# Vitamin D Deficiency in Veterans With Chronic Spinal Cord Injury

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**Chronic spinal cord injury (SCI) is associated with osteopenia, increasing the prevalence of long-bone fractures. Although disuse may be the primary cause of osteopenia, identification of any additional mechanisms of bone loss may lead to potential therapeutic interventions. We investigated the relationships of serum calcium (Ca), phosphorus ($PO_4$), albumin, alkaline phosphatase (Alk P), and parathyroid hormone (PTH) with serum 25-hydroxyvitamin D [25(OH)D] in 100 subjects with chronic SCI and 50 control subjects. In a subgroup of 50 subjects with SCI and 50 control subjects, we correlated these parameters with serum 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. Mean ages for the group with SCI and the controls were the same. In subjects with SCI, the duration of injury was 20 ± 1 years (mean ± SD). Thirty-two of 100 subjects with SCI, as compared with eight of 50 controls, had serum 25(OH)D levels less than the normal range ($\chi^2 = 4.36$, $P < .05$). In subjects with SCI, a negative correlation was demonstrated between serum 25(OH)D and PTH ($r = .29$, $P < .005$). Mean serum $1,25(OH)_2D$ levels were significantly elevated in subjects with SCI as compared with controls (61 ± 21 *v* 46 ± 18 pg/mL, $P < .0005$). Twenty of 50 subjects with SCI had serum $1,25(OH)_2D$ levels greater than 62 pg/mL, as compared with 10 of 50 controls ($\chi^2 = 4.76$, $P < .05$). A positive correlation was found between serum PTH and $1,25(OH)_2D$ in subjects with SCI and controls ($r = .41$, $P < .005$ and $r = .30$, $P < .05$, respectively). Twelve subjects with SCI had serum PTH levels greater than the normal range. In this high–serum PTH subgroup, serum 25(OH)D concentration was significantly lower ($P < .05$) and serum $1,25(OH)_2D$ and Alk P concentrations were significantly higher ($P < .005$ and $P < .05$, respectively) as compared with the subgroup with serum PTH values within the normal range. In subjects with SCI, 17 had a serum Ca concentration less than 8.5 mg/dL. In persons with SCI, depressed levels of serum 25(OH)D, as well as other factors, may result in forces inclined to reduce the serum calcium concentration. A state of mild secondary hyperparathyroidism may result, thus increasing the conversion of serum 25(OH)D to $1,25(OH)_2D$. These data suggest that in chronic SCI subjects, as in the general population, secretion of PTH and the increase of circulating $1,25(OH)_2D$ are subject to control by negative-feedback mechanisms. Higher levels of serum PTH would be expected to accelerate bone resorption of a skeleton already regionally osteoporotic as a consequence of the bone mineral loss due to acute immobilization.**


SPINAL CORD INJURY (SCI) results in immobilization and resultant disuse atrophy of bone. Calcium metabolism has been studied after acute injury, when skeletal resorption causes an elevation of serum calcium and suppression of both parathyroid hormone (PTH) release and associated 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] formation.[1] Bone mineral density determination by dual-photon absorptiometry has revealed an accelerated early loss, with mean distal femur bone depletion of 37% at 16 months after acute SCI.[2] Although bone mineral density has not been studied longitudinally during the chronic phase of SCI, it may be hypothesized that an age-related loss in skeletal mass does occur. Severe demineralization of bone increases the risk of fracture, even after negligible trauma.[3-5] Accordingly, it is vital to prevent or markedly reduce further bone loss during the chronic phase of immobilization.

Patients with chronic SCI have a tendency to avoid calcium-containing foods, which are often vitamin D–fortified. In addition, patients may be less likely to be exposed to sunlight or may be prescribed medications that induce hepatic microsomal enzymes, accelerating vitamin D metabolism. Resultant mild reductions in serum ionized calcium may stimulate PTH release, which may accelerate bone resorption. In a group of subjects with chronic SCI and control subjects, we investigated the relationships of serum 25-hydroxyvitamin D [25(OH)D] and $1,25(OH)_2D$ levels to serum calcium, phosphorus ($PO_4$), albumin, alkaline phosphatase (Alk P), and PTH levels.

