cortisol production is a foreboding challenge. Yet, securing the diagnosis is important as untreated Cushing's syndrome carries a high mortality rate. Measurement of a 24 hour urine free cortisol (UFC) is one of the most widely used screening tests for Cushing's syndrome. However, its use in the clinical setting has many shortcomings. There is significant within-patient variability and falsely elevated levels can be seen with over-collection or increased urine volumes. Reported sensitivities up to 95% are only achieved over 2–3 separate collections, which is logistically difficult for the patient. Furthermore, mild cortisol excess can be missed, a problem particularly in patients with early recurrence of Cushing's disease. In the era of liquid chromatography/tandem mass spectrometry (LCMS) this is even more of a concern. Often there are subtle excesses of cortisol metabolites in cases of Cushing's syndrome which are included in measurements using traditional radio or immunoassays, but not reported in pure free cortisol measurements in LCMS analyses. However, other testing methods are also fraught with problems, leaving the 24 hour UFC measurement still an important test in the diagnosis and management of Cushing's syndrome.

THE MYTHOLOGY OF VITAMIN D DEFICIENCY AND INSUFFICIENCY

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Vitamin D deficiency is defined as a serum 25-hydroxy-vitamin D (25(OH)D) of less than 30 nmol/L.¹ Vitamin D insufficiency is held to be present with values <75 nM.² The aim of this study was to examine the evidence supporting the use of these thresholds as surrogates of bone disease. If valid, then at a level of 25(OH)D below 30 nM, serum PTH and bone remodelling markers should be elevated, bone mineral density (BMD) reduced and microarchitecture deteriorated. Lesser degrees of these abnormalities should be present in persons with values of 25(OH)D between 30–75 nM.

We measured serum 25(OH)D, PTH, calcium and creatinine in 10,349 women and 3582 men (using blood samples obtained from Melbourne Pathology). We also critically reviewed the literature dealing with the pathogenesis and treatment of bone disease associated with vitamin D metabolism. Based on the literature, reduced serum 1,25 dihydroxy-vitamin D and calcium malabsorption was observed only at serum 25(OH)D levels below 10 nM.³ We and many other investigators report an inverse association between PTH and 25(OH)D but PTH remained within the reference range in over two-thirds (954/1416) of subjects with 25(OH)D ≤30 nM. There was no level 25(OH)D that distinguished persons with and without secondary hyperparathyroidism. PTH increased with age before and after adjusting for 25(OH)D and eGFR. The literature revealed little evidence of increased remodelling markers, reduced BMD or microarchitectural deterioration at 25(OH)D <30 nM but most

studies lacked subjects with 25(OH)D levels below 30 nM.^{4–6} Moreover, there was little evidence of hyperosteoridosis in post-mortem bone biopsy specimens from 675 deceased patients with serum 25(OH)D <30 nM (blood taken at death).⁷

The literature confirmed that administration of vitamin D increased serum 25(OH)D levels but there was little or no improvement in fractional calcium absorption.⁸ Suppression of serum PTH was achieved provided serum 25(OH)D was below 50 nM.⁹ Whether this is accompanied by reduced remodelling or slowing of bone loss is not known. In one metaanalysis (*n*=4082), fracture risk is reduced by ~8% when vitamin D is with calcium, but no benefit when administered alone.¹⁰

In summary, these null findings may be partly the result of issues in design and execution of the studies. Within these constraints, there is no serum 25(OH)D level that discriminates persons with and without calcium malabsorption, secondary hyperparathyroidism, deficits in BMD, microarchitectural decay, or evidence of osteomalacia. Nor is there robust replicated evidence of anti-fracture efficacy of vitamin D supplementation. In conclusion, the scientific basis underlying the choice of these thresholds of vitamin D deficiency and insufficiency, and indications for intervention, are poorly defined. Work is needed to identify surrogates that identify persons with bone disease with high sensitivity and specificity and demonstrate efficacy and safety of vitamin D treatment.

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