Secondary hyperparathyroidism in elderly people: combined effect of renal insufficiency and vitamin D deficiency1–3

Rosemarie Freaney, Yvonne McBrinn, and Malachi J McKenna

ABSTRACT The relative effects of renal insufficiency and vitamin D deficiency on parathyroid gland function were assessed in 29 free-living elderly subjects by using a sensitive assay for intact parathyroid hormone (PTH). Serum calcium, phosphate, alkaline phosphatase, creatinine, 25-hydroxyvitamin D [25(OH)D], and PTH were measured after an overnight fast during wintertime, after oral vitamin D therapy (20 μg cholecalciferol/d for 4 wk), and at the end of the subsequent summer. Hypovitaminosis D [serum 25(OH)D < 25 nmol/L] was evident in 86% of the subjects during wintertime and 52% had elevated PTH concentrations. Multiple-regression analysis identified serum creatinine as the strongest predictor variable for serum PTH (multiple r = 0.73, P < 0.001). Mean (±SD) serum PTH declined from 6.3 ± 2.8 to 5.0 ± 2.0 pmol/L (P < 0.001) by the end of the summer season, coincident with an increase in serum 25(OH)D. Secondary hyperparathyroidism is common in elderly people, and in Ireland is the result of both renal insufficiency and hypovitaminosis D. Am J Clin Nutr 1993;58:187–91.

KEY WORDS Elderly people, secondary hyperparathyroidism, vitamin D deficiency, renal insufficiency

Introduction

The development of a two-site immunoradiometric assay for intact parathyroid hormone (PTH 1–84) has resulted in a very sensitive assay capable of showing a response to small changes in serum calcium (1). A recent review of methodology for assay of intact PTH by using commercial kits showed remarkable concordance in intact PTH concentrations measured and close agreement between reference ranges for healthy adults (2). Reports indicate that values for serum intact PTH are higher in elderly subjects than in young adults (3–5). This finding of secondary hyperparathyroidism may reflect a degree of renal insufficiency with concomitant reduction in 1-α-hydroxylase activity and production of 1,25-dihydroxyvitamin D [1,25(OH)2D] (6, 7). Alternatively, it could be a manifestation of privational vitamin D deficiency, a common event in elderly people (8). It is conceivable that the contemporaneous presence of vitamin D deficiency and renal insufficiency could account for the high prevalence of secondary hyperparathyroidism in elderly people. This is especially so in countries where a high prevalence of vitamin D deficiency in elderly subjects exists (9, 10).

The objectives of this study were to determine the frequency of secondary hyperparathyroidism in community-dwelling elderly subjects, determine the response of PTH concentrations to vitamin D supplementation and season, and assess the relative influence of vitamin D deficiency and renal insufficiency on serum PTH concentration.

Subjects and methods

Twenty-nine ambulatory, free-living elderly white subjects (14 men, 15 women) attending a hospital clinic were studied. Their mean age was 74 y (range 65–87 y). None was suffering from any condition likely to affect vitamin D status or parathyroid function. Approval for the study was obtained from the Ethics Committee at St Michael’s Hospital. All patients gave informed consent.

Baseline blood samples were drawn after an overnight fast during wintertime (January–March) for determining serum calcium, serum phosphate, alkaline phosphatase, creatinine, 25-hydroxyvitamin D [25(OH)D], and PTH concentrations. Vitamin D therapy was administered (20 μg cholecalciferol/d as halibut liver-oil capsules) for 4 wk. A second set of blood tests was drawn after supplementation, and this was completed by early April. A third set of blood samples was drawn at the end of the subsequent summer (August–September).

Serum calcium, phosphate, and creatinine were measured as previously described (9). Serum alkaline phosphatase was measured by a kinetic method adapted for use on the American Monitor System (11). Serum 25(OH)D was measured by the competitive protein-binding method of Haddad and Chyu that incorporates both extraction and chromatographic steps before radioassay (12). Mean recovery of exogenously added 25-hydroxycholecalciferol [25(OH)D3] was 101.6 ± 11.7%; between-batch precision was 13%, 11%, and 13% at 14, 24, and 56 nmol/L, respectively. Serum 1,25(OH)2D was not measured in this study. Serum PTH was determined by using an immunoradiometric assay for intact PTH (Allegro; Nichols Institute, San Juan

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Received September 15, 1992.
Accepted for publication January 28, 1993.
Capistrano, CA). The detection limit for PTH was 0.11 pmol/L, and the between-batch precision of the method was 11.1%, 3.4%, and 3.0% at concentrations of 1.59, 3.71, and 23.7 pmol/L, respectively. The reference range defined in an adult group < 65 y of age (n = 33; 23 men, 10 women) gave a mean (±SD) concentration of 2.60 ± 1.0 pmol/L (absolute range 0.85–5.40 pmol/L).

