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CASE REPORT AND REVIEW

# Severe osteomalacia presenting with multiple vertebral fractures: a case report and review of the literature

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**Abstract** Adequate exposure to sunlight and fortification of dairy products with vitamin D have eliminated vitamin D deficiency secondary to inadequate endogenous production or nutrition in the majority of countries. Insufficient vitamin D intake secondary to using unfortified foods and social customs (such as avoiding sun exposure), however, contribute to the development of disease. Poor diet, a lack of sun exposure, and the age related decline in the dermal synthesis of 7-dehydrocholesterol are among the factors that predispose to vitamin D deficiency and consequent bone disease. Here, we present a case of severe osteomalacia presenting with multiple vertebral fractures due to poor diet and a lack of exposure to sunlight.

**Keywords** Osteomalacia · Vitamin D deficiency · Vertebral fractures · Osteoporosis

## Introduction

Osteomalacia is characterized by impaired mineralization of the bone matrix. It results from reduced availability of calcium or phosphate for incorporation into the hydroxyapatite of bone, along with deficient absorption or activation of vitamin D [1, 2]. It is possible that osteomalacia results from decreased availability of vitamin D as a consequence of insufficient ultraviolet light exposure, insufficient vitamin intake, or malabsorption in patients with gastrointestinal or biliary disorders. Vitamin D insufficiency and deficiency are highly prevalent in the general population and have potentially deleterious musculoskeletal effects [3].

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## Case report

A white 62-year-old Turkish woman presented to our Endocrinology polyclinic due to common bone pains, asthenia, and muscle weakness that had gradually increased over the last 2–3 years. The patient suffered an ischemic stroke 4 years ago, and right hemiparesis was present. The patient had been healthy until she suffered the ischemic stroke. She was able to work and had not had any additional problems or conditions. During the examination, the patient stated that she had not gone out of her house and had not been able to walk without help for the last 4 years. She could only perform activities of daily living such as feeding, bathing, and dressing. No hypertension, diabetes mellitus, cardiac arrhythmia, atherosclerotic heart disease, or other condition was present in her history. She had only suffered an ischemic stroke of unknown origin, and kyphosis and scoliosis had developed over the last year. The patient was able to live in her house with help and was often lying down. Before presenting to our polyclinic, the patient had been evaluated at external medical centers, where major depression, severe osteoporosis, and accompanying vertebral fractures were detected. Treatments for these conditions had been recommended, but the patient had rejected treatment. She had a poor appetite at home and was eating by the force of her relatives. The patient presented to our polyclinic with asthenia, a clear reduction in her motor function, and progression of her kyphoscoliosis, and the severity of her common body pains. During the first evaluation of the patient, clear asthenia, kyphoscoliosis,

