n the ionized form, 40% protein bound a decrease in total serum calcium, but they will not

Primary hyperparathyroidism and malignancy are responsible for greater than 90% of all cases of hypercalcemia. Compared with the hypercalcemia of malignancy, hyperparathyroidism tends to be associated with lower serum calcium levels (< 12 mg/dL) and a longer duration of hypercalcemia (more than 6 months). The hypercalcemic symptoms are usually fewer and subtle. Hyperparathyroidism tends to cause kidney calculi, hyperchloremic metabolic acidosis, and the characteristics of metabolic bone disease osteitis fibrosa cystica, but no anemia. In contrast, hypercalcemia of malignancy is typically rapid in onset, with higher serum calcium levels, and more severe symptoms. Patients so affected show marked anemia, but they never have kidney calculi or metabolic acidosis. Parathyroid hormone assay is the most useful test for differentiating hyperparathyroidism from malignancy and other causes of hypercalcemia. In hyperparathyroidism, serum parathyroid hormone levels will be elevated. In other cases, the high serum calcium concentration usually results in suppression of parathyroid hormone. Treatment of hypercalcemia should be started with hydration. Loop diuretics may be required in individuals with renal insufficiency or heart failure to prevent fluid overload. Calcitonin is administered for the immediate short-term management of severe symptomatic hypercalcemia. For long-term control of severe or symptomatic hypercalcemia, the addition of biphosphonate is typically required. Among intravenous bisphosphonates, zoledronic acid or pamidronate are the agents of choice. Glucocorticoids are effective in hypercalcemia due to lymphoma or granulomatous diseases. Dialysis is generally reserved for those with severe hypercalcemia complicated with kidney failure.

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physiologically active fraction. It is the main form

that is tightly regulated by the body. Fluctuations

in plasma protein levels may affect the total body

calcium without affecting the ionized calcium level.

As an example, hypoalbuminemic states such as

malnutrition or advanced liver disease may cause

necessarily present with symptoms of hypocalcemia.

Thus, the measured serum calcium concentration

INTRODUCTION

The total body calcium is distributed largely in 2 main compartments: 99% of the total body calcium is stored in the bone, while the rest is mostly found between the intracellular (1%) and extracellular (0.1%) fluid compartments. Calcium in the serum is 50% in the ionized form, 40% protein bound (mainly with albumin), and 10% as complexes to anions such as phosphate.¹⁻³ Ionized calcium is the

KIDNEY DISEASES 🛛 🕑

Hypercalcemia An Evidence-Based Approach to Clinical Cases

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Keywords. hypercalcemia, primary hyperparathyroidism, neoplasms, diagnosis, parathyroid hormonerelated protein, vitamin D, hypoalbuminemia



should be corrected for the abnormality in serum albumin concentration as calculated below⁴:

Corrected calcium $(mg/dL) = 0.8 \times [normal albumin (4.5 g/dL) - patient's albumin (g/dL) + patient's calcium (mg/dL)]$

Other factors that may affect the ionized form of calcium include acid/base disorders. Acidosis decreases protein binding and increases the ionized calcium.^{1,2,5} Alkalosis, on the other hand, increases protein binding and decreases the ionized calcium level.

ETIOLOGY AND DIAGNOSIS

The parathyroid glands are the major regulators of body calcium. An increase in the ionized calcium level stimulates the calcium-sensing receptor and acts via a negative feedback mechanism to cause a decrease in parathyroid hormone (PTH) secretion.² High magnesium levels can also stimulate the calcium-sensing receptor and decrease PTH secretion.² Parathyroid hormone increases serum calcium concentrations via 3 main mechanisms including (1) decrease in calcium excretion in urine by an increase in the renal tubular reabsorption of calcium, (2) stimulation of osteoclast-mediated resorption of bone which release calcium into serum, and (3) upregulation of $1-\alpha$ -hydroxylase enzyme which increases conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the proximal renal tubular cells which in turn increases intestinal calcium absorption.²

The vitamin D axis is the second important regulator of calcium homeostasis. Vitamin D3 is derived from dietary sources and conversion of cholesterol precursors in the skin via ultraviolet light. Vitamin D3 is converted to 25-hydroxyvitamin D3 in the liver. It is then transformed into the active form of vitamin D3 (1,25-dihydroxyvitamin D3) in the proximal renal tubular cells with the help of PTH. 1,25-dihydroxyvitamin D3 causes an increase of calcium and phosphate absorption in the intestines. It can also directly suppresses parathyroid cell function and increase bone turnover.²

