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SUPPLEMENTS

Ins and outs of drug induced nutrient depletion

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SUMMARY

Coenzyme Q10

Folic Acid

Vitamin B12

Zinc

Vitamin D

Melatonin

Magnesium

Calcium Citrate

Probiotics

COENZYME Q10 - CLINICAL PEARLS

Other Popular Names
CoQ10, Ubiquinone, Mitoquinone, Ubidecarenone

Background

Coenzyme Q10 is recognized today as an antioxidant and a crucial cofactor in a process known as mitochondrial respiration. The coenzyme helps shuttle electrons in the mitochondria of cells to form ATP.[4]

Research indicates that coenzyme Q10 supplementation benefits heart muscle by improving mitochondrial function. Furthermore, clinical studies indicate that coenzyme Q10 supplementation may benefit patients with heart failure. A one-year, double-blinded, multicenter trial conducted in 1993 aimed to study its efficacy on patients with NYHA class III and IV heart failure. Adjunctive daily treatment with 2 mg/kg of coenzyme Q10 demonstrated statistically significant declines in hospitalizations (73 vs 118, $P < 0.001$). It is important to note, however, that while the American College of Cardiology acknowledges a benefit in subjective measures (i.e., quality of life) with the use of coenzyme Q10, it does not support its use due to a lack of concrete benefit on mortality rates.[4, 10, 14]

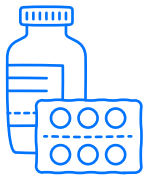
Reduction of coenzyme Q10 in muscle tissue is thought to be the cause of statin-induced myopathies (muscle pain). Statin administration has been shown to lead to lower levels of coenzyme Q10 in the muscle tissue. Mevalonic acid is the precursor needed in the production of coenzyme Q10. HMG-CoA reductase inhibitors, such as the statins, inhibit the production of this precursor.[4]

Dosing

Common Daily Dose:
10 to 300 mg/day
(Single or divided doses)[6]

Recommended Doses:
Coenzyme deficiency:
200 mg daily[4]

Maximum Total Daily Dose:
3,000 mg of ubiquinone[1]
Avoid daily doses over 300 mg in patients with liver problems (may affect liver enzymes).[1]
Nanoparticle and solubilized versions of coenzyme Q10 have better bioavailability.[1, 9]



Uses

Coenzyme Q10 deficiency – Level A Evidence for Use
Heart Failure, Hypertension – Level B Evidence for Use

Drugs Known To Deplete

Statins, gemfibrozil, tricyclic antidepressants, alpha-2-adrenergic agonists (e.g., clonidine), beta blockers (e.g., propranolol), hydralazine, thiazide diuretics, phenothiazine derivatives (e.g., chlorpromazine), thioxanthene derivatives.

Mechanisms of Depletion

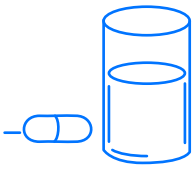
Statins – Statins block the synthesis of a precursor of coenzyme Q10, mevalonic acid. Based on studies, this effect appears to be dose related. Efficacy of coenzyme Q10 on statin-associated myopathy has not been conclusive, and administration has not been shown to impact the number of patients who remain on statin therapy.[11]

Antihypertensives – Thiazides, vasodilators, alpha-2-adrenergic agonists, and beta blockers block the synthesis of coenzyme Q10.[12] Alpha-2-adrenergic agonists have effects that possibly inhibit the action of coenzyme Q10 on the heart.[13]

Symptoms of Deficiency

Muscle pain and weakness[1]

Fatigue and/or "cloudy thinking"[1]



Administration

Split dosing: Studies indicate split dosing may be superior to single daily dosing.

