Rheumatology 2008;47:1348–1351
Advance Access publication 22 May 2008
doi:10.1093/rheumatology/ken203

Concise Report

Hypovitaminosis D among rheumatology outpatients in clinical practice

M. Mouyis[1], A. J. K. Ostor[1], A. J. Crisp[1], A. Ginawi[1], D. J. Halsall[2], N. Shenker[1] and K. E. S. Poole[1,3]

Objectives. A role for vitamin D in the pathogenesis of autoimmune and inflammatory diseases is emerging. We undertook an audit of 25-hydroxyvitamin D (25OHD) investigation and treatment in rheumatology outpatients.
Methods. Serum 25OHD requests were matched to electronic medical records from rheumatology and metabolic bone clinics (April 2006–March 2007). Data were analysed separately for two groups, 'Documented osteoporosis/osteopaenia' (Group 1) and 'General rheumatology outpatients' (Group 2, sub-divided by diagnosis). Hypovitaminosis D was defined by 25OHD levels <50 nmol/l. Values were compared with healthy adults to calculate geometric *z*-scores.
Results. A total of 263 patients were included (Group 1, n = 122; Group 2, n = 141) with an overall median 25OHD of 44 nmol/l.The 25OHD level among general rheumatology patients (median 39 nmol/l, mean z score −1.2, was statistically significantly lower than among osteoporotic/osteopaenic patients (median 49 nmol/l, mean z score of −0.9, $p < 0.05$ for the difference). 25OHD was lower in inflammatory arthritis and chronic pain/fibromyalgia than in other groups. Prescribing was recorded in 100 in Group 1 (of whom 95% were prescribed calcium/800 IU cholecalciferol) and 83 in Group 2 (91% calcium/800 IU). Only 31% of the patients with 25OHD <50 nmol/l would have been identified using general guidelines for screening patients at 'high risk' of hypovitaminosis D.
Conclusions. Improved guidelines for managing hypovitaminosis D in rheumatology patients are needed. We found a high prevalence of hypovitaminosis D among secondary care patients in rheumatology and widespread supplementation with 800 IU cholecalciferol. Substantially reduced levels of serum 25OHD were identified among patients with inflammatory arthritis and chronic pain.

Key words: Vitamin D deficiency, Vitamin D, Osteoporosis, Immunopathology, Autoimmune disease, Biochemical analysis, Inflammatory arthritis, Fibromyalgia.

Introduction

Inadequate levels of serum 25-hydroxyvitamin D (25OHD) are not only detrimental to musculoskeletal health [1] and calcium homeostasis but may also have a role in immunopathology. Understanding of the role of the active vitamin D hormone (1,25-hydroxyvitamin D) in immunodysregulation via down-regulation of Th1 immunity is increasing [2]. Indeed, it is even hypothesized that the latitude-related prevalence of autoimmune diseases is at least in part due to regional differences in the prevalence of hypovitaminosis D [2]. Recently, 25OHD levels were found to inversely correlate with disease activity scores in RA [3], inflammatory arthritis [4] and SLE [2] but little has been published regarding the assessment and management of 25OHD (the stored and readily assayed metabolite) in routine clinical practice. Just as understanding of cardiovascular risk and its profiling in rheumatological practice has increased, so rheumatologists are ideally placed to assess and manage hypovitaminosis D in the outpatient clinic setting. We wished to audit patterns of investigation and treatment of hypovitaminosis D (by serum 25OHD assay) in general rheumatology patients and osteoporotic patients among local physicians.

For rheumatology patients, there is a dearth of formal guidance on investigation for hypovitaminosis D levels in high-risk individuals (with no specific recommendations to guide routine rheumatological practice). However, from a general medical perspective, a recent consensus position statement (CSP; from Australia) identified high-risk groups in whom a serum 25OHD assay should be performed [5]. Here we assess whether these guidelines would adequately identify hypovitaminosis D in rheumatology patients.