and depressive mood were present. She was fair-skinned, and her speech was dysarthric, as a sequela of ischemic stroke. She did not have any difficulty swallowing. Her blood pressure was 110/60 mmHg, with a rhythmic pulse rate of 72/min, body temperature of 36.8°C, and rhythmic respiration at 17/min. She weighed 46 kg and was 156 cm in height, with a body mass index of 19 kg/m$^2$. Clear sensitivity to palpation was present in the long bones, and she had clear kyphosis and dextroscoliosis. She could raise her lower extremities against gravity with difficulty, and motor power was determined to be 2/5 in the right leg and 3/5 in the left leg. Motor power was determined to be 3/5 in the right upper extremity and 4/5 in the left upper extremity. The patient could not stand up from the bed or a chair by herself, and advanced proximal muscle weakness was present. Although the patient was able to stand up by herself and move despite her ischemic stroke, she had become less mobile over the last year. She arrived in the clinic in a wheelchair. Upon examination of the lungs, aeration was reduced; the cardiovascular and other system examinations were normal, and she did not have any organomegaly. She had no sensory deficits. No history of osteoporosis or bone fractures was present in her first-degree relatives. In the last few years, she had not suffered any fractures and had not suffered any low-trauma fractures. She had never smoked cigarettes or consumed alcohol. Furthermore, she had never received any treatments such as steroid or anticonvulsant drugs. She had gone through menopause when she was 51 years old and had never used any hormone replacement treatments. She had not had any diseases or complaints about pre-menopausal oligo/amenorrhea, and had given birth to one child. She stated that she had been extremely healthy and that her general condition and appetite had been good until she suffered an ischemic stroke. She did not have any dementia, and her body mass index was at the lower limit of 19 kg/m$^2$. No clear factors creating any susceptibility to osteoporosis and bone fractures were detected in her history. Considering her underlying osteomalacia with clear proximal muscle weakness, common bone pains, restricted food intake, and very little exposure to sunlight over the last 4 years, in addition to immobility seen in the physical examination, laboratory studies to clarify the diagnosis were ordered (Table 1). The results of these studies indicated hypocalcemia, hypocalciuria, hypophosphatemia, and elevated levels of alkaline phosphatase and immune-reactive parathyroid hormone (iPTH) were detected (Tables 1 and 2). Given the suspicion that vitamin D deficiency had led to osteomalacia, which was indicated by the previously mentioned laboratory studies, the serum vitamin D level was measured. Serum 25(OH)$D_3$ was very low at 6 ng/ml (normal range: 15–46 ng/ml). The serum 1,25$(OH)_2D_3$ level was within normal limits at 20 pg/ml (normal range: 15–60 pg/ml). Advanced diagnostic procedures were begun to determine the etiology of her severe osteomalacia. An upper GI endoscopy and biopsies collected from the distal duodenum were normal, and there were no findings to suggest any malabsorption syndromes. Liver function tests were normal, and hepatobiliary USG was normal, with no findings that would suggest biliary tract injury or enlargement. Pancreatic imaging was normal. The patient had never had any acute pancreatitis attacks and did not have any biochemical findings to suggest pancreatitis. She had not had any operations pertaining to the gastrointestinal system. Her fecal occult blood was checked three times and found to be negative. Since there were no symptoms or indications of Crohn's disease or ulcerative colitis, a colonoscopy was not performed. The autoimmune markers for autoimmune hepatobiliary tract diseases likely to present subclinically were negative (Table 2). Antiendomysial IgA was assayed for celiac disease and found to be negative. In renal system imaging, both kidneys were normal in size and morphological structure, and serum renal function tests were normal. Creatinine clearance was normal, and there was no glucose, protein, or blood in the urine. Hypocalciuria was present, supporting hypovitaminosis D. There were no clinical or laboratory findings of acidosis. Tubular reabsorption of phosphorus (TRP) was normal: 87% (normal range: 80–97%). Bone mineral density (BMD), conventional X-ray films, and the magnetic resonance imaging (MRI) of the vertebrae were all taken. In direct thoracolumbar and lumbosacral X-rays, osteoporotic images were generally observed in all bones. Lumbar spondylolisthesis, compression fractures leading to a clear loss of height in the T11 and T12 vertebrae, biconcave 3rd–5th lumbar vertebrae, and compression fractures in the middle sections of the spine were present. Subperiostal erosions were observed in ribs and scapulae, and also coarsening of the trabecular pattern in the spine was present in the plain radiographs. The BMD gave values for severe osteoporosis, with T-scores of L1: −5.1, L2: −5.2, L3: −4.8, L4: −5.1, and L1–4: −5.1 in the thoracic vertebrae (Table 3). MRI showed that the vertebral fractures in T11–12 constricted the spinal canal and compressed the spinal cord. It was found that the patient had osteomalacia, which led to severe osteoporosis and fractures. A consultation was ordered from the department of vertebral surgery, and it was determined that an operation would be required. This operation was planned following treatment of her metabolic bone disease. Supportive corsets were applied to the patient, and she began physical therapy. Since we diagnosed her osteomalacia both biochemically and clinically, we did not collect any bone biopsies to demonstrate osteomalacia also histopathologically. Deficient dietary nutrient intake, osteomalacia, and vertebral fractures were

