CASE REPORT

Approach to Diagnosis and Management of An Elderly Female Patient with Recurrent Hypocalcemia

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ABSTRACT

Disorders of calcium metabolism are common in the everyday clinical setting. Although hypocalcemia is not as common as hypercalcemia, it can be life-threatening if not properly recognized and treated promptly. Causes of hypocalcemia can be divided into three broad categories, such as parathyroid hormone (PTH) deficiency, high PTH levels, and other causes. There is no literature that specifically discusses the incidence and prevalence of hypocalcemia in general. In general, renal failure is the most common cause of hypocalcemia. This condition is followed by vitamin D deficiency, magnesium deficiency, acute pancreatitis, and others. The clinical presentation of hypocalcemia can vary widely, from asymptomatic to life-threatening. In an emergency, unrecognized or poorly managed hypocalcemia can cause significant morbidity or mortality. Symptomatic patients with classic clinical findings of acute hypocalcemia require immediate resuscitation and evaluation. However, most cases of hypocalcemia are found based on clinical suspicion as well as appropriate laboratory testing. Treatment of hypocalcemia depends on the presence and severity of symptoms, degree of hypocalcemia, and etiology of hypocalcemia. Most cases of hypocalcemia are clinically mild and require only supportive treatment and further laboratory evaluation. Oral calcium absorption may be indicated for outpatient treatment in mild cases. In cases of severe hypocalcemia leading to seizures, tetany, refractory hypotension, or arrhythmias, a more aggressive approach may be required, including intravenous calcium infusion.

***Keywords**: Calcium, hypocalcemia, parathyroid hormone, vitamin D*

INTRODUCTION

Hypocalcemia is one of the most diagnosed electrolyte disturbances and requires careful management and evaluation. Epidemiological studies of hypocalcemia compared with other electrolyte abnormalities have not been carried out. For the past 20 years, laboratory tests that included serum levels of calcium, ionized calcium, and parathyroid hormone (PTH) allow diagnosis to be easier. Hypocalcemia has been reported to occur due to genetic disorders or acquired from several organ and organ system disorders. Diseases that interfere with the physiology of the parathyroid glands, bones, intestines, and kidneys, which are all responsible for regulating serum calcium levels, can cause hypocalcemia.[1-3] The incidence of ionized hypocalcemia is difficult to measure. In intensive care patients, the reported rates range from 15-88%. A systematic review and meta-analysis of hypocalcemia after thyroidectomy found that the average incidence of transient hypocalcemia was 27% (range 19-38%) and permanent hypocalcemia was 1% (range 0-3%). In a series of 500 postoperative thyroidectomy patients who were operated on for hyperparathyroidism, 2% developed permanent hypocalcemia.[2]

Patients with hypocalcemia may be present with a variety of signs and symptoms. Low serum calcium levels have the potential to affect nearly all organs and organ systems. New-onset hypocalcemia can be life-threatening and requires immediate medical intervention. Meanwhile, in cases of chronic hypocalcemia, patients sometimes appear asymptomatic or have mild symptoms. Identification, clinical assessment and management of hypocalcemia are key points that need to be addressed simultaneously and carried out as soon as possible. The focus of this case report is to update the evidence on the diagnostic assessment and clinical management of hypocalcemia according to an algorithm that is useful for everyday clinical practice.[1,2]

CASE REPORT

A 72-year-old female patient came with her family to hospital, in conscious state with the main complaint of shortness of breath. Shortness of breath has been felt since the last 1 month and got worse 3 days before entering the hospital. Shortness of breath that feels like fatigue after undergoing heavy exercise, with fast and short breaths, chest feels heavy, accompanied by cold sweat. Since the last 3 days, the shortness of breath has been felt continuously with increasing intensity when carrying out normal daily activities and aggravating when lying down. Shortness of breath is felt to decrease if the patient is at rest and in a sitting position. Over the past 1 month, complaints of shortness of breath have gotten worse and more frequent. When shortness of breath occurs, the patient feels nausea, fatigue, difficulty speaking, and coughing.

Complaints of nausea have also been felt by the patient since the last 3 days after starting with aggravating complaints of shortness of breath. Nausea is not accompanied by vomiting and decreases if shortness of breath improves. Cough has also been felt since the last 2 days. Cough complaints come and go, beginning with the desire to get rid of phlegm. Cough worsens if tightness increases. Cough with thick yellow phlegm and hard to cough up. Cough and shortness of breath are reduced when given oxygen while on Triage. Apart from shortness of breath and coughing, the patient also complained of decreased appetite since the last 3 days due to the aggravating tightness. Patients can eat up to 1/2 portion but can still drink as much as 500-1,000 ml/24 hours.

The patient also complained of stiffness in the fingers of the limbs but felt the heaviest in the fingers of both hands, difficult to control, painless, difficult to move, intermittent, and one attack lasted less than 5 minutes. Complaints of stiffness have been felt since the last 1 month. Currently, for stiff complaints, attacks are less common. When an attack occurs, the fingers grip, the wrist is slightly flexed, and the upper arm is slightly extended. Consciousness

remains full during an attack. There are no conditions that exacerbate or alleviate these stiff complaints.

Other complaints such as fever, tremors, cold sweat without preceded by shortness of breath, heat intolerance, convulsions, decreased consciousness, liquid stools, decreased frequency of urination, and significant weight loss were denied by the patient. There is no problem regarding defecation. Urinate in an average of at least 1,000 cc per 24 hours, yellow, not frothy, not painful. Complaints of frequent thirst have been noticed by the patient since the last 1 month.

The patient was undergoing treatment at our hospital with complaints of pain in the right shoulder area. The patient was diagnosed with a closed fracture with dislocation of the third proximal of the right humerus. In patients, Open Reduction and Internal Fixation (ORIF) +bone graft on 5 July 2022 and discharged on 6 July 2022. History of untreated subclinical hyperthyroidism and blood calcium deficiency recognized during previous hospitalization (25 June 2022). Prior history of diabetes mellitus was denied.

The patient has a history of hypertension and congestive heart failure since the last 5 years and is taking regular medication from the heart polyclinic at Kasih Ibu Hospital in Tabanan with drugs namely candesartan 1x8mg and bisoprolol 1x5mg. The patient also had a history of goiter and had surgery in 1975. The patient said that an incision was made on the right and left side of the neck. The incision scars are still visible. There were no complaints of palpitation, cold sweat, tremor, and weight loss at that time.

There is no history of family members having similar complaints. History of hypertension, heart disease, kidney disease, thyroid gland disease, diabetes mellitus and liver disease in the family was denied by the patient. The patient works as a housewife. Everyday patients rarely consume milk. The patient does not smoke, does not consume alcohol, and has never taken herbs and pain medications.

A follow-up physical examination was carried out when the patient had moved to the Lely Room on 7/22/2022. From the physical examination, the patient's weight was 55 kg, height 160 cm, body mass index (BMI) 21.48 kg/m^2 with compos mentis awareness. Vital signs obtained: blood pressure 130/80 mmHg, pulse 89 times per minute, respiratory rate 28 times per minute and axillary temperature 37.8^{O}C, visual analog score (VAS) 0/10 and oxygen saturation was 97% in room air. On examination of the neck, it was found that there were multiple lumps in the right and left coli areas, which appeared to be more significant in the left coli region with a size of ± 3x3x4 cm. The lumps also move when swallowing, there are incision marks on the anteroinferior side of the right and left coli, and on auscultation no bruits are heard. On cardiac examination, the left heart border was enlarged, the S1 and S2 heart sounds were normal, regular, and there were no additional heart sounds. Examination of the lungs, abdomen and extremities showed no abnormalities.

