A 250 µg/week dose of vitamin D was as effective as a 50 µg/d dose in healthy adults, but a regimen of four weekly followed by monthly doses of 1250 µg raised the risk of hypercalciuria

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Abstract
The risk of vitamin D insufficiency is increased in persons having limited sunlight exposure and dietary vitamin D. Supplementation compliance might be improved with larger doses taken less often, but this may increase the potential for side effects. The objective of the present study was to determine whether a weekly or weekly/monthly regimen of vitamin D supplementation is as effective as daily supplementation without increasing the risk of side effects. Participants were forty-eight healthy adults who were randomly assigned for 3 months to placebo or one of three supplementation regimens: 50 µg/d (2000 IU/d, analysed dose 70 µg/d), 250 µg/week (10 000 IU/week, analysed dose 331 µg/week) or 1250 µg/week (50 000 IU/week, analysed dose 1544 µg/week) for 4 weeks and then 1250 µg/month for 2 months. Daily and weekly doses were equally effective at increasing serum 25-hydroxyvitamin D, which was significantly greater than baseline in all the supplemented groups after 30 d of treatment. Subjects in the 1250 µg treatment group, who had a BMI > 26 kg/m², had a steady increase in urinary Ca in the first 3 weeks of supplementation, and, overall, the relative risk of hypercalciuria was higher in the 1250 µg group than in the placebo group (P=0.01). Although vitamin D supplementation remains a controversial issue, these data document that supplementing with #250 µg/week (#10 000 IU/week) can improve or maintain vitamin D status in healthy populations without the risk of hypercalciuria, but 24 h urinary Ca excretion should be evaluated in healthy persons receiving vitamin D₃ supplementation in weekly single doses of 1250 µg (50 000 IU).

Key words: Vitamin D: Dietary supplements: Hypercalciuria: Sunlight

The debate over the dietary requirement for vitamin D continues, despite the Institute of Medicine’s re-evaluation of dietary requirements, released in 2011(1), with continuing concern that recommendations fall short of actual vitamin D requirements(2,3). Uncertainty and lack of consensus over biomarkers of sufficient and insufficient vitamin D status, and growing evidence for the role of vitamin D in diseases beyond Ca and bone health, further emphasise the importance of continued research on vitamin D nutrition. For individuals with low serum 25-hydroxyvitamin D (25(OH)D), and certain at-risk populations, such as the elderly or those with dark skin or little sunlight exposure, supplements may be advised(4). Concerns over the risks of hypervitaminosis D also continue, and the Institute of Medicine report concluded that serum concentrations of 25(OH)D > 125 nmol/l come with an increased risk of negative effects(1,4,5). One potential side effect of excess vitamin D intake is the increased risk of hypercalciuria, but despite this fact, only a few studies have examined 24 h Ca excretion.

One of the limitations of strategies to improve nutrient status through the use of vitamin supplements is poor compliance with daily supplementation(6). For this reason, large doses taken less frequently may offer advantages to some people. To assess the efficacy and safety of such an approach, we evaluated the effects of vitamin D supplementation in daily and weekly doses, and a high weekly dose followed by monthly doses, on circulating 25(OH)D and vitamin D metabolites and on Ca and related indices in healthy adults.

Abbreviations: 24,25(OH)₂D, 24,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

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We studied vitamin D₃ supplementation given the general consensus that this is more effective⁷–⁹, despite conflicting literature¹⁰. Although only vitamin D₂ is available by prescription, the Internet has opened the door to a wide availability of many doses and forms. We did achieve the aim of evaluating the efficacy and safety of daily, weekly and weekly/monthly doses of vitamin D₃ in a healthy adult population, and we describe their effectiveness at maintaining serum 25(OH)D status and discuss their likelihood of increasing urinary Ca excretion and producing vitamin D toxicity.

Subjects and methods

The present study was conducted at the Johnson Space Center in Houston, Texas, from June 2008 to September 2009. The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Johnson Space Center Committee for the Protection of Human Subjects. Participants were recruited from local advertising at Johnson Space Center. Written informed consent was obtained from all subjects.

