

Severe Myopathy Associated With Vitamin D Deficiency in Western New York

Anu Prabhala, MD; Rajesh Garg, DM; Paresh Dandona, MD

Five cases of severe myopathy associated with vitamin D deficiency are described. Each patient was confined to a wheelchair because of weakness and immobility. Two were elderly, 1 was a 37-year-old African American with type 1 diabetes mellitus, 1 was being treated for carcinoid syndrome, and 1 was severely malnourished due to poor oral intake. In each, weakness had previously been attributed to other causes, including old age, concomitant diabetic neuropathy, or general debility. Correct diagnosis was made initially by a high index of suspicion, following the demonstration of clinical proximal myopathy; confirmation was made by the demonstration of low 25-hydroxyvitamin D and elevated parathyroid hormone concentrations. Treatment with vitamin D caused a resolution of body aches and pains and a restoration of normal muscle strength in 4 to 6 weeks. Four patients became fully mobile and had normal 25-hydroxyvitamin D concentrations, and the fifth also became mobile. In the 4 fully recovered cases, parathyroid hormone levels on follow-up were lower but still elevated. This finding suggests a degree of autonomy of parathyroid secretion known to occur in cases of long-standing vitamin D deficiency. Myopathy, due to chronic vitamin D deficiency, probably contributes to immobility and ill health in a significant number of patients in the northern United States. An awareness of this condition may significantly improve mobility and quality of life in patient populations vulnerable to vitamin D deficiency.

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Vitamin D deficiency has been recognized in the United Kingdom and in northern Europe and is attributed to a lack of sunshine.¹⁻³ Immigrant communities are particularly vulnerable to this condition^{4,5} because of their limited exposure to the sun, their pigmented skin, and their vegetarian diet. In addition to osteomalacia, myopathy is a well-recognized feature of this condition and may lead to further immobility and morbidity.⁶ In the United States, the recognition of vitamin D deficiency has only recently been appreciated, especially in the northern areas bordering Canada.⁷⁻⁹ Although the presence of vitamin D deficiency in the hospital setting and in the community at large during the winter months is recog-

nized, there are few reports on the presence of myopathy in relation to vitamin D deficiency in this country.^{10,11} In this article, we present 5 cases of profound myopathy in western New York due to vitamin D deficiency. The diagnosis in these cases was either masked by the concomitant presence of neurologic disease or had been totally unrecognized because of the insidious onset of this condition.

REPORT OF CASES

CASE 1

A 37-year-old African American woman with type 1 diabetes mellitus (hemoglobin A_{1c} level, 8.6%) was seen in March 1997 with aches and pains and increasing muscle weakness. The weakness started in the lower limbs and had spread

From the Division of Endocrinology, Diabetes and Metabolism, State University of New York at Buffalo (Drs Prabhala and Dandona), and Kaleida Health (Drs Garg and Dandona), Buffalo.

Table 1. Serum 25-Hydroxyvitamin D, 1,25-Dihydroxyvitamin D, and Parathyroid Hormone Levels Before and 3 to 6 Months After Vitamin D Therapy

	Case 1		Case 2		Case 3		Case 4		Case 5	
	Before	After								
Serum calcium, mmol/L*	2.22	2.25	2.08	2.10	1.88	2.15	2.38	2.30	2.25	...
Ionized calcium, mmol/L†	1.20	1.22	...	1.28	1.02	1.22	1.32	1.32
Serum phosphate, mmol/L‡	1.0	0.87	0.81	1.0	0.84	1.26	1.0	0.94	1.39	...
Serum alkaline phosphatase, U/L§	893	563	152	148	134	101	960	940	137	...
Serum 25-hydroxyvitamin D, nmol/L	12	139	28	187	12	104	12	42	32	...
Serum 1,25-dihydroxyvitamin D, pmol/L¶	25	85	50	113
Intact parathyroid hormone, pmol/L#	88.9	82.2	13.4	13.0	60.8	12.5	74.5	62.3	12.7	...

*To convert serum calcium to conventional units (milligrams per deciliter), divide by 0.25. The reference range for serum calcium is 2.15 to 2.55 mmol/L. Ellipses indicate not measured.

†To convert ionized calcium to conventional units (milligrams per deciliter), divide by 0.25. The reference range for ionized calcium is 0.38 to 1.40 mmol/L.