On laboratory examination, there was a decrease in serum calcium and intact PTH level. The results of other laboratory tests are shown in tables 1 and 2.

Table 1. Laboratory Results of The Patient's Current Hospitalization Period

Types of Laboratory Examination	Results (Date, July 2022)				Reference	Unit
	16	17	18	20		
Whole Blood						
Leucocytes	14,7				4,1-11,0	$10^3/\mu L$
Neutrophils	12.64				2.50-7.50	$10^3/\mu L$
Lymphocytes	1.6				1.00-4.00	$10^3/\mu L$
Hemoglobin	10.1				13,5-17,5	g/dL
Hematocrite	32				41-53	%
MCV	84.7				92.20	fL
MCH	26.7				29.31	Pg
Platelets	465				150-440	$10^3/\mu L$
Blood Sugar						
RBS	208				70-140	mg/dL
HbA1C	7.3				<6.5	%
Inflammatory Markers						
Procalcitonin	2.65				<0.15	ng/mL
Liver Function Test						
SGOT	43.5				11-33	U/L
SGPT	30.8				11-34	U/L
Albumin	3.59		3.29		3.4-4.8	g/dL
Kidney Function Test						
BUN	11.4		14.9	15.6	8-23	mg/dL
Creatinine serum	1.19		1.3	1.18	0.5-0.9	mg/dL
Coagulation Test						
PPT	14.1				10.8-14.4	second
APTT	31.9				24-36	second
INR	0,99				0.9-1.1	
Serum electrolytes						
Natrium	143	144		137	136-145	mmol/L
Kalium	5.85	3.51		2.98	3,5-5,1	mmol/L
Calcium	4.4		5.2	5.1	8.4-9.7	mg/dL
Corrected calcium	4.7		5.8	5.7	8.4-9.7	mg/dL
Blood Gas Analysis						
pH	7.44					
pCO2	34				35-45	mmHg
pO2	121				80-100	mmHg
BE	-1.1				-2-2	mmol/L
HCO3	23.1				22-26	mmol/L

Table 1. Laboratory Results of The Patient's Current Hospitalization Period (Continuation)

Types of Laboratory Examination	Results					Reference	Unit
	21	23	25	26	27		
Whole Blood							
Leucocytes	7.58					4,1-11,0	10^3/µL
Neutrophils	4.97					2.50-7.50	10^3/µL
Lymphocytes	1.9					1.00-4.00	10^3/µL
Hemoglobin	9					13,5-17,5	g/dL
Hematocrit	27.5					41-53	%
MCV	84.1					92.20	fL
MCH	27.5					29.31	Pg
Platelets	353					150-440	10^3/µL
Kidney Function Test							
BUN		12.9		13.2		8-23	mg/dL
Creatinine serum		0.9		1.05		0.5-0.9	mg/dL
Serum electrolytes							
Natrium	135	139		139		136-145	mmol/L
Kalium	3.19	3.7		4.85		3,5-5,1	mmol/L
Calcium		5.7	6.6	6.9		8.4-9.7	mg/dL
Corrected calcium		6.3	7.2	7.5		8.4-9.7	mg/dL
Magnesium			1.47			1.6-2.6	mg/dL
Hormones							
Intact PTH					5.83	10-65	pg/mL
Urinary electrolytes							
24-hour urine's K				48.57		25-100	mmol/24 hour
24-hour urine's Na				273.6		30-300	mmol/24 hour
24-hour urine's Ca				2.93		2.5-8.0	mmol/24 hour
Urine osmolality				214.5		500-800	mOsm/kg H2O

MCV (mean corpuscular volume); MCH (mean corpuscular hemoglobin); RBS (random blood sugar); HbA1C (glycosylated haemoglobin); SGOT (serum glutamic oxaloacetic transaminase); SGPT (serum glutamic pyruvic transaminase); PPT (plasma prothrombin time); APTT (activated Partial Thromboplastin Time); BE (base excess); Na (sodium); K (potassium); PTH (parathyroid hormone)

Table 2. Laboratory Results of Patients In The Previous Hospitalization Period

Types of Laboratory Examination	Results	Reference	Unit
	June 27, 2022		
Reticulocyte %	1.58	0.76-2.21	%
Reticulocyte#	0.06	0.03-0.1	10^6µL
TSHs	0.15	0.27-4.2	uIU/mL
FT4	1.19	0.7-1.48	ng/dL
Albumin	3.04	3.4-4.8	g/dL
Calcium	3.8	8.4-9.7	mg/dL
ALP	98	42-98	U/L
CRP	124.4	<5	mg/dL
Vitamin D,25-OH Total	26.9	30-100	ng/dL

TSHs (thyroid stimulating hormone); FT4 (free thyroxine); ALP (alkaline phosphatase); CRP (C-reactive protein)

Furthermore, an anteroposterior (AP) plain chest X-ray examination was carried out and showed that in the lung there was bilateral consolidation on upper to middle zone of the lungs, perihilar treasure in both lung fields, increasing of vascular pattern, and cephalization. Furthermore, on the heart, it is enlarged in size, the left border is covered with opacities, and there is aortic knob calcification. Then, installed plate and screw internal fixation on the proximal third of the right humerus is found. The impression on this chest X-ray is cardiomegaly with aortosclerosis, pulmonary edema, bilateral pleuropneumonia, and installed plate and screw internal fixation on the proximal third of the right humerus.

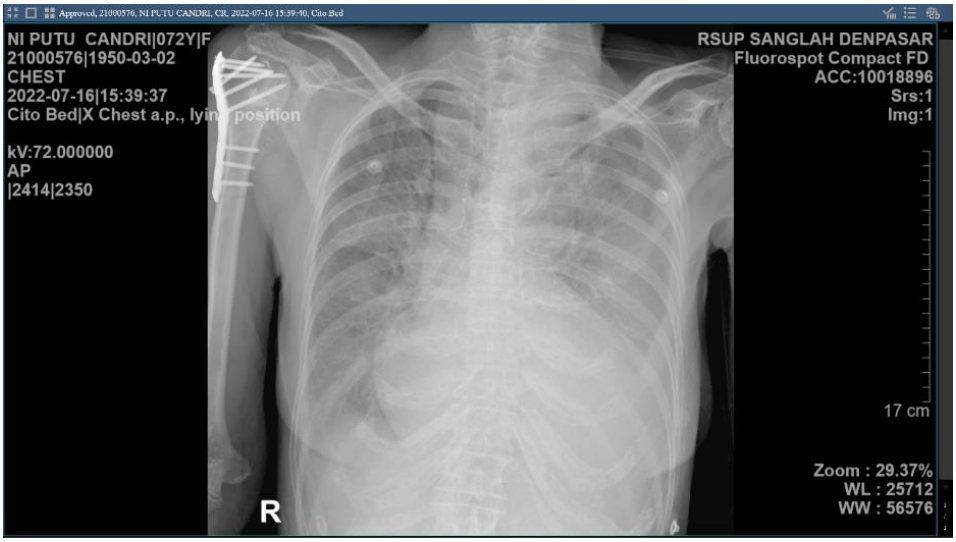

Figure 1. Photo of the patient's chest upon admission to the hospital

Bedside echocardiography also performed and showed the results of dilatation of the left atrium and left ventricle, left ventricle hypertrophy, ejection fraction 25%, mild mitral regurgitation, mild tricuspid regurgitation, low probability of pulmonary hypertension, estimated right atrial pressure (eRAP) 15 mm Hg, as well regional wall motion abnormality (RWMA). The patient also underwent cytopathological examination fine needle aspiration biopsy (FNAB) of the thyroid gland (25/7/2022) which showed a cytomorphological impression of a predisposition to a benign follicular nodule.