Take with fat-containing foods. Studies show significantly better absorption if taken with foods such as peanut butter.[8,3]

Interactions

Warfarin –Coenzyme Q10 is structurally similar to K-vitamin and can decrease the effectiveness of warfarin. Monitor INR.[2,7]

Antihypertensives – Coenzyme Q10 can increase the effects of antihypertensives.[7]

Thyroid agents – Coenzyme Q10 can interact with thyroid agents and affect hormone levels. Monitor and use with caution.[1]

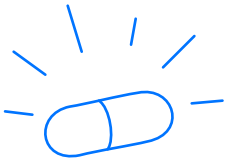
Monitor

Hypotension – can reduce blood pressure and increase the effects of antihypertensives.7

Diabetic Hypoglycemia – Coenzyme Q10.[6]

Surgeries – should discontinue two weeks prior to surgery, since it can interfere with blood pressure control.7

Monitor INR if patient is taking warfarin (can decrease INR).[7]



Adverse Reactions

Diarrhea, dyspepsia, GI discomfort, nausea, fatigue, headache.

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FOLIC ACID - CLINICAL PEARLS

Other Popular Names
Folacin, Folate, Vitamin B9

Background

Folate is a B-vitamin that is intimately involved in the production of DNA and RNA and the creation of healthy new cells — particularly red and white blood cells — by means of cellular division and transmission of genetic code.[1]

Folate is naturally occurring in many different food sources including leafy green vegetables such as spinach, broccoli, and lettuce; fruits like bananas, melons, and lemons; and dried beans, peas, and nuts. Folic acid, the synthetic form, is more bioavailable, and it is commonly used to fortify foods such as bread, cold cereals, and grains.[2]

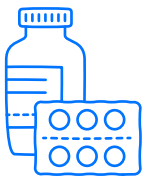
Research indicates that folate deficiency in pregnancy dramatically increases the risk of megaloblastic anemia and birth defects including spina bifida, anencephaly, and cleft palate. Folate deficiency has also been linked to the likelihood of having a premature or low birth-weight baby.[4] Clinical research shows that supplementation with folic acid during pregnancy decreases the risk of megaloblastic anemia by 79%.[5] The CDC recommends that all women, both before and during pregnancy, take 400 mcg of folic acid daily to prevent these birth defects.[4]

Dosing

Common Daily Dose:
400 mcg/day in adults ≥ 13 years, 600 mcg/day in pregnant women, 500 mcg/day in lactating women5

Recommended Doses:
Megaloblastic macrocytic anemia:
400 mcg to 1000 mcg/day6

Neural tube defects:
400 mcg to 600 mcg/day7



Uses

Megaloblastic macrocytic anemia due to folate deficiency – Level A Evidence for Use[6]
Neural tube defects – Level A Evidence for Use[7]
Methotrexate-induced toxicity – Level G Evidence for Use[6]

Drugs Known To Deplete

Methotrexate, aminosalicylic acid, carbamazepine, pancreatic enzymes (e.g., pancrelipase, pancreatin), pentamidine, barbiturates (e.g., phenobarbital, primidone), phenytoin, sulfasalazine, triamterene, trimethoprim (including SMX-TMP), valproic acid and derivatives (e.g., valproate, divalproex), isotretinoin.[5]

Mechanisms of Depletion

Methotrexate – studies show that patients treated with methotrexate have lower folic acid levels than controls (median 4.36 vs 7.37 ng/ml, $p < 0.001$) depending on the weekly administered dose.[8]

Aminosalicylic acid – treatment with aminosalicylic acid is associated with malabsorption of dietary folate, resulting in worsened deficiency in active tuberculosis patients.[9]

Antiepileptics and anticonvulsants – decreased intestinal folic acid absorption and induced hepatic enzymes, resulting in increased folate demand, associated with treatment with use of these medications (e.g., primidone, phenobarbital, phenytoin, valproic acid, carbamazepine, etc.).[10]

Pancreatic enzymes – in vivo testing shows pancreatic extracts forming insoluble complexes with folate leading to diminished dietary folate absorption.[11]

Sulfasalazine – competitively inhibits absorption of folic acid in the intestine and interferes with the breakdown of dietary folate into its absorbable form.[12]

Triamterene – competitively inhibits absorption of folic acid in the intestine and interferes with the breakdown of dietary folate into its absorbable form.[13]

Trimethoprim – inhibits the enzyme involved in the conversion of folate to its active form.[14]

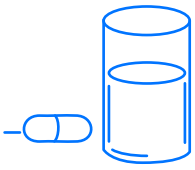
Isotretinoin – studies show significant reduction in serum folic acid in patients taking isotretinoin.[15]

Symptoms of Deficiency

Fatigue and irritability[3]

Diarrhea[3]

Smooth or tender tongue[3]



Administration

Take with or without food daily. No significant data regarding the impact of food on absorption.