For paired group analysis, one-sample Student’s t test was used. Analysis of variance was used for comparison of multiple groups, and where a significant difference was noted a Tukey test was applied for multiple comparisons. Stepwise linear-regression analysis was performed to identify predictor variables of PTH concentration from a set of independent variables—namely, age, sex, creatinine concentration, and 25(OH)D concentration. P-values were derived by using two-sided tests and values < 0.05 were considered to be significant. GB-STAT (Dynamics Microsystems, Inc. Silver Spring. MD) was used for statistical analyses.

Results

The mean (±SD) serum 25(OH)D concentration during summertime was 13 ± 12 nmol/L (Table 1). Fifty-two percent of subjects had concentrations < 5 nmol/L and 86% of values were < 25 nmol/L (Table 2). After short-term vitamin D supplementation, serum 25(OH)D increased to 25 ± 14 nmol/L and values were > 5 nmol/L in 25 of 29 patients. In these community-dwelling, ambulatory patients serum 25(OH)D concentrations rose further at the end of summertime to 38 ± 19 nmol/L. One patient failed to respond to either oral supplementation or seasonal change with a serum 25(OH)D concentration remaining < 5 nmol/L.

Initially, 15 patients (52%) had serum PTH concentrations above the upper limit of the adult reference range (0.85–5.40 pmol/L). Serum PTH was 5.8 ± 2.2 pmol/L after vitamin D supplementation. A further decrease occurred over the summertime to 5.0 ± 2.1 pmol/L; serum PTH decreased in 19 of 25 patients in whom it was measured, was unchanged in 2, and rose in 4; 72% of values fell within the reference range for younger adults.

![Table 1](https://example.com/table1)

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline (n = 29)</th>
<th>After vitamin D therapy (n = 29)</th>
<th>After summertime (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
<td>6.3 ± 2.8</td>
<td>5.8 ± 2.3</td>
<td>5.0 ± 2.0†</td>
</tr>
<tr>
<td>(pmol/L)</td>
<td></td>
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</tr>
<tr>
<td>25-Hydroxyvitamin D</td>
<td>13 ± 12</td>
<td>25 ± 14†</td>
<td>38 ± 19†</td>
</tr>
<tr>
<td>(nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>2.37 ± 0.10</td>
<td>2.35 ± 0.11</td>
<td>2.36 ± 0.08</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Phosphate</td>
<td>1.17 ± 0.26</td>
<td>1.19 ± 0.20</td>
<td>1.15 ± 0.19</td>
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<tr>
<td>(mmol/L)</td>
<td></td>
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<tr>
<td>Alkaline phosphatase</td>
<td>1.15 ± 0.57‡</td>
<td>1.20 ± 0.72‡</td>
<td>1.18 ± 0.35</td>
</tr>
<tr>
<td>(µkat/L)</td>
<td></td>
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<tr>
<td>Creatinine</td>
<td>89 ± 35</td>
<td>95 ± 34§</td>
<td>98 ± 29</td>
</tr>
<tr>
<td>(µmol/L)</td>
<td></td>
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</tbody>
</table>

* SD.
† Significantly different from baseline. P < 0.001.
‡ n = 26.
§ n = 27.

![Table 2](https://example.com/table2)

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>After vitamin D therapy</th>
<th>After summertime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
<td>52</td>
<td>55</td>
<td>28</td>
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<tr>
<td>(&gt; 5.4 pmol/L)</td>
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<td></td>
</tr>
<tr>
<td>25-Hydroxyvitamin D</td>
<td>52</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>(&lt; 5.0 nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25(OH)D</td>
<td>86</td>
<td>45</td>
<td>32</td>
</tr>
<tr>
<td>(&lt; 25 nmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>10</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>(&lt; 2.25 mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>21</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>(&gt; 1.39 mmol/L)</td>
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</tr>
<tr>
<td>Creatinine</td>
<td>10</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>(&lt; 115 µmol/L)</td>
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<tr>
<td>Alkaline phosphatase</td>
<td>14</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>(&gt; 1.57 µkat/L)</td>
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</tbody>
</table>

* Percent of abnormal results based on adult reference ranges.

