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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Mineralization refers to a process where an inorganic substance precipitates in an organic matrix. This may be due to normal biological processes that take place during the life of an organism such as the formation of bones, egg shells, teeth, coral, and other exoskeletons. This term may also refer to abnormal processes that result in kidney and gall stones.

Demineralization - it is the opposite process of mineralization, a process to reduce the content of mineral substances in tissue or organism, such as **bone demineralization**, of teeth. **Demineralization** can lead to serious diseases such as osteoporosis or tooth decay. **Osteoporosis** implies increased porosity of the bones that weakens the bone structure leading to increased tendency of bone fractures.

Osteomalacia refers to a marked softening of your bones, most often caused by severe vitamin D deficiency. The softened bones of children and young adults with **osteomalacia** can lead to bowing during growth, especially in weight-bearing bones of the legs. **Osteomalacia** in older adults can lead to **fractures**.

How to naturally prevent bone demineralization

1. Eat Lots of Vegetables. ...
2. Perform Strength Training and Weight-Bearing Exercises. ...
3. Consume Enough Protein. ...
4. Eat High-Calcium Foods Throughout the Day. ...
5. Get Plenty of Vitamin D and Vitamin K. ...
6. Avoid Very Low-Calorie Diets. ...
7. Consider Taking a Collagen Supplement.

Under "**DISEASE DIAGNOSIS"** segment we discuss Disorders Of Bone Mineralization in ample detail. As a natural corollary **"INTERPRETATION"** is discussing Nutrient Mineral Levels in a human body. And again as an offshoot, **"TROUBLESHOOTING"** highlights the normal Blood Calcium levels.

DISEASE DIAGNOSIS

DISORDERS OF BONE MINERALIZATION

Overview

Several diseases can result in disorders of bone mineralization in children, including rickets, renal diseases (renal osteodystrophy, Fanconi syndrome), tumor-induced osteomalacia, hypophosphatasia, McCune-Albright syndrome, and osteogenesis imperfecta with mineralization defect (syndrome resembling osteogenesis imperfecta [SROI]). These conditions may result in failure of osteoid calcification (rickets) in children because of a disruption in the pathway of either vitamin D or phosphate metabolism. Rickets, once thought defeated, is reappearing and remains a major health problem in many developing and developed countries.

Types of rickets include the following:

- Nutritional rickets
- Congenital rickets
- Rickets of prematurity
- Vitamin D resistance (type I and type II)
- Neoplastic rickets
- Hypophosphatemic rickets
- Drug-induced rickets

Clinical and laboratory findings

Clinical results and laboratory examination findings vary with each disorder. Low phosphate and high alkaline phosphatase levels characterize most of the disorders. Exceptions are noted in the discussion of each disorder.

Vitamin D Metabolism

The primary absorption site for vitamin D is the jejunum. The 2 main sources of vitamin D in humans are vitamin D_3 (cholecalciferol), produced by the skin after ultraviolet (UV) radiation (290-320nm) – dependent conversion of 7-dehydrocholesterol, and dietary intake of either vitamin D_2 (ergocalciferol) or vitamin D_3. Both forms of vitamin D have identical biologic actions. The initial step in the metabolic activation process is the introduction of a hydroxyl group at the side chain at C-25 by the hepatic enzyme, CYP 27 (a vitamin D-25-hydroxylase). The products of this reaction are 25-(OH)D_2 and 25-(OH)D_3, respectively. Further hydroxylation of these metabolites occurs in the mitochondria of kidney tissue, catalyzed by renal 25-hydroxyvitamin D-1α-hydroxylase to produce 1α,25-$(OH)_2$ D_2 (activated vitamin D_2 or 1,25$[OH]_2$ D_2), the primary biologically active form of vitamin D_2, and 1α,25-$(OH)_2$ D_3 (calcitriol or 1,25$[OH]_2$ D_3), the biologically active form of vitamin D_3. Of note, the kidney generates at least 30 other vitamin D metabolites, but their biologic significance is not clear. The pathophysiology of rickets is not completely understood, nor is the role of the many vitamin D metabolites. Calcitriol levels may be normal in patients with rickets, suggesting that it is not the only active form of the vitamin. Causes of rickets related to phosphate deficiency are discussed in the article Hypophosphatemic Rickets.