If serum calcium concentrations remain elevated after correction for the low serum albumin level, or the patient has a high serum ionized calcium level, then further testing such as serum PTH, PTH-

related peptide (PTHRP), and 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D measurements are indicated (Figure). Hypercalcemia is usually defined as a plasma calcium concentration greater than 10.5 mg/dL.^{1,2} Hypercalcemia can occur when the concentration of calcium overwhelms the ability of the kidneys to maintain balance.⁷ Primary hyperparathyroidism is the most common cause of hypercalcemia in the general population.⁵ People with cancer often have hypercalcemia.8 Cancers of the breast, lung, head and neck, and kidney are frequently associated with hypercalcemia. It also occurs frequently in association with certain cancers of the blood, particularly malignant myeloma. Cancer causes hypercalcemia in 2 ways: when a tumor grows into the bone, it destroys bony tissue (osteolysis), and when the bone is not involved, factors secreted by cancer cells can increase calcium levels (humoral hypercalcemia of malignancy). The two mechanisms may operate at the same time. Because immobility causes an increase in the loss of calcium from bone, patients with cancer who are weak and spend most of their time in bed are more prone to hypercalcemia.⁹

Distinguishing between primary hyperparathyroidism and malignancy can be challenging, especially in the elderly. Both diseases are age related, and primarily, hyperparathyroidism is particularly common in elderly women. Often, the duration of hypercalcemia provides a useful clue for making the distinction. Patients with primary hyperparathyroidism usually reveal mild hypercalcemia a year or two before the present episode.^{1,2,5} If so, primary hyperparathyroidism would have been a much more likely cause, since hypercalcemia of malignancy tends to have a rapid course and usually occurs late in the disease. Hypercalcemic hyperparathyroidism tends to cause kidney calculi, peptic ulcer disease, and the characteristic metabolic bone disease osteitis fibrosa cystica, but no anemia.² In contrast, patients with hypercalcemia of malignancy never have kidney calculi, but often experience weight loss, marked anemia, and frequent episodes of serious or even life-threatening hypercalcemia.^{2,9} Few patients survive for more than 6 months after the onset, particularly those with breast cancer, which, after lung cancer, is the second most common malignancy causing hypercalcemia.^{2,9}

Serum chloride measurement may provide



Diagnostic approach to hypercalcemia which is a modified algorithm published in UptoDate online.⁶ PTH indicates parathyroid hormone; PTHRP, parathyroid hormone-related peptide; 1,25 VD; 1,25-dihydroxyvitamin D; 25 VD, 25-hydroxyvitamin D; Ca/C, calcium/creatinine; HP, hyperparathyroidism; SPE, serum protein electrophoresis; UPE, urine protein electrophoresis; and TSH, thyroid stimulating hormone.

useful diagnostic information.¹⁰ Since PTH causes bicarbonate wasting, most patients with primary hyperparathyroidism have mild hyperchloremic metabolic acidosis, with chloride levels of greater than 103 mEq/L. In contrast, most patients with hypercalcemia due to malignancy have serum chloride levels less than 100 mEq/L. However, serum chloride concentration is reliable only in patients with normal kidney function, as the value becomes unreliable in patients with impaired kidney function.

The most definitive test for distinguishing primary hyperparathyroidism from malignancy is a radioimmunoassay of intact PTH in the blood.¹⁰ Intact PTH is elevated in patients with primary hyperparathyroidism and is suppressed in patients with other causes of hypercalcemia. A low serum PTH level (< 20 pg/mL) in the setting of hypercalcemia indicates the need for further evaluation for other causes of hypercalcemia. In the absence of malignancy or increased PTHRP, additional laboratory studies including serum and urinary protein electrophoresis for possible multiple myeloma and measurement of the serum phosphate concentration, urinary calcium excretion, serum thyroid stimulating hormone, and vitamin A and vitamin D metabolites will often provide the correct diagnosis.^{1,2,5,10}

Other conditions can also cause hypercalcemia. Excessive intake of vitamin D increases intestinal absorption of calcium.¹¹ Overuse of calcium carbonate can cause milk-alkali syndrome and hypercalcemia.¹² Drugs such as lithium and thiazide diuretics can also cause hypercalcemia.^{13,14} Other rare causes of hypercalcemia include: thyrotoxicosis, sarcoidosis, Addison disease, rhabdomyolysis, and familial hypercalciuric hypercalcemia (an autosomal disorder characterized by hypercalcemia resulting from increased renal tubular calcium reabsorption).¹⁵⁻¹⁹

