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CAUSES OF HYPERCALCEMIA IN CHILDREN

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Review

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Abstract

Calcium is an electrolyte that is effective in maintaining cell integrity and is found at a high rate in the body. Hypercalcemia is an uncommon but vital electrolyte disorder in childhood, unlike adults. Long-term exposure to hypercalcemia may be associated with mortality and morbidity. Hypercalcemia may develop due to many reasons and there are usually no specific findings at presentation. Therefore, when evaluating hypercalcemia cases, it should be kept in mind that there is a wide differential diagnosis list and that there are different treatment approaches.

Key Words: Hypercalcemia, Etiology, Treatment

Özet

Kalsiyum, hücre bütünlüğünün korunmasında etkili olan ve vücutta yüksek oranda bulunan bir elektrolittir. Hiperkalsemi, yetişkinlerden farklı olarak çocukluk çağında nadir görülen fakat hayati önem arz eden elektrolit bozukluğudur. Uzun süreli hiperkalsemi maruziyeti mortalite ve morbidite ile ilişkili olabilmektedir. Hiperkalsemi birçok nedene bağlı olarak gelişebilir ve genellikle başvuru anında spesifik bir bulgu göstermez. Bu nedenle hiperkalsemi vakalarını değerlendirirken geniş bir ayırıcı tanı listesinin olduğu ve farklı tedavi yaklaşımlarının olduğu akılda tutulmalıdır.

Anahtar Kelimeler: Hiperkalsemi, Etioloji, Tedavi

1. Calsium Metabolism

Calcium is a divalent cationic ion that functions in many areas, from providing cell integrity to the activity of the musculoskeletal system. Approximately 99% of calcium is associated with bone tissue and it is tried to be kept in balance with serum calcium (Diaz, 2007).

The majority of dietary calcium is not excreted in children, unlike adults, and is used for positive calcium balance. About 40% of dietary calcium is absorbed from the duodenum, and in cases that the calcium requirement increases, absorption is also provided from the ileum and colon. The amount of serum vitamin D, the type of food that is a source of calcium, and the complex salt structure taken with the food are among the factors affecting calcium absorption from the intestines. Similar-structured transmembrane proteins on the renal and gastrointestinal system surfaces are effective in calcium transport. Calcium in the intestinal lumen is transported by calcium channels called TrpV5 and TrpV6 positionedon the enterocyte surface. Calcium entering the cell is transported within the cell by binding to two calcium-binding proteins (CaBP-D9k and CaBP-D28k) called calbindin and enters the circulation via the Na-Ca (NCX1) or Ca- ATPase (PMCA1b) system. 1,25 dihydroxyvitamin D [1,25(OH)2], has the effect of increasing calcium transport by stimulating all these steps in calcium transport (Allgrove, 2015) (Figure 1).

Most of the calcium filtered by the kidneys is reabsorbed from the proximal tubule. While 70% of the calcium is transported passively from the renal tubules by hormone-independent mechanisms, only 8% of the calcium is transported by the effects of PTH and vitamin D. Calcium transport in the kidneys is similar to that on the intestinal surface; however, it is thought that the Na-Ca transporter is used in the basolateral side, where TRPV5 and CaBP-D28k are used more dominantly. In fact, TRPV5 is thought to act as a control step in renal calcium reabsorption (Lieben, Carmeliet, & Masuyama, 2011).

The ionized calcium-stimulated calcium-sensing receptor (CaSR) is found in parathyroid gland and the loop of henle as well as many different tissues. Activated by the increase of ionized calcium, the receptor functions through the intracellular G protein, decreases the efficiency of the Na/K/2Cl transporter, and decreases calcium reabsorption by lowering the positive voltage of the lumen. If the amount of peritubular calcium and magnesium is high, ionized calcium binds to CaSR, reducing calcium reabsorption in the loop of henle and the distal tubule, and therefore, reabsorption decreases and the amount of calcium excreted in the urine increases. Loss-of-function mutations in the gene encoding CaSR cause familial hypocalciuric hypercalcemia, and gain-of-function mutations cause familial hypercalciuric hypocalcemia (Edward M Brown, 1997).