After passing a general physical examination, subjects were screened for serum 25(OH)D; blood urea N; serum creatinine, Mg, P and Ca; and 24 h urinary Ca excretion. Subjects who had urinary Ca >7-5 mmol/d or a BMI >30 kg/m², who took >40 µg/d (>400 IU/d) of supplemental vitamin D or who smoked were excluded from participation. After screening, forty-eight subjects (n 31 men and n 17 women) met the eligibility criteria and were randomly assigned to one of four dosage groups: placebo, or vitamin D₃ as 50 µg/d (2000 IU/d), 250 µg (10 000 IU) once per week or 1250 µg (50 000 IU) once per week for 4 weeks and then once per month for 2 months for a total of 3 months. For reporting purposes in the tables, this group will be referred to as the group receiving once per week for 4 weeks and then once per month for 3 months. For reporting purposes in the tables, this group will be referred to as the group receiving once per week for 4 weeks and then once per month for 2 months (n 4 per group), to match the vitamin D supplement groups to make sure subjects could not know their treatment group simply by knowing their dosing regimen. Subjects with an initial serum 25(OH)D concentration >85 nmol/l were assigned to the placebo (identical in appearance and excipient to the vitamin D₃ capsules) were from Tishcon. The analysis of vitamin D and 1,25-dihydroxyvitamin D measurements. Our laboratory also participated in the Accuracy Based Vitamin D Survey by the College of American Pathologists. Liver enzymes, serum creatinine and blood urea N were analysed in a College of American Pathologists-accredited clinical laboratory at the Johnson Space Center.

Levels of 24,25-dihydroxyvitamin D (24,25(OH)₂D) were measured as described previously¹¹, using Waters MassLynx 4.1 (Waters Corp.), with quantification performed with Waters QuanLynx. For HPLC separation, a solvent gradient of 2·1 min, then 12 % A/88 % B for 5 min, and then 2 % A/98 % B for 3 min. Multiple reaction monitoring consisted of a transition of 574→3 to 298→0 for 24,25(OH)₂D with a collision energy at 18 V and a cone voltage at 25 V. Ar was used as a collision gas.

Statistical analyses

Biochemical markers of vitamin D, Ca and bone metabolism were assessed using a two-way repeated-measures ANOVA followed by a post hoc Bonferroni t test to determine differences from baseline when there was a main effect (time) or a significant interaction term. The α-level for statistical significance was set at P=0·05. Multiple linear regression was used to determine the influence of vitamin D intake and UV light exposure on serum 25(OH)D concentration. A two-way repeated-measures ANOVA followed by a Bonferroni t test
were used to determine the effects of weekly 1250 µg supplementation and BMI during the first 30 d of the study. A relative-risk test was performed to compare the relative risk of hypercalciuria in the group taking the 1250 µg dose and the placebo group once supplementation had started. For parathyroid hormone, two data points were lower than the lower limit of detection. For statistical analyses (and mean and standard deviation calculations), we used the lower limit of detection as the value for those data points.

All data reported are means and standard deviations, and all statistical analyses were completed with SigmaPlot 12.0 (Systat Inc.), unless noted otherwise.

Results

No significant group differences were found in age, BMI, body weight, dietary vitamin D intake or UV exposure (Tables 1 and 2). Compliance, as determined by pill counts and subject questioning, was >96% for all groups. The 1250 µg supplements and respective placebos were taken under supervision.

Serum 25(OH)D (Table 3) increased significantly over time (P<0.001) and was significantly higher after 30 d than at baseline in all the three groups taking vitamin D, but not in the placebo group. Serum 25(OH)D was best predicted from dietary vitamin D intake assessed at baseline and 60 d (P<0.001); UV exposure in the 24 h before blood collection had no influence on 25(OH)D (data not shown).

Serum 24,25(OH)2D (Table 3) was higher at 30, 60 and 90 d of supplementation than at baseline in all of the groups taking vitamin D; at 90 d, it was significantly higher in the groups taking 50 or 1250 µg vitamin D than in those taking 250 µg vitamin D. As a percentage of 25(OH)D, 24,25(OH)2D was significantly greater at 30, 60 and 90 d of the study than at baseline (P<0.01).

Vitamin D supplementation had no effect on serum parathyroid hormone (Table 3). However, as expected, serum parathyroid hormone was inversely correlated with 25(OH)D (r2 = 0.22, P<0.001) and 24,25(OH)2D (r2 = 0.24, P<0.001).

