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TITLE: Hypercalcemia: Causes and Laboratory Investigation

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Slide 1:

Hello, my name is Qing Meng. I am the Section Chief of Clinical Chemistry Laboratories and

Professor in the Department of Laboratory Medicine, The University of Texas MD Anderson Cancer Center. Welcome to this Pearl of Laboratory Medicine on "**Hypercalcemia: Causes and Laboratory Investigation**."

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This talk is to:

- ❑ Provide brief review on calcium homeostasis
- ❑ Discuss causes of hypercalcemia
- ❑ Identify laboratory approach to hypercalcemia

Slide 3:

Calcium is the 5th most common element and the most prevalent cation in the body. There is approximately 1 kg of calcium in human body. Of this, 99% is distributed in bones, 1% in soft tissue and 0.1% in body fluids. In blood, virtually all of the calcium is in the serum or plasma, which is approximately 8.6-10.2 mg/dL with the ionized calcium concentration 1.13-1.32 mmol/L. The intracellular concentration of calcium is 10,000 times less than that in the extracellular fluid.

Calcium exists in three physiochemical states in plasma: approximately 50% is free or ionized calcium, which is the biologically active form, approximately 40% is bound to plasma proteins, and 10% is complexed with small anions such as bicarbonate, lactate, citrate and phosphate. Of the protein-bound calcium, approximately 80% is associated with albumin and 20% associated with globulins. The calcium binding to negatively charged proteins or anions is pH-dependent.

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Calcium homeostasis is mainly regulated by parathyroid hormone or PTH and 1,25 (OH)2 vitamin D. PTH is secreted by parathyroid glands in response to low serum ionized calcium.

The physiological function of calcitonin on calcium homeostasis is not significant. Pharmacological dose of calcitonin reduces blood concentration of calcium against the action of PTH.

Calcium homeostasis is mainly regulated by these three hormones through three organs: Bone, Kidneys, and Intestine.

Circulating calcium is excreted by glomerular filtration and reabsorbed in the proximal tubules.

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This table summarize the functions of the three hormones on calcium homeostasis.

PTH:

1). Increases bone resorption to release calcium and phosphate from bones.

2). Increases renal distal tubule reabsorption of calcium, inhibits tubular reabsorption of phosphate, activates 1 α-hydroxylase and stimulates conversion of 25(OH)D to 1,25(OH)2D in kidneys

3). Increased 1,25(OH)2D enhances calcium and phosphate absorption by intestine, and thus PTH indirectly acts on intestine for calcium absorption.

PTH response is very sensitive to changes in serum ionized Ca, either being secreted or shut off as appropriate, and PTH may be the only hormone responsible for min-to-min regulation.

1,25 (OH)2 Vitamin D maintain calcium homeostasis in 3 Ways:

1). It increases calcium and phosphate absorption by the small intestine.

2). Weakly increases calcium and phosphate resorption from the skeleton.

3). Weakly promotes the reabsorption of calcium ions by the kidney.

While Calcitonin decreases plasma calcium and phosphates by:

1). Inhibiting bone resorption, stimulating incorporation of calcium and phosphate to bone, against the effect of PTH on bone resorption.

2). Reducing reabsorption of calcium and phosphate by kidneys

Overall, the physiological role of calcitonin in calcium control is not clear. It may only respond to a fairly large increase in ionized Ca (~10%). It is used clinically in treatment of hypercalcelmia and in certain bone diseases by suppressing bone resorption. It is more important in regulating bone remodeling than in Ca^{2+} homeostasis.

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There are numerous factors can cause hypercalcemia including preanalytical, analytical, biological, and pathological.