In providing plasma calcium and phosphorus balance, primarily parathormone (PTH), the active form of vitamin D [1,25(OH)2], dihydroxy vitamin D, calcitonin effective in the intrauterin period, parathormone-related peptide (PTHrp), and fibroblast growth factor 23 (FGF23), mostly providing phosphate balance, are effective (Davies, 2015).

1.1. Parathormone

Parathormone is the main hormone released by parathyroid tissue and is released as preproprarathormone (115 amino acids), and mature PTH (84 amino acids) is formed by posttranslational mechanisms. The net effect of PTH in the serum is to increase the serum calcium level and renal phosphate excretion. It provides this effect mainly through the G protein-linked PTH1R, which is detected in osteoblast and kidney epithelial cells. With the stimulation of the receptor, cyclic adenosine monophosphate (cAMP) and phospholipase C are activated, resulting in the excretion of intracellular calcium into the extracellular area. Osteoblasts activate osteoclasts, increasing calcium outflow from bone tissue. Another effect of PTH is that it increases the 1 alpha- hydroxylase enzyme activity in the kidney proximal cells, increasing the production of 1,25(OH)2D and hence the absorption of calcium from the kidney and intestine. PTH is affected even by minimal changes in serum calcium level, and serum calcium level is tried to be kept in balance.

1.2. Vitamin D

Although there are two different forms of vitamin D, cholecalciferol (animal origin) and ergocalciferol (plant origin), 90-95% it is synthesized in the skin by the effect of sun rays under the wavelength of 280-315 nm. Vitamin D, taken orally, is absorbed from the small intestine and mixes with the blood, and provitamin D is converted to previtamin D in the skin with the effect of ultraviolet B. Vitamin D transported to the liver is converted to 25-hydroxyvitamin D via the 25-hydroxylase enzyme and then to 1,25(OH)2D by the 1-alpha hydroxylase enzyme in the kidney, and this is the active form of vitamin D. In the synthesis steps, 25-hydroxylase enzyme activity acts as the rate-limiting step, and its deficiency leads to classical vitamin D deficiency.

All forms are transported in the plasma via the vitamin D binding protein and bind to the vitamin D receptor located both in the cytoplasm and in the cell nucleus. This receptor is expressed in many tissues, such as the pituitary gland, skin, breast tissue, and lymphocyte surface, apart from bone, the intestine, and the kidneys (Tsiaras & Weinstock, 2011). Vitamin D acts by

increasing the absorption of both calcium and phosphate from the intestine and kidney. When the serum calcium level is low, 1,25(OH)2D, which increases with the effect of PTH, also causes calcium release from the bone tissue, if this situation lasts for a long time, bone mineralization gradually deteriorates and the rickets table becomes obvious (Holick, 1999).

1.3. Calcitonin

Another hormone effective on calcium metabolism is calcitonin. It is released in the parafollicular cells of the thyroid gland and is thought to have a PTH-like effect. It is a peptide hormone that acts by suppressing osteoclasts and increasing excretion of calcium, sodium and potassium from the kidneys. (Greenstein & Wood, 2011).

2. Hypercalsemia

Although hypercalcemia is not common in children, it might be associated with morbidity and mortality if left untreated. A serum calcium level of 10.6 mg/dl and an ionized calcium level of over 5.2 mg/dl (1.3 mmol/l) is considered as hypercalcemia. Total serum calcium levels between 10.6-12 mg/dl can be classified as slight, 12-14 mg/dl as moderate, and >14 mg/dl as severe hypercalcemia. The causes of hypercalcemia differs in children from adults. In children, different causes can be seen in different age groups. The causes of hypercalcemia will be discussed in two groups: neonatal-infant and child-adolescent periods.

2.1. Causes of Hypercalcemia in the Neonatal and Infantile Period

In the neonatal period, hypercalcemia mostly develops due to transient and iatrogenic intravenous fluids. Transient secondary hyperparathyroidism and hypercalcemia may develop in approximately 25% of newborns exposed to maternal hypocalcemia (Loughead, Mughal, Mimouni, Tsang, & Oestreich, 1990).