The patient also had a history of hospitalization. Several examinations were carried out such as plain photos of the humerus and AP/lateral shoulder, ultrasonography (ultrasound) of thyroid gland, as well head magnetic resonance imaging (MRI). Thyroid ultrasound results (30/6/2022) showed the impression of a solid lobulated mass on the left thyroid to left thoracic inlet, according to Thyroid Imaging Reporting & Data System (TIRADS)-5 (Highly Suspicious), a solid lobulated mass on the right thyroid to right thoracic inlet according to TIRADS-4 (Moderately Suspicious), a solid mass with a cystic component on isthmus TIRADS-4 compliant (Moderately Suspicious), as well as multiple nonsuspicious lymphadenopathy on right and left coli, submental, and left submandibular regions.

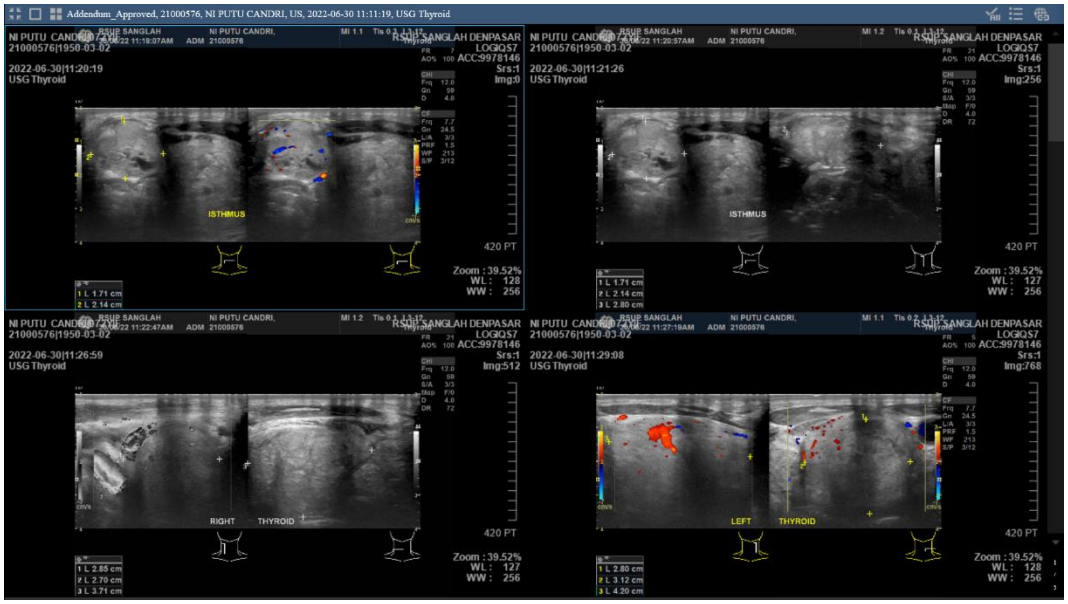

Figure 2. Result of thyroid ultrasound

Because clinically there were repetitive spastic involuntary movements, symptomatic epilepsy was suspected, an MRI of the head was performed. Head MRI results axial, sagittal, and coronal slices without contrast show an impression of small vessel ischemic changes on the right and left lateral periventricular (Fazekas 2), Pansinusitis, and mesial temporal sclerosis is not visible.

Figure 3. MRI of the head

The patient also underwent plain AP/lateral humeral photos before and after surgery. Plain radiographs before surgery show a complete displaced fractur on right anatomical neck os humerus accompanied with soft tissue swelling surroundings and osteopenia. Later, plain radiographs after surgery showed fracture attached on right anatomical neck os humerus attached with plate and internal fixation screw with good standing and apposition, accompanied with soft tissue swelling surroundings and osteopenia.

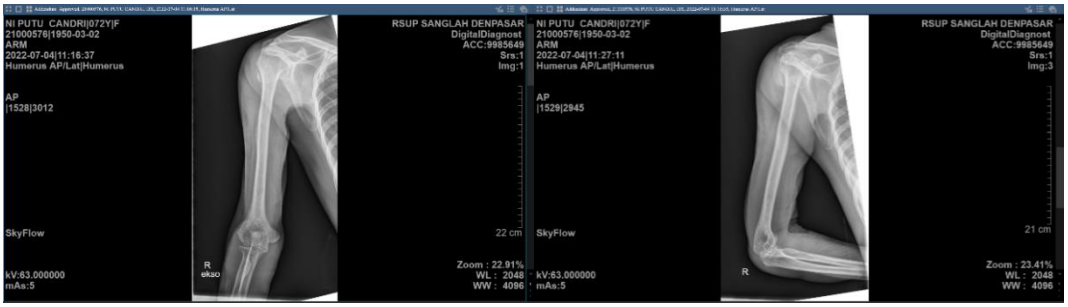

Figure 4. Photo of AP/Lateral humerus before surgery

Figure 5. Photo of AP/Lateral humerus after surgery

The patient is being treated in the intermediate ward of Penyakit Jantung Terpadu (PJT) before finally being transferred to our hospital. In intermediate ward of PJT, the patient was diagnosed with acute decompensated heart failure (ADHF) profile B; type 2 diabetes mellitus (DM); hypokalemia; acute on chronic kidney disease (ACKD) et causa prerenal on chronic kidney disease (CKD) et causa diabetic kidney disease (DKD); multiple thyroid nodule suspect malignancy, subclinical hyperthyroidism; hypocalcemia; community acquired pneumonia (STAMP). Meanwhile, in the Lely Room, the patient was diagnosed with ADHF profile B (improved); DM type 2; ACKD et causa prerenal on CKD et causa DKD (improved); benign multiple thyroid nodule; subclinical hyperthyroidism; suspect hypoparathyroidism; hypocalcemia; CAP (improved).

Therapy given in intermediate ward of PJT is an infusion of 0.9% NaCl 8 drops per minute, furosemide 3x20mg iv, insulin glulisine 3x3 units sc, insulin glargine 1x8 units sc, ceftriaxone 1x2gr iv, levofloxacin 1x750gr po, spironolactone 1x25mg po, acetosal 1x80 mg po, candesartan 1x8 mg po, bisoprolol 1x2.5 mg po, simvastatin 1x20mg po, acetylcysteine 3x200mg po, calcitriol 1x0.25mg po, lansoprazole 1x30mg iv, calcium gluconate 3x1 gram iv. Meanwhile, the therapy given in the Lely Room was an infusion of 0.9% NaCl 8 drops per minute, CKD diet nutrition 1900 kcal/day + 48 gr protein/day, calcium gluconate 3 x 1 gram IV, insulin glulisine 3 x 3 units SC, insulin glargine 1 x 8 units SC. , furosemide 40 mg IV (if there are signs of congestion), acetosal 1x80 mg po, candesartan 1x8 mg po, bisoprolol 1x2.5 mg po, spironolactone 1x25 mg po, simvastatin 1x20 mg po, calcitriol 1 x 0.5 mg po, KSR 3x600 mg po , and lansoprazole 1x30mg po. Monitoring blood sugar is done by examining fasting blood sugar and 2 hours after eating. Electrolyte monitoring is also carried out by checking natrium, kalium and calcium every 72 hours. Evaluation of kidney function was also carried out by assessing blood urea nitrogen (BUN) and serum creatinine every 72 hours and urine output in 24 hours.