**Table 1** Laboratory results upon admission and after treatment

| | On admission | 15th Day of treatment | 1st Month of treatment | Normal ranges |
|---|---|---|---|---|
| Fasting serum glucose (mg/dl) | 80 | 83 | 81 | 80–120 |
| Albumin (g/dl) | 4.8 | 4.7 | 4.6 | 3.5–5.2 |
| Alanine aminotransferase (U/l) | 32 | 39 | 35 | 5–33 |
| Aspartate aminotransferase (U/l) | 16 | 19 | 21 | 5–32 |
| Alkaline phosphatase (U/l) | 518 | 358 | 154 | 35–104 |
| Gamma-glutamyl transferase (U/l) | 28 | 31 | 26 | 5–36 |
| Creatine kinase (U/l) | 74 | 65 | 69 | 26–192 |
| BUN (mg/dl)[a] | 14 | 19 | 18 | 0–25 |
| Serum creatinine (mg/dl) | 0.36 | 0.35 | 0.36 | 0.5–0.9 |
| Serum phosphorus (mg/dl) | 2.1 | 3.1 | 3.7 | 2.7–4.5 |
| Serum calcium (mg/dl) | 7.8 | 8.1 | 9.4 | 8.6–10.2 |
| Corrected serum calcium (mg/dl)[b] | 7.1 | 7.5 | 8.9 | 8.6–10.2 |
| Lactate dehydrogenase (U/l) | 200 | 175 | 189 | 135–214 |
| Serum sodium (mEq/l) | 142 | 141 | 138 | 136–145 |
| Serum potassium (mEq/l) | 4.1 | 4.0 | 4.2 | 3.5–5.1 |
| Serum chloride (mEq/l) | 107 | 108 | 104 | 98–107 |
| Urine calcium (mg/dl/24 h) | 55 | 125 | 174 | 100–250 |
| TRP (%)[c] | 87% | 88% | 93% | 80–97 |
| Creatinine clearence (ml/min) | 135 | 129 | 131 | 90–130 |
| WBC ($\times 10^3/\mu l$)[d] | 6600 | 6500 | 6400 | 4.5–11 |
| Hemoglobin (gr/dl) | 15.9 | 15 | 15.4 | 11.7–15.5 |
| MCV (fl)[e] | 88 | 87 | 88 | 80.4–95.9 |
| Platelet ($\times 10^3/\mu l$) | 267 | 258 | 241 | 159–388 |
| Sedimantation (mm/h) | 12 | 10 | 14 | |

[a] BUN, blood urea nitrogen

[b] Corrected serum calcium was calculated by: measured serum calcium + 0.8 × (4-measured serum albumin)

[c] TRP, tubular reabsorbtion of phosphate, calculated by = 1-urine phosphorus × serum creatinine/serum phosphorus × urine creatinine

[d] WBC, white blood cell

[e] MCV, mean corpuscular volume

present in this patient, the latter two of which likely developed because the patient had very little exposure to sunlight. She was prescribed 1,000 U/day of Vitamin $D_3$ p.o, 300.000 U vitamin $D_3$ i.m single dose, and 3 × 1,000 mg of elementary calcium. The dose of vitamin D was increased upon follow-up.

