. They also suggest therapeutic mechanisms for which readers may find Fig. 1 from Harrison's article on rheumatoid arthritis helpful! There is also evidence of benefit in cystic fibrosis and asthma and a recent individual participant data (IPD) meta-analysis may be surprising, as vitamin D therapy decreased acute respiratory infections in a study recruiting participants aged 0–95 years, although it was not possible to evaluate separately upper versus lower respiratory infections [14].

In vitamin D research, as elsewhere, no sooner have manuscripts been accepted for publication than the latest (sometimes contradictory) evidence is published. With large studies and meta-analyses, recruiting ever more diverse populations and looking at variable outcome measures, we are grateful to Dr Sami and Professor Abrahamsen for their attempts to keep us up to date [15]. They note a change in focus of vitamin D research. For example, we saw a number of studies in the 1990s on fracture prevention and the role of calcium, which are still extremely influential in practice today. However, the field has expanded to consider vitamin D with or without calcium with skeletal and/or non-skeletal outcomes in a range of populations: adult, old or very old. Coming back to public health concerns, the benefits of vitamin D supplements are relatively meagre when given to the many and we should recognise there are risks to a few, particularly the very old or frail who may succumb to adverse outcomes. We have also seen recent mega-trials which have failed to show significant effects on primary outcomes but may contribute enormously to further IPD meta-analyses. More work for someone in the near future, it appears!

Compliance with Ethical Standards

Conflict of interest Terry J. Aspray has no conflict of interest to declare.

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