For preanalytical errors, these include:

Tourniquet use and venous occlusion: which is associated with increased-protein bound calcium or total calcium but not ionized calcium

- Fist clenching or forearm exercise that can decrease pH and increase in ionized calcium
- Hyperventilation causing respiratory alkalosis reduces ionized calcium without change of total calcium
- Changes in posture such as standing decreases intra-vascular water and increases protein concentration and thus total calcium
- Prolonged immobilization and bed rest increase both total and ionized calcium levels
- Contamination with calcium from corks, glassware, tubes, and drywall increases calcium levels

There are also analytical interferences such as hemolysis, icterus, lipemia on Spectrophotometer or ISE.

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There are a number of pathological disorders can cause hypercalcemia.

These are:

- Increased parathyroid hormone (PTH): due to

Primary hyperparathyroidism

Sporadic, familial, multiple endocrine neoplasia 1 (MEN 1) or MEN 2A

Secondary and Tertiary hyperparathyroidism

Coexisting malignancy and primary hyperparathyroidism

Ectopic PTH in malignancy (though very rare)

- Malignancy: which is characterized as

Humoral hypercalcemia of malignancy as mediated by

Parathyroid hormone-related protein (PTHrP)

Local osteolysis in multiple myeloma

Other malignancy such as breast cancer, lung cancer

- Increased Vitamin D, mainly 1,25[OH]2vitamin D**:**

Granulomatous disease: sarcoidosis, tuberculosis, berylliosis, coccidioidomycosis: Vitamin D intoxication

Vitamin D supplements, vitamin D metabolites or analogs

Lymphoma (1,25[OH]2D)

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- Renal Failure, for example

Chronic renal failure with treatment with calcium and 1,25[OH]2D or VitD analogs

Recovery phase of Rhabdomyolysis and acute renal failure

Renal transplant

Other Endocrine Diseases such as

Hyperthyroidism (Thyrotoxicosis)

Adrenal insufficiency

Acromegaly

Pheochromocytoma

Medications: include

Thiazide diuretics

Lithium-related release of PTH

Milk–alkali syndrome (calcium and antacids)

Vitamin A intoxication

Theophyline

Other causes such as:

Immobilization with high bone turnover (e.g., Paget's disease, bedridden child)

Familial hypocalciuric hypercalcemia

Williams Syndrome

Hyperphosphatemia

Acute hypomagnesemia

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In general,

- Primary hyperparathyroidism and cancer account for 90% of cases of hypercalcemia
- For Outpatients
  - 90% of the cases have primary hyperparathyroidism
- For Inpatients
  - 65% of the cases have cancer
  - 25% of the cases are due to primary hyperparathyroidism

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In Primary Hyperparathyroidism, the increased calcium levels are due to excessive PTH secretion from parathyroid adenoma (90%) or hyperplasia multiple gland enlargement (10%) including MEN 1, MEN 2A, Familial hyperparathyroidism, Carcinoma (<1%), and familial benign hypercalcemia (FBH).

The pathophysiological change of hypercalcemia is related to combined effects of excessive secretion of PTH and production of 1,25-(OH)2-vitamin D.

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Primary hyperparathyroidism (PHPT) is diagnosed based on:

- Intact PTH and chemistry panel
  - PTH is elevated despite elevated serum calcium
  - Serum phosphate is in the low-normal to mildly decreased range
  - Serum ALP increased, and with hyperchloremic metabolic acidosis
- Urine calcium is normal to slight increase
- 24-hour urine calcium excretion is
  - Used to rule out familial hypocalciuric hypercalcemia
  - Values below 100 mg/24 hours or a calcium creatinine clearance ratio of < 0.01 are suggestive of familial hypocalciuric hypercalcemia (FHH)
- Whether to use ionized calcium versus serum total calcium: there is still a debate….*some labs do and some labs only use total calcium as there is approximate correlation with the ionized calcium*. Also some labs especially in Europe use
  -Corrected serum calcium: there are many equations but here is the one calculated as: Serum calcium (mg/dL) +

0.8 [4-albumin (g/dL)]

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The Hypercalcemia of Malignancy is attributed to excessive bone resorption by one of three mechanisms.

