

HYPERCALCEMIA AND ECG FEATURES

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Hypercalcemia is defined as a higher-than-normal level of calcium in the blood usually more than 10.5 milligrams per deciliter of blood. It is the most common life-threatening metabolic disorder associated with cancer. The reference range of serum calcium levels is 8.7-10.4 mg/dL, with somewhat higher levels present in children. As much as 99% of the body's calcium is stored in bone tissue. A healthy person experiences a constant turnover of calcium as bone tissue is built and reshaped. The remaining 1% of the body's calcium circulates in the blood and other body fluids. Calcium in the blood plays an important role in the control of many body functions, including blood clotting, transmission of nerve impulses, muscle contraction, and other metabolic activities. Approximately 40% in the blood is bound to protein, primarily albumen, while 50% is ionized and is in physiologic active form. The remaining 10% is united to anions.

Hypercalcemia is a disorder that most commonly results from malignancy or primary hyperparathyroidism. Other causes of elevated calcium are less common and usually are not considered until malignancy and parathyroid disease are ruled out. Hypercalcemia can cause a number of nonspecific symptoms, including anorexia, nausea, polydipsia, fatigue, muscle weakness, restlessness, and confusion. Patients with hypercalcemia have a markedly greater risk of dying from cardiovascular disease than normocalcemic age- and sex-matched controls. The diagnosis of hypercalcemia often is made incidentally in asymptomatic patients. Clinical manifestations affect the neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular systems. Cardiovascular findings in hypercalcemic patients sometimes but not always include characteristic ECG changes, mainly short QoT, QaT, and QeT intervals which are measured from the beginning of the QRS complex to the origin (O), apex (A), and the end (E) of the T wave, respectively, left ventricular hypertrophy, and myocardial calcification. **(Rayner HC, Hasking DJ. Hyperparathy-**

roidism associated with severe hypercalcaemia and myocardial calcification despite minimal bone disease. Br Med J (Clin Res Ed). 1986; 293:1277-1278.). Furthermore, these subjects have a higher incidence of angina pectoris and calcification of the heart valves. Baseline screening for hypercalcemia should include ECG and echocardiography. Hypercalcemic crisis does not have an exact definition, although marked elevation of serum calcium, usually more than **14 mg/dL**, is associated with acute signs and symptoms of hypercalcemia. Treatment of the elevated calcium level may resolve the crisis.

Excessive intake of calcium may cause muscle weakness and constipation, affect the conduction of electrical impulses in the heart, lead to calcium stones (nephrocalcinosis), in the urinary tract, impair kidney function, and interfere with the absorption of iron predisposing to iron deficiency.

Etiologies of Hipercalcemia

Prevalence: Hypercalcemia affects from 0.1 to 1% of the population. The widespread ability to measure blood calcium since the 1960s has improved detection of the condition, and today most patients with hypercalcemia have no symptoms.

Hypercalcemia types:

Hypercalcemia is divided into PTH-mediated hypercalcemia (primary hyperparathyroidism) and non-PTH-mediated hypercalcemia. Women over the age of 50 are most likely to be hypercalcemic, usually due to primary hyperparathyroidism.

Primary hyperparathyroidism (pHPT): is the unregulated overproduction of PTH resulting in abnormal calcium homeostasis. In most primary hyperparathyroidism cases, the calcium elevation is caused by increased intestinal calcium absorption. This is mediated by the PTH-induced calcitriol synthesis that enhances calcium absorption. The increase in serum calcium results in an increase in calcium filtration at the kidney. Because of PTH-mediated absorption of calcium at the distal tubule, less calcium is excreted than might be expected.

In PTH-mediated hypercalcemia, bones do not play an active role because most of the PTH-mediated osteoclast activity that breaks down bone is offset by hypercalcemic-induced bone deposition. Hypercalcemia of this disorder may remain mild for long periods because some parathyroid adenomas respond to the feedback generated by the elevated calcium levels. The measurement of circulating PTH in the serum is the most direct and sensitive measure of parathyroid function. A reference range is 2-6 pmol/L. A nonsuppressed PTH level in the presence of hypercalcemia suggests a diagnosis of primary hyperparathyroidism. If the PTH level is suppressed in the face of an elevated calcium level, hyperparathyroidism is unlikely. If laboratory evidence of primary hyperparathyroidism is present, CT scan of the head, MRI, ultrasound, or nuclear parathyroid scans may be helpful. Preoperative diagnostic imaging is essential in patients with previous neck surgery.