DISCUSSION

Definition

Hypocalcemia is defined as a total serum calcium concentration <8.8 mg/dL (<2.20 mmol/L) in the presence of a normal plasma protein concentration or a serum ionized calcium concentration <4.7 mg/dL (<1.17 mmol/L). The reference range for serum calcium varies with age and sex.[2] Hypocalcemia is one

of the most common electrolyte disturbances and requires careful diagnosis and management. Calcium homeostasis in the body is a complex interaction between several different hormones and other factors. The main factors that regulate calcium homeostasis in the body are the PTH hormone, vitamin D, fibroblast growth factor 23 (FGF23), and calcitonin.[3]

The serum calcium concentration is maintained within a very narrow range. About 45% of body calcium is bound to plasma proteins, especially albumin. About 15% is bound to small anions such as phosphate and citrate. About 40% is in the free or ionized state. Most laboratories report total serum calcium concentrations ranging from 8.5 to 10.5 mg/dL (2.12 to 2.62 mmol/L). Ionized calcium can also be measured by some laboratories, where the normal range is 4.65 to 5.25 mg/dL (1.16 to 1.31 mmol/L). Any level below this range is considered hypocalcemia.[3]

In this case, the patient's total calcium level at admission was 4.4 mg/dL, with a total calcium level of 4.7 mg/dL after corrected with plasma albumin levels. Hence, the patient was diagnosed with hypocalcemia.

Epidemiology

There is no literature that generally addresses the incidence and prevalence of hypocalcemia. A systematic review and meta-analysis of hypocalcemia after thyroidectomy showed that the mean incidence of transient hypocalcemia was 27% (range, 19-38%) and that of permanent hypocalcemia was 1% (range, 0-3%).[4] In a series of 500 postoperative patients for hyperparathyroidism, as many as 2% of patients also reported having permanent hypocalcemia.[2]Hypocalcemia occurs in chronic kidney disease and acute kidney injury, vitamin D deficiency, magnesium deficiency, acute pancreatitis, hypoparathyroidism, pseudohypoparathyroidis, severe degree corona virus disease-19 (COVID-19) infections, as well as the use of calcium-free phosphate, citrate, or albumin infusions. The underlying disease causing the hypocalcemia has a greater impact on morbidity than the hypocalcemia itself.[2,6]

Etiology

Disorders causing hypocalcemia can be divided into PTH-mediated and non-PTH-mediated. The first group includes all cases of impaired parathyroid gland function resulting in reduced or overproduction of PTH. Meanwhile, in the second group are organs and other organ systems that are involved. Kidney, liver, bone, intestine, and vitamin D metabolism play a major role in this case, which is generally associated with a secondary increase in PTH levels (Table 3).[1]

Table 3. Causes of hypocalcemia

PTH-mediated causes	
Genetic disorders	**Acquired disorder**
Familial isolated hypoparathyroidism Hypoparathyroidism-associated syndrome, namely: 22q11.2deletion (DiGeorge) syndrome; Hypoparathyroidism, Sensory Neural Deafness, Renal Dysplasia Syndrome (HDR); Kearns-Sayre syndrome; Kenny-Caffey syndrome type 1 and 2; Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome; Sanjad Sakati syndrome (SSS); Mitochondrial trifunctional protein (MTP) deficiency syndrome; Autosomal Dominant Hypocalcemia (ADH) 1 and 2; Pseudohypoparathyroidism 1A and 1B; Wilson's disease; hemochromatosis	Postoperative hypoparathyroidism Hypomagnesemia Hypermagnesemia Autoimmune polyendocrine syndrome type 1 (APS1) Blood transfusion (hemosiderosis) Radiation therapy Metastasis sclerotic "Hungry bone" syndrome Vitamin D deficiency Chronic kidney disease

Table 3. Causes of hypocalcemia (continued)

Causes not mediated by PTH	
Genetic	**Got**
Vitamin D dependent rickets (VDDR) types 1 and 2 Hypocalcemia vitamin D-resistant rickets (HVDRR) Osteopetrosis Maternal hyperparathyroidism	Malabsorption End stage liver disease Critical illness Acute pancreatitis Osteoblastic metastases Citrate (blood transfusion) Drugs: loop diuretics; phosphate; foscarnet; anti-convulsant; magnesium sulfate; calcitonin, bisphosphonates, denosumab; cinacalcet

PTH deficiency (low or low normal serum of PTH)

This occurs because of decreased PTH secretion (hypoparathyroidism), which can be caused by destruction of the parathyroid glands (postoperative or autoimmune), abnormal regulation of PTH production and secretion, or abnormal development of the parathyroid glands. Postoperative procedures are the most common cause of hypoparathyroidism.

Post surgery

Postoperative hypoparathyroidism is the most common form of this condition. This surgery can include parathyroidectomy thyroidectomy, laryngectomy, or radical neck surgery.[7] This condition can be temporary, that is, it heals in the first days-months after surgery. However, this condition can be permanent if it lasts more than 6 months after surgery.[3,8] Normal parathyroid glands consist of about 30% capillary cells. This makes the parathyroid glands very sensitive to interruption of the arterial blood supply or venous drainage, which can result from mechanical, thermal, or electrical injury during a thyroidectomy procedure. In this context, early measurement of serum calcium and PTH levels after neck surgery is a good predictor of permanent postoperative hypoparathyroidism.[1]

In addition, in other cases such as severe hyperparathyroidism with significantly elevated PTH levels before surgery and cases of tertiary hyperparathyroidism in renal disease, a sudden decrease in PTH levels after surgery can lead to severe hypocalcemia. This is due to excessive osteoblast activity, causing significant calcium uptake into the bones. This condition is called hungry bone syndrome.[3,9]

Hypomagnesemia day Hypermagnesemia

Hypomagnesemia is a relatively common cause of functional hypoparathyroidism, whereas hypermagnesemia is less common in everyday clinical practice. Magnesium deficiency causes hypocalcemia by interfering with PTH end-organ action and/or by inhibiting its secretion. Both disorders can cause a decrease in PTH secretion by the parathyroid glands, which is thought to be through stimulation of the Calcium Sensing Receptor (CaSR).[1,7,8]

Autoimmune

Hypoparathyroidism can occur because of an autoimmune process. Autoantibodies against the parathyroid glands are the main cause of autoimmune hypoparathyroidism which can be a manifestation of autoimmune polyendocrine syndrome 1 (APS1). The APS1 associated with hypoparathyroidism may be affected by other endocrinopathies or immune system-mediated disorders, such as Addison disease, mucocutaneous candidiasis, Graves' disease, hypogonadism, vitiligo, malabsorption (steatorrhea), pernicious anemia, and diabetes mellitus.[7]

Abnormal Parathyroid Gland Development

X-linked or autosomal recessive hypoparathyroidism causes abnormal development of the parathyroid glands. This condition can be associated with complex congenital syndromes such as the DiGeorge syndrome, Kearns-Sayre syndrome, Kenny-Caffey syndrome type 1 and 2, and others.[1,7]

Parathyroid gland destruction

This condition can also be caused by other, rare causes, namely infiltrative diseases of the parathyroid glands such as granulomatous disease, hemochromatosis, Wilson disease, or radiation impact. Human immunodeficiency virus (HIV) infection is also a rare cause of symptomatic hypoparathyroidism. Finally, mutation activation of calcium-sensing receptors (CaSR) can decrease the set point ofCaSR, thus causing hypoparathyroidism and hypocalcemia.[3]

High PTH levels

Absolute or relative vitamin D deficiency

Vitamin D deficiency can be caused by decreased intake or malabsorption, inadequate sun exposure, liver disease, kidney disease, and decreased conversion to its active metabolite (1,25-dihydroxy vitamin D). This can lead to decreased intestinal calcium absorption and bone resorption. The resulting hypocalcemia causes a compensatory increase in PTH secretion (secondary hyperparathyroidism). Severe vitamin D deficiency results in hypocalcemia, which is commonly associated with hypophosphatemia and high serum PTH levels.[1,3]