Vitamin D supplementation had no effect on serum Ca, vitamin D-binding protein, N-telopeptide, Mg, high-sensitivity C-reactive protein, urea, P or creatinine (data not shown).

A significant group effect occurred for bone-specific alkaline phosphatase, but the post hoc Bonferroni t test yielded no significant differences between the groups (Table 3). The liver enzymes alanine transaminase and aspartate transaminase were elevated in the 250 µg/week group after 90 d of supplementation (P<0.001 and P<0.05, respectively; Table 3).

Table 1. Subject demographic data before and throughout the supplementation study

(Mean values and standard deviations)

<table>
<thead>
<tr>
<th>Dose group</th>
<th>Sex (n)</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>50 µg/d</td>
<td>6</td>
<td>6</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>250 µg/week</td>
<td>9</td>
<td>3</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>1250 µg/month*</td>
<td>10</td>
<td>2</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>Placebo</td>
<td>6</td>
<td>6</td>
<td>37</td>
<td>9</td>
</tr>
</tbody>
</table>

* The 1250 µg/month group took one 1250 µg pill each week for the first 30 d and then one pill per month for the next 2 months. There were no significant changes in body weight over time, nor were there baseline differences between the groups for age or BMI.

Table 2. Daily UV light exposure and dietary vitamin D intake for 6 d before and 1 d after blood draws

(Mean values and standard deviations, n 12 per group)

<table>
<thead>
<tr>
<th>Vitamin D intake* (µg)</th>
<th>Baseline</th>
<th>30 d</th>
<th>60 d</th>
<th>90 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 µg/d</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
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<td>250 µg/week</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>7</td>
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<tr>
<td>1250 µg/month†</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Placebo</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>7</td>
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</tbody>
</table>

MED, minimal erythemal dose; NA, not available.

* This intake did not include the study supplements. A two-way repeated-measures ANOVA was performed on vitamin D intake data that did not include the study supplements, and there were no differences between the groups or over time.

† The 1250 µg/month group took one 1250 µg pill each week for the first 30 d and then one pill per month for the next 2 months.
Of the twelve subjects, four who took 250 µg vitamin D had an alanine transaminase concentration of 0.83 µkat (50 U)/l (normal range 0.10–0.67 µkat (6–40 U/l), and three of these four subjects also had elevated serum aspartate transaminase.

Urinary Ca excretion (Fig. 1) was above the upper limit of normal for twelve samples from subjects in the 1250 µg vitamin D group when expressed as nmol/d (but not when normalised to creatinine), three samples from the 250 µg group, two samples from the 50 µg group and four samples from the placebo group. However, no significant effect of group was found for mean urinary Ca, creatinine, N-telopeptide, P or Mg excretion at any time (data not shown). When the urinary Ca data (nmol/d) from the 1250 µg/month group were analysed by BMI subgroup over the first 30 d of supplementation (the time when the supplementation was weekly in this group), mean urinary Ca increased significantly only in subjects with a higher BMI (26–30 kg/m², n 6), not in subjects with a lower BMI (20–25 kg/m², n 6). When the urinary Ca

### Table 3. Serum vitamin D status and serum concentrations of liver enzymes, parathyroid hormone and bone-specific alkaline phosphatase for subjects assigned to the different doses of vitamin D or placebo for 3 months‡

