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The worlds of primary and secondary hyperparathyroidism often collide; What effect are variable regimens of supplementing vitamin D for one problem, having on the other?

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Introduction: Primary hyperparathyroidism causes accelerated bone turnover and the consensus is to measure and act upon the 25-hydroxyvitamin D level in order to reduce the drive to PTH production, slow down BMD loss, and prevent hungry bone syndrome. How best to replace vitamin D is less clear so we chose to audit our current practice.

Method: In 12 months 120 patients with primary hyperparathyroidism were identified retrospectively, 98 of which were vitamin D insufficient (25hydroxyvitamin D <72.5nmol/l). These were audited as to the action taken and the change in 25-hydroxyvitamin D, calcium and PTH.

Results: 21.4% of the 98 cases were loaded with the equivalent to 300000U over 10weeks, this being the most common decision in the "deplete" subgroup. The majority (44.9%), especially in the subgroup 25-50nmol/l were given 20000 to 60000U monthly. The remaining 33 cases were not given any vitamin D supplementation. 30% of cases referred for surgery were not supplemented but with no detrimental effects.

There was an increment in calcium in all groups except those given <1000U daily (-0.04mmol/l). The largest mean difference of +0.13mmol/l in the subgroup loaded to 300000U by weekly doses coincided with the largest mean change in 25-OHVitD level (70.67nmo/l) without a PTH decrement (mean +0.86pmol/l). Those receiving a stat dose of 300,000U did however show reduction in the PTH (mean -2.03pmol/l), and was as safe as other regimes for calcium change (+0.05mmol/l), even with influence by an outlying result of +0.9mmol/l. A subgroup of 9 patients on 1g supplement of calcium a day demonstrated a mean rise in calcium of +0.12mmol/l, but despite minimal impact on 25-OHVitD reduced PTH by a mean of -12.47pmol/l.

Discussion: There doesn't appear to be one best regimen to use and none appear detrimental. The variable effects on PTH level would warrant further investigation.

Premise and method of retrospective notes audit

The assay of 25-hydroxyvitamin D is not very reliable [2], and there is no consensus internationally about a serum level that is replete [1,2]. Leeds teaching hospitals has a shared care policy for vitamin D supplementation with a recommended replete level of 72.5mmol/l, but due to lack of evidence, gives little direction when it comes to suplementing vitamin D in patients with primary hyperparathyroidism. In this population group with an accelerated bone turnover and renal activation of 25-hydroxyvitamin D, the only national agreement is the appropriateness to measure and act upon the 25-hydroxyvitamin D level [1] especially in the context of osteoporosis and anti-resorptive therapy [3] and to prevent hungry bone syndrome post parathyroidectomy [4]. There are valid concerns that supplementing 25-hydroxyvitamin D will promote GI calcium absorption, unmasking primary hyperparathyroidism [2], and potentially pushing the serum calcium levels up further to dangerous levels as in the index case at St James's University Hospital. The patient presented with an adjusted calcium of 3.63mmol/l 4 weeks post supplementing cholecalciferol, but only with a 64.9nmol rise in vitamin D. However, theoretically a rise in calcitriol may reduce the drive to PTH?

The second agreed national guideline is to monitor response to vitamin D supplementation at a suggested 1 month interval [2].
With a group of 10 Consultants, the variety of vitamin D administration could be identified retrospectively from 12months of Endocrine outpatient letters from March 2012-2013, using in-house filtering software of the digital dictation system.
180 cases of hyperparathyroidism were identified this way, narrowing to 122 cases of primary hyperparathyroidism that had not already gone parathyroidectomy to cure the condition, on closer look of the biochemistry system.
120 cases all had their 25-hydroxyvitamin D levels checked within a couple months of the target year and 98 were found to be insufficient. Data was collected and analysed as to the action taken, the influences of this action, the monitoring performed, and the outcome in terms of consequent change in 25-hydroxyvitamin D, corrected calcium and parathyroid hormone.