Chronic kidney disease

Chronic kidney disease (CKD) causes impaired excretion of phosphate and impaired hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxy vitamin D. This encourages PTH secretion, causing secondary hyperparathyroidism. However, due to impaired vitamin D metabolism and high phosphate levels, serum calcium will remain low even though PTH levels have increased.[3] Elevated phosphate levels result in hypocalcemia by complicating serum calcium and depositing it in bones and other tissues. Meanwhile, impaired vitamin D metabolism results in hypocalcemia by reducing calcium absorption in the digestive tract.[7]

Pseudohypoparathyroidism

Pseudohypoparathyroidism (PHP) is a genetic disorder characterized by unresponsiveness of target organs to PTH. This condition mimics a form of hypoparathyroidism due to hormone

deficiency (hormone-deficient forms of hypoparathyroidism). This condition is characterized by hypocalcemia and hyperphosphatemia, but PTH levels are increased.[1,3,7]

OTHER CAUSES

Pseudo hypocalcemia

Serum calcium is generally bound to proteins in the blood, especially albumin. Therefore, low albumin status can provide information that the total serum calcium level is also very low. In this state, ionized calcium levels are usually normal. Thus, a correction of adding 0.8 mg/dL to the serum calcium level for every 1 gram decrease of serum albumin below normal (4 g/dL) is recommended.[3]

Acidosis/alkalosis

The binding of calcium to albumin is dependent on serum pH. Thus, in conditions of severe acidosis, ionized calcium will increase and vice versa will decrease in conditions of severe alkalosis. There is no reliable correction factor to estimate this shift in ionized calcium levels. This is why direct measurement of ionized calcium is recommended in these cases to guide therapy.[3]

Acute pancreatitis

Hypocalcemia can be induced by disruption of the PTH-vitamin D axis in several conditions, such as acute pancreatitis. This condition occurs due to calcium deposition in the abdominal cavity because of ongoing inflammation. There is a process of saponification of calcium from the released fatty acids in acute pancreatitis.[1,3]

Severe sepsis/critical illness

Severe sepsis can cause hypocalcemia through mechanisms that are not clear. Impaired PTH secretion, dysregulation of magnesium metabolism, and impaired vitamin D (calcitriol) secretion have been identified as potential mechanisms of this condition. More recent reports have also shown hypocalcemia to be associated with severe COVID-19 infection.[3]

Drugs

All drugs that inhibit bone resorption used to treat hypercalcemia (eg, calcitonin, intravenous bisphosphonates, receptor activator of nuclear factor kappa B (RANK) or the RANK-L inhibitor denosumab) and calcimimetics cinacalcet or etelcalcitide Drugs used to treat hyperparathyroidism can also cause hypocalcemia.[7] Bisphosphonates and denosumab can inhibit osteoclastic bone resorption, which can lead to severe hypocalcemia in some cases. Simultaneously, taking these drugs can reduce vitamin D levels, which can also cause hypocalcemia. Patients taking this drug should check their calcium and vitamin D levels regularly.[3]

Cinacalcet is a calcimimetic agent that works by stimulating CaSR, thereby reducing PTH secretion. This drug is used in the treatment of primary and secondary hyperparathyroidism. Cisplatin, a chemotherapy drugs can also cause hypocalcemia via hypomagnesemia state. Foscarnet can also cause hypocalcemia by forming complexes with ionized calcium, thereby reducing ionized calcium levels.[3]

Massive citrate blood transfusion

Excessive transfusion of citrate blood products causes an acute and transient depletion of ionized calcium. This is because calcium binds to citrate, which is used as an anticoagulant in stored blood.[3,7]

Osteoblastic metastasis

As in the case of prostate cancer, metastatic processes can also cause hypocalcemia, through increased osteoblastic activity.[3,7] In this case, the patient had a history of goiter surgery in 1975. There were incision marks on the right and left sides of the neck. The patient's low PTH level (5.83 pg/mL) was suspected to be due to the removal of the parathyroid glands during the surgical removal of the goiter that year. This condition is temporary in most cases, but can become permanent if all 4 glands are removed without parathyroid gland autotransplantation.[3,9] In this case, it is predicted that the removal of the parathyroid glands will not be total, so that

at the start there is no significant decrease in PTH levels which causes a decrease in total calcium levels, or there is still a decrease in total calcium levels but there are no symptoms.

Impaired production and secretion of PTH from the remaining parathyroid glands can be caused by age-related decline in parathyroid cell function. In elderly patients, occurs impaired parathyroid cell function, decreased provitamin D production by the liver, impaired renal response to vitamin D activation, and increased osteoclast activity, resulting in hypocalcemia. In addition, patients have been found to have decreased magnesium levels which contribute to lower total calcium levels through decreased PTH secretion.

DIAGNOSIS

Clinical manifestations

Clinical manifestations of hypocalcemia can range from no symptoms to life-threatening symptoms such as seizures, heart failure or laryngospasm. In addition, clinical manifestations also depend on the degree of progression of hypocalcemia and its chronicity. The history and physical examination of the hypocalcemia patient should focus on identifying the symptoms present. This is because some symptoms may not be seen in some patients. In addition, it is also important to carry out provocation checks. Symptoms of hypocalcemia include[1,3,11] seizures, tetany, paresthesia, psychiatric manifestations (anxiety, depression or emotional lability), carpopedal spasms (Trousseau sign), tail sign, prolongation of the QTc interval on the ECG which in advanced circumstances can cause severe ventricular tachycardia (Torsades de pointes).[3,11]

Seizure is a life-threatening condition in association with severe hypocalcemia. A mechanism associated with the pathogenesis of seizures is that low calcium levels, through a modulatory effect mediated by CaSR signaling, can shift channels and surface charges. This can increase the influx of sodium through voltage-gated sodium channels and produce glutamate release with a secondary increase in neuronal cell activity, which may enhance epileptogenesis.[12,13]

Paresthesia is the most common clinical manifestation of chronic hypocalcemia, especially postoperative chronic hypoparathyroidism. Low serum calcium and PTH levels are hallmarks of this condition. Lack of PTH can increase urinary calcium excretion and high calcium x phosphate products can lead to ectopic calcification. Report from Underbjerg et al demonstrated that patients with postoperative hypoparathyroidism have a 4-fold increased risk of renal complications related to kidney calcification or injury.[15] Brain calcifications can also develop during chronic hypocalcemia states. This condition can play a role in the process of epileptogenesis.[16]

Table 4. Clinical manifestations of hypocalcemia.[1]

Organs/Systems	Acute	Chronic
Cardiovascular	QTc interval prolongation 2:1 atrioventricular block or atrioventricular block $2^{nd}/3^{rd}$ degree Hypotension Cardiomyopathy Heart failure	
Respiration	Laryngeal stridor, bronchospasm	
Nerves	seizures paresthesia (Tail sign and Trousseau sign) Tetanus Coma	Extrapyramidal disorders (Fahr's disease) Pseudotumor of the brain Neuropsychiatric manifestations
Kidney	Hypercalciuria	Decreased renal filtration rate Nephrocalcinosis
Ophthalmology		Cataract Corneal calcification Papilledema
Tooth		Changes in tooth morphology Tooth enamel hypoplasia
Dermatology		Alopecia Xeroderma

In this case, the patient experienced repetitive stiffness of the extremity muscles that could not be controlled by consciousness, as well as a history of fractures due to minor trauma. On physical examination found carpopedal spasm, without symptoms of severe hypocalcemia.