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean</th>
<th>Baseline SD</th>
<th>30 d Mean</th>
<th>30 d SD</th>
<th>60 d Mean</th>
<th>60 d SD</th>
<th>90 d Mean</th>
<th>90 d SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (nmol/l)*</td>
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<tr>
<td>50 µg/d</td>
<td>75 a</td>
<td>18</td>
<td>92 b</td>
<td>21</td>
<td>98 b</td>
<td>24</td>
<td>92 b</td>
<td>20</td>
</tr>
<tr>
<td>250 µg/week</td>
<td>55 a</td>
<td>13</td>
<td>72 b</td>
<td>12</td>
<td>77 b</td>
<td>10</td>
<td>78 b</td>
<td>11</td>
</tr>
<tr>
<td>1250 µg/month</td>
<td>66 a</td>
<td>19</td>
<td>114 b</td>
<td>23</td>
<td>98 b</td>
<td>19</td>
<td>100 c</td>
<td>28</td>
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<tr>
<td>Placebo</td>
<td>78</td>
<td>25</td>
<td>76</td>
<td>25</td>
<td>76</td>
<td>25</td>
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<td>22</td>
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<tr>
<td>1,25(OH)2D (pmol/l)†</td>
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<tr>
<td>50 µg/d</td>
<td>145 a</td>
<td>51</td>
<td>102 b</td>
<td>58</td>
<td>158 b</td>
<td>60</td>
<td>157 b</td>
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<tr>
<td>250 µg/week</td>
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<td>31</td>
<td>137 b</td>
<td>50</td>
<td>150 b</td>
<td>61</td>
<td>143 b</td>
<td>40</td>
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<tr>
<td>1250 µg/month</td>
<td>106 a</td>
<td>49</td>
<td>131 b</td>
<td>38</td>
<td>132 b</td>
<td>55</td>
<td>135 b</td>
<td>54</td>
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<tr>
<td>Placebo</td>
<td>110 a</td>
<td>48</td>
<td>134 b</td>
<td>72</td>
<td>124 b</td>
<td>43</td>
<td>120 b</td>
<td>34</td>
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<td>24,25(OH)2D (nmol/l)*</td>
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<tr>
<td>50 µg/d</td>
<td>12 a</td>
<td>4</td>
<td>16 b</td>
<td>5</td>
<td>18 b</td>
<td>6</td>
<td>19 b</td>
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<tr>
<td>250 µg/week</td>
<td>8 a</td>
<td>4</td>
<td>11 b</td>
<td>4</td>
<td>13 b</td>
<td>3</td>
<td>14 b</td>
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<tr>
<td>1250 µg/month</td>
<td>10 a</td>
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<td>21 b</td>
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<tr>
<td>Placebo</td>
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<td>12 b</td>
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<td>ALT (U/l)*</td>
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<td>1250 µg/month</td>
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<tr>
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<td>AST (U/l)**</td>
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<td>50 µg/d</td>
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<td>4</td>
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<td>21 b</td>
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<td>26 b</td>
<td>9</td>
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<td>24 b</td>
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</tbody>
</table>

25(OH)D, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 24,25(OH)2D, 24,25-dihydroxyvitamin D; ALT, alanine transaminase; AST, aspartate transaminase; PTH, parathyroid hormone; BSAP, bone-specific alkaline phosphatase.

a,b,c Mean values within a row with unlike superscript letters were significantly different (P < 0.05; post hoc Bonferroni test).

There was a significant group × time interaction effect: * P < 0.001, ** P < 0.05.

† There was a significant time effect (P < 0.01).

‡ Statistical analyses were performed on the monthly data (baseline and 30, 60 and 90 d time points, n 12). The 7, 14 and 21 d data are included in the table, but were not analysed statistically because of the smaller sample sizes (n 8/9 for the 50 µg group, n 5/6 for the 250 µg group, n 12 for the 1250 µg group and n 9 for the placebo group for the weekly time points). The 1250 µg/month group took one 1250 µg pill each week for the first 30 d and then one pill monthly for the next 2 months.
data normalised to creatinine were analysed, a similar trend was found, but the interaction was not significant \( (P = 0.052) \). The data were analysed using a two-way repeated-measures ANOVA \( (P < 0.05) \), and a post hoc Bonferroni t test revealed that after 3 weeks of supplementation, urinary Ca excretion was significantly greater in the group with a higher BMI. The relative risk of urinary Ca excretion being greater than 7.5 mmol/d was compared between the 1250 mg and placebo groups, and the likelihood that urinary Ca exceeded 7.5 mmol/d was higher in the 1250 mg group \( (P = 0.01) \).