In approximately 85% of cases, primary hyperparathyroidism is caused by a single adenoma. In 15% of cases, multiple glands are involved (ie, either multiple adenomas or hyperplasia). Rarely, primary hyperparathyroidism is caused by parathyroid carcinoma. The etiology of adenomas or hyperplasia remains unknown in most cases. Familial cases can occur either as part of the multiple endocrine neoplasia syndromes (MEN 1 or MEN 2a), hyperparathyroid-jaw tumor (HPT-JT) syndrome, or familial isolated hyperparathyroidism (FIHPT). Familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism also belong to this category. The molecular genetic basis of MEN 1 is an inactivating mutation of the *MEN1* gene, located on chromosome band 11q13. MEN 2a is caused by a germline mutation of the *Ret* proto-oncogene on chromosome 10. Germline mutation of *HRPT2* localized on chromosome arm 1q is responsible for HPT-JT, while FIHPT is genetically heterogeneous.

Hypertension is often present in primary hyperparathyroidism (33%) without concomitant disease of the kidney. Blood pressure became normal in approximately 10% of cases after parathyroidectomy. **(Cottino A, Marcolongo M, Osella D, et al. The electrocardiogram and arterial hypertension in primary hyperparathyroidism *Minerva Med.* 1979;70:959-964.)**

X-linked hypophosphatemia (XLH):

This genetic entity may result in hypercalcemia, hypercalciuria, nephrocalcinosis, and hyperparathyroidism. Patients with XLH should be monitored closely for the development of hypertension and left ventricular hypertrophy. An abnormal increase in diastolic blood pressure occurs at all levels of work load in XLH patients. (*Nehgme R, Fahey JT, Smith C, et al. Cardiovascular abnormalities in patients with X-linked hypophosphatemia. J Clin Endocrinol Metab. 1997; 82:2450-2454.*)

Familial hypocalciuric hypercalcemia (FHH)

A genetic mutation that affects the body's ability to regulate calcium is seen in familial hypocalciuric hypercalcemia a benign (non-cancerous) condition. FHH is caused by heterozygous inactivation of the calcium-sensing receptor, which is notably expressed in parathyroid and kidney. FHH is characterized by asymptomatic hypercalcemia and hypophosphatemia and confers minimal, if any, morbidity. High extracellular calcium levels activate the receptor resulting in modulation of several signaling pathways depending on the target tissues. Mutations in the CASR gene can result in gain or loss of receptor function. Gain of function mutations are associated to Autosomal dominant hypocalcemia and Bartter syndrome type V, while loss of function mutations are associated to Familial hypocalciuric hypercalcemia and Neonatal severe hyperparathyroidism. More than one hundred mutations were described in this gene. In addition to calcium, the receptor also interacts with several ions and polyamines. The CASR is a potential therapeutic target to treatment of diseases including hyperparathyroidism and osteoporosis, since its interaction with pharmacological compounds results in modulation of PTH secretion.

Hypercalcemia related to malignancies: Hypercalcemia is a common metabolic disorder, especially in the elderly. The most common etiologies are hyperparathyroidism or malignancy, most often of the lung, breast, kidney, multiple myeloma or hematological system diseases: hypercalcemia frequently occurs in the course of Adult T-cell leukemia/lymphoma (ATLL). Hypercalcemia associated with malignancy commonly is the result of advanced breast or lung cancer (Consider hypercalcemia in patients with multiple nonspecific complaints and an

associated lung mass.), or parathyroid carcinoma, and is caused by increased osteoclastic activity within the bone. It is a paraneoplastic hypercalcemia. **(Badertscher E, Warnica JW, Ernst DS. Acute hypercalcemia and severe bradycardia in a patient with breast cancer. *CMAJ*. 1993;148: 1506-1508.)** **(Dolgos J, Patakfalvi A, Kosa D, Farkas M, Tarsoly L. Hyperparathyroidism simulating severe hypercalcemia syndrome *Orv Hetil*. 1991;132:1369-1372.)**. Patients with multiple myeloma often present with vague, common symptoms such as back pain, bony pain, fatigue, and anemia. Other elements of the disease are hypercalcemia, pathological fractures, osteopenia, and renal failure.

Nonmetastatic (humoral-induced) - Ovary, kidney, lung, head and neck, esophagus, cervix, lymphoproliferative disease, multiple endocrine neoplasia, pheochromocytoma, and hepatoma.