For patients with low bone mass, we audited our vitamin D treatment against existing UK clinical guidelines [6]. However, it is increasingly clear that there is no 'One size fits all' approach to supplementing or treating osteoporotic patients [7], and we sought to investigate whether new guidelines are needed.

Methods

We undertook a retrospective audit of the practice of local rheumatologists and metabolic bone physicians ($n = 9$) from April 2006 to March 2007; their requests for serum 25OHD analysis (by disease category) and their prescribing of vitamin D analogues (including preparation type; ergocalciferol, cholecalciferol, IM or oral, physiological or pharmacological dose) in order to identify opportunities for improvement. By matching consultant codes to the local biochemistry database we identified 25OHD requests in 279 patients (7.3% of all trust requests) and identified diagnoses and prescribing from electronic medical records. Records were anonymized and requesting and prescribing were audited as part of standard rheumatological practice. Sixteen patients with a documented diagnosis of hyperparathyroidism were excluded leaving 263. Data were first separated into two groups, 'Documented osteoporosis/osteopaenia' (Group 1) and 'General rheumatology outpatients without documented osteoporosis/osteopaenia' (Group 2). We audited two main aspects of vitamin D management in secondary care; investigation and treatment.

Standard 1—investigation

For osteoporosis (Group 1), existing UK clinical guidelines [6] do not specify vitamin D investigation in individual patients. Neither do standards nor recommendations exist for the

[1]Department of Medicine, Division of Rheumatology, [2]Department of Clinical Biochemistry and [3]Department of Medicine, Division of Bone Research, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK.

Submitted 16 January 2008; revised version accepted 17 April 2008.

Correspondence to: K. E. S. Poole, Box 157, Department of Medicine, Division of Bone Research, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK. E-mail: kenpoole@doctors.org.uk

investigation of serum vitamin D among rheumatology patients. In the absence of satisfactory national audit standards, we used an alternative approach. Here we audited how many clinician's requests (during the year) for serum 25OHD would have satisfied the 'high risk' category recommendation of a recent CPS on vitamin D and adult bone health [5] (standard 100%). We sought to establish how many patients outside these CPS categories had hypovitaminosis D in routine practice in order to assess if these standards were appropriate for investigation of rheumatology and osteoporosis patients in the UK. 'High risk' patients selected for our audit from the CPS were therefore (i) elderly people (>70 yrs), (ii) patients with skin-related conditions where avoidance of sunlight (SLE) is required and (iii) patients with malabsorption syndromes. Data on skin colour was not available.

Standard 2—treatment

For patients with low bone mass, we chose to audit our practice against the Royal College of Physicians' amended guidelines [6]. In osteopaenic patients, the recommendation is 'adequate nutrition with calcium and vitamin D' and in osteoporotic patients 'vitamin D and calcium treatment' (as an adjunct to treatment with other bone active agents). Therefore, our first audit standard for Group 1 was documentary evidence of vitamin D supplementation or dietary modification advice in 100% of the patients. We also examined documentary evidence of vitamin D supplementation or dietary modification advice in general rheumatology patients (Group 2). A further audit standard was documentation of vitamin D prescribing in clinic letters (standard 100%).

