Vitamin D intoxication

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Vitamin D intoxication (VDI) may result from supplementation rarely, but it has been reported more frequently in recent years. This may be attributable to an increase in vitamin D supplement intake due to an understanding of the role of vitamin D (25OHD) in the pathogenesis of several diseases. The symptoms and findings associated with VDI are closely related to serum calcium concentration and duration of hypercalcemia. In patients with VDI, hypercalcemia, normal or high serum phosphorus levels, normal or low levels of alkaline phosphatase (ALP), high levels of serum 25OHD, low serum parathyroid hormone (PTH), and high urine calcium/creatinine are usually present. Serum 25OHD levels above 150 ng/ml are considered as VDI. The main goal of treatment for VDI is correction of the hypercalcemia. When the calcium concentration exceeds 14 mg/dl, emergency intervention is necessary because of the adverse effects of hypercalcemia on cardiac, central nervous system, renal, and gastrointestinal functions. However, since vitamin D is stored in fat tissues, effects of toxicity may last for months despite the removal of the exogenous source of vitamin D. Treatment for VDI includes: discontinuation of intake, a diet with low calcium and phosphorus content, intravenous hydration with saline, loop diuretics, glucocorticoids, calcitonin, and bisphosphonates. In conclusion, the diagnosis of vitamin D deficiency rickets (VDDR) without checking serum 25OHD level may cause redundant treatment that leads to VDI. All patients who are clinically suspected of VDDR should be checked for serum vitamin D status and questioned for previous vitamin D administration before starting vitamin D therapy. On the other hand, parents of all infants should be asked whether they are using dietary or oral supplements, and serial questioning may be required during supplementation to avoid excessive intake.

Key words: vitamin D, intoxication, hypercalcemia, children.

Vitamin D intoxication (VDI) usually develops due to high doses of vitamin D given by health care providers, before a clear diagnosis of vitamin D insufficiency or rickets is established. In addition, patients may improperly ingest high maintenance doses recommended by a physician. Another cause of VDI is the inappropriate administration of high doses of vitamin D in infants by families for complaints such as delayed teething, ‘late walking’, and ‘knock-kneed gait’. VDI resulting from supplementation has been reported rarely but may now occur more frequently. This may be attributable to an increase in vitamin D supplement intake due to the findings that deficiency is common and has been associated with a number of disease states¹⁻³.

Vitamin D intoxication (VDI) differs from hypervitaminosis D; the normal serum vitamin D levels and clinical definitions are shown in Table I. According to the American Academy of Pediatrics, serum vitamin D levels above 250 nmol/L (100 ng/ml) are considered as hypervitaminosis D, whereas serum levels above 375 nmol/L (150 ng/ml) are associated with VDI⁴.

Hypervitaminosis D is a condition where an increase in the 25-hydroxyvitamin D (25OHD) levels is associated with either hypercalcemia or hypercalciuria, or both. VDI occurs in patients with one or more of the clinical findings listed in Table II, together with the laboratory findings of hypervitaminosis D. Hypervitaminosis D may also result from subcutaneous fat necrosis.

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and sarcoidosis, in addition to excess oral or parenteral intake of vitamin D. There is no consensus on the dose of oral vitamin D that leads to intoxication; individual variability must be considered with VDI. In studies conducted on animals, the toxic dose has been reported as 0.5 mg/kg (20,000 IU/kg), whereas the lethal dose (LD50) has been reported as 88 mg/kg (3.5 millions IU/kg). However, in humans, the mean lethal dose (LD50) of vitamin D has been reported as 21 mg/kg (840,000 IU/kg). In 2011, the American Medical Institute estimated tolerable upper limits of vitamin D, taking into account oral maintenance doses causing no hypercalcemia, hypercalciuria or ectopic calcification. Administration of vitamin D has been reported to be safe at 1000 IU/day for ages 0-1, 2500 IU/day for ages 1-3, 4000 IU/day for age 9 and above, adults and pregnant women. Iatrogenic subclinical hypervitaminosis D is more commonly recorded than acute VDI. However, individual variation is important to consider with regard to VDI; vitamin D receptor polymorphisms may be associated with the development of this condition.