Prognosis of hypercalcemia associated with malignancy is poor; the 1-year survival rate is 10-30%. Hypercalcemia is the most common life-threatening metabolic disorder associated with neoplastic diseases, occurring in an estimated 10% to 20% of all adults with cancer. It also occurs in children with cancer, but with much less frequency (approximately 0.5%-1%). The fundamental cause of cancer-induced hypercalcemia is increased bone resorption with calcium mobilization into the extracellular fluid and, secondarily, inadequate renal calcium clearance. Two types of cancer-induced hypercalcemia have been described: osteolytic and humoral hypercalcemia. Osteolytic hypercalcemia results from direct bone destruction by primary or metastatic tumor. Humoral hypercalcemia is mediated by circulating factors secreted by malignant cells without evidence of bony disease. It is now believed that hypercalcemia results from the release of factors by malignant cells that ultimately cause calcium reabsorption from bone.

One such factor is a PTH-like protein known as parathyroid hormone-related protein or peptide (PTHrP). PTHrP is a primitive protein that appears to have important roles in calcium transport and developmental biology. It shares partial amino acid sequence and conformational homology with normal PTH, binds with the same receptors on skeletal and renal target tissues, and affects calcium and phosphate homeostasis, as does PTH. Increased blood levels of PTHrP have been found in patients with solid tumors but not in patients with

hematologic malignancies who develop hypercalcemia. These tumors produce PTH-related peptide (PTHrP) which increases blood calcium. Circulating growth factors may also mediate hypercalcemia. Potential mediators include transforming growth factor- α and - β , interleukin-1 and -6, and tumor necrosis factor (TNF)- α and - β .

Several clinical symptoms are associated with cancer-related hypercalcemia. Symptoms may appear gradually and often look like signs of other cancers and diseases. The symptoms of hypercalcemia are not only related to the elevated level of calcium in the blood, but—more importantly—to how rapidly the hypercalcemia develops. The severity of the symptoms is often dependent upon factors such as previous cancer treatment, reactions to medications, or other illnesses a patient may have. Most patients do not experience all of the symptoms of hypercalcemia, and some may not have any signs at all. Rapid diagnosis of hypercalcemia may be complicated because the symptoms are often non-specific and are easily ascribed to other factors. These symptoms include: decreased muscle tone and muscle weakness, delirium, disorientation, incoherent speech, and psychotic symptoms such as hallucinations and delusion, constipation, fatigue, anorexia, nausea and/or vomiting, polyuria and polydipsia and pain.

Lithium-associated hypercalcemia The drug lithium, used in treating bipolar disorder, may increase PTH release and cause hypercalcemia. Little notice has been paid in the surgical literature to problems with psychoeffective lithium, which by interfering with adenylate cyclase affects thyroid and parathyroid function, causing hypercalcemia, hyperparathyroidism, and hypothyroidism. (Wolf ME, Ranade V, et al. Hypercalcemia, arrhythmia, and mood stabilizers. *J Clin Psychopharmacol.* 2000; 20:260-264. (Wolf ME, Moffat M, Ranade V, Somberg JC, Lehrer E, Mosnaim AD. Lithium, hypercalcemia, and arrhythmia. *J Clin Psychopharmacol.* 1998; 18:420-423.)

Vitamin D intoxication (Ashizawa N, Arakawa S, Koide Y, et al. Hypercalcemia due to vitamin D intoxication with clinical features mimicking acute myocardial infarction. *Intern Med.* 2003;42:340-344.)

Hypervitaminosis D symptoms appear several months after excessive doses of vitamin D are administered. An excess of vitamin D causes abnormally high blood concentrations of calcium, which can eventually cause severe damage to the bones, soft tissues, and kidneys. The clinical manifestations of this intoxication are dehydration, vomiting, polydipsia, polyuria, anorexia, irritability, constipation and fatigue. Is observed kidneys disorders (65.0%), with kidney damage and kidney stones (secondary to hypercalciuria) and renal insufficiency (51.0%), gastrointestinal tract disorders (23.0%), arterial hypertension (52.0%). are observed in vitamin D intoxication.