SIGNS AND SYMPTOMS

Many patients with mild hypercalcemia have no symptoms and the condition is discovered during routine laboratory screening.^{1,2,20} Gastrointestinal symptoms include loss of appetite, nausea, vomiting, constipation, and abdominal pain. There may be a blockage in the bowel. If the kidneys are involved, the individual will have to urinate frequently during both the day and night and will be very thirsty. As the calcium levels rise, the symptoms become more serious. Calculi may form in the kidneys and waste products can build up. Blood pressure rises, heart rhythm may change, and muscles become increasingly weak.²¹ The individual may experience mood swings, confusion, psychosis, and eventually, coma and death.

TREATMENT

Treatment of hypercalcemia depends on how high the calcium level is and what is causing the elevation.²² Hypercalcemia can be life-threatening and rapid reduction may be necessary.23 If the patient has normal kidney function, fluids can be given intravenously to clear the excess calcium. The amount of fluid taken in and eliminated must be carefully monitored. Drugs such as furosemide can be given after adequate fluid intake is established. These drugs inhibit calcium reabsorption in the kidneys and promote urine production. Drugs that inhibit bone loss, such as calcitonin, zolendronate acid, and pamidronate, are helpful in achieving long-term control.²⁴⁻²⁶ Anti-inflammatory agents such as steroids are helpful in patients with lymphoma or granulomatouse diseases and toxic levels of vitamin D. Dialysis is generally reserved for those with severe hypercalcemia complicated with kidney failure.²⁷

Treatment of the underlying cause of the hypercalcemia will also correct the imbalance. Hyperparathyroidism is usually treated by surgical removal of one or more of the parathyroid glands and any tissue, other than the glands themselves, that is producing excessive amounts of the hormone. The hypercalcemia caused by cancer is difficult to treat without controlling the cancer. Symptoms can be alleviated with fluids and drug therapy as outlined above.

CLINICAL QUIZ

The following clinical quiz was first published by the author in 2008 in a book entitled *Clinical Decisions in Pediatric Nephrology: A Problem-Solving Approach to Clinical Cases*,²⁸ and hereby is presented with some modification with the written permission of the publisher.

Case 1

You are asked to see a 19-year-old female college student in the emergency room with hypercalcemia and kidney failure. She notes the onset of mild polyuria and nocturia 6 to 8 months earlier. Headache, constipation, and malaise became apparent approximately 6 weeks earlier. She began using a tanning salon 4 weeks before. Yesterday, she visited her mother who noted that she was "not herself" and seemed confused. She brought her to the emergency room for evaluation. Past medical history is significant for passing a single kidney calculus 2 years before. She has a 1-year history of mild hypertension for which was treated with hydrochlorothiazide, 50 mg/d. She does not smoke or drink alcohol. She denies the use of any other medications or over-the-counter supplements. She denies any hormonal therapy and avoids all dairy products. On examination, she appears in no acute distress. Blood pressure is 140/92 mm Hg; Pulse, 86 per minutes; respiratory rate, 12 per minutes; body temperature, 37°C; body weight, 62.5 kg; and height, 159 cm. Heart rate is regular with no murmurs, the lungs are clear, the abdomen is soft with no masses, and there is no pitting edema. Neurological examination shows mild depression and some cognitive dysfunction. Laboratory studies show the following: hematocrit, 46%; leukocyte count, 5.6×10^9 /L; blood urea nitrogen, 61 mg/ dL; serum creatinine, 3.0 mg/dL; serum sodium, 140 mEq/L; serum potassium, 3.9 mEq/L; serum chloride, 101 mEq/L; serum bicarbonate, 22 mEq/L; serum calcium, 13.8 mg/dL; serum phosphate, 3.9 mg/dL; serum magnesium, 1.9 mg/dL; and serum albumin, 4.2 g/dL. Urinalysis shows trace protein, no glucose, no blood, 2 to 4 hyaline casts per highpower field, but no erythrocytes or leukocytes.

Question 1. Which of the following treatment modalities would you like to order now (select all that apply)?