Serum creatinine was 89 ± 35 µmol/L; three patients had a considerable diminution in renal function as judged by a serum creatinine concentration > 140 µmol/L. The mean serum creatinine for the group was not significantly different from the basal value after supplementation and at the end of the summertime. Serum alkaline phosphatase was high in four patients (14%) at the outset. No significant changes in alkaline phosphatase were recorded. Multiple-regression analysis identified serum creatinine (multiple r = 0.73) as the only significant predictor of serum PTH. There were no significant differences between men and women with respect to age, creatinine, 25(OH)D, or PTH.

Discussion

Elevated PTH concentrations in the absence of hypercalcaemia is synonymous with secondary hyperparathyroidism. This parathyroid hyperactivity occurs in response to a hypocalcaemic stimulus that could arise in a variety of clinical circumstances. The latter can be divided broadly into three categories: renal insufficiency with reduced capacity for 1α-hydroxylation, privalional hypovitaminosis D, and intestinal diseases with calcium malabsorption (13). In the past, if renal impairment was present PTH assays were not reliable estimates of parathyroid gland activity; therefore, indirect indexes such as nephrogenic cyclic AMP (cAMP) and the tubular maximum reabsorption of phosphate were used (13). Intact PTH, unlike C-terminal or midmolecule PTH fragments, is not dependent on renal clearance for removal, and therefore is a better indicator of parathyroid function. Furthermore, close agreement between intact PTH assays from different centers enables comparisons in clinical studies (2).

It has been suggested for some time that PTH concentrations increase with age (14, 15). This finding has been corroborated by studies with intact PTH assays from different laboratories (3, 5). Most investigators tend to conclude that secondary hyper-
PTH status in elderly people reflects a decline in renal function (16, 17). It is conceivable that privational vitamin D deficiency could account for secondary hyperparathyroidism, especially in regions where hypovitaminosis D is prevalent (10). We found that renal function was the major predictor variable of parathyroid status as assessed by multiple-regression analysis.

We compared studies that reported vitamin D status and parathyroid status in elderly people (4, 6, 18–21). Results are presented as a bivariate plot of mean PTH vs mean 25(OH)D (Fig 1), which is a diagrammatic demonstration of the relationships between hypovitaminosis D and secondary hyperparathyroidism but does not draw interlaboratory comparisons. The plot of the mean values for both serum 25(OH)D and serum PTH shows an inverse relationship. Mean PTH concentrations were higher in regions where hypovitaminosis D is prevalent (eg, Ireland, France, and Wales) compared with countries where hypovitaminosis D is less common (eg, North America) (Fig 1). Institutionalized elderly people in the United States (20) had higher PTH concentrations than did community-dwelling elderly subjects in the United States (4, 19). In the United States serum PTH values in healthy elderly people are considered to be higher than in younger normal adults and a decline in PTH concentrations over the summer season has been reported (22). After vitamin D therapy and the summer season in the Dublin group, the coordinate for 25(OH)D and PTH shifted toward the North American values but was still different. Supplementation with a similar vitamin D dose for a longer period (18 mo) in a French group of housebound elderly people led to a marked decline in serum PTH (Fig 1 and Fig 2) (21).

These observations have two implications with respect to 1) the establishment of a reference range for PTH, and 2) the correction and prevention of hypovitaminosis D. A reference range for PTH in elderly people must take into account both renal function and vitamin D status. In selecting patients to define a reference range, we suggest that the glomerular filtration rate exceed 50 mL/min and that serum 25(OH)D exceed 25 nmol/L. This cutoff concentration for hypovitaminosis D was advocated in 1982 (8) and found to be relevant in clinical studies (9, 10), but some advocate an even higher cutoff concentration (23).

It is still likely that the range for PTH values will be higher than in young adults. At this point, in evaluating influences on parathyroid activity in elderly people, one must distinguish between factors that are part of the aging process and those that are due to disease. Diseases may readily respond to therapy, such as those that result in hypovitaminosis D, or they may be difficult to remedy—renal insufficiency is one such disease. Secondary hyperparathyroidism ensuing as part of the aging process is assumed to be consequent on a decline in 1,25-dihydroxyvitamin D activity, but may, as our study shows, be moderated by vitamin D supplementation.