Milk-alkali syndrome, milk-drinker's syndrome or Burnett's syndrome

This syndrome is caused by excessive consumption of milk (which is high in calcium) and soluble alkali-like antacids, especially sodium bicarbonate (baking soda) over a prolonged period of time. It is an acquired condition including high levels of calcium (hypercalcemia) and a shift in the body's acid/base balance towards alkaline metabolic alkalosis. Milk-alkali syndrome is often a side effect of treating a peptic ulcer. Nausea, headache, weakness, confusion, and kidney damage with renal insufficiency, may result. A complex of symptoms associated with prolonged excessive intake of milk and soluble alkali, including hypercalcemia, metabolic alkalosis, conjunctivitis, and calcinosis. The ECG reveal sometimes a shortened QT interval, a J wave, a broad T wave, and a U wave (**Jenkins JK, Best TR, Nicks SA, Milk-alkali syndrome with a serum calcium level of 22 mg/dl and J waves on the ECG. South Med J. 1987; 80:1444-1449.**)

Cardiac sarcoidosis and others Granulomatous disorders

High levels of calcitriol may be found in patients with sarcoidosis, berylliosis, tuberculosis, leprosy, coccidioidomycosis, and histoplasmosis. Iatrogenic disorders of calcium levels may increase secondary to the ingestion of many medications. **Chapelon-Abric C, de Zuttere D, Duhaut P, Veyssier P, Wechsler B, Huong DL, de Gennes C, Papo T, Bletry O, Godeau P, Piette JC. Cardiac sar-**

coidosis: a retrospective study of 41 cases. *Medicine (Baltimore)*. 2004;83:315-334.

Liver granulomatosis is not an exceptional cause of hypercalcemia with hypoparathyroidism in dialysis patients. The biological pattern of low bone turnover disease (hypercalcemia and normal intact PTH) associated with cholestasis should evoke liver granulomatosis, which should be confirmed by a liver biopsy and lead to a treatment by corticosteroids. The masking effect of previous corticoid therapy for transplantation should be pointed out. Serial monitoring of plasma calcitriol show a relation between decreasing high normal calcitriol with prednisone and normalization of calcemia, suggesting the role of inappropriate synthesis of calcitriol by the granuloma. Liver granulomatosis should be looked for in dialysis patients on the association of unexplained hypercalcemia and normal PTH with anicteric cholestasis, and confirmed by a liver biopsy. Although still of unknown etiology, its evolution is favorable under corticotherapy. (**Hardy P, Moriniere PH, Tribout B, et al. Liver granulomatosis is not an exceptional cause of hypercalcemia with hypoparathyroidism in dialysis patients. *J Nephrol*. 1999; 12:398-403.**)

Tertiary hyperparathyroidism is a state of excessive secretion of (PTH) after a long period of secondary hyperparathyroidism and resulting in hypercalcemia. When the hyperparathyroidism can not be corrected by medication one calls it tertiary hyperparathyroidism. The treatment of choice is surgical removal of one or more parathyroidal glands. However the basis of treatment is still prevention in chronic renal failure, starting medication and dietary restrictions long before dialysis treatment is initiated.

Post renal transplant and initiation of chronic hemodialysis: Bone disease is a common clinical problem following renal transplantation. In renal transplant recipients, multiple underlying factors determine the extent of bone loss and the subsequent risk of fractures. In addition to the well-recognized risk to bone disease posed by steroids, calcineurin inhibitors and pre-existing bone disease, persistent hyperparathyroidism contributes to post-transplant bone loss. Hyperparathyroidism is usually treated with vitamin D supplements combined with calcium. Patients whose hyperparathyroidism is associated with hypercalcemia

pose a difficult therapeutic dilemma which often requires parathyroidectomy. Cinacalcet, a calcium mimetic agent, offers a unique pharmacologic approach to the treatment of patients with post-transplant hypercalcemia and HPT.

Male gender, high levels of blood urea nitrogen, beta2-microglobulin (beta2MG), hypercalcemia, and hyperphosphatemia are identified as independent risk factors for the development of severe pruritus in chronic hemodialysis patients, whereas a low level of calcium and intact-parathyroid hormone were associated with reduced risk. Severe uremic pruritus caused by multiple factors, not only affects the quality of life but may also be associated with poor outcome in chronic hemodialysis patients. (**Narita I, Alchi B, Omori K, et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. *Kidney Int.* 2006; 69:1626-1632.)**

Immobilization: It is an frequently unrecognized cause of recurrent hypercalcemia. Immobilization hypercalcemia must be considered after the exclusion of other discernible causes and frequently is successfully treated with rehabilitative exercises and bisphosphonates. Clinical alertness to immobilization as a possible cause of hypercalcemia may avoid unnecessary and invasive examinations, life-threatening complications and annoying recurrences. (**Cheng CJ, Chou CH, Lin SH. An unrecognized cause of recurrent hypercalcemia: immobilization. *South Med J.* 2006; 99:371-374.**). Prolonged immobilization or physical inactivity has been shown to produce increased bone resorption due to enhanced osteoclastic activity and diminished bone formation. These skeletal changes are a typical complication in tetraplegic patients, who are at risk of developing hypocalcemia. Hypercalciuria is the most characteristic symptom. However, some patients develop hypercalcemia, which is infrequent in these patients, and the hypercalcemia can become a life-threatening complication. Until now, it has been unclear why a small percentage of immobilized patients develop hypercalcemia. Treatment with pamidronate (Aredia) reduced the serum calcium to normal values.