If taken for the indication of megaloblastic anemia, folic acid must never be administered without an appropriate dose of B12.

Interactions

Anticonvulsants and antiepileptics – Folic acid may decrease the serum concentrations of Phenytoin and Barbiturates like Phenobarbital, resulting in a reduced effect. Use of folic acid is cautioned in patients on these medications and increased monitoring is recommended when used.[5]

Pyrimethamine – Folic acid can antagonize the antiparasitic effects against toxoplasmosis and Pneumocystis carinii pneumonia causing a diminished therapeutic effect.[5]

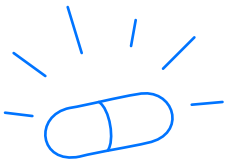
Methotrexate – There is evidence that folic acid supplements may reduce efficacy of methotrexate in the treatment of acute lymphoblastic leukemia, and theoretically could reduce its efficacy in the treatment of other cancers.[5]

Monitor

Monitor B12 levels as high folic acid intake can mask vitamin B12 deficiency.[2]

Seizures – Folic acid should be taken with caution by patients being treated for seizures as it could reduce serum concentration of these medications.[5]

Cardiovascular events – High daily doses of folic acid are linked to an increase in adverse cardiovascular events.[5]



Adverse Reactions

Abdominal cramps, diarrhea, nausea, rash, altered sleep patterns, irritability, bitter taste in mouth.[5]

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VITAMIN B12 - CLINICAL PEARLS

Other Popular Names
Cyanocobalamin, Methylcobalamin

Background

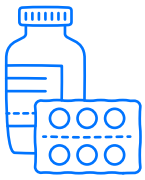
Vitamin B12 exists in many forms and contains the mineral cobalt resulting in compounds containing B12 being called "cobalamins."[1]

Vitamin B12 is necessary for proper red blood cell formation, protein metabolism, neurological function, and DNA synthesis.[2] It is found naturally in animal products, including meat, poultry, fish, eggs, and milk products. Some foods are also fortified with vitamin B12, most notably breakfast cereals.[3]

Although uncommon, vitamin B12 deficiency can be a result of malabsorption from food, postsurgical malabsorption, and pernicious anemia. People following diets that are deficient of vitamin B12, such as vegan and vegetarian diets, are also at a much higher risk of developing a deficiency.[3] If vitamin B12 deficiency is left untreated it could result in a variety of complications including anemia, muscle weakness, fatigue, nerve damage, mood disturbances, and intestinal problems.[2]

Dosing

Recommended Doses:
Vitamin B12 deficiency:
1000 to 2000 mcg/day oral [1]
Pernicious anemia:
1000 to 2000 mcg/day oral9



Uses

Vitamin B12 deficiency – FDA Indication[4]
Pernicious anemia – FDA Indication[4]

Drugs Known To Deplete

Aminosalicylic acid, H2 blockers (e.g., cimetidine, ranitidine, nizatidine, famotidine), metformin, phenytoin, phenobarbital, primidone, proton pump inhibitors (e.g., omeprazole, pantoprazole, lansoprazole), colchicine.[1]

Mechanisms of Depletion

Aminosalicylic acid – Studies have shown that aminosalicylic acid can reduce absorption of dietary vitamin B12 by up 55%.[5]

H2 blockers/Proton pump inhibitors (PPIs) – The reduction of gastric acid and pepsin caused by H2 blockers and PPIs can result in reduced absorption of dietary vitamin B12, but it does not interfere with supplemental vitamin B12.[6,8]

Metformin – Can reduce serum levels of vitamin B12 by decreased intrinsic factor secretion, reduced uptake of vitamin B12-intrinsic factor complexes, altered bowel motility, and bacterial overgrowth.[7]

Symptoms of Deficiency

Weakness/fatigue[3]

Constipation[3]

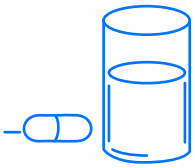
Loss of appetite/weight loss[3]