Pathophysiology

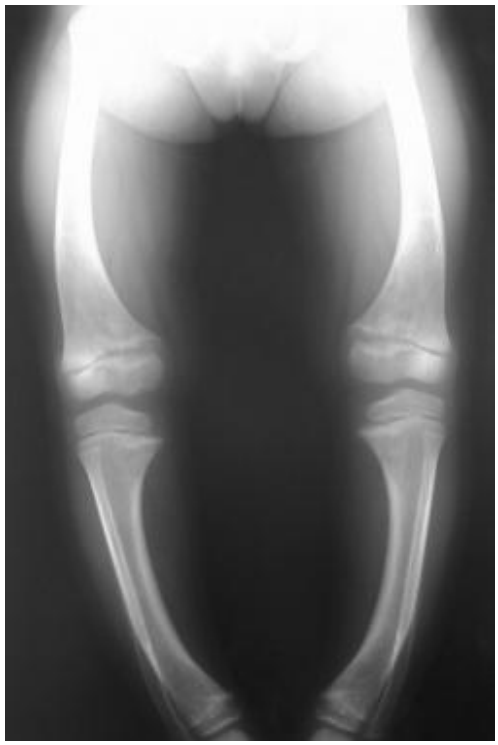
Calcification of osteoid depends on adequate levels of ionized calcium and phosphate in the extracellular fluid. Vitamin D influences these levels after its dihydroxylation into calcitriol (at the 25 position in the liver and the 1 position in the kidney). If the enzyme that controls either of these steps is deficient because of a mutation, vitamin D function is less than normal. In addition, a renal tubular defect that reduces reabsorption may alter phosphate metabolism. Finally, a genetic absence of the receptor for calcitriol results in deficient calcification. X-linked hypophosphatemic rickets and autosomal recessive hypophosphatemic rickets are the result of mutations in *PHEX* (a phosphate-regulating gene with homologies to endopeptidases on the X chromosome) and dentin matrix protein 1 (*DMP1*), respectively. Degradation of matrix extracellular phosphoglycoprotein (MEPE) and DMP-1 and release of acidic serine-rich and aspartate-rich MEPE-associated motif (ASARM) peptides are chiefly responsible for the hypophosphatemic rickets mineralization defect and changes in osteoblast-osteoclast differentiation. In patients with oncogenic osteomalacia, intact and C-terminal fibroblast growth factor-23 (FGF-23) levels are elevated, and the tumors responsible for this disease show increased expression of FGF-23 messenger ribonucleic acid (mRNA).

Rickets

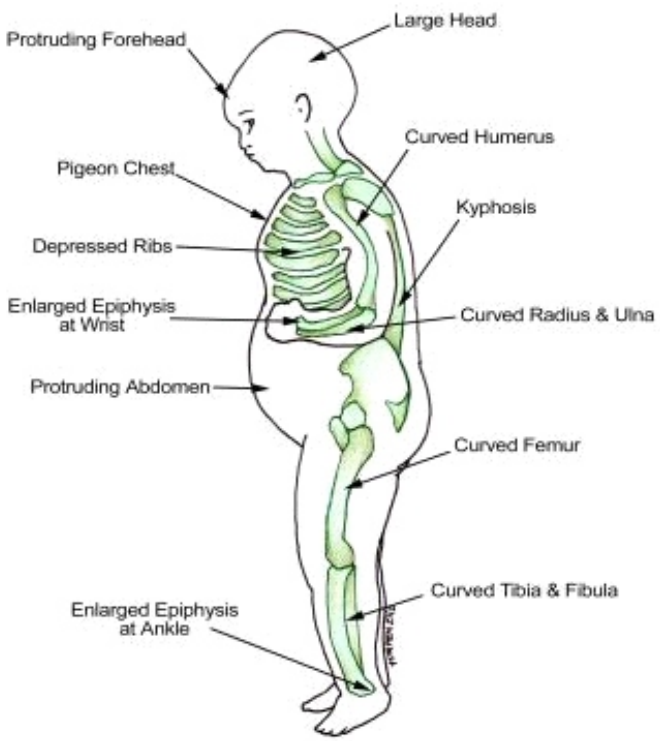
Nutritional rickets

A recommended daily allowance (RDA) for vitamin D has not been defined. Because no strong data support an RDA, recommendations for vitamin D intake actually refer to "adequate intake." Dietary rickets can be a consequence of inadequate intake of calcium, vitamin D, phosphate, or a combination of these. Infants fed exclusively with mother's milk can develop nutritional rickets because of the low content of vitamin D in breast milk (4-100 IU/L). In premature infants, insufficient amounts of calcium and phosphorus may cause nutritional rickets. Furthermore, reserves of vitamin D in the neonate highly depend on the mother's vitamin D status. Infants with low or no sun exposure may develop rickets, particularly if they have dark skin, because of decreased vitamin D production by the skin after exposure to UV light. Maternal hypovitaminosis D may cause congenital rickets in infants. In infants, clinical features of hypocalcemia and hyperphosphatemia include seizures, apnea, and tetany. In children, clinical features of rickets include the following (see the images below):

- Delayed motor milestones
- Hypotonia
- Enlargement of wrists
- Progressive bowing of long bones
- Rachitic rosary
- Harrison sulcus
- Violin case deformity of the chest
- Late closure of anterior fontanelle
- Parietal and frontal bossing
- Craniotabes
- Craniosynostosis
- Delay in teeth eruption
- Enamel hypoplasia
- Decreased bone mineral density
- Myopathy with normal deep tendon reflexes
- Propensity for infections - As a consequence of impaired phagocytosis and neutrophil motility



Radiograph in a 4-year-old girl with rickets depicts bowing of the legs caused by loading.



Findings in patients with rickets.

