Calcium Homeostasis, Hypocalcemia, and Hypercalcemia in Children: Diagnosis and Treatment

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Calcium is an essential mineral. With a pivotal role in bone growth and neuromuscular development, it is of crucial importance in the pediatric population. This article envisages highlighting the significance of calcium homeostasis in children and gives an overview of the pathological states associated with abnormal calcium levels such as hypocalcemia and hypercalcemia.

Definition

Calcium is a critically important mineral and the most abundant mineral in the human body. It affects many diverse bodily functions and is indispensable for life. Calcium levels in the blood are strictly controlled by hormones and affected by a change in blood levels of pH and albumin (see image).

Calcium exists in the body in two forms: ionized and free. A tight control mechanism ensures optimum levels of ionized and total calcium. Subtle changes in calcium levels can have significant repercussions. Calcium homeostasis is a tightly regulated essential
The maintenance of calcium levels within a narrow range ensures optimal functioning of critical organs such as the kidney and of neurons. This regulation is multifactorial, with a large number of checkpoints and important quality-control measures.

The key elements of calcium homeostasis are as follows:

- Parathyroid hormone (PTH)
- PTH receptor
- Vitamin D
- Calcium-sensing receptor

**Vitamin D**

The discovery of vitamin D dates back to the early 20th century, when Elmer McCollum and Marquerite Davis isolated it from cod liver oil in their search for a cure for rickets in children.

Vitamin D comprises a family of secosteroids that regulate the absorption of calcium, magnesium, and phosphate in the human body and affect a number of biological processes.
The most important variant is vitamin D₃, or cholecalciferol. The next most relevant secosteroid is ergocalciferol, or vitamin D₂. Vitamins D₂ and D₃ are present in dietary supplements. The absorption of dietary vitamin D is a complex process involving both spatial and temporal separation.

Vitamind D₂ and D₃: Key Steps in the Process and Their Site of Occurrence

Most vitamin D is ingested; however, the majority of human vitamin D needs are satisfied via its synthesis from 7-dehydrocholesterol in the skin through UV ray–dependent chemical conversions (see table).

<table>
<thead>
<tr>
<th>Metabolic Step</th>
<th>Explanation</th>
<th>Site of occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake</td>
<td><strong>Dietary intake:</strong> Vitamin D can be ingested in the form of vitamins D₂ and D₃. Main sources are plants, fish, fungi, and yeast. This state is, however, metabolically inactive. Vitamin D is absorbed via chylomicrons and the lymphatic system. It then moves through the circulation with vitamin D–binding protein. <strong>Synthesis of skin:</strong> 7-dehydrocholesterol is converted first into previtamin D₃ and then vitamin D₃, where the heat from the sun’s ultraviolet B (UVB) rays acts as a catalyst.</td>
<td>Dietary intake of Vitamin D is absorbed in the small intestine. Vitamin D₃ is synthesized in the epidermis, specifically in the stratum basale and stratum spinosum.</td>
</tr>
<tr>
<td>Hydroxylation</td>
<td>The active form of vitamin D is created during this step. 25-hydroxycholecalciferol and 25-hydroxyergocalciferol are the end products. These hydroxylated vitamin D metabolites are assessed in an individual’s serum to procure an estimate of the vitamin D level.</td>
<td>Liver</td>
</tr>
</tbody>
</table>
Hydroxylation

25-hydroxycholecalciferol is further hydroxylated to form 1,25 hydroxycholecalciferol. The latter is the biologically active form of vitamin D and is also known as calcitriol. It acts on the nuclear receptors in various cells and plays a role in many biochemical cascades. By regulating this hydroxylation reaction, PIF, Ca+2, fibroblast growth factor-23, and related factors maintain the level of the active vitamin. PTH also acts as a regulator.

Kidney

Excretion

24-hydroxylase enzyme is responsible for the breakdown of calcitriol into calcitroic acid. Calcitronic acid is excreted in the urine. PTH inhibits the excretion of calcitroic acid in urine.

Action

Calcitriol acts on nuclear receptors in different cells to activate various chemical cascades.

Osteoblast: Both calcitriol and PTH act on osteoblast which, through receptor activator of nuclear factor \( \kappa \) B (RANK) and RANK ligand interaction, activates preosteoclast to form osteoclast. Osteoclast acts on the bones to bring about calcium and phosphorus release.