Numbness of hands and feet[3]

Depression[3]

Confusion[3]

Poor memory[3]



Administration

IM or deep SQ are preferred routes of administration. Oral administration can cause variability in absorption but is effective in anemia if patient does not tolerate or refuses IM/SQ.[9]

Interactions

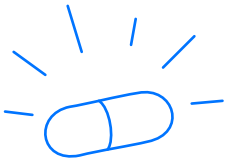
Chloramphenicol – Case reports indicate that parenteral chloramphenicol can interfere with red blood cell response to supplemental vitamin B12.[3]

Vitamin C – Coadministration of vitamin B12 and vitamin C may reduce the available amount of vitamin B12. To avoid, take vitamin C two or more hours after Vitamin B12.[2]

Monitor

General: Vitamin B12 and peripheral blood counts should be monitored one month after beginning treatment, and every three to six months thereafter.[9]

Pernicious anemia: Monitor normal hematological parameters, serum potassium, and platelet counts during treatment.[9]



Adverse Reactions

Allergic reactions (erythema, urticaria), nausea, vomiting, dysphagia, dizziness, headache.[1,2]

References

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ZINC - CLINICAL PEARLS

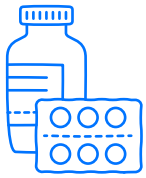
Other Popular Names
Zinc Sulfate, Zinc Gluconate, Zinc Acetate

Background

Zinc in an important trace mineral utilized by the body to promote normal human functioning. It is involved in various physical processes in the body and utilized as an enzyme cofactor to aid in the maintenance of cell membrane integrity.

Since the body has no specialized zinc storage system, zinc must be regularly consumed as part of the diet. Good food sources of zinc are animal proteins including beef, pork, lamb, poultry, and fish. Other food sources include nuts, whole grains, legumes, and yeast. Vegetables and fruits are not good sources of zinc since the zinc in plant proteins is not as available as animal proteins for use by the human body.[1,2]

Zinc deficiency is best characterized by loss of appetite, growth retardation, and impaired immune function. Severe cases of zinc deficiency can lead to hair loss, hypogonadism, impotence, and eye and skin lesions. Many of the symptoms are non-specific thus medical examination is necessary to determine whether a deficiency in zinc is present. While a deficiency is uncommon in North America, groups that are more prone to zinc deficiency are people with GI diseases, pregnant and lactating women, vegetarians, people with alcohol use disorder, and people with sickle-cell disease.[3]



Uses

Wilson's Disease – FDA Indicated[15]
Zinc deficiency – FDA Indicated[15]

Drugs Known To Deplete

Quinolone and Tetracycline antibiotics, Thiazide Diuretics, ACE inhibitors.

Dosing

Common Daily Dose: (Recommended Daily Allowance):
11 mg/day in males 14 years and older, 9 mg/day in females 14 to 18 years, 8 mg/day in females 19 years and older, 11 mg/day in pregnant women, and 12 mg/day in lactating women.[2]

Recommended Doses:
Zinc deficiency: 2-3 times the RDA in mild deficiency for six months and four to five times the RDA for moderate deficiency for six months.16

Wilson's Disease:
Zinc acetate 50mg (expressed as elemental zinc) three times daily.16
Zing salts that contain roughly 50mg elemental zinc17
Zinc acetate (dehydrate) 168mg
Zinc chloride 104mg
Zinc citrate (trihydrate) 160mg
Zinc gluconate 348mg
Zinc lactate 186mg
Zinc sulfate (heptahydrate) 220mg

Mechanisms of Depletion

Deferoxamine – studies show that deferoxamine increases urinary excretion of zinc in a dose-dependent manner therefore lowering serum levels in some patients.[5]

Penicillamine – forms chelates with zinc leading to increased urinary excretion. Case reported of severe, symptomatic zinc deficiency after two years of treatment with up to 2 g/day of penicillamine.[7]

Propofol – contains 0.005% EDTA which chelates zinc resulting in an increased excretion of zinc in severely ill patients who already have increased zinc excretion.[8]