2.1.1. Neonatal Severe Primary Hyperparathyroidism (NSHPT)

CaSR, which is very rare in the neonatal period, is a condition that develops as a result of homozygous inactivating mutations and may be associated with mortality, and its definitive treatment is total parathyroidectomy. There is information about a few case series with limited patient numbers in the literature. Patients usually have severe hypercalcemia, normal or high PTH, and low fractionated serum calcium excretion (Al- Shanafey, Al-Hosaini, Al-Ashwal, & Al-

Rabeeah, 2010; Sadacharan et al., 2020). Spontaneous fractures may occur due to resorption in bone tissue.

2.1.2. Subcutaneous Fat Necrosis

Another cause of hypercalcemia that can be seen in the neonatal period is subcutaneous fat necrosis, which occurs secondary to hypoxia-related conditions. It has been shown to occur in 40% of newborns who have undergone hypoxic-ischemic involvement and received therapeutic hypothermia (Strohm, Hobson, Brocklehurst, Edwards, & Azzopardi, 2011). It occurs as a late sign of treatment, and hypercalcemia becomes evident in the resolution phase of fat necrosis that occurs in the subcutaneous tissue in the parts of the body that are exposed to pressure. Hypercalcemia is thought to be due to the 1,25(OH)2D vitamin released from the granulomatous tissue in fat necrosis, and steroids are used in addition to hydration in the treatment.

2.1.3. Causes of Hypercalcemia Due to Metabolic Diseases

2.1.3.1. Hypophosphatasia

It is a group of diseases that occur with different levels of bone deformity and hypercalcemia as a result of a defect in the gene encoding the tissue non- specific alkaline phosphatase isoenzyme. In its early-stage symptomatic form, respiratory distress due to chest deformity often develops and may result in mortality. Hypercalcemia, hypercalciuria, a low serum alkaline phosphatase level, and concomitant urinary phosphoethanolamine excretion support the diagnosis. Asfotase alfa therapy, which has recently been used, has been shown to increase survival (Whyte et al., 2016).

2.1.3.2 Congenital Lactase Deficiency

It is stated that increased calcium absorption due to metabolites accumulating secondary to enzyme deficiency in the intestinal lumen and the developing metabolic acidosis exacerbate hypercalcemia, and normocalcemia was observed with the initiation of a lactose-free diet after diagnosis (Saarela, Similä, & Koivisto, 1995).

2.1.3.3. Blue Diaper Syndrome

It is a rare metabolic disease that results from a defect in tryptophan metabolism.

2.2. Causes of Hypercalcemia in Child and Adolescent Period

2.2.1. Primary Hyperparathyroidism

Unlike adults, hyperparathyroidism is rarely seen in children with a rate of 2- 5/100000 (Harman et al., 1999; Kollars et al., 2005). However, the etiology is similar and the most common cause is adenoma developing in one gland (Belcher, Metrailer, Bodenner, & Stack, 2013; Mallet, 2008) . Parathyroid adenomas may occur sporadically or may be associated with multiple endocrine neoplasia (MEN). Four types of MEN have been described and all are observed to be associated with parathyroid tumors. Primary hyperparathyroidism cases often show nonspecific symptoms at the time of admission, and this may cause a delay in diagnosis (Kollars et al., 2005; Mallet, 2008). Cases exposed to prolonged PTH elevation may present due to bone deformity and even fracture.