Intestine: Calcium and phosphate absorption is brought about by calcitriol.

Relation of Calcium to Other Constituents in Blood

Calcium exists in the body in three forms: ionized, bound to albumin, and bound to anions. A subset (45%) of total circulating calcium is in ionized form. This ionized active calcium is responsible for the mineral’s physiochemical effects and chemical interactions. The level of ionized calcium is, in turn, dependent on other constituents of the serum. Consequently, an estimate of “true” ionized calcium level needs to be considered in relation to these key regulatory elements.

The table below outlines the interaction of calcium with the other key constituents of human serum.

<table>
<thead>
<tr>
<th>Constituents of Serum</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td>Has a negative regulatory authority on calcium. An increase in phosphate levels culminates in a decrease in serum calcium levels.</td>
</tr>
<tr>
<td>Magnesium</td>
<td>A fall in serum magnesium levels induces hypocalcemia.</td>
</tr>
<tr>
<td>Albumin</td>
<td>Some circulating calcium is bound to albumin. A 1 g reduction in serum albumin levels necessitates an 0.8 mg/dL increase in serum calcium levels. Total calcium levels therefore need to be corrected if there is low albumin.</td>
</tr>
</tbody>
</table>
Functions

Calcium has broad effects throughout the body, and therefore its range must be tightly maintained to keep action potentials working across nerve cells. **The most significant functions of calcium are the following:**

- Bone mineralization
- Metabolic functions
- Neuromuscular functions
- Regulation of clotting mechanisms
- Effective intracellular messenger for a variety of substances such as insulin

Normal calcium levels are outlined in the table below.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma total calcium level</td>
<td>9.0–10.5 mg/dL</td>
</tr>
<tr>
<td>Serum ionized calcium concentration</td>
<td>4.5–5.6 mg/dL</td>
</tr>
</tbody>
</table>

Subtle changes in calcium levels can lead to a distinct constellation of symptoms and signs, and therefore immediate management is critically important.

Pathology: Hypocalcemia

Definition

The state of low serum calcium is called hypocalcemia. Mild disease is asymptomatic. However, **severe hypocalcemia can be potentially life-threatening and can present as one or more of the following symptoms:**

- Seizure
- Tetany
- Diffuse spasm
- **Arrhythmia**
- Chvostek’s and Trousseau’s sign

Diagnosis

**For a patient with unexplained hypocalcemia, the following laboratory tests can be helpful:**

- 1,25 OH vitamin D
- 25 OH vitamin D
- Serum intact PTH
- Basic metabolic panel
- Magnesium and phosphate
- Alkaline phosphate
- Urine calcium:creatinine ratio

Causes

Laboratory tests such as those noted above can uncover the most common and relevant causes of hypocalcemia (see table below).
**Diagnosis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Phosphate</th>
<th>PTH</th>
<th>25 OH Vitamin D</th>
<th>1,25 OH Vitamin D</th>
<th>Other Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
<td>Increase in alkaline phosphatase levels with decreased urine calcium</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
<td>Increase in urine calcium levels</td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
<td>↑</td>
<td>↑↑</td>
<td>↔</td>
<td>↓</td>
<td>Increase in urine calcium levels</td>
</tr>
<tr>
<td>Renal failure</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
<td>Increase in creatinine (hallmark of renal failure)</td>
</tr>
</tbody>
</table>

Other useful tests include the following:

- Electrocardiogram can detect prolonged QRS interval (risk for arrhythmia)
- Calcium, PTH, and phosphate levels that reflect hypoparathyroidism may indicate DiGeorge syndrome
- Physical exam and X-ray of chest and extremities may show signs of rickets

**Management**

Hypocalcemia, when mild, can be managed through oral calcium supplementation alone. However, severe hypocalcemia calls for dedicated multi-pronged treatment to avoid serious morbidity and even mortality.