## Discussion

In adult patients with osteomalacia, diffuse bone pain and muscle weakness are often present. In addition, fractures and deformities can be observed in the ribs, long bones, and vertebrae. When a radiological examination is performed, a reduction in bone density, loss in trabecular bone, and various reductions in cortical bone thickness can be observed, but these findings cannot distinguish osteomalacia from osteoporosis [4]. Thus, it is difficult to diagnose osteomalacia in adults using only clinical symptoms and conventional studies. We began our examination of this patient by investigating the possible reasons that could cause severe osteoporosis and multiple vertebral fractures at such an early age. In our examination of the endocrine system, there were no symptomatic or laboratory findings of thyrotoxicosis, Cushing's syndrome, adrenal insufficiency, acromegaly, or diabetes mellitus. There were no symptoms and findings of rheumatoid arthritis or ankylosing spondylitis in her rheumatological examination. She did not have any existing hematological diagnoses, and her complete blood count, sedimentation, and immunoglobulin electrophoresis were normal. There were no hereditary diseases in her family, and she had not used any medications. She had never smoked cigarettes or used alcohol, and her body mass index was normal but at the lower limit. She had suffered from a cerebrovascular event 4 years ago and had hemiparesis on the left side and

**Table 2** Advanced and differential diagnostic laboratory results upon admission and after treatment

| | On admission | 15th Day of treatment | 1st Month of treatment | Normal ranges |
|---|---|---|---|---|
| Basal serum cortisol (μg/dl) | 14 | – | – | 6.2–19.4 |
| iPTH (pg/ml)[a] | 848 | 135 | 59 | 15–65 |
| sTSH (μgIU/ml)[b] | 1.05 | – | – | 0.27–4.2 |
| Urine blood | Negative | Negative | Negative | |
| Urine sugar | Negative | Negative | Negative | |
| Urine protein | Negative | Negative | Negative | |
| Urine pH | 6 | 6 | 6 | |
| Blood pH | 7.39 | – | – | 7.35–7.45 |
| Serum 25(OH)$D_3$ (ng/ml) | 6 | – | 14 | 15–46 |
| Serum 1,25$(OH)_2D_3$ (pg/ml) | 20 | – | – | 15–60 |
| Anti-endomysium antibodies | Negative | – | – | |
| Anti-gliadin Ab Ig A (RU/ml) | <2 | – | – | <2 |
| Anti-LKM Ab (Type 1–2)[c] | Negative | – | – | |
| Anti-mitochondrial Ab | Negative | – | – | |
| Anti-smooth muscle Ab | Negative | – | – | |
| Serum Ig G (mg/dl) | 743 | – | – | 650–1600 |
| Serum Ig A (mg/dl) | 229 | – | – | 45–380 |
| Serum Ig M (mg/dl) | 119 | – | – | 50–300 |
| Serum electrophoresis | Normal | – | – | |

[a] iPTH, immune reactive parathormone

[b] sTSH, sensitive thyroid stimulating hormone

[c] LKM, liver/kidney microsomal antibody

**Table 3** Chart of bone density showing bone mineral content, T- and Z-scores

| | Bone mineral density (g/$cm^2$) | T-scores | Z-scores |
|---|---|---|---|
| L1 | 0.511 | −5.1 | −3.5 |
| L2 | 0.427 | −5.2 | −4.9 |
| L3 | 0.504 | −4.8 | −4.1 |
| L4 | 0.425 | −5.1 | −4.6 |
| L1–L4 | 0.464 | −5.1 | −4.3 |
| Femur neck | 0.424 | −4.5 | −3.4 |
| Wards | 0.295 | −4.7 | −2.9 |
| Trochanter | 0.403 | −3.2 | −2.8 |

dysarthria. The patient had developed a depressive mood after her ischemic stroke and rejected the use antidepressants recommended by her psychiatrist. In general, the patient tended to lie in her house, had poor appetite and did not go out at all. She had very little exposure to sunlight. As a result of her evaluation, the only risk factors that could be identified for severe and multiple vertebral fractures were immobilization, insufficient nutrition, and reduced exposure to sunlight. In her laboratory examinations, however, hypocalcemia, hypophosphatemia, hypocalciuria, high iPTH, and very low levels of 25(OH)$D_3$ were detected (Table 1). Her other laboratory findings were normal. She had biconcave compression fractures leading to a clear loss of height in the T11 and T12 thoracic vertebrae and the 3rd–5th lumbar vertebrae. In addition, there were compression fractures in the middle sections of the spinal column (Fig. 1). In light of these laboratory findings, it was determined that the severe osteoporosis and fractures seen in this patient were secondary to metabolic bone disease, i.e., to osteomalacia.