## SUBJECTS AND METHODS

One hundred subjects with chronic SCI (49 subjects with paraplegia and 51 with quadriplegia) were studied at the Veterans Affairs Medical Center, Bronx, NY. A gender- and age-matched group of 50 able-bodied veteran controls were also studied. In the group with SCI, there were 27 blacks, 72 whites, and one Asian; in the control group, there were 20 blacks and 30 whites. All subjects were without a history of malabsorption, liver disease, or renal failure.

After an overnight fast, blood samples were collected for determination of serum Ca, $PO_4$, albumin, Alk P, PTH, and 25(OH)D. Blood samples were drawn without regard to season in both the SCI group and the control group. In a subset of 50 subjects, serum $1,25(OH)_2D$ level was measured. Serum Ca, $PO_4$, albumin, Alk P, and creatinine levels were measured by SMAC (Technicon Instruments, Tarrytown, NY). Blood samples for measurement of serum PTH, 25(OH)D and $1,25(OH)_2D$ levels were collected in chilled glass tubes and promptly separated by centrifugation at 4°C. The plasma samples were kept at −30°C until assayed. Serum intact PTH (immunoradiometric assay), 25(OH)D (competitive protein-binding assay), and $1,25(OH)_2D$ (radioreceptor assay) were quantified by radioimmunoassay kits (Nichols Institute Diagnostics, San Juan Capistrano, CA).

All results are expressed as the mean ± SD. An unpaired Student's *t* test was performed between the groups: SCI versus control, paraplegia versus quadriplegia, and black versus white were the variables. Chi-square analyses were used to determine differences in distribution of depressed serum 25(OH)D or Ca and

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elevated serum $1,25(OH)_2D$ or PTH by group, as well as differences in distribution of these variables by race within each group. Simple linear regression analyses were performed between serum Ca and albumin, serum 25(OH)D and PTH, serum 25(OH)D and $1,25(OH)_2D$, serum PTH and $1,25(OH)_2D$, and serum PTH and duration of injury. A multiple regression analysis was performed to control for the effect of race on serum $1,25(OH)_2D$ concentration between the groups. Stepwise regression analyses were performed to determine the relative influences of age, race, SCI, and serum $1,25(OH)_2D$ on serum PTH or serum 25(OH)D.

## RESULTS

Characteristics of the study group are shown in Table 1. No significant differences were noted between SCI subjects and controls for age, but significant differences between the groups were noted for height and body mass index (Table 1). Subgroups with paraplegia or quadriplegia were significantly different in age (56 ± 13 *v* 47 ± 13 years, $P < .005$) and duration of injury (23 ± 14 *v* 17 ± 12 years, $P < .05$); for the total group, duration of injury ranged from 1 to 48 years.

The mean serum 25(OH)D level was not significantly lower in the group with SCI as compared with controls (Table 2). However, 32 of 100 subjects with SCI, as compared with eight of 50 controls, had serum 25(OH)D levels less than the normal range ($\chi^2 = 4.36$, $P < .05$). In these subgroups with depressed serum 25(OH)D levels, the mean value was significantly lower in those with SCI than in controls (8 ± 3 *v* 14 ± 1 ng/mL, $P < .0001$); 11 had elevated serum PTH and 10 had elevated serum $1,25(OH)_2D$ levels.

Mean serum $1,25(OH)_2D$ levels were significantly elevated in subjects with SCI as compared with controls (Table 2). Twenty of 50 subjects with SCI had serum $1,25(OH)_2D$ levels greater than 62 pg/mL, as compared with 10 of 50 controls ($\chi^2 = 4.76$, $P < .05$). In these subgroups with elevated serum $1,25(OH)_2D$ levels, the mean level was significantly higher in the group with SCI than in controls (83 ± 15 *v* 71 ± 4 pg/mL, $P < .05$). There were no significant differences between the groups for serum Ca, albumin, $PO_4$, Alk P, or PTH. Serum creatinine was significantly higher in controls than in subjects with SCI (1.2 ± 0.2 *v* 0.9 ± 0.3 mg/dL, $P < .0001$). For the metabolic parameters, no significant differences were noted between subgroups with paraplegia or quadriplegia.