The most relevant aspects of management of hypocalcemia include the following:

- 10% calcium gluconate bolus, for severe hypocalcemia
- Supplemental calcium and vitamin D, as needed
- Calcitriol (1,25 OH vitamin D) for renal failure, hypoparathyroidism, and McCune-Albright syndrome

**Pathology: Hypercalcemia**

**Definition**

Hypercalcemia encompasses the constellation of signs and symptoms that occur when calcium levels escalate beyond the physiological upper limit. The familiar saying "stones, bones, abdominal groans, and psychiatric overtones" poetically encapsulates the major features of hypercalcemia.

Severe hypercalcemia is characterized by calcium levels > 14 mg/dL. There is a potential risk of complete neuro-musculoskeletal breakdown and cardiac and renal system collapse. Severe hypercalcemia calls for rapidly integrated management.

**Etiology**

Various etiologies are associated with hypercalcemia.

In infants, the most relevant pathologies associated with hypercalcemia include the following:

- Maternal hypocalcemia
- Williams syndrome
- Familial hypocalciuric hypercalcemia
- Fat necrosis
Signs and Symptoms

The signs and symptoms of hypercalcemia in pediatric patients include the following:

- **Vomiting**
- Dehydration from **polyuria**
- Dysmorphic symptoms associated with **Williams syndrome**

Causes

The circumstances in which older children develop hypercalcemia can vary widely. Major causes include the following:

- **Sarcoidosis**, **tuberculosis**, and other causes of granulomas
- Malignancy
- **Hyperparathyroidism**
- Vitamins and medications, such as increased vitamin A and D, **thiazides**, and lithium

Diagnosis

Hypercalcemia can be diagnosed based on blood tests alone. Assessment of serum calcium and serum PTH level is sufficient to establish the diagnosis and confirm the most common etiologies. Once escalated calcium levels are documented, uncovering the cause begins with determining the PTH level. The table below outlines the algorithm used to do this.

<table>
<thead>
<tr>
<th>PTH Level</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Decreased</td>
<td>Next step is to determine the PTH-related peptide levels</td>
</tr>
<tr>
<td>Normal</td>
<td>Seen in familial hypocalciuric hypercalcemia</td>
</tr>
</tbody>
</table>

Management

As noted, severe hypercalcemia is a threat to the critical cellular pathways essential for survival. The key features in the management of hypercalcemia include the following:

- The most important primary step is to bring about volume expansion and avoid dehydration.
- Calcitonin may be thought of as an antidote to hypercalcemia. However, repeated use of calcitonin should be avoided, as this is associated with tachyphylaxis.
- Bisphosphonates can be used.
- Dialysis should be considered in cases of severe renal inflection.
- Steroids may be effective for granulomatous disease.
- Parathyroidectomy may be used in patients with hyperparathyroidism.

Summary

Calcium is an essential mineral element and a crucial building block of life. Calcium homeostasis is largely determined by vitamin D, PTH, PTH receptor, and calcium-sensing receptor. Strict regulation of calcium levels within a relatively narrow range is important
for optimal functioning of the neuromuscular system.

Vitamin D is procured by the body through diet and dietary supplementation as cholecalciferol and ergocalciferol. The skin produces vitamin D using UVB rays from sunlight. This vitamin D configuration is biologically inactive. Further hydroxylation in the liver and then the kidneys results in the synthesis of the active form of vitamin D, also known as calcitriol. PTH regulates vitamin D synthesis and activation.

Ionized calcium is responsible for the physiochemical effects of calcium. Ionized calcium levels are altered as a result of interaction with other constituents of blood serum, such as phosphate and magnesium. For every 1 g/dL fall in albumin, 0.8 mg/dL of calcium needs to be added to the total calcium estimate to obtain the true level of calcium.

Calcium is indispensable for survival. It serves a multitude of functions, including the regulation of bone mineralization, clotting mechanism activation, and regulation of various processes and steps in the neuromuscular system.

Total calcium level is approximately 9.0–10.5 mg/dL. Serum ionized calcium assessment reveals that about half of serum calcium exists in ionized form.

Pathological aberrations in the level of calcium in the blood can be dangerous. While mild abnormalities are relatively well tolerated, severe fluctuations can inflict significant harm on the cardiac, neuromuscular, and skeletal systems. Both hypocalcemia and hypercalcemia present with a unique set of symptoms and signs. Quick recognition of these signs and symptoms and dedicated management can help avoid long-term damage.

References


Nelson’s textbook of Pediatrics.

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