Fractures occur in older infants and toddlers with overt rickets and can be seen using radiography. Of note, the fractures do not resemble nonaccidental trauma fractures. Radiologic features include widening of the epiphysial plate, cupping, and deformities in the shaft of long bones. Of note, radiographs of the costochondral junction are not useful in the diagnosis of rickets. The healing process is characterized by broadened bands of increased density. Different treatment modalities are available for nutritional rickets. Oral doses of 5,000-15,000 IU/day of vitamin D for 4 weeks are generally safe and effective. If compliance cannot be assured, 100,000-500,000 IU can be given orally or intramuscularly every 6 months or 600,000 IU may be given in a single intramuscular dose. Calcium intake must be optimized at the same time. Calcium, phosphorus, and parathyroid hormone concentrations should normalize within 1-3 weeks. Radiologic lesions and clinical symptoms improve rapidly with treatment, although alkaline phosphatase levels may remain elevated for several months after radiologic resolution.

Vitamin D–dependent rickets (type I)

Also known as vitamin D–pseudodeficiency rickets (PDDR), this disorder results from a genetic deficiency in the enzyme that converts calcidiol to calcitriol in the kidney. Inheritance is autosomal recessive, and the gene is located in band 12q13.3. Clinical and laboratory examination findings are similar to those associated with nutritional rickets, with low levels of $1,25(OH)_2$ vitamin D. Levels of $1,25(OH)_2$ vitamin D may be normal but inadequately low for the levels of calcium, phosphorus, and parathyroid hormone. These patients develop rickets despite receiving vitamin D at the recommended preventive doses. Medical treatment consists of oral calcitriol (0.5-1.5mcg/day). These patients may also respond to pharmacologic doses of vitamin D (5,000-10,000U/day).

Receptor defect rickets (type II vitamin D–dependent rickets)

Receptor defect rickets (hereditary 1,25-dihydroxyvitamin D–resistant rickets [HVDRR]) results from a recessively inherited abnormality in the calcitriol receptor, causing an end-organ resistance to the vitamin. The clinical picture, which is evident early in life, consists of rickets with very severe hypocalcemia and alopecia, although a variant without alopecia has been reported. Patients without alopecia appear to respond better to treatment with vitamin D metabolites. Serum levels of $1,25(OH)_2$ vitamin D_3 are typically elevated. HVDRR can be lethal in the perinatal period. Because calciferol receptors are in many tissues, other, more subtle dysfunctions may occur. Patients are hypocalcemic and usually normophosphatemic. Several mutant forms of receptor defect rickets are recognized, with a wide range of severity and response to calcitriol therapy. Some patients are totally resistant to therapy. Some others have benefited from intravenous calcium (400-1400mg/m /day) followed by oral therapy with high doses of calcium (with secondary risk of nephrocalcinosis, hypercalciuria, nephrolithiasis, and cardiac arrhythmias). Patients with mutations in the ligand-binding domain (LBD) region of the receptor are more likely to respond to high-dose vitamin D treatment than are patients with mutations in the deoxyribonucleic acid (DNA)–binding domain (DBD) region of the receptor.

Defective 25-hydroxylase

Two cases of 25-hydroxylase deficiency have been reported, one involving a family in the United States and the other involving a family in

Germany. Inheritance is likely autosomal recessive. The clinical picture resembles that observed in nutritional rickets, with a later age of onset. Treatment with calcidiol in physiologic amounts is sufficient for this condition. Calcidiol is a natural metabolite of vitamin D. Calcidiol is hydroxylated once at the 25 position and is the circulating form for vitamin D in plasma.

Familial hypophosphatemia

Several different familial and acquired conditions may lead to hypophosphatemia in children. In familial hypophosphatemia, the kidneys fail to reabsorb sufficient phosphate, leading to low levels of serum phosphate. This is usually evident only after age 6-10 months. Prior to this occurrence, the glomerular filtration rate is low, which sustains an adequate phosphate level. Once renal maturity is reached, phosphate levels are usually less than 3.5mg/dL and are often less than 2.5mg/dL. Levels of $1,25(OH)_2$ vitamin D are actually normal in these patients, owing to an abnormal response to hypophosphatemia, in which levels of $1,25(OH)_2$ vitamin D should increase. Mutations in *PHEX* and *DMP1* result in X-linked hypophosphatemic rickets and autosomal recessive hypophosphatemic rickets, respectively. (Most families of patients with familial hypophosphatemia exhibit X-linked dominant inheritance.) *PHEX*, a phosphate-regulating gene, codes for a protease, which is an enzyme that catalyzes the hydrolysis of a protein. Degradation of MEPE and DMP-1 and release of ASARM peptides are chiefly responsible for the hypophosphatemic rickets mineralization defect and changes in osteoblast-osteoclast differentiation. FGF-23 has been implicated in the renal phosphate wasting in tumor-induced osteomalacia and autosomal dominant hypophosphatemic rickets. Mutations in the gene that codes for the main renal sodium-phosphate cotransporter (NPT2a) have been reported in some patients with familial renal calcium stones and hypophosphatemia due to a decrease in renal phosphate reabsorption. These patients have hypercalciuria and elevated levels of $1,25(OH)_2$ vitamin D_3. Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a metabolic disorder caused by homozygous loss-of-function mutations in the *SLC34A3* gene, which encodes the renal type IIc sodium-phosphate cotransporter (NaPi-IIc). The typical presentation is severe rickets, hypophosphatemia, and hypercalciuria. Autosomal recessive and autosomal dominant inheritance have each been found and have been associated with the same clinical phenotype. In approximately one third of patients, the disease appears to occur as a consequence of a new mutation. Clinical findings are similar to those of nutritional rickets, but without proximal myopathy. These patients usually have high bone density. As hypophosphatemia is usually clinically evident at a later age, infantile skull defects are not apparent. Because calcium levels remain normal, neither tetany nor secondary hyperparathyroidism are present.