Hypophosphatemia: It is observed in patients with total parenteral nutrition. Prevalence of hypophosphatemia in postoperative patients with total parenteral nutrition is high and needs timely monitoring. Factors related to hypophos-

phatemia are hypokalemia, hypomagnesemia, hypercalcemia, female sex, neoplasia, 96-hour postoperative period and duration of nutrition.(**Martinez MJ, Martinez MA, Montero M, et. al. Hypophosphatemia in postoperative patients with total parenteral nutrition: influence of nutritional support teams. Nutr Hosp. 2006; 21:657-660.**)

Miscellaneous: primary infantile hyperparathyroidism, Williams syndrome, (**Bragg K, Fedel GM, DiProsperis A. Cardiac arrest under anesthesia in a pediatric patient with Williams syndrome: a case report. AANA J. 2005; 73:287-293.**), AIDS, and advanced chronic liver disease

ECG FEATURES IN HYPERCALCAEMIA

Hypercalcemia may produce ECG abnormalities related to altered trans-membrane potentials that affect conduction time. QT interval shortening is common secondary to absence of the ST segment. The QoT, QaT, and QeT intervals which are measured from the beginning of the QRS complex to the origin (O), apex (A), and the end (E) of the T wave, respectively are very short. At very high levels, the QRS interval may lengthen, T waves may flatten or invert, and a variable degree of heart block may develop.

Heart rate (HR) Symptomatic sinus node dysfunction: It is very rarely observed. **Shah AP, Lopez A, Wachsner RY, et.al.Sinus node dysfunction secondary to hyperparathyroidism. J Cardiovasc Pharmacol Ther. 2004;9:145-147.** There is description of tachy-brady syndrome. (**Carpenter C, May ME, Case report: cardiotoxic calcemia.Am J Med Sci 1994; 307: 43-44.**);

PR or PQ interval is prolonged in some cases. The PQ interval tended to be prolonged in the case of hypercalcemia, but the change was statistically insignificant. (**Saikawa T, Tsumabuki S, Nakagawa M, QT intervals as an index of high serum calcium in hypercalcemia. Clin Cardiol. 1988;11:75-78.**)

ST segment: Absence of the ST segment or almost absent is the rule. **ST** reduce or retrench in length or duration. When ST is present could be depressed

or with ST segment elevation mimicking acute myocardial infarction. (**Nishi SP, Barbagelata NA, Atar S, Birnbaum Y, Tuero E. Hypercalcemia-induced ST-segment elevation mimicking acute myocardial infarction. *J Electrocardiol.* 2006 Jul;39(3):298-300.**) (**Littmann L, Taylor L 3rd, Brearley WD Jr. ST-segment elevation: a common finding in severe hypercalcemia. *J Electrocardiol.* 2007;40:60-62.**) (**Turhan S, Kilickap M, Kilinc S ST segment elevation mimicking acute myocardial infarction in hypercalcaemia. *Heart.* 2005;91:999.**) (**Ashizawa N, Arakawa S, Koide Y, ET AL . Hypercalcemia due to vitamin D intoxication with clinical features mimicking acute myocardial infarction. *Intern Med.* 2003; 42:340-344.**) J point is the isoelectric union of QRS complex with ST segment. It represents the end of depolarization and the beginning of repolarization. Prominent and positive J point level is named J wave, considered typical but not pathognomonic of severe hypothermia, because it has also been described in hypercalcemia **Carrillo-Esper R, Limon-Camacho L, Vallejo-Mora HL, et al. Non-hypothermic J wave in subarachnoid hemorrhage *Cir Cir.* 2004;72:125-129.** and others clinical circumstances: Non-hypothermic J wave or the "normothermic" Osborn wave (**Otero J, Lenihan DJ. The "normothermic" Osborn wave induced by severe hypercalcemia. *Tex Heart Inst J.* 2000;27:316-317**): . Electrocardiographic J wave could be result of hypercalcemia aggravated by thiazide diuretics (**Topsakal R, Saglam H, Arinc H, Eryol NK, Cetin S. Electrocardiographic J wave as a result of hypercalcemia aggravated by thiazide diuretics in a case of primary hyperparathyroidism. *Jpn Heart J.* 2003;44(6):1033-1037.**;