‡The reference range for serum phosphate is 0.81 to 1.45 mmol/L. To convert serum phosphate to conventional units (milligrams per deciliter), divide by 0.323. §The reference range for serum alkaline phosphatase is 30 to 165 U/L.

||To convert 25-hydroxyvitamin D to conventional units (nanograms per milliliter), divide by 2.496. The reference value for 25-hydroxyvitamin D is greater than 37 nmol/L.

¶To convert 1,25-dihydroxyvitamin D to conventional units (picograms per milliliter), divide by 2.4. The reference range for 1,25-dihydroxyvitamin D is 41 to 145 pmol/L.

#To convert intact parathyroid hormone to conventional units (picograms per milliliter), divide by 0.1053. The reference range for intact parathyroid hormone is 1.3 to 7.6 pmol/L.

to the upper limbs. She had increasing difficulty combing her hair since January 1997 and was confined to a wheelchair. She had proliferative retinopathy, peripheral neuropathy with multiple amputations of the toes, proteinuria (1 g/d), a serum creatinine level of 239 $\mu\text{mol/L}$ (2.7 mg/dL) (reference range, 44-133 $\mu\text{mol/L}$ [0.5-1.5 mg/dL]), and hypertension. Examination revealed decreased proximal muscle strength (3/5) and tone in all 4 limbs. There was diminished pinprick sensation in the lower extremities. Her deep tendon reflexes were 1+ in the upper extremities and 1+ at the knees and absent at the ankles. Doppler pressure was normal in the dorsalis pedis and posterior tibial arteries. Other relevant results are as shown in **Table 1**. She was treated with 50 000 IU of oral ergocalciferol once a week for 6 weeks. She lost her aches and pains, regained her strength, became mobile in 3 to 4 weeks, and is now able to walk and climb stairs.

CASE 2

A 71-year-old man was seen in December 1997 with a history of severe pain in both his lower limbs and difficulty in walking even short distances within his home. Outside the home, he used a wheelchair. He was being investigated for his "back-ache." He had type 2 diabetes melli-

tus (hemoglobin A_{1c} level, 6.9%) with nonproliferative retinopathy, nephropathy (urine for microalbumin, 138 $\mu\text{g}/\text{min}$), a serum creatinine level of 115 $\mu\text{mol/L}$ (1.3 mg/dL), and peripheral and autonomic neuropathy. A gastrojejunostomy was performed many years ago, and he had been taking phenytoin for 6 months for recent-onset seizure disorder. Muscle strength was markedly diminished in all proximal muscle groups, with relative preservation of power in distal muscles. Vibratory and pinprick sensations were diminished to midcalf in the lower extremities. His deep tendon reflexes were present in the upper extremities and at the knees but were absent at the ankles. Dorsalis pedis pulsation was absent in both limbs. A clinical diagnosis of proximal myopathy and diabetic peripheral neuropathy was made. Table 1 shows the relevant laboratory investigation reports. He was treated with ergocalciferol, 50 000 IU orally, each week for 6 weeks. His weakness and bone pains resolved within 6 weeks. He currently walks 2 to 3 blocks on his own without support.

CASE 3

A 77-year-old white woman presented with an "upset stomach" and fatigue for the last 2 to 3 months. She had lost 13.5 kg during the last 2 years. She was confined to a wheel-

chair because of "aches and pains all over and weakness in her lower extremities." Billroth type II gastrectomy was performed 40 years ago, and she was taking replacement doses of vitamin B₁₂ (cyanocobalamin) for recently discovered vitamin B₁₂ deficiency. In 1995, she incurred a fracture of the distal radius in her right forearm while she was being held by an attendant to prevent a fall. A prosthetic femoral head had been placed in her left hip, and she was being treated for osteoporosis with alendronate sodium. On examination, she weighed 43 kg. She also had profound proximal muscle weakness in the pelvic and shoulder girdles (power 3/5).