Level 25-OH Vitamin D (nmol/L)	Number of patients	Action taken	Percentage of group	Number of patients in which osteoporosis diagnosed	Patients for whom surgery planned	Range of PTH values (pmol/L)	Effect on 25-OH Vit D in patient with highest PTH (nmol/L)	Effect on calcium in patient with highest PTH (mmol/L)
<25	22	Loading	45	1	2	8.1-102.6	12 to 129	2.98 to 3.36
		Maintenance	36	3	3	9.9-34.8	13.7 to 86	2.56 to 2.74
		No action	5	1	0			
		Not commented	14	1	2			
25-50	47	Loading	23	4	3	2.2-43.3	46.7 to 90.3	2.8 to 2.88
		Maintenance	53	10	7	5.3-43.4	29 to 45.8	3.07 to 2.82
		No action	13	1	1			
		Not commented	11	1	2			
50-72.5	29	Loading	0	0	0			
		Maintenance	38	5	2	5.4-47.5	57.5 to 57.9	3.08 to 2.9
		No action	41	2	2			
		Not commented	21	4	1			
Total patients	98			33 (out of 87 where stated or with DEXA); 23 receiving action for insufficiency	25 surgical candidates; 17 receiving action for insufficiency			

Figure 1. Table of action taken and whether a diagnosis of osteoporosis, plans for surgery, or PTH baseline level is associated with a particular method of supplementation. Where PTH activity is highest, how the vitamin D and adjusted calcium level changed with supplementation.

Figure 2

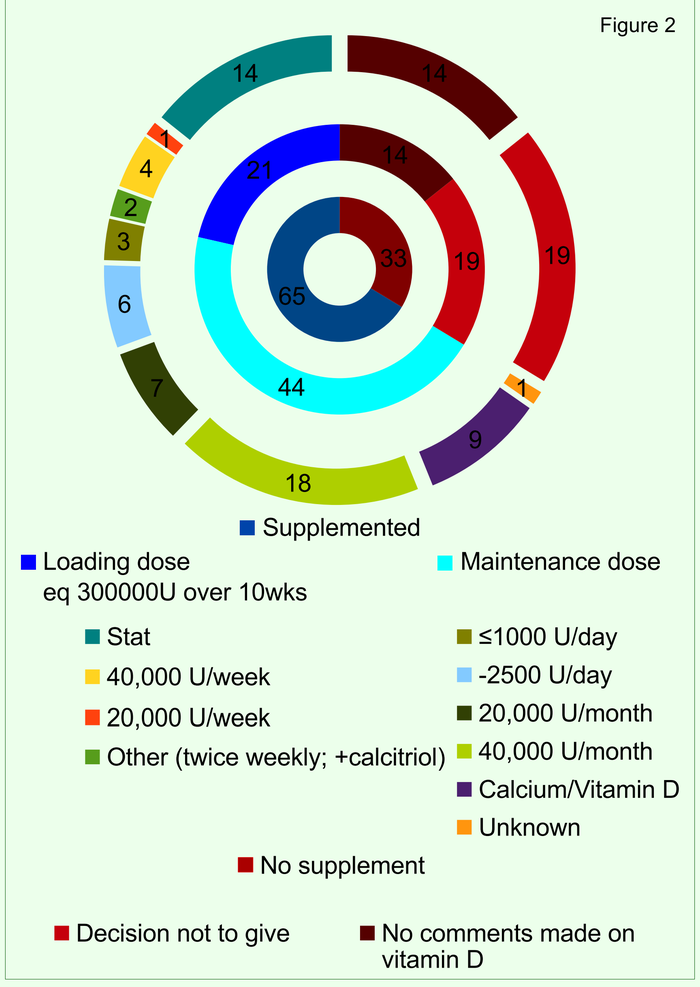
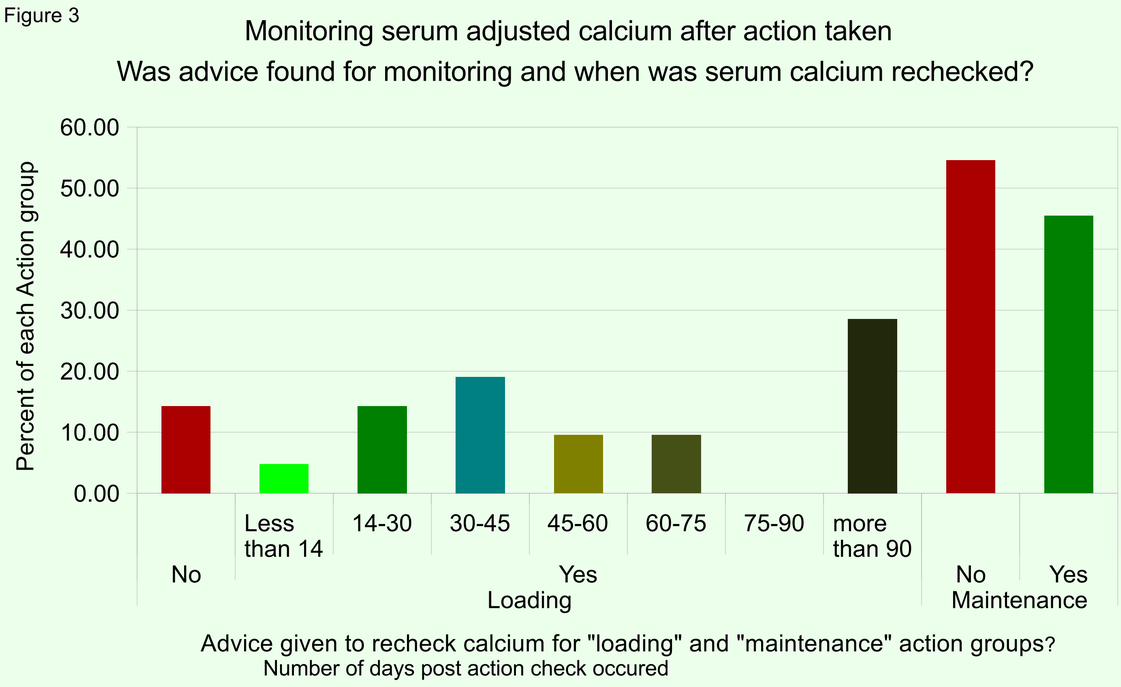