(a). Calcitonin

- (b). Intravenous saline solution
- (c). Surgical consult
- (d). Mitramycin
- (e). Pamidronate/zoledronate

The correct answer is *b*. The initial treatment of symptomatic hypercalcemia should have 3 elements to provide some efficacy, both initially and several days later. Virtually all patients with significant hypercalcemia have some element of extracellular fluid volume contraction. For this reason, it is important to start therapy with intravenous saline.²³ Calcitonin is effective in approximately 70% of patients. It is safe and relatively nontoxic, and it acts to lower serum calcium within several hours. For this reason, it should be the initial agent of choice to provide some benefit before the more potent bisphosphonates become maximally effective.²⁴ It typically loses its effectiveness within 48 hours in most patients. For this reason, it is important to begin therapy with a bisphosphonate at this time, as well.

Bisphosphonates block the hypocalciuric effect of PTH. They act by interfering with metabolic activity of osteoclasts; they are cytotoxic to osteoclasts. Pamidronate, zoledronic acid, and etidronate are the currently available agents that are recommended for the treatment of malignancyassociated hypercalcemia. Zoledronate appears to be the most efficacious with a maximum effect occurring in 48 to 72 hours.²⁶

Question 2. Which of the following signs and symptoms are due to the effects of hypercalcemia per se (select all that that apply)?

- (a). Polyuria
- (b). Muscle weakness
- (c). Brand keratopathy
- (d). Shortening of the QT interval
- (e). Constipation
- (f). Shortness of breath
- (g). Cognitive dysfunction
- (h). Supraventricular tachycardia

The correct answers are *a*, *c*, *d*, *e*, and *g*. Chronic hypercalcemia leads to a defect in concentrating ability that may induce polyuria and polydipsia in up to 20% of patients. This is due to downregulation of aquaporin-2 water channels and activation of the normal calcium-sensing receptor in the loop of

Henle, which reduces sodium-chloride reabsorption in this segment and thereby impairs the interstitial osmotic gradient.²⁹

Hypercalcemia directly shortens the myocardial action potential, which is reflected in a shortened QT interval.³⁰ Band keratopathy, a reflection of subepithelial calcium phosphate deposits in the cornea, is a very rare finding in patients with hypercalcemia.³¹ It extends, as a horizontal band across the cornea in the area that is exposed between the eyelids. Calcium salts probably precipitates in that site because of the higher local pH induced by the evaporation of CO₂.

Constipation is the most common gastrointestinal complaint in patients with hypercalciuria. It is likely related to decreased smooth muscle tone.^{1,20} Personality changes and affective disorders have been described at a serum calcium level above 12 mg/dL. Confusion, organic psychosis, hallucinations, somnolence, and coma are seen until serum calcium concentration is above 16 mg/dL.^{1,20}

Question 3. Which of the following factors may be contributing to kidney failure at the initial presentation (select all that that apply)?

- (a). Extracellular fluid volume contraction
- (b). Hypercalcemia-induced renal vasoconstriction
- (c). Nephrocalcinosis
- (d). Granulomatous glomerulonephritis

The correct answers are *a*, *b*, *c*, and *d*. Mild hypercalcemia is only rarely associated with renal insufficiency. Higher elevations in serum calcium concentration (12 mg/dL to 15 mg/dL) can lead to a reversible fall in glomerular filtration rate that is mediated by direct renal vasoconstriction and natriuresis-induced volume contraction.³²

Long-standing hypercalcemia and hypercalciuria lead to the development of chronic hypercalcemic nephropathy, which may be irreversible and continue to progress despite cure of the underlying conditions such as hyperparathyroidism. Calcification, degeneration, and necrosis of the tubular cells lead to cell sloughing and eventual tubular atrophy and interstitial fibrosis and calcification.³³ These changes are most prominent in the medulla but can also be seen in the cortex.

Interstitial calcium deposition can be detected by radiographic imaging studies. Nephrocalcinosis that can be detected by plain radiography of the abdomen is advanced and reflects severe renal parenchymal involvement.³² Ultrasonography or computed tomography can detect earlier stages of the disease. An interstitial nephritis with granuloma formations is common in sarcoidosis, but the development of clinical disease manifested by renal insufficiency is unusual.

While the patient is receiving therapy and you are monitoring the serum calcium, it is time to begin ordering diagnostic studies.

Question 4. Which of the following would you order first (select all that apply)?