Vitamin D and PTH interpretation

Serum 25OHD was measured by RIA (IDS Ltd, Boldon, UK) in a UK Clinical Pathology Accreditation (CPA) approved laboratory. Coefficients of intra-assay ($n=10$) and inter-assay ($n=25$) variation provided by the manufacturer were <10% across the assay range (12.5–374 nmol/l). RIA under-recovers the plant sterol vitamin D metabolite $25OHD_2$ (an important issue if patients have been supplemented with ergocalciferol prior to assay), such that cross-reactivity with $25OHD_2$ is 75% at 50% binding of the zero calibrator (compared with 100% for $25OHD_3$ and 24,25 dihydroxyvitamin D_3, manufacturer's data on file at http://www.idsltd.com/Downloads/AA-35PL-A.pdf). 25OHD is non-normally distributed, so geometric (transformed) z-scores of 25OHD were calculated for each patient by comparison with the monthly mean and S.D. of 25OHD (after log-transformation to achieve normalization) of the local adult reference interval for healthy older adults (derived by measuring 96 healthy adults of mean age 69 ± 2.9 bimonthly for a year; Fig. 1) with JMP software v5.0 (SAS Institute, Cary, USA) [8] and methods detailed previously [9]. The reference intervals determined were validated for the IDS assay by linear regression studies (data not shown). The use of z-scores meant that measurements were no longer season dependent. The mean geometric z-scores of groups could then be compared using analysis of variance (ANOVA) and Tukey Kramer all-pairs honest standard deviation (HSD) analysis. Definitions of hypovitaminosis D (a level insufficient to prevent secondary hyperparathyroidism) are controversial. In our reference interval, the local winter mean nadir in our older [median age 69, interquartile range (IQR) 67–71] healthy subjects was 50 nmol/l (Fig. 1), which we used as a conservative cut-off for defining hypovitaminosis D. PTH was measured using a Siemens Advia Centaur autoanalyser (Deerfield, IL USA) using reagents and protocols provided by the manufacturer.

Regional ethics committee (REC) approval was gained for the healthy volunteer study. The audit was conducted in accordance with the local code of conduct for clinical audit and data protection rules and written confirmation was received that the audit was outside the remit for consideration by the REC.

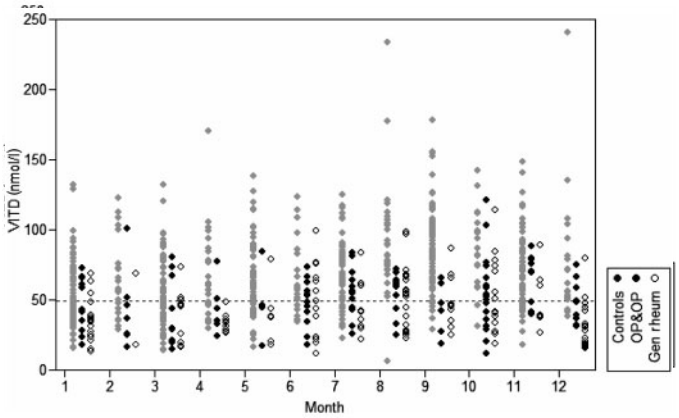

FIG. 1. Healthy reference interval for older East Anglian adult controls (grey filled circles) by month [8]. General rheumatology outpatients ($n=263$) are shown for Group 1 (black filled circles) and Group 2 (open circles).

Results

A total of 263 patients with 25OHD requests during the audit period were identified from the biochemistry database. One hundred and twenty-two (46%) had documented osteoporosis/osteopaenia (Group 1: osteoporosis 109, osteopaenia 13). The remaining 141 (54%, mean age 54 ± 18 yrs) comprised the general rheumatology group (Group 2: CTDs 24, chronic pain/FM 15, degenerative and OA 25, GCA/PMR 11, inflammatory arthritis 29, soft tissue disorders 13, Others 24). Overall (general rheumatology and osteoporosis groups combined), 25OHD was non-normally distributed (Shapiro Wilk goodness of fit $P_W < 0.0001$), with median 25OHD 44 nmol/l (IQR 31–63). In Group 1, median 25OHD was 49 nmol/l (IQR 35–66) and in Group 2, 39 nmol/l (IQR 27–56). Overall, the ANOVA for means comparison of geometric transformed z-scores was statistically significant ($P=0.0331$). Hypovitaminosis D was more prevalent in the general rheumatology patient Group 1 (Fig. 2, mean z-score −1.2; 95% CI −1.4, −1.1) than in the osteoporosis/osteopaenia Group 2 (mean z-score −0.9; 95% CI −1.1, −0.7; $P=0.002$). The mean z-score of 25OHD was lower in inflammatory arthritis (mean z-score −1.6; 95% CI −2.0, −1.2; $P<0.05$) and chronic pain/fibromyalgia (mean z-score −1.8; 95% CI −2.3, −1.2; $P<0.05$) than other rheumatology and osteoporotic patients. PTH levels were requested in 94/263 (36%) patients with a median result of 42.5 ng/l (IQR 29–56). Linear regression with JMP software version 5.0 (SAS Institute) was performed, using methods published by Bates *et al*. [10] (in UK participants aged 65–84 yrs). Linear regression indicated an inverse linear relationship between PTH and 25OHD on a $\log_e - \log_e$ scale for the whole sample (log PTH ng/l = 5.58 − 50*log Vit D nmol/l; $r^2=0.14$; $P=0.0002$).