Supporting examination

Most cases of hypocalcemia are found based on clinical manifestations and appropriate laboratory tests. Examination of albumin, liver function, and coagulation parameters should be performed to assess for liver dysfunction and hypoalbuminemia. Examination of BUN and serum creatinine should also be done to determine kidney dysfunction.[2]

Other necessary laboratory tests are serum phosphate and magnesium. Impaired renal function is generally associated with increased serum phosphate levels. Assessment of serum magnesium is necessary in these patients because hypomagnesemia is a frequent cause of reduced PTH secretion.[1] In patients with hypocalcemia, measurement of serum albumin is essential to differentiate true hypocalcemia, which involves a reduction in serum ionized calcium with factitious hypocalcemia, which is defined as a decrease in total serum calcium, but not serum ionized calcium.[2] PTH levels should also be checked as early as possible. Vitamin D levels should also be measured if a deficiency is suspected. In patients with PTH deficiency, alkaline phosphatase levels tend to be normal or slightly decreased. However, these serum levels are often elevated in patients with osteomalacia and rickets. If a diagnosis of osteomalacia is suspected, a bone biopsy can determine the final diagnosis.[2] Other biomarkers can also

provide information such as serum lipase examination in suspected acute pancreatitis.[3] An ECG examination must be carried out to determine whether there is a QTc interval prolongation. If there is, then it is a risk factor for malignant arrhythmias.[3]

Necessary imaging studies include x-ray or computed tomography (CT) scan. On x-ray examination, abnormalities associated with rickets or Looser Zone on osteomalacia may be found, which is highly pathognomonic and can be observed on the pubic ramus, upper femoral bone, and ribs. X-ray examination may also reveal osteoblastic metastases from certain tumors (eg: breast, prostate, lung cancer). CT scan of the head may show calcification of the basal ganglia, which is associated with extrapyramidal neurologic symptoms.[2]

In this case, decreased levels of total calcium, magnesium, PTH, and total vitamin D,25-OH were found, without impaired liver and kidney function. On radiological examination, also found the impression of osteopenia which is suspected of being the cause of the patient's previous fracture. The overall results strengthen the patient's diagnosis, that the hypocalcemia that occurs is mainly due to decreased PTH levels.

Hypocalcemia Diagnostic Algorithm

Assessment of medical history, family, pharmacology, as well as physical examination, is very important in patients with hypocalcemia (Figure 6). Identification of drugs that induce hypocalcemia is also important to know. In this context, careful evaluation needs to be carried out on each patient. Below is an algorithm for diagnosing hypocalcemia.

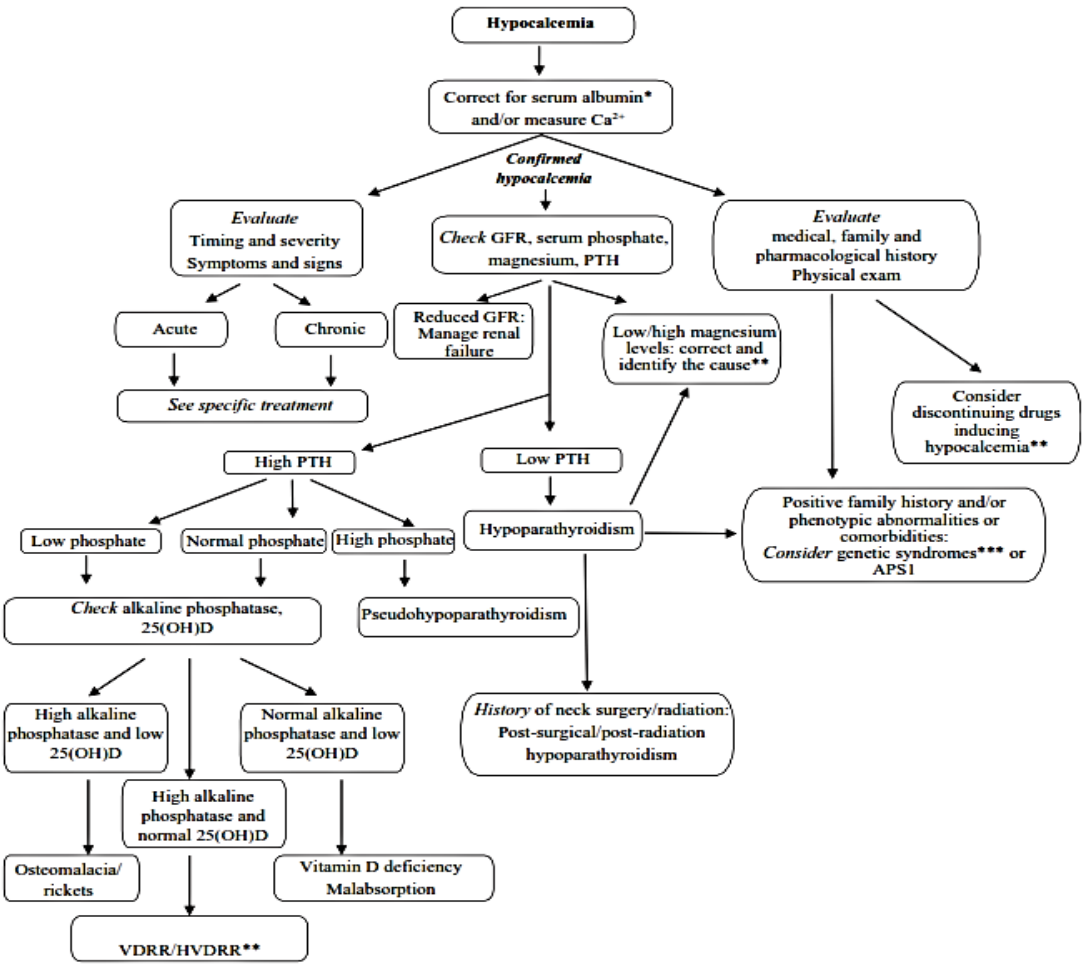

Figure 6. Diagnostic flowchart and differential diagnosis of hypocalcemia

In this case, the flow of diagnosis begins with an exploration of the signs and symptoms experienced by the patient. Patients with a history of fracture due to minor trauma, accompanied by recurrent muscle rigidity, direct the clinician to check the total calcium level. Total calcium levels were found to be low even after corrected with serum albumin levels. No impaired liver, kidney, and urinary calcium function was found, and an impression of osteopenia was found on radiological examination, causing plasma magnesium, vitamin D, and intact PTH levels to be examined. Low PTH levels with a history of thyroidectomy and low vitamin D levels suggest hypoparathyroidism as the diagnosis.