Seventeen subjects with SCI had depressed serum Ca concentrations (<8.5 mg/dL). There was a significant reduction, albeit mild, in serum albumin concentration in this low-serum calcium subgroup as compared with those with levels in the normal range (3.9 ± 0.3 *v* 4.1 ± 0.3, $P < .05$). Of the subjects with these low serum Ca levels, seven had serum 25(OH)D levels less than the normal range. In 11 of 17 hypocalcemic subjects who had serum $1,25(OH)_2D$ determinations performed, seven had elevated values.

**Table 1. Characteristics of the Study Group**

| Characteristic | Control (n = 50) | SCI (n = 100) |
|---|---|---|
| Age (yr) | 51 ± 13 | 51 ± 14 |
| Height (cm) | 175 ± 8 | 178 ± 7* |
| Weight (kg) | 82.2 ± 14.6 | 78.2 ± 15.5 |
| BMI (kg/m²) | 26.7 ± 4.4 | 24.6 ± 4.5* |
| DOI (yr) | — | 20 ± 13 |

NOTE. Values are expressed as the mean ± SD.
Abbreviations: BMI, body mass index; DOI, duration of injury.
*$P < .05$.

**Table 2. Parameters of Calcium Metabolism in SCI Subjects and Controls**

| Parameter | Control (n = 50) | SCI (n = 100) | Normal Range |
|---|---|---|---|
| Ca (mg/dL) | 8.8 ± 0.4 | 8.7 ± 1.0 | 8.5-10.5 |
| $PO_4$ (mg/dL) | 3.1 ± 0.4 | 3.1 ± 0.6 | 2.5-4.5 |
| Albumin (g/dL) | 4.0 ± 0.3 | 4.1 ± 0.3 | 3.0-5.5 |
| Alk P (U/L) | 73 ± 19 | 76 ± 28 | 30-115 |
| PTH (pg/mL) | 40 ± 19 | 38 ± 20 | 10-65 |
| 25(OH)D (ng/mL) | 25 ± 9 | 27 ± 26 | 16-74 |
| $1,25(OH)_2D$ (pg/mL) | 46 ± 18 | 61 ± 21*† | 18-62 |

NOTE. Serum values are expressed as the mean ± SD.
*$P < .0005$.
†n = 50.

In subjects with SCI, a negative correlation was demonstrated between serum 25(OH)D and PTH ($r = .29$, $P < .005$; Fig 1). A positive correlation was found between serum PTH and $1,25(OH)_2D$ in SCI patients ($r = .41$, $P < .005$; Fig 2) and controls ($r = .30$, $P < .05$). In the subgroup of patients with serum 25(OH)D levels not greater than the mean value of the total group with SCI (27 ng/mL), significant negative correlations were found between serum 25(OH)D and both PTH ($r = .35$, $P < .005$) and $1,25(OH)_2D$ ($r = .34$, $P < .05$). In the total group, a positive correlation was found between duration of injury and serum PTH ($r = .32$, $P < .001$). In subjects with SCI and controls, a positive correlation was found between serum Ca and albumin ($r = .22$, $P < .05$ and $r = .72$, $P < .0001$).