Malabsorption of intestinal origin and diseases pertaining to the hepatobiliary tree and pancreas are the most frequent reasons for the development of vitamin D insufficiency and osteomalacia [4]. Furthermore, patients who have had a partial and total gastric operation [5, 6] or gastroileal bypass surgery for obesity are at high risk for osteomalacia [7, 8]. Therefore, diagnostic tests to explain the hypovitaminosis D in our patient were ordered, with a focus on screening the gastrointestinal system. Our patient had not had any gastric or intestinal bypass surgery and did not have any gastrointestinal complaints such as nausea, vomiting, diarrhea, melena, hematochezia, or gastritis. Antiendomysial IgA was measured for celiac disease and found to be negative. An upper GI endoscopy and biopsies collected from the distal duodenum were both normal. Her hepatological evaluation showed no symptoms or laboratory findings of cirrhosis, biliary fistule, or chronic pancreatic insufficiency. Autoimmune markers pertaining to

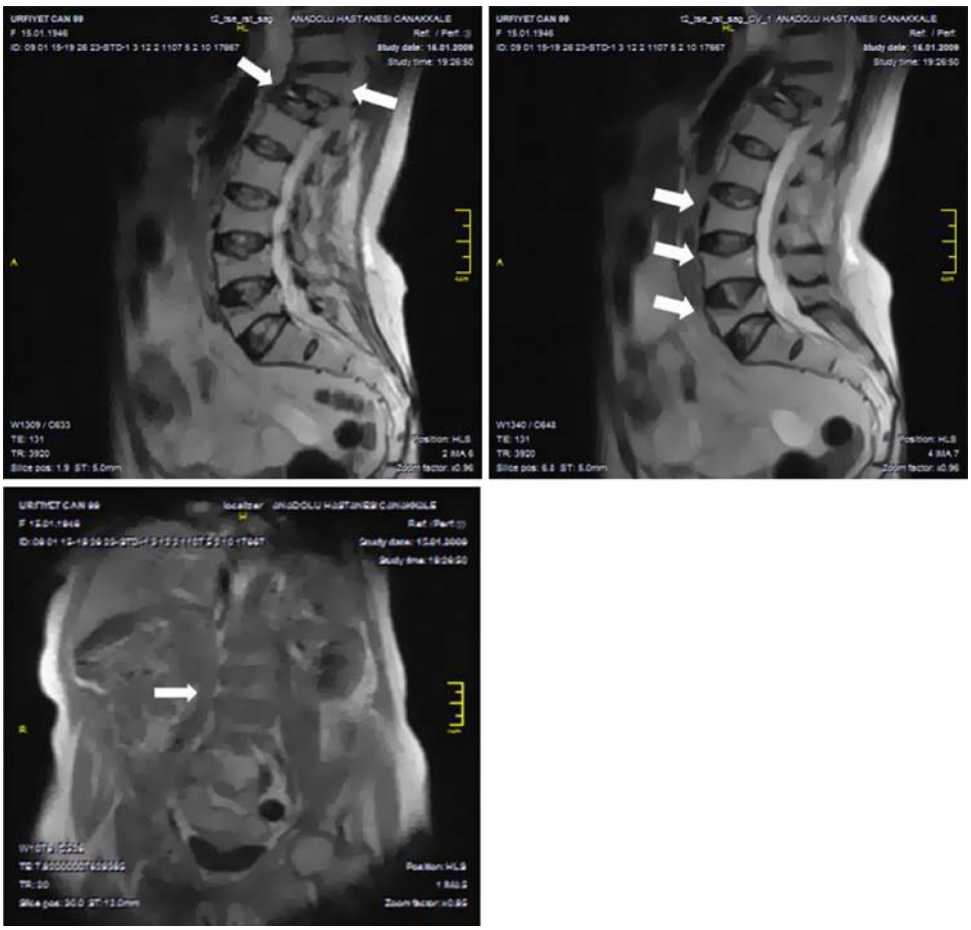

**Fig. 1** There were biconcave compression fractures leading to a clear loss of height in the T11 and T12 vertebrae and the 3rd–5th lumbar vertebrae, and there were compression fractures in the middle sections of the spinal column

the hepatobiliary tract were negative. She had never suffered any attacks of pancreatitis. In light of these results, we ruled out diseases pertaining to the gastrointestinal, hepatobiliary, or pancreatic systems as causes of osteomalacia in this patient. Meanwhile, osteomalacia secondary to genetic renal tubular acidosis (RTA) frequently develops [9, 10]. Such renal tubular acidoses show autosomal recessive and dominant inheritance patterns. Since autosomal recessive RTA is rapidly diagnosed in the infantile period, we did not consider it in our patient. As a rule, the autosomal dominant form of RTA occurs in adults in the 3rd–5th decades