2.2.2. Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia was first introduced in 1972 to describe individuals belonging to the same family with benign hypercalcemia (Foley, Harrison, Arnaud, & Harrison, 1972). The clinical picture occurs due to a heterozygous mutation in the 3q13.3-q21 region of the third chromosome. There is an inactivating mutation in one of the alleles of the CaSR gene. It is an autosomal dominant disease that is mostly asymptomatic, and therefore its true prevalence is not known, but it is estimated to be 1/78,000. Heterozygous mutations are often asymptomatic, while homozygous mutations show indications from the neonatal period. It has three types: FHH Type 1 is the most common type seen as a result of the development of mutations in the gene encoding CaSR. The mutation occurring in the GNA11 gene encoding the Gs alpha 11 subunit of CaSR is called type 2, while the mutation occurring in the AP2S1 gene encoding the adapter-related protein 2 is called type 3. It has been found that cognitive changes and more severe hypercalcemia are seen in FHH type 3 than in other types (Szalat et al., 2017). Mutations that cause a loss of function in CaSR reduce the suppressive effect of calcium on PTH. A higher blood calcium level is needed to act on PTH. Reabsorption of calcium from the renal tubules increased. Urinary calcium excretion decreased, approximately 80% of patients have a urinary calcium creatinine ratio <0.01. However, the PTH level is normal or high. Serum magnesium level is slightly high. While no specific treatment is usually required, the use of cinacalcet in the treatment of symptomatic cases is successful in providing normocalcemia (E. M. Brown, 2000; Mayr, Schnabel, Dörr, & Schöfl, 2016).

The incidence of vascular calcification, hypertension, and Alzheimer's disease is increased in association with hypercalcemia in individuals with CaSR mutations. In some studies, it has been shown that CaSR plays a tumor suppressor role in tumors such as parathyroid tumors and neuroblastoma and a proto-oncogene role in breast and prostate cancers (Díaz-Soto, Rocher, García-Rodríguez, Núñez, & Villalobos, 2016; Vahe et al., 2017). Therefore, regular follow-up of individuals with CaSR defect is required.

2.2.3. Idiopathic Infantile Hypercalcemia

It is thought that idiopathic infantile hypercalcemia is mainly due to a defect in vitamin D metabolism. It is a diagnosis that was first established in the 1950s by observing cases with hypercalcemia, hypercalciuria, suppressed PTH, and an inappropriate elevation in the active form of vitamin D in children after the use of vitamin D-fortified formula (Misselwitz, Hesse, & Markestad, 1990; Pronicka et al., 1988; Samuel, 1964). Although there is no high dose of vitamin D taken, the development of hypercalcemia in some individuals has brought to mind the idea that there may be an underlying vitamin D metabolism disorder. Two subtypes were defined as Lightwood (slight form) and Fanconi (severe form), and the severe form was thought to be similar to Williams Syndrome (Mitchell, 1960). With the increase in genetic diagnosis methods, it has been shown that there are new gene defects associated with IHH in recent years, and new classifications have been made. Defects in the Cyp24A1 (IHH Type 1) gene encoding the 24 alpha hydroxylase enzyme and, more rarely, the SLC34A1 (IHH Type 2) gene, which encodes the renal sodium-phosphate cotransporter (NaPi-IIa), have been demonstrated in the onset of this disease (Rajagopal et al., 2014; Schlingmann et al., 2016). It has been observed that adult individuals with heterozygous mutations in the Cyp24A1 gene can be asymptomatic and normocalcemic. It has been thought that the fact that IHH cases are more common in infancy may be related to the low glomerular filtration rate and higher prevalence of vitamin D intake in childhood (Molin et al., 2015).

2.2.4. Excess Vitamin D Intake

Hypervitaminosis D may occur due to, for instance, accidental or deliberate excess intake of vitamin D or excessive maternal vitamin D intake. The absence of vitamin D intoxication as a result of sun exposure is related to the fact that UV-B rays break down vitamin D at the same time and convert it into inactive products called lumisterol and tachysterol (Kovacs et al., 1996). The

highest daily dose of vitamin D is recommended as 1000-2500 IU/day in infants and 3000-4000 IU/day in older children (Ross et al., 2011). A serum 25OHD level above 150 nmol/L is considered vitamin D hypervitaminosis (Özkan, Hatun, & Bereket, 2012). It is thought that in excess intake of vitamin D, increased 25OHD in the serum liberates 1.25(OH)2 D over VDBP and hypercalcemia develops as a result of the increase in the free form of 1.25(OH)2Din the serum. Hypercalcemia, hyperphosphatemia, and hypercalciuria develop depending on the increasing in serum vitamin D level. Permanent nephrocalcinosis may develop due to long-term hypercalciuria. Depending on its storage in adipose tissue, hypercalcemia may continue for a long time.