Treatment

Optimal therapy consists of oral phosphate to provide 1-3g of elemental phosphate per day in 5 divided doses plus oral calcitriol (0.5-1.5mcg/day). Calcitriol (Rocaltrol) prevents increases in parathyroid hormone caused by phosphate therapy. The phosphate mixture contains mineral salts of phosphoric acid. Raising the concentration of plasma phosphate facilitates calcification of osteoid. Of note, phosphate half-life in serum is short, which usually causes low phosphate levels in fasting serum samples, despite proper therapy. Efficacy is reflected by proper linear growth. Minor changes in calcitriol dose may produce hypercalcemia and renal damage. The calcium-creatinine (mg/mg) ratio in urine must be closely monitored at first and then every 3-6 months. An elevated phosphate intake may produce secondary hyperparathyroidism. Therefore, only experienced practitioners should treat these patients.

Drug-induced rickets

Different medications may affect bone in different ways. Chronic anticonvulsant therapy (particularly with phenobarbital and phenytoin) may cause rickets, regardless of appropriate vitamin D intake. The main mechanism is related to induction of hepatic cytochrome P-450 hydroxylation, generating inactive metabolites. Levels of 25-hydroxyvitamin D_3 were reported to be low in children on long-term anticonvulsant therapy. Fractures were associated with the use of anticonvulsants in patients with cerebral palsy. A down-regulation of 25-hydroxylation by phenobarbital may explain, at least in part, the increased risk of osteomalacia, bone loss, and fractures associated with long-term phenobarbital therapy. Conversely, calcitriol levels in plasma are reportedly not low in patients taking medication for seizures. The dose of vitamin D required to prevent this type of rickets is unclear. Supplementation may not be needed. Approximately 800-1000 IU/day, plus good calcium intake, may be sufficient.

Renal Causes

Fanconi syndrome

Fanconi syndrome is a disorder of proximal renal tubular transport. Phosphate, amino acid, glucose, bicarbonate, and uric acid wasting characterize this disorder. Dysfunctions in tubular phosphate reabsorption via the sodium-phosphate cotransporter, endocytotic reabsorption of the vitamin D–vitamin D–binding protein complex mediated by megalin and cubilin, and acid-base regulation are the most important factors that cause bone mineralization defects in these patients. Lowe disease and Dent disease are familial forms of Fanconi. Two different genes have been identified as being involved in the development of Dent disease. *CLCN5* is affected in Dent disease type 1 and *OCRL1* is affected in Dent disease type 2. Other genes may also be involved, because mutations in *CLCN5* and *OCRL1* are not found in some patients. In Fanconi syndrome, which includes cystinosis and tyrosinemia, renal phosphate wasting may occur, along with aminoaciduria and glycosuria. Fanconi syndrome can have a genetic cause (as in Lowe and Dent disease), or it may be acquired from various toxins, including heavy metals (eg, mercury, lead) and drugs. The clinical picture varies with age and cause and includes severe hypophosphatemic rickets, failure to thrive, and metabolic acidosis. A potential drug-induced Fanconi syndrome has been noticed in children treated with ifosfamide, a derivative of cyclophosphamide. The syndrome presents with radiologic changes compatible with rickets. Most patients respond to a combination of managing the underlying cause when possible and vitamin D therapy. These patients do not necessarily appear to require treatment with calcitriol. Renal tubular acidosis, through phosphate wasting, may also cause rickets.

Renal osteodystrophy

In end-stage renal disease, renal 1-hydroxylase is diminished or lost, and excretion of phosphate is defective. This leads to low levels of $1,25(OH)_2$ vitamin D, hypocalcemia, and failure of osteoid calcification.

Osteodystrophy (ie, renal rickets) is the only type of rickets with a high serum phosphate level. It can be adynamic (a reduction in osteoblastic activity) or hyperdynamic (increased bone turnover). Calcium receptors (CaRs) have been discovered in bone, kidney, and intestine and also in organs not directly related to calcium regulation. Mutations that cause loss of function in the CaRs result in familial benign hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. Familial benign hypocalciuric hypercalcemia is usually associated with heterozygous inactivating mutations of the *CAR* gene, whereas neonatal severe hyperparathyroidism is usually due to homozygous inactivation of the *CAR* gene. Familial benign hypocalciuric hypercalcemia is generally asymptomatic and is characterized by mild to moderate, lifelong hypercalcemia; relative hypocalciuria; and normal intact parathyroid hormone. Individuals with neonatal severe hyperparathyroidism frequently develop life-threatening hypercalcemia.

Treatment of these patients includes phosphate binders, a low phosphate intake, and calcitriol and other vitamin D analogs.