Treatment

Treatment of hypocalcemia can vary based on the severity, degree, and underlying cause of hypocalcemia. In acute and chronic hypocalcemia, the goals of treatment are to increase serum calcium within the normal range and to treat or minimize symptoms. Identifying the etiology of hypocalcemia is critical to establishing optimal management (Table 5).[3,17]

Table 5. Treatment options for hypocalcaemia.[17]

Agent	Dosage Information	Notes
Acute Management		
Parenteral Calcium Infusion		
Calcium chloride	10 mL ampoule (272 mg elemental calcium) diluted in 200 mL 5% dextrose in water given intravenously over 30-90 minutes	CaCl solutions can irritate adjacent tissues if extravasation occurs, so these agents should be administered via a central venous catheter, if possible.
Calcium gluconate	10 mL ampoule (93 mg elemental calcium); 1-3 ampoules diluted in 200 mL of 5% dextrose or normal saline given intravenously over 30-90 minutes	Therapy should be individualized and guided by frequent determinations of serum ionized calcium
Calcium gluconate infusion	10 ampoules (930 mg elemental calcium) diluted in 1 L dextrose 5% in water	The infusion rate should be 1-3 mg/kg/hour to maintain serum calcium levels within the targeted range
Long Term Management		
Calcium Supplements		
Calcium carbonate	40% elemental calcium by body weight	Best absorbed in small doses, multiple doses with food, and on an acidic stomach.
Calcium citrate	21% elemental calcium by body weight	The preferred option for patients with achlorhydria
Vitamin D Preparation		
D_2 (ergocalciferol) D_3 (cholecalciferol)	2000-100,000 IU once a day; onset action 10-14 days; offset action 14-75 days	The wide dosage range reflects the use of these agents in a variety of disorders. Careful attention to serum levels of calcium, phosphorus and creatinine is required for safe use
25-Hydroxyvitamin D_3 (calcifediol)	20-200 µg daily; onset action 5-10 days; offset action 14-75 days.	This drug is used in cases of liver failure when renal function is intact to ensure 1-alpha hydroxylation is available to activate this metabolite.
Dihydrotachysterol	0.2-1 mg once a day; onset action 4-7 days; offset action 7-21 days	Active D metabolite that does not require renal conversion
1α(Alpha)-hydroxyvitamin D_3 (alfacalcidol)	0.5-3 µg daily; onset action 1-2 days; offset action 5-7 days.	Converts rapidly to active 1,25-dihydroxyvitamin D3live

● 1,25-Dihydroxyvitamin D_3 (calcitriol)	● 0.25-1 µg once or twice daily; onset of action 1-2 days; offset action 2-3 days	● Active D metabolite that does not require renal conversion - agent of choice
● Thiazide diuretic		
● Hydrochlorothiazide ● Chlorthalidone	● 25-100 mg daily ● 25-100 mg daily	● Administered concomitantly with a low sodium diet (80-100 mmol per day) to increase renal calcium retention. Hypokalemia and hyponatremia are side effects of using this drug.

In this case, the patient was given calcium gluconate 3 x 1000 mg IV and vitamin D supplementation with calcitriol 1 x 0.5 mg po. The target of intravenous calcium supplementation is to pass through the acute phase during hospitalization, and it is planned to continue with the administration of 3x500mg po calcium carbonate as a long-term treatment. Calcitriol supplementation is given by monitoring total vitamin D, 25-OH levels periodically every 3-6 months. Because the patient's hypoparathyroidism is permanent, the provision of supplementation is not time-limited, only based on periodic monitoring for dose adjustments.

Parenteral administration of calcium is recommended for patients with severe symptoms, evidence of QTC prolongation, or in asymptomatic patients who have had acute hypocalcemia for a short time. Parenteral infusion of calcium gluconate or calcium chloride is indicated when rapid correction of serum calcium levels is required. Although calcium chloride provides nearly four times more elemental calcium than an equivalent amount of calcium gluconate, calcium gluconate is the salt of choice most often for administration in the peripheral vein. This is because calcium chloride can cause tissue necrosis if local extravasation occurs. Initially, 1 g calcium chloride (272 mg calcium) or up to 3 g calcium gluconate (279 mg calcium) may be given over 30-90 minutes to control symptoms (Table 3). However, a single intravenous injection of calcium is generally only effective for a few hours. Continuous calcium gluconate infusions will be necessary to fully control symptoms and achieve a safe and stable ionized calcium level, which is usually above 1.0 mmol/L.[17]

In patients receiving parenteral calcium replacement, serum ionized calcium levels should be measured every 1-2 hours until the patient's condition stabilizes. Then, these serum levels should be measured every 4 to 6 hours for monitoring of therapy. Recurrence of symptoms of hypocalcemia requires an increase in the infusion rate, but it should always correlate with the ionized calcium level. The rate of infusion should not exceed 1-2 mg/min because of the potential risk of cardiac arrhythmias associated with rapid calcium infusion. Alkaline solutions such as those containing bicarbonate and phosphorus should be avoided in the same infusion stream to prevent precipitation of calcium salts. Oral calcium and vitamin D should be started as soon as possible, and the intravenous calcium infusion should be tapered off slowly (over 24-48 hours or longer), while oral therapy should be further adjusted.[3,17]

If the symptoms of hypocalcemia are mild such as paresthesia or are asymptomatic, then oral calcium supplementation can be given. Calcium carbonate (40% elemental calcium) or calcium citrate (21% elemental calcium) are the most used calcium preparations. The aim of this preparation is to provide 1500 to 2000 mg of elemental calcium daily in 2 to 3 divided doses. Calcium carbonate requires an acidic medium for its absorption, so administration of this drug should be avoided in patients taking this class of proton pump inhibitor (PPIs) drugs. Vitamin D supplementation is often recommended to be given together with calcium to promote better absorption.[3]

Treatment of chronic hypocalcemia must be adjusted to the underlying etiology and almost always relies on oral calcium supplements, vitamin D, and (sometimes)

thiazide diuretics. Although calcium supplementation of all types can be used for hypocalcemia, the most efficient supplementation is in the form of carbonate or citrate salts. A reasonable initial dose that can be given is 0.5-1 g of elemental calcium, two or three times daily. Subsequent doses may be adjusted based on patient compliance, side effects, and clinical goals. Calcium carbonate should be taken during or after meals to ensure optimal absorption. Calcium carbonate can interfere with the absorption of other drugs, for example L-thyroxine, so special instructions should be given to the patient in this case. Calcium citrate also has the advantage of optimal absorption regardless of food intake.[1,17] Vitamin D deficiency is common in most clinical scenarios leading to hypocalcemia conditions. Vitamin D supplementation should be given in this condition. In subjects with good renal function, ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) can be selected to give. Patients who choose to avoid consumption of animal products should be aware that cholecalciferol is an animal product. The recommended regimen to achieve a 25-hydroxyvitamin D concentration of 25-30 ng/mL is giving 50,000 IU vitamin D weekly for 8-12 weeks. Ergocalciferol 50,000 IU daily can be administered safely for 5 days at the start of therapy in patients with severe vitamin D deficiency. Because of its long-term storage in fat, this form of vitamin D has a long tissue half-life (up to months) and toxicity may be difficult to anticipate and/or correct quickly. Hypercalcemia (if it occurs) can persist for weeks after vitamin D supplementation is discontinued. For this reason, administration of calcitriol (although the cost is greater than vitamin D), this drug is preferred by many doctors because its fast onset and offset work.[1,3,17]

Serum calcium, phosphorus, and creatinine along with measurements of urinary calcium excretion should be monitored regularly to avoid toxicity from calcium and vitamin D therapy. In patients with hypercalciuria (urine excretion of calcium > 300 mg/day), thiazide diuretics (along with a low salt diet) can be used to increase urinary calcium retention. The effective dose of hydrochlorothiazide is generally between 50 and 100 mg/day. Patients should be monitored for changes in serum kalium, natrium and magnesium. Soft tissue calcification and nephrocalcinosis can be prevented by keeping the serum calcium phosphate product below 55 mg/dL. Hyperphosphatemia can be managed by reducing the patient's intake of phosphate-rich foods (eg, meat, eggs, and dairy products) and if necessary, by oral phosphate binders (oral phosphate binders).[17]

Most patients will develop hypocalcemia following a thyroidectomy or parathyroidectomy due to hyperparathyroidism, which is usually transient. Prophylactic treatment with calcium after surgery is recommended. Administration of calcium can prevent severe symptomatic hypocalcemia in most cases. Calcium levels should be monitored closely after surgery and the calcium dose gradually reduced as indicated.[3]