2.2.5 Williams Syndrome

Williams Syndrome occurs as a result of gene deletion in the 7q11.23 region. Growth and development retardation, mental retardation, malar hypoplasia, epicanthus facial appearance, congenital heart defect associated with 80%, renal artery and celiac artery stenosis can be seen (De Rubens Figueroa, Rodríguez, Hach, Del Castillo Ruíz, & Martínez, 2008). In addition to all these, hypercalcemia is observed in 15% of cases. Hypercalcemia is usually slight and resolves by the age of four; PTH may be suppressed or normal. The reason for the development of hypercalcemia has not been clearly revealed, but there are publications showing that TRPC3 expression, which is effective in transporting calcium to lymphocytes, may be associated with an increase in calcium absorption from the gastrointestinal tract and renal system as a result of this increase (Letavernier, Rodenas, Guerrot, & Haymann, 2012). Hypercalciuria may occur without the development of hypercalcemia, which increases the risk of nephrocalcinosis (Cunniff et al., 2001).

2.2.6. Immobilization

Hypercalcemia and hypercalciuria may occur as a result of immobilization secondary to a spinal cord injury or extremity fracture. This is due to a decrease in osteoblast activity and an increase in osteoclast activity. While hypercalciuria develops in the acute phase of immobilization, hypercalcemia develops within 1-3 weeks. Affected patients may present with complaints of nausea, vomiting, constipation, polyuria, and polydipsia (Bergstrom, 1978).

2.2.7. Malignancy-Associated Hypercalcemia

Malignancy-associated hypercalcemia is a very rare cause of hypercalcemia in children. In studies, it can be observed in 1% of children with cancer and in the course of leukemia, lymphoma, neuroblastoma, hepatoblastoma, and rhabdomyosarcoma (McKay & Furman, 1993). There are two reasons for hypercalcemia developing in malignancy follow-up. The first is the invasion of bone tissue by tumoral tissue. The second is therelease of PTHrP from the tumoral tissue. PTHrP is structurally similar to PTH and increases calcium release from bone tissue.

2.2.8. Renal Tubular Diseases

Distal renal tubular acidosis is a disease with metabolic acidosis, hypokalemia and hypercalciuria caused by insufficient H ion excretion from renal collecting ducts.In infancy and childhood, distal renal tubular acidosis may rarely be accompanied by hypercalcemia, and the possibility of nephrocalcinosis increases in the presence of hypercalcemia. It is a condition that should be kept in mind in infant cases presenting with growth retardation and metabolic acidosis (Rodriguez-Soriano, Garcia-Fuentes, Vallo, & Álvarez-Granda, 2000). Bartter syndrome is a disease that occurs with hypercalciuria, metabolic alkalosis, hypokalemia, and nephrocalcinosis secondary to mutations in the Na/K/2Cl transporter. Slight to moderate hypercalcemia can be seen accompanying in the childhood age group (Bettinelli et al., 2000).

2.2.9. Other Causes

Lithium stimulates the parathyroid gland, long-term use of vitamin A can increase osteoclastic bone resorption, and thiazide-derived diuretics increase renal calcium absorption and therefore cause hypercalcemia. Adrenal insufficiency and hyperthyroidism are also endocrine disorders that may cause the development of hypercalcemia.

3. Treatment

In cases of hypercalcemia, the choice of treatment is made according to the serum calcium level, the acute or chronic occurrence of hypercalcemia, and the presence of symptoms. Generally, patients with slight hypercalcemia can be treated as outpatients with oral hydration, while those with moderate to severe hypercalcemia require hospitalization.

Usually, the first approach is to provide hydration and increase the glomerular filtration rate to increase renal excretion. Furosemide, which provides renal Na/K/2Cl channel inhibition with

a similar mechanism, can be used (1-2mg/kg/dose). However, as long-term use increases the risk of nephrocalcinosis, the duration of treatment should be carefully adjusted.

The mechanism of action of calcitonin is to suppress osteoclastic activity and inhibit renal calcium reabsorption. It can be administered as an intravenous infusion or injection (1-4 units/kg). In addition to its rapid effect, the rapid development of tolerance to its effect limits its use.