For audit Standard 1 (investigation), only 35% (92/263) of requests would have satisfied the 'high risk' category recommendation of a recent CPS on vitamin D and adult bone health. Of the 92 that did fulfil the audit standard, 71 were aged >70 yrs. The remaining 21 were younger than 70 yrs but had either SLE or a malabsorption syndrome. The CPS standard would have identified only 48/156 (31%) patients with vitamin D insufficiency (<50 nmol/l) of 263 patients sampled at their clinicians discretion in secondary care. For audit Standard 2 (treatment), vitamin D prescribing details were documented for 100/122 (82%) in Group 1 and 83/141 (59%) in Group 2, well below our audit standard of 100%. Of those with documented prescribing, 95 (95%) patients in Group 1 were prescribed cholecalciferol 800 IU/calcium 1.25–1.5 g (only three had received additional pharmacological dose ergocalciferol) during the year and four had documented intolerance. Among the 100 Group 1 patients, 51 were on supplements at the time the serum 25OHD was checked

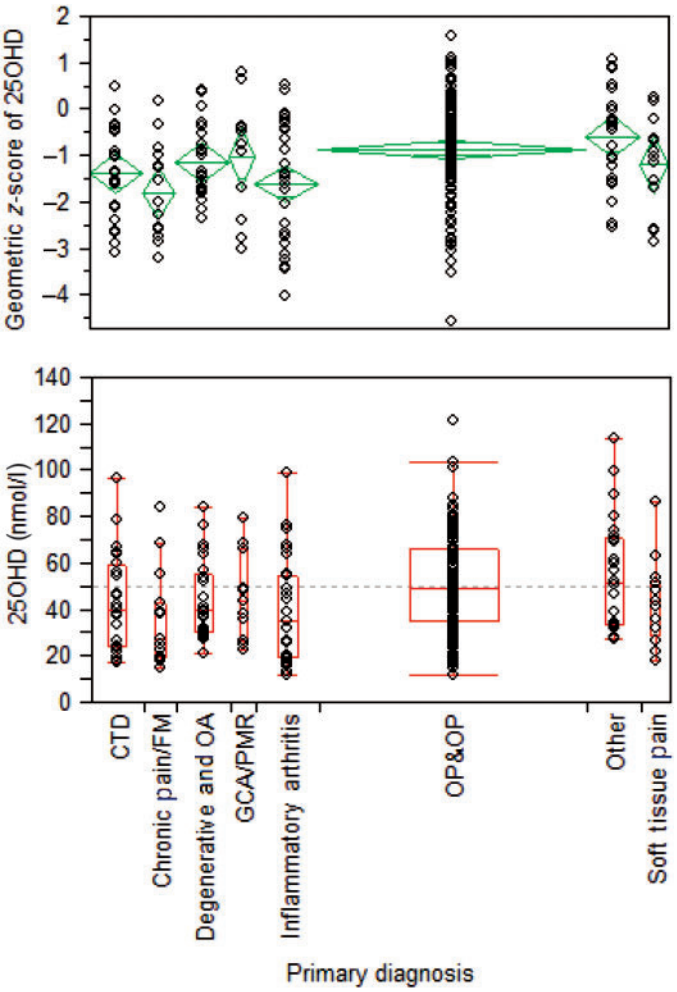

FIG. 2. Geometric *z*-score (upper, with mean/S.D. plot) and 25OHD (lower, with quantile plot) by rheumatological diagnosis in all patients. ANOVA for means comparison of *z*-scores was significant ($P = 0.0331$). Patients with inflammatory arthritis and chronic pain/fibromyalgia had lower mean *z*-scores (of statistical significance using all pairs Tukey Kramer analysis). OP&OP: osteoporosis and osteopaenia.

(median 25OHD 61 nmol, IQR 42–70) and 49 were not (median 48 nmol/l, IQR 32–63, $P = 0.043$). Among the 83 Group 2 patients 20 were on supplements at the time the serum 25OHD was checked (median 50 nmol/l, IQR 39–68) and 63 were not (median 38 nmol/l, IQR 25–57, $P = 0.08$). In Group 2, 91% of the patients were prescribed treatment during the year.

Discussion

Vitamin D has pleiotropic effects beyond its calcaemic homeostatic actions. The importance of adequate levels of vitamin D underlies musculoskeletal health and immune function [1, 2, 11]. 