of life. The patient history showed no renal disease, and her renal function was normal based on clearance measurements and 24-h urine collection. The patient had never passed any renal calculi, and no proteinuria or glucosuria was present. There were no symptoms or laboratory findings of acidosis, and her renal morphology and structures were normal based ultrasound studies. In light of these results, we eliminated chronic renal insufficiency, distal tubular acidosis, and structural anomalies of the kidney as possible causes of osteomalacia in this patient. The hypophosphatemia present in this patient could have contributed to her osteomalacia. Low levels of serum phosphorus may occur due to inadequate intake or excessive loss via the urine. Since many foods contain sufficient amounts of phosphorus, the amount of phosphorus taken from food typically prevents the development of phosphorus deficiency as long as there is no excessive loss. It is difficult to produce a selective deficiency in phosphorus by dietary means alone because most foods contain this element at concentrations that are sufficient to prevent hypophosphatemia and bone disease. Nevertheless, in cases of antacid use, which is not absorbed at high doses, phosphorus chelation may occur, and hypophosphatemia and osteomalacia secondary to phosphorus deficiency may develop [11, 12]. No antacid was present in our patient. In the literature, however, there is an X-linked form of hypophosphatemic rickets, which may begin in childhood or in adulthood due to excessive loss of phosphorus from the renal and gastrointestinal systems. This disease can either be X-linked or sporadic. Nevertheless, after RTA, GI causes and tumor-related osteomalacia are eliminated as the reasons for primary vitamin D deficiency, a biochemical diagnosis can be made based on an abnormally low serum phosphorus level, high discharge of urine phosphorus and the presence of osteomalacia. We