T wave becomes flatten or invert in hypercalcemia. Secondly, flattened or biphasic T waves are prominent in moderate to severe hypercalcemia, mimicking those seen in myocardial ischemia (**Douglas PS, Carmichael KA, Palevsky PM. Extreme hypercalcemia and electrocardiographic changes. *Am J Cardiol* 54: 674–675, 1984.**). Changes in T wave morphology, polarity, and amplitude either appeared with development of hypercalcemia or disappeared with normalization of serum calcium level. In addition to shortening the QT interval, severe to extreme hypercalcemia can cause development of inverted, biphasic, or notched T wave with a marked decrease in amplitude of T waves. (**Ahmed R, Yano K, Mitsuoka T, Ikeda S, Ichimaru M, Hashiba**

K. Changes in T wave morphology during hypercalcemia and its relation to the severity of hypercalcemia. J Electrocardiol 1989; 22: 125–132.

QT or QTc interval: the QT interval sometimes is shortened. The corrected QT intervals (QTc), particularly the QaTc interval, are reliable indicators of clinical hypercalcemia (**Ahmed R, Hashiba K. Reliability of QT intervals as indicators of clinical hypercalcemia. Clin Cardiol 1988; 11: 395–400.**)(**Nierenberg DW, Ransil BJ. Q-aTc interval as a clinical indicator of hypercalcemia. Am J Cardiol 1979;44: 243–248.**), From 74 patients (hypocalcemia: 41 patients, hypercalcemia 13 patients, 20 patients as control) without heart disease examined, a prolongation of the relative QT-interval was found in 90% and a flat or inverted T-wave in 25% of the patients with hypocalcemia. In 77% of the patients with hypercalcemia the QT-interval was shortened. A good, clinically useful correlation between the QT-interval and the serum calcium-concentration could be established in patients with hypocalcemia and hypercalcemia.(**So CS, Batrice L, Volger E. Electrocardiographic changes in electrolyte imbalance. Part 2: Alterations in serum calcium Med Klin. 1975;70:1966-1968.**).

Sensitivity of QoTc, QaTc, and QeTc in predicting high serum calcium concentration is 83%, 57%, and 39%, respectively, and specificity is 100%, 100%, and 89%. These observations suggest that QT intervals can serve as an indicator of high serum calcium concentration and that the QoTc seems to be a good indicator of the three QTc's. (**Saikawa T, Tsumabuki S, Nakagawa M, QT intervals as an index of high serum calcium in hypercalcemia. Clin Cardiol. 1988; 11:75-78.**)

Q-aTc: Very short **Q-aTc** interval. This interval is measured from the beginning of QRS complex to apex of T wave corrected for heart rate. Q-aTc interval is the more easily and precisely measured at elevated calcium levels and exhibited the strongest correlation over the range of calcium levels measured. The relation is linear and could be used to estimate serum calcium levels from measured Q-aTc intervals. When all other factors known to affect the Q-T interval are ruled out, the shortening of the Q-aTc interval (≤ 270 ms) appears to be a useful clinical indicator of hypercalcemia. Hypermagnesemia normalizes the QaTc interval, which is usually shortened by isolated hypercalcemia. Combined

hypercalcemia and hypermagnesemia can be caused by swallowing excessively salty water.

Q-oTc: Very short **Q-oTc** interval. This interval is measured from the beginning of QRS complex to onset of T wave corrected for heart rate.

Moderate hypercalcemia, in spite of causing a shortening of the repolarization phase (QT-interval), has no clinically significant effect on cardiac conduction. (*Rosenqvist M, Nordenstrom J, Andersson M, et al. Cardiac conduction in patients with hypercalcaemia due to primary hyperparathyroidism. Clin Endocrinol (Oxf). 1992; 37:29-33.*);

The correlation between serum ionized calcium (Ca⁺⁺) levels and three ECG QT intervals (Q-oTc, Q-aTc and Q-eTc) was assessed in 20 adult patients. The relationship between each QT interval and Ca⁺⁺ level, based on 209 Ca⁺⁺ determinations through a range of 1.0 to 4.0 mEq/liter, is best described by a hyperbolic function. Although Q-oTc, and Q-aTc predict Ca⁺⁺ levels more accurately than Q-eTc, all QT intervals are clinically unreliable as guides to the presence of hypercalcemia. Similarly, the usefulness of the QT intervals in the diagnosis of hypocalcemia is limited by the wide distribution of normal values. (*Rumancik WM, Denlinger JK, Nahrwold ML, et al. The QT interval and serum ionized calcium. JAMA. 1978;240:366-368.*).