Tumor-Induced Osteomalacia

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome with hypophosphatemia secondary to decreased renal phosphate reabsorption, normal or low serum 1,25-dihydroxyvitamin D concentration, osteomalacia, and myopathy. Several mesenchymal tumors of bone or connective tissue (including nonossifying fibromas, fibroangioma, and giant cell tumors) secrete a phosphaturic substance (parathyroidlike protein) that results in rickets. The age of onset has been late childhood, adolescence, or young adulthood. The clinical characteristics are similar to those associated with familial hypophosphatemia. FGF-23 causes renal phosphate wasting in tumor-induced osteomalacia. Treatment is surgical removal of the tumor (if it can be located), with excellent results.

Other Causes

Hypophosphatasia

This autosomal recessive condition, which results in low activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP), causes rickets without disturbance of calcium and phosphate metabolism. Levels of TNSALP substrates, namely pyridoxal-5'-phosphate (PLP), inorganic pyrophosphate (PPi), and phosphoethanolamine (PEA) in serum and urine, are increased. Clinical severity widely varies, ranging from death in utero to pathologic fractures first presenting only in adulthood. Six clinical forms of hypophosphatasia have been distinguished, although form assignment may be challenging in some cases. This classification is based on the age at which skeletal lesions are discovered: perinatal (lethal), infantile, childhood, and adult. Two particular forms include odontohypophosphatasia (only biochemical and dental manifestations are present, with no clinical changes in long bones) and pseudohypophosphatasia. The effects of bone marrow transplant in hypophosphatasia are transient, and bone lesions may recur 6 months after the transplant. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used in patients with childhood hypophosphatasia with some clinical improvement. The US Food and Drug Administration has approved asfotase alfa as the first permitted treatment for perinatal, infantile and juvenile-onset hypophosphatasia. A study by Whyte et al found that asfotase alfa enzyme replacement therapy is effective and safe for treating children with hypophosphatasia.

McCune-Albright syndrome

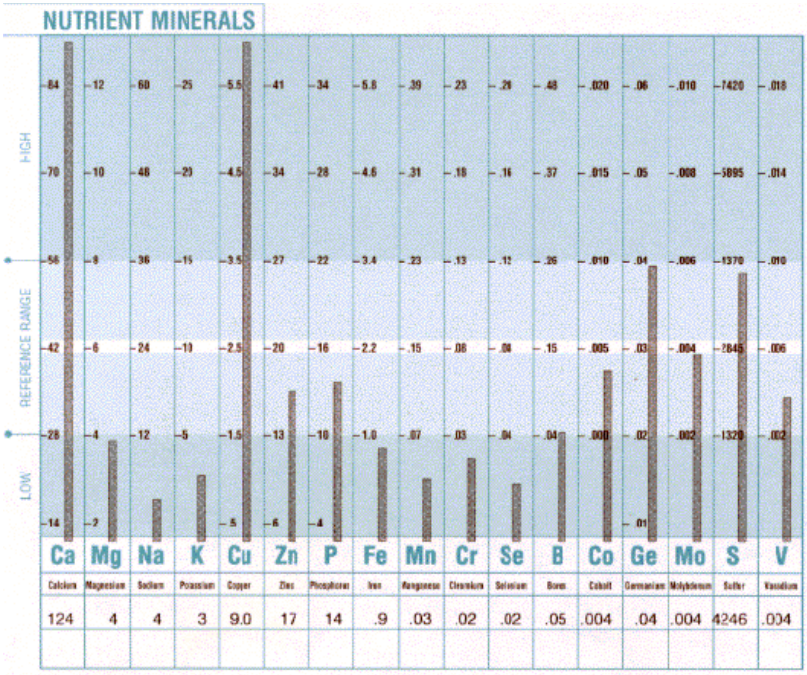
Patients with McCune-Albright syndrome may have hypophosphatemia secondary to urinary phosphate leak, which may cause osteomalacia. Fasting phosphate levels should always be monitored in these patients, and phosphate supplements prescribed when indicated.

Syndrome resembling osteogenesis imperfecta

Syndrome resembling osteogenesis imperfecta (SROI) with mineralization defect is clinically indistinguishable from moderate to severe osteogenesis imperfecta. (This rare form, in fact, has been termed type VI osteogenesis imperfecta.) It can only be diagnosed with bone biopsy, in which a mineralization defect that affects the bone matrix and sparing growth cartilage are evident. These patients have neither dentinogenesis imperfecta nor Wormian bones. Despite the histologic mineralization defect, no radiologic signs of growth plate involvement are seen. The pattern of inheritance is not clear, but a case of 2 siblings from healthy consanguineous parents has been described, suggesting gonadal mosaicism or a somatic recessive trait. No mutations of *COL1A1* and *COL1A2* genes have been found in these patients, and collagen structure appears to be normal. This form shares several characteristics with fibrogenesis imperfecta ossium. A mild, rare form of this condition may occur (3 patients in a series of 128 bone biopsies performed to assess bone fragility). These patients do not appear to respond well to treatment with intravenous bisphosphonates.