Thiazide diuretics – increases urinary zinc excretion by 50-60%, likely to be sustained during at least three years of treatment with thiazides. Prolonged thiazide treatment may also deplete tissue zinc.[9]

Symptoms of Deficiency

Poor appetite[2]

Problems with sense of taste and smell[2]

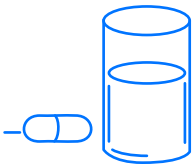
Frequent infections[2]

Slowly healing wounds[2]

Hypogonadism in males[2]

Loss of hair[2]

Skin sores[2]



Administration

Zinc acetate should be taken on an empty stomach at least one hour before or two to three hours after meals.[15]

Interactions

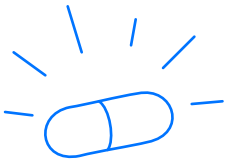
Cephalexin – Zinc may decrease cephalexin levels by chelating cephalexin in the gut preventing its absorption. This decrease in cephalexin levels may run the risk of treatment failure.[12]

Tetracycline and quinolone antibiotics – Tetracyclines form complexes with zinc in the GI, thus reducing absorption of both zinc and tetracycline when taken at the same time.[10,11]

Integrase inhibitors – Studies have shown that other divalent cations, such as iron and calcium, can decrease blood levels of integrase inhibitors. Theoretically zinc can cause the same effect since it is also a divalent cation.[13]

Monitor

When administered with antibiotics, monitor levels of both zinc and the antibiotic as it could affect the absorption of the antibiotic.[12]



Adverse Reactions

Nausea, vomiting, diarrhea, copper deficiency, indigestion, headache, irritation and corrosion of the GI tract, acute renal tubular necrosis, interstitial nephritis, and flu-like CNS symptoms.[1, 4]

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VITAMIN D - CLINICAL PEARLS

Other Popular Names
Ergocalciferol (Vitamin D2), Cholecalciferol (Vitamin D3)

Background

Vitamin D is a fat-soluble vitamin with two physiologically significant forms, ergocalciferol (vitamin D2), and cholecalciferol (vitamin D3). Vitamin D undergoes hydroxylations in the body in order to convert into the active metabolite calcitriol.[1] By promoting calcium absorption in the gut, vitamin D maintains the proper amount of serum calcium and phosphate to enable correct bone mineralization. Vitamin D is also needed for bone growth and remodeling by the osteoclasts and osteoblasts. Other roles of vitamin D include reduction of inflammation, modulation of cell growth, and neuromuscular and immune growth.[2]

There are three main sources of vitamin D: dietary sources, supplements, and through the skin. Common foods that are high in vitamin D are egg yolks and fish. There are also a variety of foods that are fortified with vitamin D, most commonly milk and cereals. Also, the body forms vitamin D after exposure to sunlight via the skin.[3]

It is fairly common for people to become vitamin D deficient. The most common ways are not getting enough from diet and not enough exposure to sunlight. Other less common reasons are a malabsorption problem, the liver and kidneys being unable to convert vitamin D to its active form, and drugs that interfere with vitamin D conversion and/or absorption.[3]

Two notable complications that can result from vitamin D deficiency are rickets and osteomalacia, both of which are associated with weak bones. Groups of people at increased risk are breastfed infants and older adults.[2]

For the treatment of nutrient depletion, the vitamin D forms of Colecalciferol and Ergocalciferol are preferred. They exhibit a slow onset of action and a long duration. The two most common forms of Vitamin D are considered interchangeable regarding their dosing and administration.[19]

Dosing

Common Daily Dose: (Recommended Daily Allowance):
400 IU/day in patients from birth to 12 months, 600 IU/day in patients 1 year to 70 years, 800 IU/day in adults 71 years and older.[3]

Recommended Doses:
Hypoparathyroidism: 50,000 – 200,000 IU Vitamin D3 daily14
Rickets: 12,000 – 500,000 IU Vitamin D2 daily14
Vitamin D deficiency treatment: 6000 – 50,000 IU Vitamin D3 weekly14

Drugs Known To Deplete

Orlistat, carbamazepine, cholestyramine, corticosteroids, phenobarbital, phenytoin, rifampin, stimulant laxatives, sunscreens.[1]