**Diagnosis**

**History:** VDI should be considered and sought in the differential diagnosis of symptoms and findings mentioned in Table II. Unless specifically asked, overdose of vitamin D may go unnoticed. In a study conducted at our clinic, the characteristics of 27 patients with VDI were followed and reviewed. The common complaints were: vomiting (85.7%), loss of appetite (57.1%), weight loss (47.6%), thirst (42.8%), excessive water intake/polyuria (38%), and constipation (33.3%). With a careful review of the patient history, unnecessary evaluations can be avoided. Complications that may develop due to hypercalcemia may be prevented with early diagnosis and appropriate treatment.

**Clinical Findings:** VDI has serious consequences due to the degree of hypercalcemia and subsequent hypercalciuria/nephrocalcinosis. Rizzoli et al. demonstrated enhanced bone resorption by increased fasting urinary calcium excretion in patients with VDI. Sequential biochemical measurements in the hypoparathyroid patient with VDI showed the persistence of abnormally elevated fasting urinary calcium and of serum 25OHD concentrations, even after normalization of plasma calcium, emphasizing that enhanced bone resorption is a prominent feature of vitamin D action. Active vitamin D [1,25(OH)2 D3] is a potent stimulator of osteoclastogenesis in vitro, and administration of high doses of 1,25(OH)2 D3 can exert an osteoclastogenic and bone-resorbing effect in wild type animals in vivo. Thus, 1,25(OH)2 D3 can increase RANKL release and decrease OPG release from osteoblastic cells and stimulate osteoclastogenesis, resulting in bone resorption. Consequently, hypercalcemia in a VDI state predominantly results from bone resorption due to the effect of vitamin D rather through the direct participation of intestinal absorption.

The symptoms and findings associated with VDI are closely related to the patient’s age, serum calcium concentration and duration of hypercalcemia. If the serum calcium level is below 12 mg/dl (<3 mmol/L), it is classified as mild, between 12-14 mg/dl (3-3.5 mmol/L) as moderate, and above 14 mg/dl (>3.5 mmol/L) as severe hypercalcemia. Most cases with mild and moderate hypercalcemia are usually asymptomatic. However, the effects of severe hypercalcemia can be observed on the gastrointestinal, renal, central nervous, cardiovascular, and musculoskeletal systems, the eyes, and the skin, depending on the level of hypercalcemia. If the level of calcium

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>25(OH)-D nmol/L</th>
<th>ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe deficiency</td>
<td>12.5</td>
<td>5</td>
</tr>
<tr>
<td>Deficiency</td>
<td>37.5</td>
<td>15</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>37.5 - 50</td>
<td>15-20</td>
</tr>
<tr>
<td>Normal</td>
<td>50-250</td>
<td>20-80</td>
</tr>
<tr>
<td>Excess</td>
<td>250</td>
<td>100</td>
</tr>
<tr>
<td>Intoxication</td>
<td>375</td>
<td>150</td>
</tr>
</tbody>
</table>

*Table I. Clinical Definitions of 25 (OH)-D Levels*
x phosphorus is above 60 mg/dl, calcium phosphate crystals start to accumulate within the soft tissues of the body; impairment in renal function, vascular calcification and renal hypertension may develop\(^{15,16}\). Clinical findings associated with hypercalcemia are provided in Table II. Since vitamin D is lipophilic and stored in fat tissues, the effects of toxicity (hypercalcemia/hypercalciuria) may last for months despite the removal of the exogenous source of vitamin D\(^{15,16}\). On the other hand, especially in infants with Down syndrome or hypothyroidism, hypercalcemia may easily develop due to either increased intestinal absorption or decreased vitamin D metabolism\(^{17,18}\). Therefore, in these cases, vitamin D and calcium supplementation should be carefully provided.