Hypocalcemia in CKD is generally the result of a lack of vitamin D. This condition can be corrected by supplementing it with vitamin D or its active metabolite, calcitriol. Patients with significant vitamin D deficiency should be given ergocalciferol 50,000 units weekly for 8 to 12 weeks followed by cholecalciferol at a lower dose, ie, 1000 to 5000 units daily.[3]

PTH Linked to Vitamin D Metabolism

Calcium is important for many physiological processes, including blood clotting, platelet adhesion, neuromuscular activity, endocrine and exocrine secretory functions, and bone metabolism. The adult human body contains about 1000 g of calcium. About 40-50% of calcium in the blood is bound to plasma proteins, especially albumin. An equivalent amount is ionized or "free" and the remainder is complexed into phosphate, citrate, bicarbonate, and other ions. Only free calcium is physiologically active. Thus, it is a better indicator of the functional status of calcium metabolism than the total calcium level. The

normal range for ionized serum calcium concentration is 1.20-1.30 mmol/L.[17]

Regulation of ionized calcium concentration can be achieved mainly by the coordinated action of PTH and calcitriol at the three main sites of calcium transport, namely intestine, bone, and kidney (Figure 7). PTH and Vitamin D play important roles in calcium and phosphate homeostasis and the development and maintenance of healthy bones. PTH is the main stimulator of vitamin D synthesis in the kidney, while vitamin D provides negative feedback on PTH secretion. The main function of PTH is to maintain serum calcium within the normal range. PTH has a reciprocal effect on phosphate metabolism. Conversely, vitamin D has a stimulatory effect on calcium and phosphate homeostasis, which plays a key role in providing sufficient minerals for normal bone formation.[18]

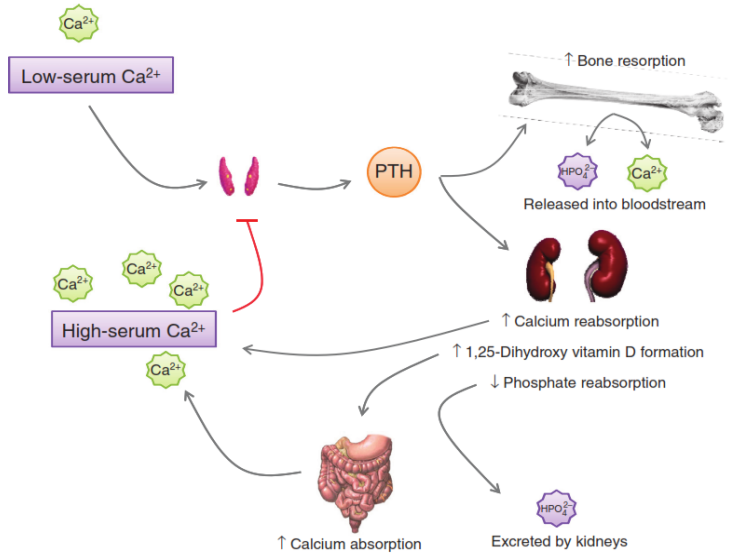

Figure 7. Regulation of Serum Calcium by PTH.[18]

Calcium-sensing receptors on the parathyroid cell surface constantly influence the extracellular ionized calcium concentration. Figure 7 describes the levels of Ca^{2+} Low serum levels will stimulate the synthesis and release of PTH from the parathyroid glands. PTH exerts effects on several target organs. The first organ is the skeleton, in which PTH enhances osteoclast-mediated bone resorption. This will lead to the release of Ca^{2+} and $HPOs_4^{2-}$ into the bloodstream. The next organ is the kidney, where PTH will increase Ca reabsorption^{2+} into the extracellular space of the distal convoluted tubule and decrease HPO_4^{2-} reabsorption from the proximal convoluted tubule. In addition, PTH also increases the activity of renal 1α-hydroxylase, which increases the conversion of 25-hydroxyvitamin D to its active form (calcitriol). Vitamin D is activated in the kidney by 1α-hydroxylase, causing increased Ca absorption^{2+} from the intestines. Ca^{2+} The recovered serum provides a negative feedback signal to the parathyroid glands, which stops PTH release.[17,18]

Vitamin D can be synthesized in the skin by breaking down the B ring of cholesterol through the medium of ultraviolet (UV) light. Animal sources of vitamin D are D3, and plant sources of vitamin D are D2. The two forms are basically equivalent in terms of biological activity. The clinical consequences of vitamin D deficiency are rickets/osteomalacia (lack of adequate minerals and osteoid), osteoporosis (reduced bone mass, reduced mineral and osteoid), secondary hyperparathyroidism, as well as muscle pain, weakness, bone pain, and fractures.[17]

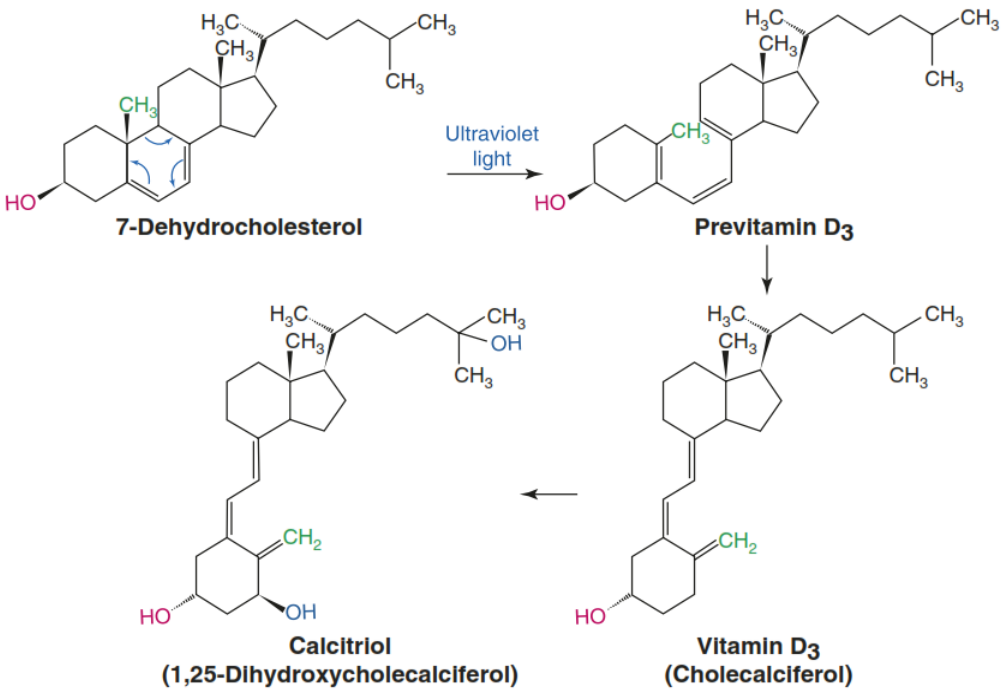

Figure 8. Vitamin D synthesis[19]

CONCLUSION

Hypocalcemia is one of the most common electrolyte disturbances and requires careful diagnosis and management. Some of the main factors that regulate calcium homeostasis in the body are PTH and vitamin D. Postoperative procedures on the neck (specifically: goiter) are the most common cause of hypoparathyroidism. In addition, autoimmune diseases and abnormal development of the parathyroid glands can be causes of hypoparathyroidism. Severe vitamin D deficiency results in hypocalcemia, which is associated with hypophosphatemia and hyperparathyroidism. Treatment of hypocalcemia can vary based on the severity and the underlying cause. The goal of treating hypocalcemia is to increase serum calcium within the normal range and to treat or minimize the symptoms it causes. Identifying the etiology of hypocalcemia is critical to establishing optimal management.

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