Mechanisms of Depletion

Orlistat – decreases the absorption of fat-soluble vitamins, including Vitamin D, which can reduce serum levels.[6,7]

Antiepileptics – antiepileptics such as carbamazepine, phenytoin, phenobarbital, etc., increase the hepatic metabolism of vitamin D into inactive compounds, reducing calcium absorption.[8]

Cholestyramine – decreases the absorption of vitamin D which can reduce the serum levels.[9]

Corticosteroids – dose equivalent to 7.5 mg or more of prednisone can cause significant bone loss increasing with duration of therapy; therefore, vitamin D supplementation is recommended.[6,10]

Rifampin – increases the hepatic metabolism of vitamin D which reduces its serum levels.[11]

Stimulant Laxatives – studies have shown that prolonged use of stimulant laxatives can reduce the absorption of dietary vitamin D and calcium.[12]

Sunscreens – frequent and extensive use of sunscreen can cause a reduction of vitamin D in the skin and plasma levels.[13]

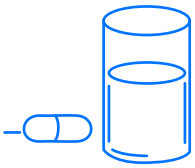
Symptoms of Deficiency

Bone pain and tenderness[4]

Muscle weakness[4]

Bone fracture[4]

Difficulty walking[4]



Administration

The FDA recommends using droppers that deliver no more than 400 IU per dose for administration to infants.[14]

Interactions

Aluminum – Coadministration can result in increased absorption of aluminum which can result in aluminum toxicity in people with renal failure.[15]

CYP3A3 Substrates (e.g., Atorvastatin) – Vitamin D possibly induces CYP3A4 which can cause a reduction in bioavailability of atorvastatin and other CYP3A4 substrates.[6,16]

Calcipotriene – combination with vitamin D supplements may cause hypercalcemia since calcipotriene is a vitamin D analog.[6]

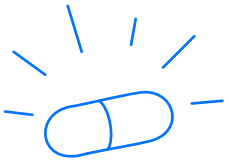
Digoxin – high doses of vitamin D can result in hypercalcemia. This increase in serum calcium increases the risk of fatal arrhythmias with digoxin.[6]

Diltiazem and Verapamil – high doses of vitamin D can result in hypercalcemia. Hypercalcemia in combination with diltiazem or verapamil can result in atrial fibrillation.[17]

Thiazide diuretics – Thiazides decrease urinary calcium excretion which, in combination with vitamin D supplements, can cause hypercalcemia.[18]

Monitor

Monitor serum calcium and phosphorus at least every two weeks.[14]
X-ray bones monthly until stabilized.[14]
Monitor for signs and symptoms of vitamin D intoxication.[14]



Adverse Reactions

Nausea, vomiting, constipation, poor appetite, fatigue, hypercalcemia, weight loss.

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MELATONIN - CLINICAL PEARLS

Other Popular Names
Pineal Hormone

Background

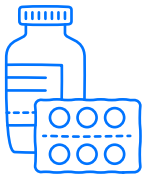
Melatonin is a neurohormone produced in the brain by the pineal gland from the amino acid tryptophan. The synthesis and release of melatonin into the blood and cerebrospinal fluid are stimulated by darkness and suppressed by light. This suggests the involvement of melatonin in the circadian rhythm among other body functions.[1,2]

Deficiency in melatonin can occur overtime as secretion of the hormone decreases as we age. Besides its association with old age, reduced melatonin levels have also been observed in patients with various diseases such as dementia, mood disorders, cancer, severe pain, and diabetes mellitus type 2.[3] Melatonin is used to help correct sleep disturbances most commonly caused by jet lag, shift work sleep disorder, and diseases with associated pain (e.g., cancer).

Dosing

Common Daily Dose:
2-3 mg before bedtime

Recommended Doses:
Jet Lag: 5 mg daily for three days prior to departure (between 10 a.m. and 6 p.m. local time), 5 mg daily for an additional four days (between 10 p.m. and midnight local time) beginning the day of the flight.



