Reduced Vitamin D in Acute Stroke

Kenneth E.S. Poole, BM, MRCP; Nigel Loveridge, PhD; Peter J. Barker, MSc; David J. Halsall, PhD, MRCP; Collette Rose; Jonathan Reeve, DM, BSc, FRCP; Elizabeth A. Warburton, MA, DM, MRCP

Background and Purpose—Stroke leads to a reduction in bone mineral density, altered calcium homeostasis, and an increase in hip fractures. Vitamin D deficiency is well documented in long-term stroke survivors and is associated with post-stroke hip fractures. Less is known regarding levels in acute stroke.

Methods—We compared the serum 25-dihydroxyvitamin D levels of 44 patients admitted to an acute stroke unit with first-ever stroke with results obtained by measuring 96 healthy ambulant elderly subjects every 2 months for 1 year. Statistical Z scores of serum vitamin D were then calculated after seasonal adjustment for the month of sampling.

Results—The mean Z score of vitamin D in acute stroke was −1.4 SD units (95% CI, −1.7, −1.1), with 77% of patients falling in the insufficient range.

Conclusions—Reduced vitamin D was identified in the majority of patients with acute stroke throughout the year and may have preceded stroke. Vitamin D is a potential risk marker for stroke, and the role of vitamin D repletion in enhancing musculoskeletal health after stroke needs to be explored. (Stroke. 2006;37:243-245.)

Key Words: rehabilitation ▪ stroke

T here is a substantial increase in hip fractures in both sexes and across all age ranges after stroke.1 Reduced vitamin D levels may further increase risk for bone loss and fractures. In long-term stroke survivors, there are associations between low vitamin D, low bone mineral density, and post-stroke hip fracture.2 Insufficient vitamin D can impair bone mineralization, increase bone loss through secondary hyperparathyroidism, impair muscular function, increase the likelihood of falling, and contribute to the risk of hip fracture.3 Seasonal periodicity in vitamin D is recognized in northern and southern hemisphere populations.4,5 We tested the hypothesis that vitamin D was reduced in acute stroke patients when compared with healthy elderly subjects after controlling for seasonal variation. A further aim was to establish baseline vitamin D levels in hemiplegic stroke patients before entry into a randomized controlled trial of preventing bone loss after stroke using an intravenous bisphosphonate. Recent case reports have highlighted the risk of developing hypocalcaemia after administering intravenous bisphosphonates to patients with vitamin D deficiency.5 Vitamin D assessment and repletion might therefore be necessary before they can be administered routinely in stroke.

Methods

Serum samples were taken from 44 patients within 30 days of a first-ever stroke (Table). Patients were previously healthy and independently mobile. Inclusion criteria were hemiplegia involving the lower limb, computed tomography–confirmed stroke, inability to walk independently 1 week after stroke, and ability to give informed consent. Exclusions were cognitive impairment, aphasia, previous hip fracture, bone disease, steroid treatment, vitamin D/calcium supplementation, and renal or liver impairment. Serum 25-hydroxyvitamin D (25OHD) levels were measured by radioimmunoassay (IDS Ltd). Coefficients of intra-assay and interassay variation were <8% and 10% across the range of 25OHD concentrations measured. A total of 96 healthy free-living elderly volunteers had serum samples taken every 2 months for 1 year to establish a normal range (Barker et al, Proceedings UK NEQAS meeting, Cardiff, 1996). An adjusted Z score of 25OHD was calculated for each stroke patient by comparison with the monthly mean and SD of 25OHD (after log-transformation to achieve normalization) from the reference range. Baseline dual-energy x-ray absorptiometry scans of both hips (Lunar Prodigy) and parathyroid hormone (PTH) measurements were performed. The Z scores were tested against a hypothesized mean Z score of 0 using Student t test. The protocol was approved by the local ethics committee.

Results

The mean Z score of 25OHD for acute stroke patients was −1.4 (95% CI, −1.7, −1.1). This was statistically significant (Figure 1; P<0.0001). Thirty-four of the 44 patients (77%) had serum 25OHD <50 nmol/L, regarded by many as the lower limit for good health (Figure 2). Demographics are shown in the Table. In stroke patients, there was no relationship between 25OHD level and the length of time between stroke and 25OHD sampling (adjusted r² = −0.02; P=0.77). PTH and 25OHD levels did not correlate with total hip bone mineral density or with each other (adjusted r² = 0.04; P=0.15).