'Sufficient' stores of the pre-hormone (25OHD) are commonly defined in studies of local populations as a level that prevents the serum PTH from increasing, at around 50 nmol/l in northern Europe [12]. Irrespective of the time of year, patients from our general rheumatology clinics had a lower mean vitamin D level than healthy East Anglian adults. Out of 263 patients, 156 (59%) in whom serum 25OHD was requested had an insufficient 25OHD level (<50 nmol/l). Increasing the threshold of serum 25OHD requiring therapy to 75 nmol/l (as many advocate for optimal health) [13] would mean that 236/263 (90%) of rheumatology and metabolic bone disease outpatients were vitamin D insufficient from this sample of patients (sampled at a clinicians discretion) in secondary care.

These findings from routine clinical practice are in agreement with a study performed by Orbach *et al.* [11], where patients with various autoimmune diseases had low levels of 25OHD. One possible explanation for this low vitamin D level is the sun avoidance recommended for patients with photosensitivity secondary to CTDs, and similarly the use of sun block that decreases vitamin D production in the skin (factors not assessed in our audit). Medications used in SLE and inflammatory arthritis have also been found to adversely affect vitamin D metabolism (e.g. HCQ inhibits the conversion of 25OHD to $1,25OHD_2$ [14]).

Patients with osteomalacia can present with diffuse pain that may be misdiagnosed as fibromyalgia. For example, 22/26 (85%) patients proven to have osteomalacia on bone biopsy (with only 7/26 (27%) having pseudo fractures on radionuclide bone scan) presented with regional or widespread pain [15]. Ninety-three percent of the patients presenting to a primary care facility with persistent unexplained pain were found to have low vitamin D levels (mean 30 nmol/l) [16]. Our findings confirm the association of a low vitamin D level and unexplained pain. An unanswered question is whether replacing this low vitamin D will alleviate the pain.

Our findings in patients with inflammatory arthritis are in agreement with Patel *et al.* [4] who found associations with 25OHD insufficiency and clinically assessed disease activity in early polyarthritis. Of particular relevance, higher stores of 25OHD appear to confer protection from (or a reduction in the severity of) certain autoimmune diseases and OA [1, 3, 11]. The median level among our patients with OA/degenerative disease was 40.4 (IQR 31–55), also within the insufficient range, and particularly interesting in light of associations between low 25OHD and incident radiographic hip OA [17].