Uses

Jet lag – Level B Evidence for Use[4]
Cancer – Level B Evidence for Use[4]

Drugs Known To Deplete

NSAIDs, caffeine, beta blockers.[1,16]

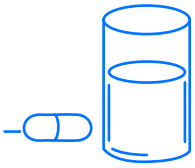
Mechanisms of Depletion

Caffeine – A few studies suggest a possible association between caffeine consumption and decrease in melatonin production although this evidence is not concrete.[6]

Beta blockers – Studies indicate that beta blockers decrease melatonin release via specific inhibition of adrenergic beta1-receptors.[15]

Symptoms of Deficiency

Sleep disturbances[3]



Administration

Advise patients to treat melatonin as they would any sleeping pill.[7]

Patients should avoid driving or other activities requiring mental alertness or coordination until drug effects are realized, as drug may cause drowsiness.[4]

Advise patients to take after they have eaten and avoid alcohol.[4]

Interactions

Anticoagulants/antiplatelets – isolated case reports of increased bleeding and decreased prothrombin activity in people taking melatonin with warfarin.

Anticonvulsant – clinical evidence indicates melatonin may increase seizure frequency in patients, particularly neurologically disabled children.[9]

Antidiabetic medications – some studies suggest melatonin may affect glucose utilization and increase insulin resistance while other studies find no effect on glucose levels.[1]

Antihypertensives – evidence shows that melatonin worsens blood pressure in patients who are taking antihypertensive medications possibly reducing the effectiveness of the medications.[10]

Contraceptives – concomitant use of oral contraceptives with melatonin supplements may increase levels of endogenous melatonin resulting in increase of adverse effects.

CYP1A2/2C19 substrates – melatonin is metabolized in the liver by CYP1A2 and 2C19. Combination of melatonin and drugs metabolized by CYP1A2/2C19 may reduce the metabolism of these drugs thus increasing their serum levels.[11]

Fluvoxamine – can significantly increase serum melatonin levels with cases reported of increase of exogenously administered melatonin by 20 times.[12]

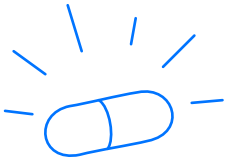
Immunosuppressants – melatonin can possibly stimulate immune function and interfere with immunosuppressant therapy.[13]

Nifedipine GITS – melatonin can decrease the effectiveness of nifedipine GITS. Immediate-release melatonin 5 mg at night in combination with nifedipine GITS 30-60 mg daily increases systolic blood pressure an average of 6.5 mmHg and diastolic by an average of 4.9 mmHg. Concomitant use with melatonin also increases heart rate by 3.9 bpm.[14]

Monitor

Monitor improvements of sleep (e.g., reduced sleep latency, and improved quality of sleep and morning alertness).[4]

Monitor possible side effects.[4]



Adverse Reactions

Headache, dizziness, nausea, drowsiness, transient depressive symptoms, mild tremor, mild anxiety, abdominal cramps, irritability, reduced alertness, confusion or disorientation, and hypotension.[1,4,7]

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MAGNESIUM - CLINICAL PEARLS

Background

Magnesium is an abundant element in the body that plays an important part in normal bone structure development. It is also an essential cofactor in over 300 cellular and chemical reactions including protein synthesis, blood glucose control, blood pressure regulation, and muscle/nerve function. Magnesium is also a requirement for energy production, glycolysis, and oxidative phosphorylation. In addition, it plays an important role in the active transport of calcium and potassium ions affecting nerve impulse conduction, normal heart rhythm, and muscle contraction.[1,2]

Besides its availability in dietary supplements, magnesium is available in a variety of different food sources. Leafy green vegetables, including spinach, as well as legumes, nuts, seeds, and whole grains are all great sources of magnesium. Other sources include fortified breakfast cereals and tap, mineral, and bottled waters depending on water source and brand.[2]

Symptomatic magnesium deficiency is uncommon in the United States due to the kidney's ability to limit excretion.[2] Most commonly, magnesium deficiency is prevalent in groups who typically consume insufficient amounts of magnesium or cannot properly absorb magnesium. Some examples of these populations are people with gastrointestinal disease, type 2 diabetics, and people with alcohol use disorder.