Bisphosphonates have recently proven to be effective and have become a frequently used treatment option. Unlike calcitonin, its effect is delayed, repeated doses can be administered as an intravenous slow infusion (0.5-1 mg/kg/dose) (Srivastava & Alon, 1999).

Corticosteroids act by suppressing 1 alpha hydroxylase enzyme activity and can be applied orally or intravenously (1-2 mg/kg/day). It can be used, especially in cases secondary to vitamin D intoxication or inflammatory diseases. Although ketoconozole is an antifungal, it can be preferred as it has a corticosteroid-like effect (3-9 mg/kg/day), but it may cause liver toxicity.

Cinacalcet is a treatment agent in the calcimimetic group that acts by suppressing PTH secretion by causing an increase in CaSR level sensitivity. Due to its mechanism of action, it is often preferred in FHH patients and in cases with high PTH.

Dialysis and surgical treatment options are the methods that can be preferred in cases that are resistant to treatment or associated with malignancy.

Denosumab is used as a monoclonal RANKL receptor inhibitor and is shown as useful in refractory and malignancy-associated hypercalcemia (Mamedova et al., 2020).

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Conflicts of interest

None

References

Al-Shanafey, S., Al-Hosaini, R., Al-Ashwal, A., & Al-Rabeeah, A. (2010). Surgical management of severe neonatal hyperparathyroidism: one center's experience. J Pediatr Surg, 45(4), 714-717. doi: 10.1016/j.jpedsurg.2009.08.005

Allgrove, J. (2015). Physiology of calcium, phosphate, magnesium and vitamin D. Calcium and BoneDisorders in Children and Adolescents, 28, 7-32.

Belcher, R., Metrailer, A. M., Bodenner, D. L., & Stack, B. C., Jr. (2013). Characterization of hyperparathyroidism in youth and adolescents: a literature review. Int J PediatrOtorhinolaryngol, 77(3), 318-322. doi: 10.1016/j.ijporl.2012.12.008

Bergstrom, W. H. (1978). Hypercalciuria and hypercalcemia complicating immobilization. Am J DisChild, 132(6), 553-554. doi: 10.1001/archpedi.1978.02120310017001

Bettinelli, A., Ciarmatori, S., Cesareo, L., Tedeschi, S., Ruffa, G., Appiani, A. C., . . . Sacco, M. (2000). Phenotypic variability in Bartter syndrome type I. Pediatric Nephrology, 14(10), 940-945.

Brown, E. M. (1997). Mutations in the calcium-sensing receptor and their clinical implications.Hormone Research in Paediatrics, 48(5), 199-208.

Brown, E. M. (2000). Familial hypocalciuric hypercalcemia and other disorders with resistance to extracellular calcium. Endocrinol Metab Clin North Am, 29(3), 503-522. doi: 10.1016/s0889-8529(05)70148-1

Cunniff, C., Frias, J., Kaye, C., Moeschler, J., Panny, S., & Trotter, T. (2001). Health care supervision for children with Williams syndrome. Pediatrics, 107(5), 1192-1204.

Davies, J. H. (2015). Approach to the Child with Hypercalcaemia. Calcium and Bone Disorders inChildren and Adolescents, 28, 101-118.

De Rubens Figueroa, J., Rodríguez, L. M., Hach, J. L., Del Castillo Ruíz, V., & Martínez, H. O. (2008). Cardiovascular spectrum in Williams-Beuren syndrome: the Mexican experience in 40 patients. Tex Heart Inst J, 35(3), 279-285.

Díaz-Soto, G., Rocher, A., García-Rodríguez, C., Núñez, L., & Villalobos, C. (2016). The Calcium-Sensing Receptor in Health and Disease. Int Rev Cell Mol Biol, 327, 321-369. doi:10.1016/bs.ircmb.2016.05.004

Diaz, R. (2007). Calcium disorders in children and adolescents in Lifshitz Pediatric endocrinology (pp.475-495). Newyork: İnforma healthcare.