What is apparent from our audit data is that new guidelines for the request of serum 25OHD in high-risk patients with osteoporosis and rheumatological diseases are needed. We used a general audit standard over 1 yr for defining a population at high risk for hypovitaminosis D [5]. This standard would have identified only 48/156 (31%) patients with vitamin D insufficiency (<50 nmol/l) of 263 patients sampled at their clinicians discretion in secondary care. For newly diagnosed osteoporosis in the UK, Ryan [7] recently made a strong case for assessing serum 25OHD in all, with repeated measurements to ensure normalization of serum values (because of emerging evidence that 'standard' preparations of calcium and vitamin D may not be universally effective at normalizing 25OHD). In our patients with osteoporosis/osteopaenia, 95% received 800 IU cholecalciferol from combined calcium/vitamin D tablets and those taking supplements at the time of serum sampling for 25OHD assay had a significantly higher level than those yet to commence on supplements. We were unable to ascertain exactly when supplements were commenced, but our results are generally supportive of Ryan's study; a median 25OHD of 61 nmol (IQR 42–70) among supplemented patients may not be in the optimal range for bone health, and more pharmacological doses of ergocalciferol or cholecalciferol as well as follow-up assessment of their efficacy may be required.

With regard to treatment of 25OHD insufficiency and the prevention or alleviation of rheumatic disease, little is known in human disease. The vitamin D receptor is highly concentrated in the CD8-positive T cells of the thymus [18] and active vitamin D analogues are capable of suppressing human [19] and animal models of T-cell diseases (by suppressing the enhanced activity of such cells) [20]. Although no randomized clinical trials of supplementation have been conducted in arthritis, in healthy British adults of Bangladeshi origin CRP levels were noted to decrease by 23% in patients with hypovitaminosis D who received an approximate daily dose of 547 IU vitamin D (by intermittent IM bolus) for 2.5 yrs. This suggests a dose-dependent anti-inflammatory effect of vitamin D [21] that warrants clinical trial evaluation in the setting of inflammatory arthritis.

Our findings have a number of important limitations. Osteoporosis is often associated with low vitamin D levels and standard treatment in clinical practice includes oral calcium and vitamin D supplementation or bisphosphonates. The patients in Group 1 of our study were mostly (95%) receiving vitamin D treatment but we were unable to ascertain exactly when the treatment was commenced; it may have been initiated at primary care, well before the patient was referred to our institution. This is undoubtedly a weakness of the present study. Neither do we have data on compliance with supplements. A further caveat to the generalized applicability of our audit results was that although 91% of Group 2 patients were prescribed treatment, only 57% of clinicians documented their prescribing in electronic records, a reason for repeating the audit cycle and improving our local practice in this regard. Around 30% (77/257) of UK laboratories use RIA to measure vitamin D according to the last vitamin D external quality assessment scheme (DEQAS) report of 27 October 2007 (in spite of the fact that the RIA technique for 25OHD under-recognizes D2 analogues such as ergocalciferol) [22]. The latter is unlikely to affect overall applicability of the results since only 3/263 patients were receiving ergocalciferol, the remainder D3 analogues (cholecalciferol). Definitions of hypovitaminosis D (a level insufficient to prevent secondary hyperparathyroidism) are controversial, with some advocating a clinical cut-off of 75 nmol/l is necessary to prevent bone pathology. Raising the threshold of vitamin D adequacy would only strengthen the case for insufficiency among rheumatology patients. Finally, we had insufficient numbers to investigate by individual disease category; for instance, our inflammatory arthritis group included AS, PsA and RA. Determining 25OHD levels for individual conditions should now be a priority for further work.

Conclusion

We found a high prevalence of hypovitaminosis D among secondary care patients in rheumatology and near-universal supplementation with 800 IU daily cholecalciferol. Substantially reduced levels of serum 25OHD were identified among patients with inflammatory arthritis and chronic pain. 25OHD levels were low in all rheumatology conditions when compared with a local healthy reference interval. It is clear that clinical studies are needed to fully assess the impact of vitamin D in patients with the relevant rheumatological diagnoses. In light of the metabolic and physiological effects of hypovitaminosis D in musculoskeletal and immune health, a consensus on the requesting and treatment of serum 25OHD levels is also needed, leading to improved guidelines for rheumatologists.