Comparisons of serum Ca, $PO_4$, albumin, Alk P, 25(OH)D, and $1,25(OH)_2D$ between the subgroups with SCI with normal (n = 88) and high (n = 12) serum PTH are presented in Table 3. Mean serum 25(OH)D concentration in the high-PTH subgroup was significantly lower ($P < .05$) and mean serum $1,25(OH)_2D$ and Alk P concen-

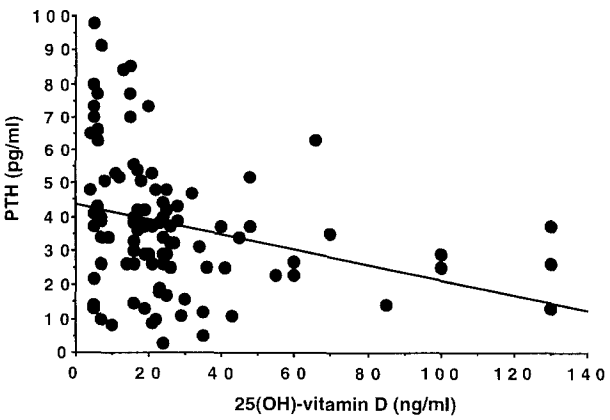


**Fig 1. Simple linear regression analysis between 25(OH)D and PTH in subjects with SCI ($r = .29$, $P < .005$).**

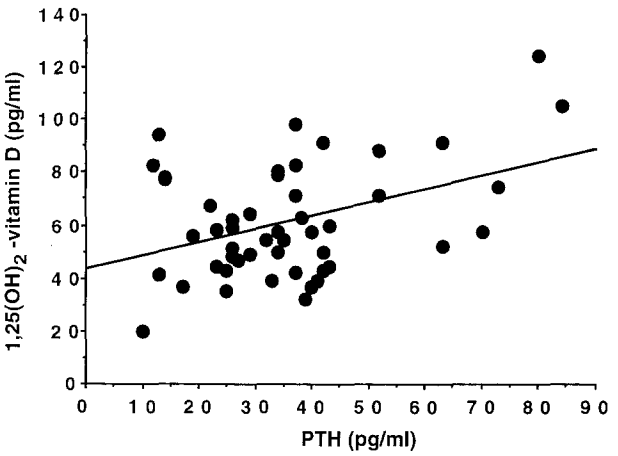


**Fig 2. Simple linear regression analysis between PTH and $1,25(OH)_2D$ in subjects with SCI ($r = .41, P < .005$).**

trations were significantly higher ($P < .005$ and $P < .05$, respectively) as compared with the subgroup with PTH values within the normal range (Table 3). In the subgroup of controls with high serum PTH values (n = 7), only mean serum $1,25(OH)_2D$ approached significance as compared with the subgroup with normal serum PTH (n = 43) values ($58 \pm 18$ *v* $44 \pm 17$ pg/mL, $P = .06$).

There was no significant difference in distribution of race between groups. Differences within each group for race were determined for variables of calcium metabolism. Mean serum 25(OH)D levels tended to be lower in blacks than in whites in SCI or control groups ($23 \pm 31$ *v* $28 \pm 25$, NS, and $22 \pm 9$ *v* $27 \pm 10$ ng/mL, $P = .09$, respectively). A significant difference in the distribution of black or white subjects with low serum 25(OH)D levels (<16 ng/mL) was found in subjects with SCI ($\chi^2 = 21.6$, $P < .0001$) and in controls ($\chi^2 = 4.9$, $P < .05$). Mean serum $1,25(OH)_2D$ levels tended to be higher in blacks than in whites in SCI or control groups ($69 \pm 22$ *v* $58 \pm 20$ pg/mL, $P = .08$, and $50 \pm 17$ *v* $43 \pm 18$ pg/mL, NS, respectively). Differences in serum $1,25(OH)_2D$ levels between the groups may have been influenced by race. Controlling for the effect of race, the group with SCI had significantly higher ($P < .0001$) mean serum $1,25(OH)_2D$ levels than whites. There were no significant differences for race in mean serum PTH or Ca levels.