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Hemiplegic patients from an acute stroke unit had 25OHD levels substantially lower than healthy elderly subjects throughout the year. Only 3 of 44 patients had values that exceeded mean control values. The prevalence of vitamin D insufficiency among these patients was greater than that observed in general medical inpatients without stroke, and because of our strict inclusion criteria, we may even have underestimated the extent of vitamin D insufficiency in clinical practice.

The biological half-life of 25OHD is ≈3 weeks. Acutely reduced 25OHD attributable to a decline in hormone synthesis or existing stores (largely found in body fat) seems unlikely because there was no relationship between 25OHD and time between stroke and 25OHD sampling. Therefore, it is probable that the observed reductions in vitamin D preceded stroke, most likely resulting from limited access to sunlight or poor dietary intake of vitamin D. The usual relationship between log 25OHD and log PTH was not observed in this group of stroke patients, in agreement with reports suggesting that because of increased bone resorption secondary to stroke, increased ionized calcium suppresses PTH secretion.

Vitamin D insufficiency is common in acute stroke patients, may precede admission, and is highly prevalent in the years after stroke as sun exposure and dietary vitamin D decline. Vitamin D as a potential risk marker for stroke warrants investigation because the serum values reported here are likely to have preceded stroke. It has been suggested that the relevant risk factor for stroke associated with 25OHD insufficiency is hypertension attributable to compensatory secondary hyperparathyroidism.

Vitamin D repletion might provide health benefits to the musculoskeletal system in acute stroke patients by conserving bone, restoring muscle strength, and reducing falls, although no trials have been conducted to date. In 1

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**Study Populations, Stroke Types, and Functional Scales**

<table>
<thead>
<tr>
<th>Study population</th>
<th>Stroke Patients n or Median (IQR)</th>
<th>Healthy Controls n or Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>44</td>
<td>96</td>
</tr>
<tr>
<td>Age</td>
<td>73 (60–81)</td>
<td>69 (67–71)</td>
</tr>
<tr>
<td>Day of sampling</td>
<td>14.5 (10.0, 22.8)</td>
<td>…</td>
</tr>
<tr>
<td>Males:females</td>
<td>28:16</td>
<td>…</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.2 (24.5, 30.6)</td>
<td>47.49</td>
</tr>
<tr>
<td>Stroke type</td>
<td>Infarction 36</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic 8</td>
<td>…</td>
</tr>
<tr>
<td>Functional scales</td>
<td>Barthel score (/100)</td>
<td>37.5 (20–55)</td>
</tr>
<tr>
<td></td>
<td>SSS* (/48)</td>
<td>27.5 (20–33)</td>
</tr>
</tbody>
</table>

*Scandinavian Stroke Scale, long-term score. IQR indicates interquartile range; BMI, body mass index.

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**Discussion**

Hemiplegic patients from an acute stroke unit had 25OHD levels substantially lower than healthy elderly subjects throughout the year. Only 3 of 44 patients had values that exceeded mean control values. The prevalence of vitamin D insufficiency among these patients was greater than that observed in general medical inpatients without stroke, and because of our strict inclusion criteria, we may even have underestimated the extent of vitamin D insufficiency in clinical practice.

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**Figure 1.** Seasonally adjusted Z scores of 25OHD in acute stroke patients.

**Figure 2.** 25OHD by month in stroke patients compared with the mean±2SD of healthy elderly subjects. To produce the mean and ±2SD curves, log 25OHD levels of healthy subjects were regressed against the sine day of year and 3 curve equations (mean, ±2SD, −2SD) were produced from the linear regression and back transformed.
study of 122 women (mean age 85.3 years) in long-stay geriatric care, a single intervention with vitamin D and calcium supplementation over a 3-month period reduced the risk of falling by 49% and increased muscular function compared with calcium alone. In addition, stroke patients should be screened for vitamin D deficiency before intravenous bisphosphonate therapy is considered. We recommend that a larger prospective study of vitamin D status in acute stroke patients is undertaken and meanwhile that consideration be given to vitamin D replenishment in patients with hemiplegic stroke.

References
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