Rheumatology key messages

- Hypovitaminosis D is common among rheumatology patients.
- Particularly low levels are seen in inflammatory arthritis and chronic pain/fibromyalgia.
- Vitamin D supplementation studies in specific rheumatic conditions are needed.

Acknowledgements

K.E.S.P. acknowledges the support of the Arthritis Research Campaign (Clinician Scientist Fellowship).

Funding: This study was supported by the National Institute for Health Research Biomedical Research Centre (Cambridge, Musculoskeletal).

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
2 Cutolo M, Otsa K. Review: vitamin D, immunity and lupus. Lupus 2008;17:6–10.
3 Cutolo M, Otsa K, Uprus M, Paolino S, Seriolo B. Vitamin D in rheumatoid arthritis. Autoimmun Rev 2007;7:59–64.
4 Patel S, Farragher T, Berry J, Bunn D, Silman A, Symmons D. Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. Arthritis Rheum 2007;56:2143–9.
5 Vitamin D and adult bone health in Australia and New Zealand: a position statement. Med J Aust 2005;182:281–5.
6 Compston JE. Prevention and treatment of osteoporosis: clinical guidelines and new evidence. J R Coll Physicians 2000;34:518–21.
7 Ryan PJ. Vitamin D therapy in clinical practice. One dose does not fit all. Int J Clin Pract 2007;61:1894–9.
8 Barker PJ, Carr C, Raggatt PR. A reference range for 25-hydroxyvitamin D. In: Proceedings UK NEQAS Endocrinology Meeting. Cardiff 1996.
9 Poole KE, Loveridge N, Barker PJ *et al.* Reduced vitamin D in acute stroke. Stroke 2006;37:243–5.
10 Bates CJ, Carter GD, Mishra GD, O'Shea D, Jones J, Prentice A. In a population study, can parathyroid hormone aid the definition of adequate vitamin D status? A study of people aged 65 years and over from the British National Diet and Nutrition Survey. Osteoporosis Int 2003;14:152–9.
11 Orbach H, Zandman-Goddard G, Amital H *et al.* Novel biomarkers in autoimmune diseases: prolactin, ferritin, vitamin D, and TPA levels in autoimmune diseases. Ann NY Acad Sci 2007;1109:385–400.
12 Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 2001;22:477–501.
13 Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr 2003;22:142–6.
14 Huisman AM, White KP, Algra A *et al.* Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia. J Rheumatol 2001;28:2535–9.
15 Reginato AJ, Falasca GF, Pappu R, McKnight B, Agha A. Musculoskeletal manifestations of osteomalacia: report of 26 cases and literature review. Semin Arthritis Rheum 1999;28:287–304.
16 Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc 2003;78:1463–70.
17 Lane NE, Gore LR, Cummings SR *et al.* Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. Arthritis Rheum 1999;42:854–60.
18 Deluca HF, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J 2001;15:2579–85.
19 Andjelkovic Z, Vojinovic J, Pejnovic N *et al.* Disease modifying and immunomodulatory effects of high dose 1 alpha (OH) D3 in rheumatoid arthritis patients. Clin Exp Rheumatol 1999;17:453–6.
20 Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis 2007;66:1137–42.
21 Timms PM, Mannan N, Hitman GA *et al.* Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? Q J Med 2002;95:787–96.
22 Glendenning P, Taranto M, Noble JM *et al.* Current assays overestimate 25-hydroxyvitamin D3 and underestimate 25-hydroxyvitamin D2 compared with HPLC: need for assay-specific decision limits and metabolite-specific assays. Ann Clin Biochem 2006;43:23–30.