It is a good time to be involved with vitamin D. Under-recognized for so long, the past few years have seen a flurry of research activity and the realization that this prohormone and its metabolites are involved in far more than just calcium and bone metabolism. Perhaps this is not that surprising when one considers that the vitamin D receptor is expressed in a wide variety of body tissues, including brain, heart, skin, gut, gonads, prostate, breast and immune cells, as well as bone, intestine, kidney and parathyroid [1]. Correspondingly, vitamin D deficiency has been linked to an increased risk of a number of malignancies, cardiovascular disease, depression, schizophrenia and autoimmune and inflammatory disease [2]. Of course, rheumatologists have known about the key role of vitamin D in bone disease for a long time, and thus it is perhaps surprising that the exciting discovery of a potential role for vitamin D in the development of other rheumatological conditions such as RA and SLE is a relatively recent one [3, 4].

In this issue, Mouyis et al. [5] lend weight to this, finding vitamin D deficiency to be in fact significantly more prevalent amongst general rheumatology outpatients than their osteoporotic or osteopenic patients, irrespective of whether they were receiving vitamin D supplementation at the time of measurement. It is acknowledged that this may be partly accounted for by certain features of rheumatological diseases, such as photosensitivity leading to sun avoidance and effects of medication, and not exclusive evidence of a direct aetiological role for vitamin D in their pathogenesis. However, this does not negate the need to recognize and treat vitamin D deficiency in these patients.

The authors go on to explore and touch upon a number of issues pertaining to vitamin D in routine clinical practice. The first is the definition of a low vitamin D concentration. A hypovitaminosis cut-off for serum 25-OH vitamin D (25-OH D) concentration of <50 nmol/l was chosen by the authors based on the lowest monthly median value from a control population. They acknowledged that their population and seasonal-based cut-off is conservative and that other authors recommend a higher cut-off of 75 nmol/l [6]. Such limits are often based on the curvilinear population relationship seen between 25-OH D and PTH with the cut-off selected as the point where increasing 25-OH D concentrations do not produce a decrease in PTH concentrations. What is seldom commented upon is the degree of individual spread about the central tendency of such data—it is very large. Thus, some patients with clearly replete 25-OH D concentrations will have PTH concentrations well within its reference interval as well as elevated, and the same is seen with clearly deficient 25-OH D concentrations. Accordingly, adverse effects on skeletal and non-skeletal health may still be seen above 75 nmol/l, and thus some authorities even suggest a 25-OH D concentration of ~90–100 nmol/l as optimal for most endpoints [7]. To overcome problems of local reference intervals including season, latitude, dress custom and skin pigmentation, many routine laboratories have recently adopted clinical action points of above 50 nmol/l and/or subdivide hypovitaminosis D into deficient and insufficient states, although some may be slow to use this on account of the extremely high prevalence in their population when these definitions are used. To add to the confusion over what limit to use, analytical issues (discussed subsequently) will unfortunately have a bearing on which cut-off to use.

The second issue that the authors explore is the lack of clear cut advice about when to request 25-OH D, even in patients with known osteoporosis. There is a clear need for general guidance regarding when 25-OH D should be requested. When estimated glomerular filtration rate was introduced into the General Medical Services contract, our laboratory saw an ~1000% increase in 25-OH D requests from primary care [8]. The absence of specific guidelines for when to measure vitamin D in rheumatology patients means that Mouyis et al.’s [5] article, conceived as an audit, uses an Australian consensus statement for general medical patients as the standard [9]. A necessity for a more dedicated set of guidelines is revealed, in that the majority of cases of vitamin D deficiency would not have been identified if only patients deemed at ‘high risk’ of vitamin D deficiency had been screened. Despite the fact that screening for vitamin D deficiency is often advocated, the Australian consensus statement appears to be the only formalized guideline yet to be published, possibly reflecting the fact that factors influencing vitamin D status are varied, complex and not easily generalizable on a national level (due to the effects of seasonal variation and latitude, for example). This study goes some way to stratifying patients according to disease type, identifying inflammatory arthritides and chronic pain/fibromyalgia as particularly likely to be accompanied by hypovitaminosis D, while acknowledging the need for larger studies to break this down further to and beyond individual disease entities.

Informing patients to increase their exposure to the sun needs to be tailored to avoiding being burnt; however, there is decrease in the production of cholecalciferol precursors by skin in the elderly [10]. Therefore, the third issue is what type and dose of vitamin D supplementation to use, assuming that it is available in view of the current UK-wide shortage of pharmacological vitamin D in tablet form. It has been argued that in certain populations, near-universal supplementation with calcium and physiological doses of vitamin D is justified as the prevalence of deficiency is so high [11]. Such treatment is unlikely to cause toxicity, but the flip side is that there is a great deal of inter-individual variability in response to this standard treatment, with under-treatment actually being the real risk in most, not over-treatment. The authors acknowledge that the majority of their patients prescribed vitamin D were receiving 800 U of cholecalciferol (D3) daily, yet for these patients median 25-OH vitamin D concentration was well below 75 nmol/l, with a significant degree of variation. It is indeed true that one dose may not fit all [12], and as universal treatment with physiological doses fails many patients, significantly higher vitamin D doses often need to be employed to ensure that an adequate vitamin D concentration is achieved. Efforts have been made to develop algorithms to calculate the expected response to different dosing regimen [13], but unfortunately these are confounded by factors such as pre-treatment 25-OH D concentration, and real-life issues such as compliance and vitamin D from other sources may limit their usefulness in clinical practice. With so many unknowns, it is likely that future policy will follow a strategy of test–treat–retest, allowing individually tailored treatment for optimum results and patient safety. Such a policy is also more likely to pick up patients with undiagnosed primary hyperparathyroidism than near-universal supplementation.

Unfortunately it is more complicated than this, as not all vitamin D assays are equivalent. Available techniques employed to measure vitamin D include various forms of immunoassay, high-performance liquid chromatography and tandem mass spectrometry. Such methods differ significantly when it comes to reagent, capital and staffing costs. Before 25-OH D can be measured, it needs to be separated from its binding protein, which adds an extra
step to the analysis of 25-OH vitamin D. This and other reasons account for the quite high precision seen when using some of these analysers. Added to this are the D$_2$ and D$_3$ forms, which means calibration is problematic especially as there is no agreed calibrant for 25-OH D. As a result of such issues, 25-OH D concentrations can vary depending on which analysers they are measured on, and the sources of the vitamin D (D$_2$ or D$_3$). For example, the RIA used in the study has been shown to under-report 25-OH vitamin D$_2$, meaning that samples from ergocalciferol-treated patients would produce spuriously low results [14]. However, it is Mouyis et al.’s practice to treat using cholecalciferol, meaning that the treatment effect in their study should be accurately determined. Nevertheless, there is clearly a need for further standardization and in view of potential overdosing, perhaps the Medicines and Healthcare products Regulatory Agency should take a lead role as it regulates both medicines and in vitro diagnostic devices. In the meantime, clinicians should be aware of the limitations of the assay employed in their laboratory.

The audit by Mouyis et al. [5] has therefore focused attention on the problems associated with vitamin D investigation and treatment and they should be thanked for this. Much more clinical research is required to determine the benefits and risks of treating patients with 25-OH D preparations. Improved professional guidance concerning such issues as when to measure 25-OH D and in what patients, clinical action points, minimum assay standards, reference material and a reference method are sorely needed for routine clinical practice. In view of the issues involved, a cross-professional group is probably the best way to take this forward. A review of the current evidence base and clinical priorities would be an excellent start.

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