- Humoral hypercalcemia of malignancy: over-expression of PTH-related protein (PTHrP) affects bone and kidney similar to PTH. Increased expression of PTH-rP is seen in
  - Squamous cell carcinoma: lung, head and neck, esophagus, cervix, etc.
  - Carcinoma: ovarian, breast, renal, etc.

- Increased 1,25-(OH)2-D synthesis by lymphomas

- Local osteolytic hypercalcemia in multiple myeloma, this accounts for 20% of all hypercalcemia of malignancy

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A number of laboratory tests can be used for assessment of hypercalcemia. These include:

Serum total calcium: which is valuable as a screen and monitoring ambulatory persons.

Ionized calcium: which is more accurate assessment of calcium status

Albumin: corrected calcium

PTH:

25 (OH)vitamin D and 1,25 (OH)2D:

Acid-base status

Electrolytes, Magnesium, Bicarbonate

Serum BUN and creatinine

Serum phosphate

Serum (urine) protein electrophoresis

24 hour urinary calcium, calcium to creatinine ratio

Urine creatinine

Urinary cyclic adenosine monophosphate (cAMP): cAMP is increased in primary hyperparathyroidism

PTHrP: is ordered in suspected malignancy

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More specifically, the following Initial laboratory tests should be ordered:

- Total Calcium: is reliable

  You may correct calcium value if albumin decreased:

  - Corrected Ca = Ca (mg/dl) + 0.8 (4-albumin [g/dl])

- If calcium elevated above 11.0 mg/dL – then order intact PTH

Along with other tests such as:

- Ionized calcium
- Electrolytes– including BUN and creatinine
- Phosphorus

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If PTH is:

- Elevated or normal – suggests hyperparathyroidism (elevated calcium should suppress PTH); then order 24-hour urine calcium
  - If urine calcium is High – suggestive of primary hyperparathyroidism
  - If Low (<50-100 mg) – then familial hypocalciuric hypercalcemia (FHH)
- If PTH is Low – then order PTHrP or consider other testing for vitamin D excess, milk-alkali syndrome, and hyperthyroidism

If PTHrP is:

- Low or normal – order vitamin D: 25-(OH)D and 1,25-(OH)2D
  - If Vitamin D level is High – suggestive of lymphoma or granulomatous disease (sarcoidosis, Wegener granulomatosis, Tuberculosis)
  - If Low – consider testing for cancer

- If PTHrP is High – it is suggestive of cancer

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If needed, additional tests or exanimations should be performed.

For example:

- Chest X-ray: for lung cancer or metastases, sarcoidosis, or tuberculosis
- Renal function test: for renal failure, milk-alkali syndrome, or renal impairment in primary hyperparathyroidism or myeloma
- Complete blood count: in hematological malignancy or anemia
- Erythrocyte sedimentation rate or CRP: may be increased in cancer
- Serum alkaline phosphatase: may be increased in primary hyperparathyroidism, Paget's disease with immobilization, myeloma, or bone metastases
- Liver function tests: for liver metastases; chronic liver failure is also a rare cause of hypercalcemia.
- Thyroid function tests: for Thyrotoxicosis
- Serum cortisol: though Addison's disease is a rare cause.

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Here is the algorithm we have developed for the investigation of hypercalcemia. Due to time constraint, I won't repeat as most of the tests and procedures we have already discussed.

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In Summary:

- Primary hyperparathyroidism and cancer are the most common causes of hypercalcemia
- Intact PTH is the most important test in the differential diagnosis of hypercalcemia
- 24 hour urine calcium and calcium to creatinine ratio are helpful
- PTHrP should be measured if cancer is suspected
- Tests for other causes of hypercalcemia should be ordered for differential diagnosis
- An investigation algorithm should be established in each institution

Slide 19: References

Slide 20: Disclosures

Slide 21: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Hypercalcemia: Causes and Laboratory Investigation**."