**Table 3. Parameters of Calcium Metabolism in SCI Subgroups: Normal PTH Compared With High PTH**

| Parameter | Normal (n = 88) | High (n = 12) |
|---|---|---|
| Ca (mg/dL) | 8.7 ± 1.0 | 8.9 ± 0.6 |
| $PO_4$ (mg/dL) | 3.1 ± 0.6 | 3.1 ± 0.6 |
| Albumin (g/dL) | 4.1 ± 0.3 | 4.0 ± 0.2 |
| Alk P (U/L) | 75 ± 25 | 95 ± 41* |
| 25(OH)D (ng/mL) | 29 ± 27 | 10 ± 5* |
| $1,25(OH)_2D$ (pg/mL) | 59 ± 19‡ | 90 ± 30†§ |

NOTE. Values are expressed as the mean ± SD.
*$P < .02$.
†$P < .005$.
‡n = 46.
§n = 4.

Stepwise regression analyses were performed to determine the relative influences of age, race, SCI, and serum $1,25(OH)_2D$ on serum PTH or serum 25(OH)D. A significant relationship was found for SCI and serum $1,25(OH)_2D$ on serum PTH ($r = .38$); age and race were removed with the stepwise regression analysis. No significant relationship was found between these variables and serum 25(OH)D.

## DISCUSSION

Approximately one third of our subjects with SCI were vitamin D–deficient, a significantly greater percentage than in the control group. Also, in those with SCI, a significant inverse relationship was found between 25(OH)D and PTH. A previous study[6] found that 38 patients with SCI and pressure ulcers were, on average, vitamin D–deficient as compared with 54 SCI subjects without pressure ulcers or 28 controls. However, those with SCI without pressure sores were not compared with controls.

Vitamin D deficiency states have been well described. The major form of vitamin D in the circulation is 25(OH)D, representing the major storage form.[7] Reduced levels of 25(OH)D have been used as a reliable indicator of vitamin D deficiency and may result in depressed serum calcium concentrations. Among the most common cases of vitamin D deficiency are institutionalized patients on anticonvulsants or individuals on other medication known to induce hepatic microsomal metabolism (specifically the cytochrome P-450 fraction),[8-10] alcoholics,[11] the elderly,[12-14] persons with dark skin or deprived of sunlight,[15] those on low–vitamin D diets,[16,17] and individuals with gastrointestinal malabsorption syndromes,[18,19] severe liver disease,[20] and/or renal failure.[21,22]

SCI should probably be added to this list of conditions that predispose to vitamin D deficiency, since several of the predisposing factors may be present. Persons with SCI may not be institutionalized in the traditional sense, but have a more limited mobility and are often home-bound or hospital-associated for much of their lives. Head trauma may have occurred at the time of the catastrophe that resulted in SCI, and as such, many patients are also on anticonvulsants; other medications may also be prescribed more commonly in this population that may increase vitamin D metabolism, especially benzodiazepams.[23] Alcohol abuse has been reported to be more common at the time of injury in this group,[24] but there is no report addressing the prevalence of abuse in chronic SCI. The condition of SCI has been called a model of premature aging,[25] and it is possible that a disturbance not unlike that which reduces the bioavailability of vitamin D in the elderly also afflicts those with SCI.

Calcium intake is often restricted in patients with SCI. During the acute period after SCI, resorbing bone releases calcium, increasing urinary calcium excretion,[26,27] suppressing PTH,[1] and decreasing intestinal calcium absorption, regardless of limitations of dietary calcium intake.[28] Healthcare professionals, under the misguided belief that increased calcium intake generally will increase renal lithiasis, instruct patients with chronic, as well as acute, SCI to avoid dairy products. Renal lithiasis during the chronic stage of this condition is usually related to infection, not to

calcium consumption. Dairy products fortified with this vitamin are an excellent source of vitamin D,[29] which would be unavailable to those on low-dairy diets.

It is not unreasonable to assume that those with SCI may have a lower exposure to sunlight than the general population. Conversion of vitamin D precursors to active vitamin D requires sunlight. A large percentage of our patients were black, another factor that may decrease effective sunlight exposure. Although not significantly different, blacks tended to have lower serum 25(OH)D levels as compared with whites, regardless of group. It might also be mentioned that blacks have a higher incidence of lactose intolerance than those of other races, which may have caused them to avoid milk products as well.[30] The gastrointestinal tract of SCI subjects is thought to absorb nutrients in a normal fashion, but motility disturbances have been described by our group,[31] and no investigation has yet been reported with regard to the efficiency of vitamin D absorption in this population. None of our subjects had known liver or renal disease, and as such these etiologies were not responsible for our findings.