- (a). Parathyroid hormone level
- (b). Calcitriol level
- (c). Calcidiol level
- (d). Parathyroid hormone-related peptide level
- (e). Abdominal computed tomography
- (f). Abdominal flat plate
- (g). Bone marrow examination
- (h). Serum electrophoresis

The correct answers are *a*, *b*, and *f*. Diagnosis of primary hyperparathyroidism is always high on the list in an outpatient presenting with hypercalcemia.²⁰ Granulomatous disease is certainly a possibility given the hilar adenopathy and hypercalcemia of several years duration. Measurement of calcitriol is therefore a good idea.³⁴ An abdominal flat plate to look for nephrocalcinosis is reasonable in case of the history of kidney failure.

The PTH level was 2 pg/mL (reference range, 10 pg/mL to 65 pg/mL) and the 1,25-dihydroxyvitamin D (calcitriol) was 72 ng/mL (reference range, 9 ng/mL to 47 ng/mL). The abdominal flat plate shows bilateral nephrocalcinosis.

Question 5. Which of the following is the most likely diagnosis (select all that apply)?

- (a). Nephrocalcinosis
- (b). Primary hyperparathyroidism
- (c). Malignancy
- (d). Granulomatous disease
- (e). Milk-alkali syndrome
- (f). Ultraviolet light toxicity

The correct answers are *a*, *d*, and *f*. The elevated calcitriol and low PTH levels are consistent with

granulomatous disease.³⁴ There is hilar adenopathy on the radiography image which makes the diagnosis of sarcoidosis very likely. It is very unlikely that exposure to a tanning salon alone would lead to elevated calcitriol level as calcitriol production is normally feedback regulated. However, in a patient with a granulomatous disease where calcitriol production is not feedback regulated, increased production of calcidiol, 25-hydroxyvitamin D, would aggravate hypercalcemia.³⁴

Question 6. Which of the following would be appropriate as part of the therapeutic regimen for this patient (select all that apply)?

- (a). Low calcium diet
- (b). Low oxalate diet
- (c). Pamidronate
- (d). Low-dose corticosteroid therapy
- (e). Avoidance of tanning salon
- (f). Furosemide administration

The correct answers are *a*, *b*, *d*, and *e*. Treatment of hypercalcemia or hypercalciuria is aimed at reducing intestinal calcium absorption and calcitriol synthesis.^{17,18,22} This can be achieved by reducing calcium intake (no more than 400 mg/d), reducing oxalate intake, elimination of dietary vitamin D supplements, avoidance of sun exposure, and lowdose glucocorticoid therapy (prednisone, 10 mg/d to 30 mg/d). Serum calcium concentration typically begins to fall in 2 days, but the full hypocalcemic response may take 7 to 10 days depending upon the prednisone dose. Inhibition of calcitriol synthesis by the activated mononuclear cells is thought to play a major role in this response, although inhibition of intestinal calcium absorption and of osteoclast may also actively contribute.17,18,22

Concurrent restriction of dietary oxalate is required to prevent a marked increase in oxalate absorption and hyperoxaluria.³⁵ The latter may increase the risk of kidney calculus formation, even though urinary calcium excretion is reduced. Oxalate absorption is normally limited by the formation of insoluble calcium oxalate salts in the intestinal lumen. Dietary calcium restriction leads to more free oxalate than can then be absorbed if oxalate intake is unchanged.³⁵

Case 2

A 45-year-old woman returns for her annual

checkup. When seen last year, physical examination and laboratory studies showed no abnormality. Routine bone densitometry revealed low bone density (more than 2.5 standard deviations below normal) and she was placed on alendronate. She now returns with no complaints. Laboratory studies shows the following: hematocrit, 46%; blood urea nitrogen, 14 mg/dL; serum creatinine, 1.1 mg/dL; serum sodium, 140 mEq/L; serum potassium, 3.9 mEq/L; serum chloride, 105 mg/ dL; serum bicarbonate, 26 mEq/L; serum calcium, 11.3 mg/dL; serum phosphate, 3.4 mg/dL; serum magnesium, 1.9 mg/dL; and serum albumin, 4.2 g/ dL. Urinalysis shows trace protein, no glucose, no blood, no casts, and no erythrocyte or leukocyte. The 24-hour urinary calcium excretion is 463 mg. The PTH level is 57 pg/mL (reference range, 10 pg/mL to 65 pg/mL).

Question 1. What is the most likely diagnosis based upon the laboratory studies?

- (a). Familial hypovalciuric hypercalcemia
- (b). Primary hyperparathyroidism
- (c). Malignancy
- (d). Granulomatous disease
- (e). I am not sure, I would like to order a sestamibi scan for verification

The correct answer is *b*. A PTH level in the high normal range is inappropriate in a patient with hypercalcemia and indicates the presence of primary hyperparathyroidism. This occurs in 5% to 20% of patients with this condition.²⁰

Question 2. What would you like to do now?