**Laboratory Investigation:** In patients with VDI, hypercalcemia, normal or high serum phosphorus levels, normal or low levels of alkaline phosphatase (ALP), high levels of serum 25OHD, low serum parathyroid hormone (PTH), and high urine calcium/creatinine are usually present. Initial and follow-up laboratory findings of 27 patients diagnosed with VDI, in a study performed at our clinic, are shown in Table III\(^3\).

Out of the 27 patients with VDI, seven were identified with nephrocalcinosis over a one-year follow-up period. Long-term hypercalciuria typically results in calcium storage in the epithelial basement membrane and tubular cells in the loop of Henle, as well as calcification at the corticomedullary junction. Medullary nephrocalcinosis can be detected on ultrasound better than in X-ray or computed tomography (CT) images. The urine calcium-creatinine ratio should be followed in patients with hypervitaminosis D to monitor for the development of nephrocalcinosis\(^3,19,20\).

**Treatment**

The main goal of treatment in VDI is correction of the hypercalcemia. Since hypercalcemia leads to serious problems in children, rapid
and effective treatment is important. When the calcium concentration exceeds 14 mg/dl, emergency intervention is necessary because of the adverse effects of hypercalcemia on cardiac, central nervous system, renal, and gastrointestinal functions. Sustaining normocalcemia is as important as the acute treatment of hypercalcemia with regard to the prevention of the development of hypercalciuria and nephrocalcinosis.\(^5\)\(^,\)\(^2\)\(^0\).

Treatment for vitamin D toxicity includes: discontinuing intake, a diet with low calcium and phosphorus content, intravenous (IV) hydration, loop diuretics, glucocorticoids, and calcitonin.\(^{19-30}\) More recently, oral and IV bisphosphonates have been proven to be effective in the treatment of VDI.\(^{22,23}\) IV hydration and diuretics are used for mild cases. Patients with moderate and severe hypercalcemia must be followed closely after being hospitalized. When the calcium level exceeds 12 mg/dl, dehydration develops. The hydration used for treatment increases the glomerular filtration, which leads to calcium being filtered out of the system through the glomeruli. The sodium in the fluid prevents the tubular reabsorption of calcium. Thus, IV normal saline, given at 1.5 to 2.5 times the maintenance dose, is administered during hydration treatment. Serum calcium level can be reduced by as much as 2 mg/dl by a well-planned and well-administered fluid protocol. Caution should be exercised in patients with cardiac and renal disease with regard to excessive fluid loading. Loop diuretics such as furosemide and ethacrynic acid, added to the treatment after hydration, inhibit the reabsorption of urinary calcium, and reduce the calcium level by increasing urinary calcium excretion. To this end, furosemide can be administered at a dose of 1-2 mg/kg/day every 4-6 hours. Performing electrolyte and ECG follow-up during treatment is important.\(^{21-27}\)

In patients with severe hypercalcemia, IV hydration and diuretic treatment should be accompanied by glucocorticoids, calcitonin or preferably bisphosphonates treatment. Glucocorticoids and calcitonin have been used in the past with limited success. Glucocorticoids suppress the activity of calcitriol, and reduce the production of 1,25(OH)\(_2\)D\(_2\) and intestinal absorption of calcium. In addition, reabsorption through the renal tubules is prevented, facilitating the renal excretion of calcium. The effects are observed 24-72 hours after the start of treatment. Prednisolone, at a dose of 1-2 mg/kg/day (20-40 mg/m\(^2\)/day), can be administered orally in four doses.\(^{28-31}\)

Calcitonin inhibits osteoclast activity and reduces bone resorption by increasing urinary calcium excretion. Calcitonin, at a dose of 2-4 IU/kg/dose, is administered subcutaneously in 2-4 doses. It is effective over a period of 2-4 hours and has a low risk of side effects. Intermittent administration is recommended due to the development of resistance (tachyphylaxis) after its initial rapid effects.\(^28\)