Discussion

The dosing regimens of 50 mg/d, 250 mg/week and 1250 mg/month for 4 weeks and then 1250 mg/month for 2 months were all similarly effective in raising circulating 25(OH) vitamin D concentrations. Of the subjects, one-third taking the weekly rather than the daily dose of vitamin D ended the 90 d study with high levels of alanine transaminase, but this effect was not noted in the subjects taking the monthly dose. One pathway by which the body protects itself against vitamin D toxicity is the conversion of 25(OH)D to 24,25(OH)\(_2\)D. Vitamin D supplementation did increase serum 24,25(OH)\(_2\)D concentrations in all of the supplemented groups. The mean 24 h urinary Ca excretion was not significantly different after 30, 60 or 90 d of taking vitamin D or placebo, but the urinary Ca excretion of all subjects was positively correlated with their serum 25(OH)D concentration \( (P < 0.001) \). Further, more subjects in the 1250 mg vitamin D group than in the other groups had 24 h urinary Ca excretion above the normal range at some time during the study, with 40% \( (n = 5/12) \) of the subjects in this group showing 24 h urinary Ca excretion typically defined as hypercalciuric \( (i.e. > 300 \text{mg/d}) \) by study day 30. Subjects in the placebo group who had elevated urinary Ca (Fig. 1) at baseline had serum 25(OH)D concentrations of 91 and 78 nmol/l. When we examined the group receiving the 1250 mg/month dose in the first 30 d of the study, we noticed that some subjects’ urinary Ca increased steadily over the first 3 weeks of supplementation, and others’ urinary Ca did not. When the subjects in that dose group were divided into categories of higher or lower BMI (greater or less than 26 kg/m\(^2\), which was the median BMI), only the subjects with a higher BMI had an elevation in urinary Ca after the third week of 1250 mg vitamin D\(_3\) supplementation. This interesting result will need further study with more subjects to determine whether it is true that subjects with a higher BMI have an increase in urinary Ca with a weekly dose of 1250 mg/month.

The fact that there were no differences in 25(OH)D responses between the dose groups was not surprising because the total doses were very similar. Total daily doses (calculated from the actual analysed content of the supplements) for the three groups averaged to 70.1, 44.1 and 103 mg/d for the 50 mg/d, 250 mg/week and 1250 mg/month groups. In recent studies conducted in Antarctica on vitamin D\(_3\) supplementation (50 mg/d or 250 mg/week), we found that the efficacy of the supplement was influenced by BMI\(^{(1)}\) in that the greater the BMI, the smaller the change in
Dosing regimens of vitamin D supplementation

serum 25(OH)D. Given the results from that study and the
present study, people with a higher BMI may be likely to
take larger doses of vitamin D to increase their vitamin D
status, and they are also more likely to have an acute increase
in urinary Ca.

Increased urinary Ca excretion is a potential adverse effect
of high-dose vitamin D supplementation. Transient elevations
in 24 h urinary Ca may not have clinical relevance to healthy
individuals, but they are relevant to populations at risk for
renal stones. It is worth noting that urinary Ca excretion of
>250 mg/d (>6.24 mmol/d) is associated with increased
renal stone risk (relative to the general population)\(^1\)\(^4\). In
light of the greater acute urinary Ca response in subjects
with a higher BMI, their potential for increased renal
stone risk with a long-term intermittent high-dose vitamin D
supplementation seems clear, and this should be studied
further. The present study illustrates the importance of
collecting urine for 24 h multiple times when evaluating
hypercalciuria risk with intermittent vitamin D supplemen-
tation. Despite the fact that hypercalciuria is a primary concern
for some populations and warrant further study.

One of the limitations of the present study is that we did not
collect dietary intake information (other than vitamin D).
Beyond this, the results of the present study should be con-
sidered preliminary because of our relatively small number
of subjects and samples; nonetheless, the relationships identified raise con-
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Conclusions

Taking fewer supplements in higher doses conferred no
advantage with regard to circulating vitamin D. We found no
overt signs of chronic vitamin D toxicity during the study.
The data that we report here document a relationship between
high-dose vitamin D supplementation and urinary Ca
excretion in a subset of individuals. For remote populations,
such as space travellers, Antarctic winter crews, submariners
and others whose access to medical facilities is limited, the
convenience of less frequent supplementation does not
seem worth any acute increased risk of hypercalciuria.

Given the limited direct evidence of a relationship between
vitamin D supplementation and renal stone incidence, it
seems that further research on appropriate and safe amounts
of supplemental vitamin D for patients at risk for renal
stones is warranted.

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to vitamin D supplementation during Antarctic winter is
related to BMI, and supplementation can mitigate Epstein-

intake needed to maintain target serum 25-hydroxyvitamin
zation. Despite the fact that hypercalciuria is a primary concern
of the twenty-nine subjects had an increase >20 mg/d\(^2\)\(^1\).