- (a). Order a sestamibi parathyroid scan
- (b). Call the surgeon
- (c). Follow the patient and schedule follow-up in 6 months

The correct answer is *b*. This patient has primary hyperparathyroidism and fulfills the criteria for surgical removal of parathyroid glands, because his 24-hour urinary calcium excretion is greater than 250 mg and her serum calcium is greater than 1 mg/dL above the normal level.²⁰ The indications for surgery in patients with hyperparathyroidism include³⁵: (1) a serum calcium concentration of 1.0 mg/dL or more above the upper limit of normal, (2) hypercalciuria (urinary calcium excretion greater

than 400 mg/d) while having a usual diet, (3) a creatinine clearance 30% or more below the agematched normal level, (4) bone density at the hip, lumbar spine, or distal radius that is more than 2.5 standard deviations below peak bone mass (T score < -2.5), (5) age less than 50 years old, and (6) problem with periodic follow-up.

Case 3

A 38-year-old man with a positive human immunodeficiency virus test notes the onset of blurring of vision since several weeks before. Ophthalmology examination reveals white, fluffy retinal lesions, located close to the retinal vessels and associated with hemorrhage. Cytomegalovirus retinitis is diagnosed and he starts on intravenous therapy with foscarnet, 120 mg/kg twice daily, for 2 weeks, to be followed by maintenance therapy with an intravenous dosage of 90 mg/kg, once daily.

He complains of several episodes of numbness and tingling, particularly around his mouth with the first several treatment protocols. This morning, he experiences a generalized seizure immediately following completion of his treatment. Laboratory studies show the following: hematocrit, 28%; leukocyte count, 4.6×10^9 /L; blood urea nitrogen, 8 mg/dL; serum creatinine, 1.0 mg/dL; serum sodium, 140 mEq/L; serum potassium, 4.0 mEq/L; serum chloride, 106 mEq/L; serum bicarbonate, 25 mEq/L; serum calcium, 9.9 mg/dL; serum phosphate, 3.5 mg/dL; serum magnesium, 1.9 mg/ dL; and serum albumin, 3.7 mg/dL. His physicians are concerned and confused. His symptoms sound like hypocalcemia, but his serum calcium concentration and serum albumin level are within reference ranges.

Question. What would you recommend to be done next (select all that apply)?

- (a). Measure a PTH level
- (b). Reduce the foscarnet dose and measure serum ionized calcium at the end of the next infusion
- (c). Measure serum calcidiol level
- (d). Measure serum ionized magnesium level
- (e). Order computed tomography of the head
- (f). Check blood gas during the infusion

The correct answers are *b*, *e*, and *f*. Foscarnet



(trisodium phosphonoformate) has been shown to chelate calcium. The plasma ionized calcium (but not the total calcium) typically falls by 0.29 mmol/L with a 120 mg/kg dose. These changes are clinically significant and can be associated with paresthesia and seizures.³⁷ Acute respiratory alkalosis associated with hyperventilation due to pain or anxiety can also reduce the ionized calcium concentration. This is because the binding of calcium to protein is pH-dependent.

Case 4

A 15-year-old boy presents with hypercalcemia and a 6-month history of leukemia.

Question. The pathologic effects of his leukemia that results in hypercalcemia include which of the following mechanisms?

- (a). Increased bone resorption induced by prostaglandin production
- (b). Interleukin-6-induced bone resorption
- (c). Parathyroid hormone-related proteininduced increase in bone resorption and reduction in calcium excretion
- (d). Tumor necrosis factor-induced activation of osteoblast proliferation
- (e). Transforming growth factor-β induced increase in osetoclast activity

The correct answer is *c*. The pathophysiology underlying hypercalcemia of malignancy can be compared with its counterpart-primary hyperparathroidisim.^{5,10} Both syndromes are humoral in nature, with one being caused by PTH and the other by PTHRP.¹⁰ Both are associated with hypercalcemia, accelerated osteoclastic bone resorption, and reductions in renal phosphate reabsorption; both display increases in nephrogenous cyclic adenosine monophosphate excretion as a result of the interaction of PTH or PTHRP with the proximal tubular PTH/PTHRP receptor/adenyl cyclase complex.^{2,7}

CONFLCT OF INTEREST

None declared.

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