Figure 3



Top Right; Figure 2. Exploded pie chart of action taken for the 98 patients with 25-hydroxyvitamin D levels less than 72.5nmol/L. Includes a break down of the methods used.
Left; Figure 3. Column chart representing the percentage of 21 patients receiving a loading dose of vitamin D, and 44 patients receiving maintenance dose, that had documented advice to monitor serum calcium. Further demonstration of how many days after loading it was that calcium was actually measured.
Bottom Left; Figure 4. For each of the 65 patients who had vitamin D supplemented, change in serum adjusted calcium plotted against change in 25-hydroxyvitamin D. Highlighted points of the Index case, and 2 apparent outliers.
Bottom Right; Figure 5. Box plot of the range and quartiles of the difference in adjusted calcium after each method of vitamin D supplementation. An additional group that removes the index case.

Figure 4

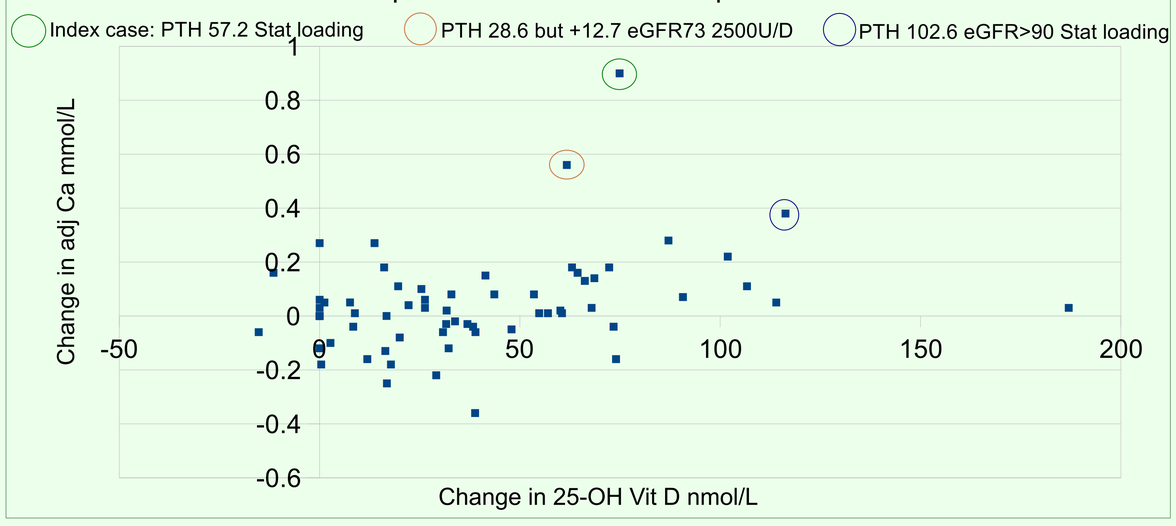
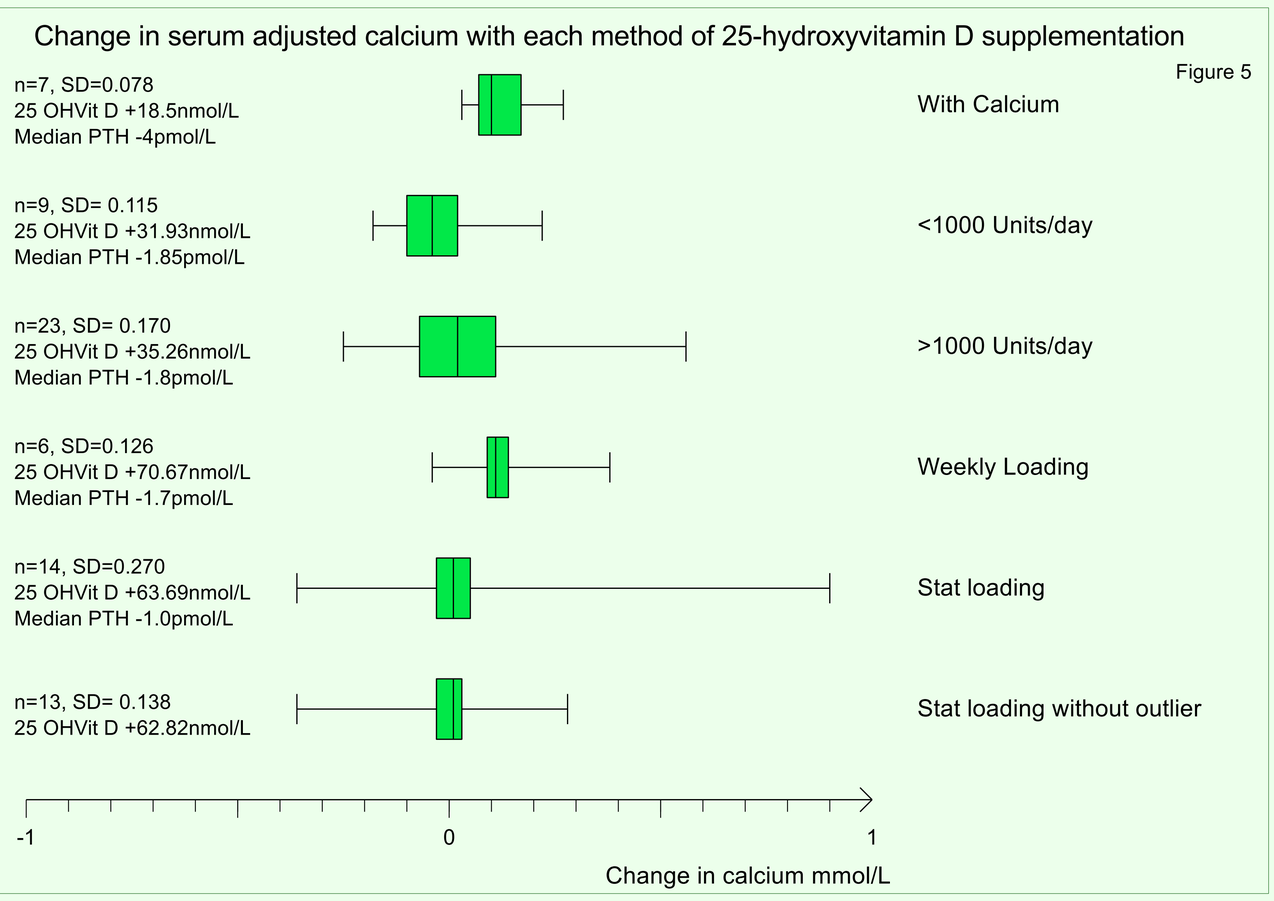


Figure 5



Discussion

The department appears to act below a vitamin D replete level of 50nmol/l, and in the main replaces vitamin D weekly or monthly with good monitoring of the calcium levels after loading doses have been given. Most patients had decisions made at Consultant level and although the relationship of method of supplementing to osteoporosis and planned surgery was difficult to analyse in detail because of the low patient numbers, there were low vitamin D levels that were not acted upon in 10/33 of the former and 8/25 of the later group. The highest baseline PTH levels were found in combination with lower 25-hydroxyvitamin D levels, and one outlying case implies caution required in giving large doses of vitamin D in the context of a high PTH. There doesn't appear to be one best regime to use in terms of keeping calcium stable, but with different standard deviations, a statistical test on the groups was not possible. No method in isolation appears detrimental and therefore with a large difference in increment of vitamin D between the loading and maintenance methods, the choice should perhaps be based on the aim of the vitamin D. The analysis, although understandably in small numbers, of the group remaining on calcium supplementation, supports the understanding that this increments the calcium, but shows no value in improving vitamin D. However this group demonstrated a large mean and median drop in the PTH level whereas the other methods' effects on PTH level were more slight, with median and mean varying and could be explained by the limitations of the assay. Given that this goes against the evidence in treating purely secondary hyperparathyroidism it would be worth more investigation. The index case is an outlier in the group that received stat loading of vitamin D and therefore not predictable.

References
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