Corrected QT intervals were determined in 13 patients with severe chronic hypercalcemia. The Qo-Tc interval was short in only 2 of 14 instances; Qa-Tc in 5 of 15 instances, and Qe-Tc in 5 of 16 instances. The correlations between serum calcium and the QTc measurement were not significant when evaluating either linear or curvilinear (quadratic) relationships. Small and inconsistent changes were found when comparing the QT intervals before the development of the hypercalcemic episode, during hypercalcemia, or after successful treatment. The authors conclude that shortening of the QT interval is an unreliable index of clinical (chronic) hypercalcemia. (*Wortzman J, Frank S. The QT interval in clinical hypercalcemia. Clin Cardiol. 1981; 4: 87-90.*).

The Q-Tc interval is not a useful clue to the presence of hypercalcemia.

Hypercalcemia of greater than 13 mg/dl (3.25 mM/L) was unaccompanied by ECG changes. (**Ellman H, Dembin H, Seriff N. The rarity of shortening of the Q-T interval in patients with hypercalcemia. Crit Care Med. 1982;10:320-322**).

Exceptionally Long QT interval was described in severe hypercalcemia. **Ortega-Carnicer J, Ceres F, Sanabria C. Long QT interval in severe hypercalcaemia. Resuscitation. 2004;61:242-243.**

Acute hyperparathyroidism developed in a previously normocalcemic 64-year-old woman during the first week after a coronary operation. Prolonged QT interval in the ECG and hypercalcemia were documented on the fourth postoperative day. Neck exploration on the fifth postoperative day revealed a lower right parathyroid adenoma. Parathyroidectomy resulted in rapid and dramatic improvement of the clinical picture and normalization of laboratory values. (**Siclari F, Herrmann G, Dralle H. Acute hypercalcemic crisis after an open heart operation. Ann Thorac Surg. 1990;50:831-832.**)

Heart Rate Variability: Primary hyperparathyroidism (pHPT) patients lacked the circadian rhythm of the low frequency to high frequency ratio, suggesting an increased sympathetic drive to the heart at nighttime. A modulation of the adrenergic control of circulation seems to be associated with hypercalcemia and/or chronic PTH excess, but its biological relevance needs further investigations. (**Barletta G, De Feo ML, Del Bene R, et al. Cardiovascular effects of parathyroid hormone: a study in healthy subjects and normotensive patients with mild primary hyperparathyroidism. J Clin Endocrinol Metab. 2000 May; 85:1815-1821.**). Sympathetic vascular tone, is modulated in part by calcium in normal man. Calcium contributes to the regulation of rhythmic oscillations in blood pressure. (**Munakata M, Imai Y, Mizunashi K, et al. The effect of graded calcium infusions on rhythmic blood pressure oscillations in normal man. : Clin Auton Res. 1995; 5:5-11.**)

QT dispersion: hypercalcemia affect ventricular repolarization, is not associated with increased QT dispersion. (**Yelamanchi VP, Molnar J, Ranade V, et al. Influence of electrolyte abnormalities on interlead variability of ventricular repolarization times in 12-lead electrocardiography. Am J Ther. 2001 ; 8:117-122.**).

Arrhythmias and Hipercalcemia:

Holter monitoring was performed in eight patients with advanced breast cancer and paraneoplastic hypercalcemia. In spite of several reports of cardiac arrhythmias, none were found in these patients. (**Lazzari R, Pellizzari F, Brusaferrri A, et al. Hypercalcemia and changes in cardiac rythm Minerva Med. 1991;82:255-257.**). Hypercalcemia seemed to decrease atrial activity and increase ventricular activity, as evidenced by the appearance of bradycardia, sinus arrest, and Premature Ectopic Beats. Vagal activity seemed altered by the changes in plasma calcium concentrations and involved in the production of the arrhythmia, because atropine could abolish the arrhythmia created by the infusion of the calcium solutions. (**Littledike ET, Glazier D, Cook HM. Electrocardiographic changes after induced hypercalcemia and hypocalcemia in cattle: reversal of the induced arrhythmia with atropine. Am J Vet Res. 1976; 37:383-388.**). Rarely in Hipercalcemia was observed: spontaneous attacks of ventricular tachycardia: **Chang CJ, Chen SA, Tai CT, et al. Ventricular tachycardia in a patient with primary hyperparathyroidism. Pacing Clin Electrophysiol. 2000; 23: 534-537** and exceptionally ventricular fibrillation. Only one case described in the literature **Kiewiet RM, Ponsen HH, Janssens EN, et al. Ventricular fibrillation in hypercalcaemic crisis due to primary hyperparathyroidism. Neth J Med. 2004;62:94-96.**

The electrocardiographic abnormalities in combined hypercalcaemia and hypokalaemia are: absence of the ST segment, prolonged T wave, a shortened Q-aTc interval and prominent U waves. (**Chia BL, Thai AC. Electrocardiographic abnormalities in combined hypercalcaemia and hypokalaemia--case report. Ann Acad Med Singapore. 1998; 27:567-569.**).