did not initially consider the diagnosis of X-linked hypophosphatemic rickets in our patient, given that it is typically diagnosed in childhood and that she had no family history of the disease. Since her serum phosphorus levels were not abnormally low, her TRP was within normal limits and she had no family history, we eliminated sporadic hypophosphatemic osteomalacia (phosphorus diabetes). Post-treatment levels of phosphorus were normal to slightly high, while TRP was within normal limits. In addition, it was necessary to eliminate the possibility of tumor-related osteomalacia, which can sometimes be present. In tumor-related osteomalacia, hypophosphatemia, increased phosphorus clearance, normal levels of calcium, normal level of iPTH, and very low levels of $1,25(OH)_2D_3$ are typically present. Since a very low $25(OH)D_3$ level was found and there were no tumor foci identified, in addition to hypocalcemia, a normal level of $1,25(OH)_2D_3$, and an excessively high level of iPTH in this patient, we eliminated a diagnosis of tumor-related osteomalacia. In vitamin D-dependent type 1 and type 2 rickets, it is typical to see very low and very high levels, respectively, of $1,25(OH)_2D_3$. Based on the patient's history, a normal serum level of $1,25(OH)_2D_3$, and her response to the recommended dose of vitamin D treatment, we eliminated the possibility of rickets. In light of these studies, we could not find any cause of osteomalacia or etiology of vertebral fractures in our patient other than age, insufficient vitamin D intake and calcium in the diet, insufficient exposure to sunlight, and immobilization. The first biochemical symptom of vitamin D deficiency is an increase in iPTH levels. An iPTH value of 848 ng/ml was present in our patient. In cases of osteomalacia that develop due to primary hyperparathyroidism, the biochemical data of primary hyperparathyroidism can be present. In the thyroid and neck USG examinations of this patient, nothing was found to indicate a parathyroid adenoma. Nevertheless, since the sensitivity and specificity of USG in the diagnosis of parathyroid adenomas are low, the post-treatment levels of iPTH and other parameters in this patient were reevaluated. Since iPTH was decreased to normal and no hypercalcemia was observed after treatment, we also eliminated the possible diagnosis of primary hyperparathyroidism. Normal vitamin D levels were not detected on scientific grounds. In general, values below 20 ng/ml are considered low [13, 14]. A serum $25(OH)D_3$ level between 21 and 29 ng/ml indicates a relative deficiency, while values >30 ng/ml suggest an adequate level of vitamin D [15]. Given these values, vitamin D deficiency or insufficiency is present in approximately 1 billion people around the world [13, 14, 16]. Nevertheless, not every low serum $25(OH)D_3$ level leads to the development of histopathological osteomalacia. Parfitt [17] defined three stages of vitamin D deficiency: (1) reduced intestinal calcium absorption resulting in osteoporosis in the absence of osteomalacia-related bone changes; (2) reduced intestinal calcium absorption resulting in osteoporosis and early osteomalacia-related changes in the skeletal system; and (3) clinical osteomalacia. Our patient had clinical stage 3 osteomalacia based on her fractures. In the treatment of osteomalacia, researchers recommend weekly or daily vitamin $D_2$ or $D_3$ treatment. What must be considered, however, is that treatment with vitamin $D_2$ is only 30% as efficient as treatment with vitamin $D_3$ [18, 19]. When treating vitamin $D_2$, it must be given at three times the dose of vitamin $D_3$. As a starting treatment, 1,000 U/day of vitamin $D_3$ and 1,000 mg of elemental calcium three times per day were initiated in our patient, and a target value for serum $25(OH)D_3$ level was set at >30 ng/ml. Since serum calcium rapidly turns into bone in patients with severe vitamin D deficiency, acute hypocalcemia was suspected, and serum calcium, phosphorus and iPTH levels were followed closely during the first week of treatment. No hypocalcemia developed and iPTH levels decreased back to normal. At the end of the second week of treatment, there were clear clinical developments in the patient. Her bone pains were reduced, and she began to sit and walk comfortably by herself. In addition, serum and 24-h urine calcium, phosphorus, and iPTH values approached normal limits. At the end of the first month of treatment, the serum $25(OH)D_3$ level increased to 14 ng/ml. Follow-up and treatment of this patient continue. Patients taking vitamin D for a long period of time should be followed closely. Hypercalcemia and hypercalciuria are potential complications of vitamin D treatment, and unless it is followed carefully, nephrocalcinosis and nephrolithiasis are likely to develop. There is no way to estimate in which patients and when vitamin D intoxication may develop. Serum $25(OH)D_3$ levels >150 ng/ml together with hypercalcemia and hyperphosphatemia indicate intoxication [20, 21]. The best treatment for osteomalacia is sufficient intake of vitamin D at recommended doses based on age and physiological condition in order to prevent the development of osteomalacia.

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