Hypovitaminosis D per se does not indicate vitamin D deficiency; it merely reflects a high risk of having a deficiency state or of developing it soon (10, 13). A diagnosis of vitamin D deficiency, in addition to the finding of low circulating 25(OH)D concentrations, is made when there is evidence of muscle or bone disease. The former is more difficult to measure and relies on clinical judgement of symptoms and signs. The presence of bone disease can be appraised by a variety of laboratory methods (13, 24, 25). Quantitative microscopy of bone after intravital double tetracycline labeling affords evaluation according to definitive criteria (13, 25). The natural history of vitamin D-related bone disease, discerned from bone histomorphometry, encompasses an initial stage of high bone turnover that is superseded gradually by a defect in mineralization (26). The high bone turnover is the result of secondary hyperparathyroidism and is a phase of irreversible bone loss (13, 26, 27). Three recent studies support the view that minor degrees of vitamin D deficiency
account for loss of bone in the vertebral spine and femoral neck (18, 28, 29). A recent double-blind trial of vitamin D (20 μg/d) and calcium supplementation demonstrated a significant reduction in hip fracture (21). Although, some contest that vitamin D deficiency in elderly people, unless very severe, has no harmful effect on bone (30).

Indexes of secondary hyperparathyroidism, direct and indirect, are considered to be sensitive markers of vitamin D deficiency (13). In this regard, the new serum PTH assays appear to be the most sensitive markers of vitamin D deficiency (31). Biochemical markers of bone disease, particularly serum alkaline phosphatase and serum osteocalcin, correlate with abnormalities in bone (13). In our study, abnormalities in PTH were more common than in alkaline phosphatase. Hypovitaminosis D was evident in 86% of subjects, and 52% had evidence of secondary hyperparathyroidism.

Low-dose vitamin D is efficacious and safe in correcting and preventing hypovitaminosis D and in lowering serum PTH concentrations in elderly people (32–35). The combined benefit of vitamin D supplementation and summertime reduced the frequency of secondary hyperparathyroidism. Still, a substantial proportion of subjects had persistent secondary hyperparathyroidism. This raises the issue of suppressibility of the parathyroid glands once overactivity has been established. In Asian immigrants PTH concentrations remained elevated after hypovitaminosis D was corrected, although the assay did not measure intact PTH (36). In our elderly patients it would appear that they require vitamin D supplementation for prolonged periods, as judged by the findings of a recent French trial (21). Pharmacological therapy for example with analogues of 1,25(OH)2D might be required for a period of time to achieve maximum suppression of PTH concentrations. It is still unclear whether the minimum concentration of serum 25(OH)D necessary to correct secondary hyperparathyroidism is similar to or greater than the concentration necessary to prevent secondary hyperparathyroidism; however, it now appears that serum 25(OH)D should be kept well in excess of 25 nmol/L without any risk of hypercalcemia (Figs 1 and 2).

Finally, regarding the matter of the optimum biochemical index of vitamin D status, the choice rests between 1,25(OH)2D and 25(OH)D (8, 10). Serum 1,25(OH)2D concentration in serum shows a variable response to 25(OH)D status. Because 25(OH)D is the substrate for 1-α-hydroxylase activity, it is necessary to have an adequate supply of it. However, in conditions of 25(OH)D scarcity the 1-α-hydroxylase enzyme activity is enhanced and 1,25(OH)2D may be normal or even elevated for a limited period of time, masking a vitamin D deficiency state. Conversely, any decline in 1-α-hydroxylase activity due to renal impairment may give a spurious indication of vitamin D deficiency. This is all the more apparent in elderly people. Serum 25(OH)D is the foremost indicator of vitamin D status (8, 10).

In conclusion, secondary hyperparathyroidism is common in elderly people in Ireland and is the result of both renal insufficiency and hypovitaminosis D. This state is corrected in part by low-dose vitamin D supplementation. Further research is required to explore the extent of the reversibility of secondary hyperparathyroidism in elderly people.

We acknowledge the assistance of Patricia McNally, St Michael's Hospital, and helpful discussions with J Stuart Woodhead. University of Cardiff College of Medicine. Cardiff, Wales.

References