Foley, T. P., Jr., Harrison, H. C., Arnaud, C. D., & Harrison, H. E. (1972). Familial benign hypercalcemia.J Pediatr, 81(6), 1060-1067. doi: 10.1016/s0022-3476(72)80232-4

Greenstein, B., & Wood, D. (2011). The Endocine System at a Glance (3 ed., pp. 104-107): Blackwell Publishing.

Harman, C. R., van Heerden, J. A., Farley, D. R., Grant, C. S., Thompson, G. B., & Curlee, K. (1999).Sporadic primary hyperparathyroidism in young patients: a separate disease entity Archives of surgery, 134(6), 651-656.

Holick, M. (1999). Vitamin D. In O. J. Shills ME, Shike M, Ross CA (Ed.), Modern Nutrition in Health and Disease (9 ed., pp. 329-345). Baltimore: Williams & Williams.

Kollars, J., Zarroug, A. E., van Heerden, J., Lteif, A., Stavlo, P., Suarez, L., . . . Rodeberg, D. (2005). Primary hyperparathyroidism in pediatric patients. Pediatrics, 115(4), 974-980. doi: 10.1542/peds.2004-0804

Kovacs, C. S., Lanske, B., Hunzelman, J. L., Guo, J., Karaplis, A. C., & Kronenberg, H. M. (1996). Parathyroid hormone-related peptide (PTHrP) regulates fetal–placental calcium transport through a receptor distinct from the PTH/PTHrP receptor. Proceedings of the National Academy of Sciences, 93(26), 15233-15238.

Letavernier, E., Rodenas, A., Guerrot, D., & Haymann, J. P. (2012). Williams-Beuren syndrome hypercalcemia: is TRPC3 a novel mediator in calcium homeostasis? Pediatrics, 129(6), e1626-1630. doi: 10.1542/peds.2011-2507

Lieben, L., Carmeliet, G., & Masuyama, R. (2011). Calcemic actions of vitamin D: effects on the intestine, kidney and bone. Best practice & research Clinical endocrinology & metabolism,25(4), 561-572.

Loughead, J. L., Mughal, Z., Mimouni, F., Tsang, R. C., & Oestreich, A. E. (1990). Spectrum and natural history of congenital hyperparathyroidism secondary to maternal hypocalcemia. Am JPerinatol, 7(4), 350-355.

Mallet, E. (2008). Primary hyperparathyroidism in neonates and childhood. The French experience (1984-2004). Horm Res, 69(3), 180-188. doi: 10.1159/000112592

Mamedova, E., Kolodkina, A., Vasilyev, E. V., Petrov, V., Belaya, Z., & Tiulpakov, A. (2020). Successful Use of Denosumab for Life-Threatening Hypercalcemia in a Pediatric Patient with PrimaryHyperparathyroidism. Hormone Research in Paediatrics, 93(4), 272-278.

Mayr, B., Schnabel, D., Dörr, H. G., & Schöfl, C. (2016). Genetics in Endokrınology: Gain and loss of function mutations of the calcium-sensing receptor and associated proteins: current treatment concepts. Eur J Endocrinol, 174(5), R189-208. doi: 10.1530/eje-15-1028

McKay, C., & Furman, W. L. (1993). Hypercalcemia complicating childhood malignancies. Cancer,72(1), 256-260.

Misselwitz, J., Hesse, V., & Markestad, T. (1990). Nephrocalcinosis, Hypercalciuria and Elevated Serum Levels of 1, 25-Dihydroxyvitamin D in Children Possible Link to Vitamin D Toxicity. ActaPædiatrica, 79(6-7), 637-643.

Mitchell, R. (1960). The prognosis in idiopathic hypercalcaemia of infants. Archives of disease inchildhood, 35(182), 383.

Molin, A., Baudoin, R., Kaufmann, M., Souberbielle, J. C., Ryckewaert, A., Vantyghem, M. C., . . .

Kottler, M. L. (2015). CYP24A1 Mutations in a Cohort of Hypercalcemic Patients: Evidence for a Recessive Trait. J Clin Endocrinol Metab, 100(10), E1343-1352. doi: 10.1210/jc.2014-4387

Özkan, B., Hatun, S., & Bereket, A. (2012). Vitamin D intoxication. The Turkish journal of pediatrics,54(2), 93.