INTERPRETATION

NUTRIENT MINERAL LEVELS



This section of the report may discuss those nutritional mineral levels that reveal moderate or significant deviations from normal. The light blue area's of each graph section represents reference ranges based upon statistical analysis of apparently healthy individuals. The following section, however, is based upon clinical data, therefore, a mineral that is moderately outside these reference ranges may not be commented on unless determined to be clinically significant.

NOTE: For those elements whose levels are within the normal range, it should be noted that nutritional status is also dependent upon their critical balance with other essential nutrients. If applicable, discussion regarding their involvement in metabolism may be found in the ratio section (s) of this report.

CALCIUM (Ca)

Your tissue calcium level is elevated above normal. High tissue calcium does not necessarily indicate excessive calcium, but rather the calcium is not being properly utilized. Proper utilization is often dependent upon calcium's relationship with other essential minerals, such as phosphorus and magnesium. A deficiency of either or both can result in excessive calcium deposition into tissues other than the primary storage sites of calcium (bones and teeth). Deposition of calcium into the soft tissues, includes not only the hair, but also the skin, joints, arteries, lymph nodes, gallbladder, etc... If soft tissue deposition of calcium continues for an extended period of time, certain conditions may develop, such as:

Depression
Anemia
Muscle Cramps
Premature Aging of the Skin
Joint Stiffness
Insomnia
Fatigue

SOME FACTORS THAT MAY CONTRIBUTE TO HIGH CALCIUM LEVELS

Low Thyroid Activity
Low Protein Intake
Tissue Alkalinity
Low Adrenal Activity
High Carbohydrate Intake
Low Phosphorus Retention

PROTEIN AND HIGH TISSUE CALCIUM

High tissue calcium levels, such as found in this case, are often the result of low protein intake or errors in protein metabolism. A reduction of hydrochloric acid production by the body and deficiencies of essential vitamins and minerals will contribute to an increased retention of calcium.

HYPOGLYCEMIA PROFILE

According to this laboratory's research, slow metabolizers are prone to hypoglycemia (low blood sugar). This condition has become relatively common in modern society due to a number of factors, one of which is an improper diet. Hypoglycemia can be contributed to by dietary factors other than the commonly known factors of eating excess refined carbohydrates and sugars. Dairy products, fruit juices and foods high in fat content may also produce hypoglycemic symptoms. For this reason, observance of the dietary recommendations is of special importance for individuals at risk of hypoglycemic episodes.

The most common symptoms associated with hypoglycemia include, headaches, mood swings, lethargy, loss of concentration, and mid-afternoon loss of energy.

HYDROCHLORIC ACID PRODUCTION AND PROTEIN DIGESTION

Your mineral profile may be reflective of a deficiency in hydrochloric acid (HCL) production, which can result in inadequate protein digestion. Hydrochloric acid in sufficient amounts is necessary for the complete digestion and utilization of dietary protein. Symptoms, such as, bloating of the stomach, flatulence and constipation may be observed with an HCL deficiency, especially following high protein meals.

SODIUM (Na)

The current tissue sodium level of 4 mg% is below normal. Sodium is vital for the maintenance of body fluids and the acid-alkaline balance. Sodium is also necessary for the transport of nutrients across the cell membrane, especially glucose and the essential amino acids. Low sodium in the slow metabolizer (Type #1), such as in this case, can be indicative of either a decreased ability to retain and utilize sodium, or most likely, a decrease in dietary sodium intake.

CONDITIONS ASSOCIATED WITH LOW TISSUE SODIUM

Poor Digestion
Constipation
Low Blood Pressure
Fatigue
Flatulence
Low Adrenal Cortical Activity
Dry Skin

SOME FACTORS THAT MAY CONTRIBUTE TO A LOW TISSUE SODIUM LEVEL

High Calcium Intake
Slow Metabolism
High Magnesium Intake
Low Sodium Intake
Chronic Diarrhea

POTASSIUM (K)

Low tissue potassium may be due to poor retention of this mineral, even though dietary intake of potassium may be adequate. Poor potassium retention can result from adrenal and thyroid insufficiency, prolonged diarrhea, or from the use of medications, such as diuretics and laxatives. Non-steroidal over-the-counter anti-inflammatories will also suppress adrenal function.

ELECTROLYTE LEVELS AND ENERGY

When both sodium and potassium TMA levels are below normal, it is further indication that adrenal response may be diminished. If this pattern becomes chronic, emotional changes may occur due to a lack of sufficient energy production by the adrenal glands. When energy levels are extremely low, the ability to cope with stress may become markedly reduced.

COPPER (Cu)

Your copper profile is indicative of excess copper in the tissues. This element will have an antagonistic effect upon the functions of other essential elements. In particular, copper has a direct antagonistic effect on zinc activity within the body. Excess accumulation of copper may produce signs of zinc deficiency, even though zinc intake may be adequate or even if the tissue zinc level is within the normal range.

ELEVATED BODY BURDENS OF COPPER

In women, chronically high tissue copper levels increase the tendency toward, or are associated with one or more of the following symptoms:

Anemia
Allergies
Hair Loss
Appetite Disturbance
Hyperactivity
Low Thyroid Activity
Iron Deficiency
Headaches (frontal)
Skin Conditions
Constipation
Learning Disability

NOTE:

- Excess copper is frequently associated with endometriosis and premenstrual syndrome.
- During or following pregnancy, copper accumulation frequently increases.