Investigations revealed the following values: hemoglobin, 115 g/L (reference range, 120-160 g/L); mean corpuscular volume, 101.4 fL (reference range, 84-99 fL); albumin, 40 g/L (reference range, 35-50 g/L); and serum creatinine, 88.4 $\mu\text{mol/L}$ (1 mg/dL). Vitamin D deficiency was strongly suspected because of severe proximal myopathy, bony tenderness, and history of gastrojejunostomy. Results shown in Table 1 support the diagnosis of vitamin D deficiency in this patient. She was given oral ergocalciferol (50 000 IU/wk) for 6 weeks, with a dramatic improvement in her aches and pains. There was improved mobility, decreased weakness, and ability to forsake the wheelchair in 6 weeks.

CASE 4

A 67-year-old white woman with a history of carcinoid syndrome with extensive metastasis to the liver, spine, pelvis, and ribs was seen for severe diarrhea and difficulty walking. She had had resection of the terminal ileum for a carcinoid tumor 20 years ago. She was being treated with a long-acting somatostatin analogue (Sandostatin LAR) for her carcinoid syndrome. She was using the wheelchair to get around. Examination revealed a thin woman who weighed 50.4 kg and had severe, painful proximal myopathy at the hip girdle. Deep tendon reflexes were 1+ at the biceps, brachioradialis, knees, and ankles. There was diffuse tenderness of bones, especially the ribs and the shins. Investigations revealed the following values: hemoglobin, 112 g/L; mean corpuscular volume, 90.4 fL; albumin, 32 g/L; serum creatinine, 53 $\mu\text{mol/L}$ (0.6 mg/dL); aspartate aminotransferase, 32 U/L (reference range, 0-50 U/L); alanine aminotransferase, 23 U/L (reference range, 0-50 U/L); and alkaline phosphatase, 960 U/L (reference range, 30-165 U/L) with a marked increase in the hepatic fraction. Abdominal sonograms and magnetic resonance imaging revealed multiple metastatic lesions in both lobes of the liver. Vitamin D deficiency was strongly suspected, and after confirming the diagnosis, the patient was treated with 50 000 IU of ergocalciferol each week for 6 weeks. Her pain and weakness improved significantly in 8 weeks, and she was able to forsake her wheelchair.

CASE 5

A 46-year-old white woman had a history of psoriasis with arthropathy for 10 years. She had been given intermittent corticosteroid therapy and methotrexate and an experimental treatment with photopheresis. She was referred for severe pain all over the body, especially the back, and severe osteoporosis with rib fractures for which she was taking 300 mg/d of calcium with vitamin D (400 IU/d) and nasal calcitonin. She had to use a wheelchair for ambulating, and reported "each movement was painful." She also had intermittent

diarrhea, had a poor appetite, and was losing weight. She was amenorrheic for 15 years and in her teens had an illness characterized by anorexia and repeated vomiting. Examination revealed a frail woman who weighed 44 kg and had severe pallor, psoriatic lesions all over the body, and severe psoriatic arthritis of small joints. She was investigated for osteoporosis, and a dual-energy x-ray absorptiometry study in July 1998 revealed a T score of -4 SD at the lumbar spine and -5 SD at the hip. Other investigations revealed iron deficiency anemia.

Additional investigations revealed the following values: hemoglobin, 100 g/L; mean corpuscular volume, 76 fL; serum iron, 2.68 $\mu\text{mol/L}$ (15 $\mu\text{g/dL}$) (reference range, 4.48-30.4 $\mu\text{mol/L}$ [25-170 $\mu\text{g/dL}$]); total iron binding capacity, 55.1 $\mu\text{mol/L}$ (308 $\mu\text{g/dL}$) (reference range, 44.8-80.5 $\mu\text{mol/L}$ [250-450 $\mu\text{g/dL}$]); iron saturation, 5% (normal range, 15%-55%); and ferritin, less than 5 $\mu\text{g/L}$ (reference range, 10-160 $\mu\text{g/L}$). Other investigations suggestive of malnutrition revealed the following values: serum vitamin B₁₂, 133 pmol/L (180 pg/mL) (reference level, >148 pmol/L [>200 pg/mL]); folate, 3.8 nmol/L (1.7 ng/mL) (reference range, 3.4-45 nmol/L [1.5-20 ng/mL]); albumin, 32 g/L; alanine aminotransferase, 31 U/L; aspartate aminotransferase, 78 U/L; and creatinine, 26 $\mu\text{mol/L}$ (0.3 mg/dL). The fat content of her 72-hour stool sample was 1.8 g/d, which ruled out malabsorption. Her 24-hour urinary N-telopeptide level was 395-nmol/L bone collagen equivalent (BCE) per nanomoles of creatinine (reference range, 14-76 nmol/L BCE per nanomoles of creatinine). Investigations showed severe vitamin D deficiency (Table 1). She was treated with 500 000 IU of ergocalciferol given intramuscularly for her vitamin D deficiency and was treated appropriately with vitamin B₁₂, folate, calcium, iron, and energy (caloric) supplements. Four weeks after the dose of vitamin D, her weakness had improved, and she was able to walk with support.