Pronicka, E., Kulczycka, H., Lorenc, R., Prószyoska, K., Grdzka, J., & Rowioska, E. (1988). Increased serum level of 1, 25-dihydroxyvitamin D3 after parathyroid hormone in the normocalcemicphase of idiopathic hypercalcemia. The Journal of pediatrics, 112(6), 930-933.

Rajagopal, A., Braslavsky, D., Lu, J. T., Kleppe, S., Clément, F., Cassinelli, H., . . . Bergadá, I. (2014). Exome sequencing identifies a novel homozygous mutation in the phosphate transporter SLC34A1 in hypophosphatemia and nephrocalcinosis. The Journal of Clinical Endocrinology & Metabolism, 99(11), E2451-E2456.

Rodriguez-Soriano, J., Garcia-Fuentes, M., Vallo, A., & Álvarez-Granda, J. (2000). Hypercalcemia in neonatal distal renal tubular acidosis. Pediatric nephrology (Berlin, Germany), 14(4), 354-355.

Ross, A. C., Manson, J. E., Abrams, S. A., Aloia, J. F., Brannon, P. M., Clinton, S. K., . . . Shapses, S. A. (2011). The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab, 96(1), 53-58.doi: 10.1210/jc.2010-2704

Saarela, T., Similä, S., & Koivisto, M. (1995). Hypercalcemia and nephrocalcinosis in patients with congenital lactase deficiency. The Journal of pediatrics, 127(6), 920-923.

Sadacharan, D., Mahadevan, S., Rao, S. S., Kumar, A. P., Swathi, S., Kumar, S., & Kannan, S. (2020). Neonatal Severe Primary Hyperparathyroidism: A Series of Four Cases and their Long-term Management in India. Indian J Endocrinol Metab, 24(2), 196-201. doi: 10.4103/ijem.IJEM_53_20

Samuel, H. (1964). Infantile Hypercalcaemia, Nutritional Rickets, And Infantile Scurvy In Great Britain. A British Paediatric Association Report. British medical journal, 1(5399), 1659-1661.

Schlingmann, K. P., Ruminska, J., Kaufmann, M., Dursun, I., Patti, M., Kranz, B., . . . Konrad, M. (2016). Autosomal-Recessive Mutations in SLC34A1 Encoding Sodium-Phosphate Cotransporter 2A Cause Idiopathic Infantile Hypercalcemia. J Am Soc Nephrol, 27(2), 604-614. doi: 10.1681/asn.2014101025

Srivastava, T., & Alon, U. S. (1999). Bisphosphonates: from grandparents to grandchildren. Clinicalpediatrics, 38(12), 687-702.

Strohm, B., Hobson, A., Brocklehurst, P., Edwards, A. D., & Azzopardi, D. (2011). Subcutaneous fat necrosis after moderate therapeutic hypothermia in neonates. Pediatrics, 128(2), e450-452. doi: 10.1542/peds.2010-3508

Szalat, A., Shpitzen, S., Tsur, A., Koren, I. Z., Shilo, S., Tripto-Shkolnik, L., . . . Meiner, V. (2017).

Stepwise CaSR, AP2S1, and GNA11 sequencing in patients with suspected familial hypocalciuric hypercalcemia. Endocrine, 55(3), 741-747.

Tsiaras, W. G., & Weinstock, M. A. (2011). Factors influencing vitamin D status. Acta dermato-venereologica, 91(2), 115-124.

Vahe, C., Benomar, K., Espiard, S., Coppin, L., Jannin, A., Odou, M.-F., & Vantyghem, M.-C. (2017). Diseases associated with calcium-sensing receptor. Orphanet J Rare Dis, 12(1), 1-9.

Whyte, M. P., Rockman-Greenberg, C., Ozono, K., Riese, R., Moseley, S., Melian, A., . . . Hofmann, C. (2016). Asfotase Alfa Treatment Improves Survival for Perinatal and Infantile Hypophosphatasia. J Clin Endocrinol Metab, 101(1), 334-342. doi: 10.1210/jc.2015-3462