Following hydration and diuretics, IV or oral bisphosphonates should be started in persistent cases. Bisphosphonates lead to osteoclast apoptosis by binding to the cell surface membrane. In addition to their effects on the lifespan of osteoclasts, they also inhibit osteoclast-induced bone resorption. The half-life of bisphosphonates is less than several hours and they are rapidly excreted from the circulation. Therefore, medications such as Pamidronate are administered at a dose of 0.5-1 mg/kg/dose by IV infusion.\(^{24}\) This dose may be repeated at intervals depending on the serum calcium level. In 2003, we demonstrated for the first time that an oral

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At admission</th>
<th>At six months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca (mg/dl)</td>
<td>12.1 ± 2.8</td>
<td>9.6 ± 0.5</td>
</tr>
<tr>
<td>P (mg/dl)</td>
<td>6.1 ± 1.2</td>
<td>4.1 ± 0.5</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>351 ± 224</td>
<td>538 ± 128</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>15 ± 9.2</td>
<td>48 ± 41</td>
</tr>
<tr>
<td>25OHD (ng/ml)</td>
<td>247 ± 117.8</td>
<td>110.2 ± 72</td>
</tr>
<tr>
<td>Calcium / Creatinine</td>
<td>2.47 ± 1.03</td>
<td>0.11 ± 0.12</td>
</tr>
</tbody>
</table>

Ca: Calcium. P: Phosphorus. ALP: Alkaline phosphatase. PTH: Parathyroid hormone. 25OHD: 1,25-Dihydroxyvitamin D.
bisphosphonate, alendronate, is safe and effective for achieving rapid decreases in hypercalcemia and hypercalciuria in infants with VDI. After this report, a few other cases of infantile VDI successfully treated with oral Alendronate were reported. Alendronate sodium may be started at a dose of 5 mg/day and increased to 10 mg/day. Experience with the administration of oral and IV bisphosphonates in children with severe hypercalcemia has increased over the past several years. In a recent study, Sezer et al. compared prednisolone vs alendronate treatment in six infants (aged 8.0 ± 2.1 months) with VDI. Average time to achieve normocalcemia with prednisolone treatment was 14.2 ± 6.7 days (7-23 days), whereas alendronate-treated patients achieved normocalcemia 3.5 ± 1.7 days after single oral alendronate administration (p<0.01). It was concluded that alendronate treatment achieves normocalcemia four times earlier than prednisolone treatment and shortens the hospital stay in infants with VDI. Bisphosphonates may cause flu-like illness including fever as an acute adverse effect. Long-term adverse effects are not well known at present; however, no significant long-term adverse effects have been reported yet. Response to bisphosphonate treatment is rapid and the duration of treatment is short in most cases, which decreases the possibility of long-term side effects.

Hemodialysis can be used in patients with severe hypercalcemia who do not respond to medical treatment; it can rapidly reduce the serum calcium levels (Table IV). Since recurrent hypercalcemia may develop, hemodialysis is the preferred treatment in patients with hypercalcemic crisis and acute and/or chronic renal failure.

Vitamin D is stored in fat tissue. Its half-life in fat tissue is approximately two months, whereas it is 15 days in the circulation. Hypercalcemia may continue for more than six months following VDI. Thus, patients with VDI should be followed until the 25OHD and the calcium levels return to normal due to the risk of recurrence.

In conclusion, the diagnosis of vitamin D deficiency rickets (VDDR) without checking serum 25OHD level may cause redundant treatment that leads to VDI. All patients who are clinically suspected of VDDR should be checked for serum vitamin D status and questioned for previous vitamin D administration before starting vitamin D therapy. On the other hand, parents of all infants should be queried as to whether they are using dietary or oral supplements, and serial questioning may be required during supplementation to avoid excessive intake.

**REFERENCES**