COMMENT

These case reports clearly show the presence of profound proximal my-

opathy with a deficiency of vitamin D of marked severity and secondary hyperparathyroidism of moderate or marked severity. In each of the cases, there was a prompt and rapid response to vitamin D therapy, with a resolution of muscle weakness and a restoration of mobility. These severe cases, which presented in our endocrine unit over a period of 18 months, are likely due to vitamin D deficiency, especially those with moderate symptoms, and are probably common. Since the diagnostic workup is simple, a high index of suspicion should be maintained in patients with bony aches and pains and muscle weakness. As is evident from the case histories presented, the cause of weakness is masked behind other "diagnostic labels." Two of the cases had concomitant history of long-standing diabetic neuropathy. In both of these cases, the weakness had been attributed to the neuropathy until the correct diagnosis was made. Although diabetic neuropathy is common, it is largely sensory; rarely does it cause weakness profound enough for someone to be immobilized. In 2 cases, the long-standing complications of a gastrojejunostomy with a blind loop syndrome had probably resulted in a progressive deficiency of several nutrients, including vitamin D, vitamin B₁₂, and iron. Since this decompensation had presumably occurred throughout 4 decades, the possibility that patients' immobility and body aches and pains may have been due to severe vitamin D deficiency was not appreciated.

Case 4 had carcinoid syndrome with extensive ileal resection and hepatic metastasis. Loss of the terminal portion of the ileum can lead to bile salt malabsorption, with an impaired absorption of fats and vitamin D. Carcinoid syndrome is also known to be a cause of myopathy¹²; however, the diagnosis and treatment of vitamin D deficiency were carried out while this patient's carcinoid syndrome was stable under long-term treatment with octreotide acetate. Prompt clinical response to ergocalciferol in this case is consistent with vitamin D deficiency as a cause of myopathy. This cause also raises the possibility that the vitamin D deficiency may underlie "carcinoid myopathy." Indeed, we

Table 2. Differential Diagnosis of Proximal Muscle Weakness

Condition	Clinical Features	Diagnosis
Hyperthyroidism and hypothyroidism Cushing syndrome	Clinical features of hyperthyroidism or hypothyroidism Centripetal obesity, moon-shaped face, buffalo hump, plethora bruising	Thyroid function tests Cortisol hypersecretion
Carcinomatous myopathy	Proximal muscle weakness, exercise-induced fatigue	Associated malignant neoplasm, electromyogram, muscle biopsy
Carcinoid syndrome	Cutaneous flushing, diarrhea, valvular heart disease, proximal myopathy	Clinical features, elevated urinary 5-hydroxyindoleacetic acid, plasma or platelet serotonin
Polymyositis or dermatomyositis	Proximal or diffuse muscle weakness, often pain, tenderness, and skin changes	Elevated creatinine kinase, electromyogram, muscle biopsy
Muscular dystrophies	Muscle weakness throughout years, rarely after age 30 y, positive family history	Elevated creatinine kinase, electromyogram, muscle biopsy
Myotonic dystrophy	Proximal muscle weakness, characteristic facies, grip myotonia, positive family history	Clinical features, electromyogram, muscle biopsy
Myasthenia gravis	Muscle weakness and fatigability, exercise-induced fatigue	Electromyogram

have since observed another patient with carcinoid syndrome and ileal resection, who developed severe proximal myopathy in association with severe vitamin D deficiency and secondary hyperparathyroidism. We have not included him in this series, since he died before we could demonstrate objective improvement in his clinical state following vitamin D therapy.