SOME SOURCES OF COPPER THAT MAY CONTRIBUTE TO AN ELEVATED COPPER LEVEL

Excess copper accumulation can be contributed to by several factors:

* Foods high in copper
* Drinking water run through copper water pipes
* Prolonged copper supplementation
* Zinc deficiency
* Vitamin B6 Deficiency
* Vitamin C Deficiency
* Oral Contraceptive Use
* Copper IUD

NOTE:

- Exogenous contamination can occur from frequently swimming in pools or spas where copper sulfate has been added as an algicide.
- During pregnancy, the fetus inherits many of the mother's mineral profiles. Research studies have shown that children of high copper profile women have a much greater frequency of acquiring higher levels of copper, than from those women whose levels were normal.

COPPER (Cu) AND SCOLIOSIS

Elevated hair levels of copper have been correlated with ligamentous abnormalities. Excess copper is frequently seen in cases of scoliosis (spinal curvature). These cases are usually seen in families and will affect the female more often than the male. Other members of the family may be tested, especially if they are in the growing stages.

METABOLIC FACTORS ASSOCIATED WITH HIGH COPPER (Cu)

Tissue copper retention can occur in the body in the absence of excessive dietary copper intake. High copper levels have been found to be a result of past incidence of hepatitis, mononucleosis, decreased liver or gallbladder function and adrenal insufficiency. Excessive tissue copper levels may have been present for several years, as a result of an inability to eliminate the metal rather than just recent excessive dietary intake. However, it is still recommended that excessive intake of those foods that contain appreciable amounts of copper be avoided. The Dietary Section will contain a listing of high copper foods to temporarily avoid or limit in the diet.

CANDIDIASIS

The following conditions are associated with a predisposition toward yeast and/or fungal manifestation:

* Brownish Discoloration with thickening or grooving of the nails.
* Eczema like Skin Conditions
* Abdominal Bloating
* Fatigue
* Inflammation of the nail bed
* Vaginal Discharge

FACTORS CONTRIBUTING TO CANDIDIASIS

The following factors may contribute to or predispose an individual to recurring fungal and/or yeast manifestations:

Hypothyroidism
Oral Contraceptives
Following Major Surgery
Zinc Deficiency
Iron Deficiency
Antibiotics
Following Pregnancy
Stress
Copper Excess

HIGH COPPER (Cu) AND APPETITE DISTURBANCE

Abnormal taste perception and appetite changes can occur in the presence of a zinc deficiency or a relative zinc-copper imbalance. Excess copper retention relative to zinc can often lead to increased craving for sweets, since unlike other foods, the taste acuity for sweets is least affected by zinc deficiency. This may eventually contribute to hinging and other appetite disturbances as well.

IRON (Fe)

Low tissue iron can be due to several factors other than low intake or excessive iron loss. Iron deficiency can be a result of any one or a combination of the following factors:

Vitamin C Deficiency
Excess Calcium
Excess Zinc
Excessive Aspirin Use
Excessive Tea Intake
Excess Copper
Vegetarian Diet
Excess Toxic Metals
Antacids
Excessive Milk Intake

MANGANESE (Mn) AND BLOOD SUGAR REGULATION

Low manganese levels are fairly common, however, a level of 0.03 mg% is significantly below normal. The mineral manganese in combination

with certain vitamins and minerals is essential for many biochemical reactions, including carbohydrate metabolism and energy production. Manganese deficiency is frequently related to such manifestations as, low blood sugar levels, ligamentous problems and reproductive dysfunction.

CHROMIUM (Cr)

Tissue chromium deficiency is increasingly becoming more common among those people tested in the United States, Canada and Western Europe. This may be due to the excessive consumption of refined carbohydrates and sugar in these areas. Low chromium levels have been implicated in producing a decreased carbohydrate tolerance. Chromium appears to increase the effectiveness of insulin. A deficiency may be a contributing factor to hypoglycemia as well as other blood sugar disturbances. Increasing protein in the diet should aid in improving sugar regulation, as well as chromium status.

SELENIUM (Se)

The tissue selenium level is below normal, which is indicative of bio-unavailability of this essential element. Selenium has anti-oxidant properties that is similar to vitamin E, and will prevent free radical damage to the cells. This important element also activates certain essential enzymes. Selenium has been found to be necessary for healthy hearts and in some cases has been shown to be an anti-cancer agent by reducing and preventing tumor growth in animal studies. A low tissue level of selenium may reduce the body's ability to protect against possible mercury and cadmium toxicity.

TUNGSTEN (W)

The current level of tungsten is below the established reference range. Currently, there is no information regarding whether tungsten is essential for optimum biochemical function.

TROUBLESHOOTING

BLOOD CALCIUM

Reference Range

Calcium concentration, both total and free, is characterized by a high physiological variation, depending on age, sex, physiological state (eg, pregnancy), and even season (owing to the seasonal variation of vitamin D, which is directly involved in the regulation of calcium concentration). Therefore, separate reference intervals have been established according to the age and sex of the individual being tested.