The electrocardiographic abnormalities in combined hypercalcaemia and hypermagnesemia:

Combined hypercalcemia and hypermagnesemia can be caused by swallowing excessively salty water. Common findings included P wave changes, tendency for prolongation of P-R interval, prolongation of QRS complex, infra-His conduction disturbances, tendency for broadening and inversion of T wave, and the ap-

pearance of a prominent U wave. Hypermagnesemia normalizes the QaTc interval, which is usually shortened by isolated hypercalcemia. (**Mosseri M, Porath A, Ovsyshcher I, et al. Electrocardiographic manifestations of combined hypercalcemia and hypermagnesemia. J Electrocardiol. 1990; 23:235-241.**)

Digoxin effects are amplified in Hypercalcemia.

The combined effects of digoxin and hypercalcaemia were studied in the canine heart in situ on the sinoatrial (SA) and atrioventricular (AV) nodes. Measurements were made of heart rate, of conduction time in the AV node by the endocavitary recording of the His bundle potentials, and of the effective refractory period of this node by the extrastimulus method. In the presence of acetylcholine released by vagal endings or infused into the coronary blood, an increase in plasma calcium concentration from 2.50 to 4.60 mmol/l after a 80 micrograms/kg dose of digoxin considerably depressed conduction in the AV node and automatism in the SA node. In the absence of acetylcholine, no bradycardia occurred under the influence of digoxin alone or digoxin and hypercalcaemia, and hypercalcemia enhanced to a lesser extent digoxin-induced depression of conduction in the AV node. These results evidence a potentiation by acetylcholine of the combined effects of digoxin and hypercalcaemia on the SA and AV nodes. (**Lang J, Lakhal M, Timour Chah Q, et al. Vagal role in potentiation by Ca²⁺ ions of the action of cardiac glycosides on the atrial specialised tissue. J Pharmacol. 1985;16:125-137.**)

History:

Symptoms of hypercalcemia depend on the underlying cause of the disease, the time over which it develops, and the overall physical health of the patient. Mild elevations in calcium levels usually have few or no symptoms.

Increased calcium levels may cause the following:

- 1) Nausea;
- 2) Vomiting;

- 3) Alterations of mental status;
- 4) Abdominal or flank pain (The workup of patients with a new kidney stone occasionally reveals an elevated calcium level.);
- 5) Constipation;
- 6) Lethargy
- 7) Depression;
- 8) Weakness and vague muscle/joint aches;
- 9) Polyuria;
- 10) Headache;
- 11) Coma: With severe elevations in calcium levels;
- 12) Elderly patients are more likely to be symptomatic from moderate elevations of calcium levels.
- 13) Hypercalcemia of malignancy may lack many of the features commonly associated with hypercalcemia caused by hyperparathyroidism. In addition, the symptoms of elevated calcium level may overlap with the symptoms of the patient's malignancy.
- 14) Hypercalcemia associated with renal calculi, joint complaints, and ulcer disease is more likely to be caused by hyperparathyroidism.

Physical examination: Hypercalcemia has few physical examination findings specific to its diagnosis.

- 1) Often it is the symptoms or signs of underlying malignancy that bring the patient with hypercalcemia to seek medical attention.
- 2) The primary malignancy may be suggested by lung findings, skin changes, lymphadenopathy, or liver or spleen enlargement.
- 3) Hypercalcemia can produce a number of nonspecific findings, as follows: Hypertension and bradycardia may be noted in patients with hypercalcemia, but this is nonspecific. Abdominal examination may suggest pancreatitis or the possibility of an ulcer. Patients with long-standing elevation of serum calcium may have proximal muscle weakness that is more prominent in the lower extremities; they

also may have bony tenderness to palpation. Hyperreflexia and tongue fasciculations may be present. Long-standing hypercalcemia may cause band keratopathy, but this is rarely recognized in the ED.

- 4) If hypercalcemia is caused by sarcoidosis, vitamin D intoxication, or hyperthyroidism, patients may have physical examination findings suggestive of those diseases.