Case 5 had vitamin D deficiency due to malnutrition and lack of exposure to sunshine. She had features of anorexia nervosa, which has previously been shown to be associated with vitamin D deficiency¹³ and osteopenia.¹⁴

These 5 cases also exemplify one other major feature of the pathogenesis of vitamin D deficiency and relative immobility, especially in the elderly,⁹ which magnifies this defect, because such patients cannot get out into the sunshine even during summer. Four of our patients were elderly, 1 was mentally challenged, and 2 had concomitant profound sensory diabetic neuropathy. In one case, the skin pigmentation may also have prevented cutaneous vitamin D biosynthesis.¹⁵ Another aspect of vitamin D deficiency in the elderly is that the resulting secondary hyperparathyroidism may not be associated with compensatory rise in 1,25-dihydroxyvitamin D due to diminished activity of renal 1 α -hydroxylase. These subjects may also be unable to increase osteocalcin, important for adequate bone formation.¹⁶ Although parathyroid hormone concentrations decreased, they did not normal-

ize despite several months of vitamin D therapy and the normalization of serum 25-hydroxyvitamin D. This has previously been described in patients with long-standing vitamin D deficiency.⁴ The nonnormalization of parathyroid hormone concentrations despite normalization of 25-hydroxyvitamin D suggests a degree of autonomy of the parathyroid glands due to long-standing vitamin D deficiency.⁴

Proximal myopathy is diagnosed clinically following the demonstration of (1) weakness in proximal (shoulder and/or hip girdle) limb muscles with preservation of distal limb muscles, (2) preserved reflexes, (3) absence of sensory impairment, and (4) absence of pain or tenderness in muscles as a major clinical feature. Electromyograms are performed whenever there is confusion in arriving at the diagnosis but not when the pattern of loss of neurologic features is typical. Electromyograms show a myopathic pattern without a distinct diagnostic pattern related to the cause of myopathy, including vitamin D deficiency. Muscle biopsy is performed when myositis is suspected, usually when pain and tenderness are present. In the series of cases presented, 2 had concomitant diabetic neuropathy; these patients had absent ankle reflexes and a loss of pain and temperature sensations extending up to the knees.

The diagnosis of vitamin D deficiency as the cause of proximal myopathy should be suspected in the following clinical circumstances: (1)

presentation in regions with prolonged winters, a relative lack of sunshine, and exposure to it; (2) concomitant body aches and pains, especially in the shins and the ribs; (3) associated malabsorption, eg, ileal disease (Crohn disease), blind loop syndrome, celiac disease, chronic cholestasis, and pancreatic disease; (4) malnutrition, including anorexia nervosa; (5) exclusion of sunlight by wearing dark garments for social or religious reasons¹⁷; and (6) chronic renal failure. The differential diagnosis of proximal myopathy involves several conditions, each with its clinical and biochemical features (**Table 2**).

The most important message of this article is that severe myopathy due to vitamin D deficiency is relatively common, insidious in onset, and easy to treat once diagnosed. It may be masked by other diagnoses that are not treatable and, thus, may lead to morbidity and frustration. We have seen other milder cases that have been labeled fibromyalgia, depression, and chronic fatigue syndrome. An active inclusion of this diagnosis in causes of weakness and fatigue is important. When diagnosing this condition, it is also important to consider that the reference level of 25-hydroxyvitamin D is the biologically relevant concentration of 37 nmol/L, since it is concentrations greater than this that ensure absence of secondary hyperparathyroidism. Any concentration less than 37 nmol/L is often associated with secondary hyperparathyroidism.^{8,9}

In conclusion, we have demonstrated 5 cases of profound myopathy due to vitamin D deficiency that resulted in immobilization and severe morbidity. The diagnosis was missed because of either a gradual development of the syndrome or the concomitant presence of another neurologic condition. Since this condition has not been described in the United States or in ambulatory patients with endemic vitamin D deficiency in the northern United States, especially during the winter months, myopathy due to this deficiency may be relatively frequent. This report will increase the awareness of this condition, which when suspected can easily be diagnosed and treated, with gratifying results.

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Reprints: Paresh Dandona, MD, Division of Endocrinology, Diabetes and Metabolism, State University of New York at Buffalo, 3 Gates Cir, Buffalo, NY 14209 (e-mail: pdandona@mshs.edu).

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