Total calcium reference ranges in males are as follows:

- Younger than 12 months: Not established
- Age 1-14 years: 9.6-10.6 mg/dL
- Age 15-16 years: 9.5-10.5 mg/dL
- Age 17-18 years: 9.5-10.4 mg/dL
- Age 19-21 years: 9.3-10.3 mg/dL
- Age 22 years and older: 8.9-10.1 mg/dL

Total calcium reference ranges in females are as follows:

- Younger than 12 months: Not established
- Age 1-11 years: 9.6-10.6 mg/dL
- Age 12-14 years: 9.5-10.4 mg/dL
- Age 15-18 years: 9.1-10.3 mg/dL
- Age 19 years and older: 8.9-10.1 mg/dL

Free (ionized) calciumreference ranges in males are as follows:

- Younger than 12 months: Not established
- 1-19 years: 5.1-5.9 mg/dL
- Age 20 years and older: 4.8-5.7 mg/dL

Free (ionized) calciumreference ranges in females are as follows:

- Younger than 12 months: Not established
- 1-17 years: 5.1-5.9 mg/dL
- Age 18 years and older: 4.8-5.7 mg/dL

Calcium (urine) reference ranges are as follows*:

- Males: 25-300 mg/24-hour urine collection
- Females: 20-275 mg/24-hour urine collection
- Hypercalciuria: >350 mg/specimen
- *Values are for persons with average calcium intake (ie, 600-800 mg/day)

BOUQUET

Brain Teasers

1. **Which of the following tests employs carbon particles as detection/testing system for diagnosing syphilis?**
   A. RPR
   B. TPHA
   C. Immunochromatography
   D. Latex agglutination.

2. **Which of the following diseases can cause false positive reactions with an RPR testing kit for diagnosing syphilis?**
   A. Leprosy
   B. Malaria
   C. Infectious mononucleosis
   D. Any of the above.

3. **In which of the following typhoid antigens in a Widal set do you expect coarse agglutination?**
   A. TO C. AH
   B. TH D. BH.

4. **Which of the following typhoid antigens is species-specific?**
   A. TO C. AH
   B. TH D. BH.

ANSWER: 1.A, 2.A, 3.A, 4.A

BOUQUET

In Lighter Vein

Aftr engagemnt!

Girl:Now stop looking at girls,

u r commited now!

Boy:Oho what do u

mean,if i m on diet,

that doesnt mean that

i cant look at MENU . .

Lalu ji ek mahina obama ke pas se engish ki training lekar vaps aaye
ek din unhe ek call aaya.

lalu ji bole

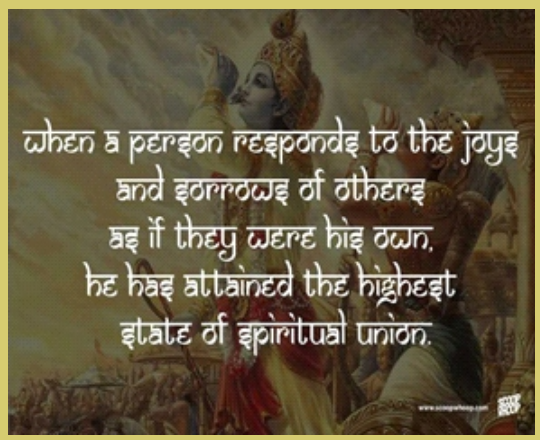
"Who is speaking?".

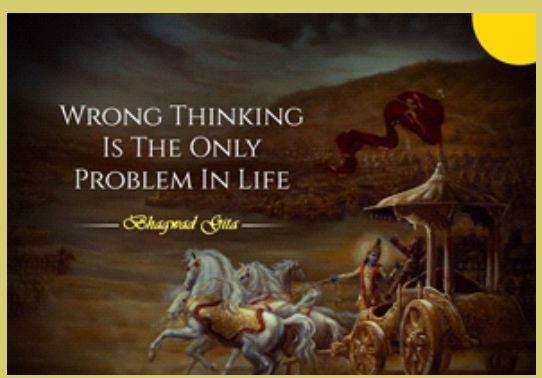
jawab aaya

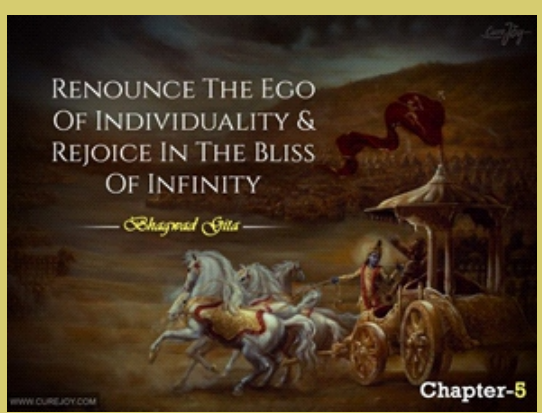
"Hum Sasura Obama bol raha hun".

A Husband & Wife Were Arguing Over Some Issue.
After Much Of Discussion,
Wife Finally Said:
"Tell Me Dear ,
Do You Want To Win
OR
Do You Want To Be
Happy . . ?
Argument Ended

Wisdom Whispers







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