The mean serum calcium concentration in subjects with SCI was 8.7 mg/dL. Seventeen subjects with SCI had levels less than the lower limit of normal. The mean serum albumin concentration was slightly lower in the subgroup with low serum calcium levels, but this fails to explain the marked depression in serum calcium concentration, suggesting that perhaps ionized calcium was indeed depressed. A reduction in serum calcium concentration to less than 8.8 mg/dL has been reported to prompt a proportional increase in PTH release.[32] In a prior report,[33] serum total calcium and albumin concentrations were depressed but ionized calcium concentration was virtually identical in 40 male subjects with SCI as compared with 14 able-bodied male controls. In the report herein, the depression in serum total calcium concentration probably was not due to a reduction in albumin concentration; however, since ionized calcium concentration was not addressed in this report, the question of bioavailability of circulating calcium remains unresolved.

The average serum $1,25(OH)_2D$ level was significantly elevated in subjects with SCI as compared with controls. Forty percent of those with SCI as compared with 20% of controls had elevated values for serum $1,25(OH)_2D$, a significant difference between the groups. Furthermore, the degree of serum $1,25(OH)_2D$ elevation was greater in those with SCI than in controls. This elevation undoubtedly reflects an augmented PTH effect on 1-α-hydroxylase activity in the renal tubular cell. Subjects with SCI and absolute elevations in serum PTH levels had significantly lower serum 25(OH)D levels and significantly higher $1,25(OH)_2D$ and Alk P levels. A secondary etiology of depressed serum 25(OH)D levels may be postulated to be increased metabolic clearance due to the activation of 25(OH)D-25-hydroxylase by elevated serum $1,25(OH)_2D$ levels.[34] In the subgroup of subjects with SCI and serum 25(OH)D at or less than the mean value, a significant negative correlation was found between serum 25(OH)D and $1,25(OH)_2D$ levels.

In this study, blacks tended to have lower serum 25(OH)D levels than whites, and a significantly greater number of blacks had values less than the lower limit of normal. Compared with whites, blacks tended to have higher serum $1,25(OH)_2D$ levels. A study comparing serum $1,25(OH)_2D$ levels in normal black or white children found higher levels in blacks.[35,36] In this study, serum $1,25(OH)_2D$ levels were higher in the group with SCI, independently of race.

Prior investigators have also found a significant positive correlation between PTH and serum $1,25(OH)_2D$.[33] In contrast to our findings, these investigators have reported[33] that men with long-standing SCI have a significant depression in serum PTH and $1,25(OH)_2D$, presumably due to excessive ongoing skeletal calcium release. This apparent difference in physiology between the previous study[33] and this study is not easily explained. Differences in racial mix (~one third of our subjects were black), diet, and sunlight exposure (our study was performed in New York, whereas the previous study was in southern California) may provide some insight.

Our findings suggest that approximately one third of our subjects with SCI were vitamin D–deficient. In a subgroup of subjects with chronic SCI, vitamin D depletion with associated mild secondary hyperparathyroidism has been identified. A substantial number were also hypocalcemic, although ionized calcium determinations were not performed to provide the necessary evidence of the biologic importance of this finding. In chronic SCI subjects, as in the general population, secretion of PTH and the increase of circulating $1,25(OH)_2D$ are subject to control by negative-feedback mechanisms related to serum calcium level, which is in turn influenced by 25(OH)D level. Higher levels of PTH would be expected to accelerate bone resorption of a skeleton already regionally osteoporotic as a consequence of the bone mineral loss due to acute immobilization. Patients identified with this deficiency state should be aggressively treated with adequate vitamin D and calcium supplementation.

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