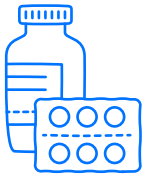
Dosing

Common Daily Dose: (Recommended Dietary Allowance):
410 mg (males) and 360 mg (females) ages 14-18 years, 400 mg (males) and 310 mg (females) ages 19-30 years, 420 mg (males) and 320 mg (females) ages 31+ years.[2]

Recommended Doses:
Indigestion: 400 to 800 mg of magnesium oxide orally in a 24-hour period.

The earliest signs of a deficiency in magnesium are loss of appetite, nausea, vomiting, and fatigue. It is important to note that severe cases of magnesium deficiency can result in hypocalcemia or hypokalemia due to disruptions in mineral homeostasis.[2]

Preparations available for magnesium supplementation are commonly provided as tablets coated with aluminum hydroxide to balance out magnesium's laxative effect.



Uses

Constipation – FDA Indication[4]
Hypomagnesemia – FDA Indication[4]
Indigestion – FDA Indication[4]

Drugs Known To Deplete

Amphotericin-B, pentamidine, tacrolimus, proton pump inhibitors, aminoglycosides, carboplatin, cisplatin, cetuximab, cyclosporine, digoxin, diuretics, estrogens (including contraceptives), foscarnet, panitumumab.[1]

Evidence of Depletion

Amphotericin-B – electrolyte disturbance, including low serum magnesium levels, develop in a large proportion of patients and may be associated with nephrotoxicity.[5]

Pentamidine – symptomatic hypomagnesemia can occur as a result of renal tubular injury leading to increased urinary losses of magnesium.[6]

Tacrolimus – reduces tubular reabsorption of magnesium leading to hypomagnesemia in a significant proportion of patients.[7]

Proton Pump Inhibitors – all PPIs are thought to inhibit active transport of magnesium into the intestine resulting in an increased risk of hypomagnesemia.[2]

Aminoglycosides – causes nephrotoxicity that leads to increased urinary losses of electrolytes including magnesium.[9]

Carboplatin and Cisplatin – cause hypomagnesemia due to renal tubular damage that increases urinary magnesium losses.[10]

Cetuximab – causes renal magnesium wasting, leading to lowered magnesium levels in 50% to 97% of patients.[11]

Cyclosporine – can cause a significant loss of magnesium in the urine due to reduced tubular reabsorption and damage.[12]

Digoxin – decreases tubular reabsorption of magnesium and increases excretion in the urine which can result in increased risk of arrhythmias.[13]

Diuretics – loop diuretics (and thiazides to a lesser extent) interfere with magnesium reabsorption in the kidneys which increases urinary losses and decreases serum levels of magnesium.[14]

Estrogens – estrogens including contraceptives enhance magnesium uptake by soft tissue and bones thus lowering serum levels leading to hypomagnesemia.[15]

Foscarnet – can cause hypomagnesemia due to chelation and increased elimination of magnesium.[16]

Panitumumab – causes renal magnesium wasting leading to lowered serum magnesium levels in 39% of patients.[17]

Symptoms of Deficiency

Nausea[2, 3]

Vomiting[2, 3]

Loss of appetite[2, 3]

Fatigue/weakness[2, 3]

Numbness/tingling[2, 3]

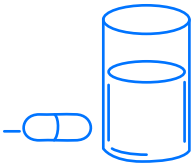
Muscle cramps[2, 3]

Seizures[2, 3]

Personality changes[2, 3]

Abnormal heart rhythms[2, 3]

Hypocalcemia and/or hypokalemia[2, 3]



Administration

Shake liquid formulations well before each use.[4]
Do not take within two hours (either before or after) of other medications.[4]

Interactions

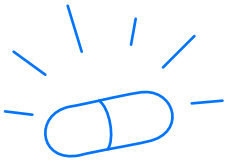
Bisphosphonates – Cations, including magnesium, can decrease bisphosphonate absorption. Must separate doses of magnesium and bisphosphonates by at least two hours.[18]

Digoxin – Treatment with oral magnesium hydroxide or magnesium trisilicate reduces absorption of digoxin from the intestines leading to a decrease in digoxin in the blood.[19]

Sulfonylureas – Magnesium-based antacids elevate gastrointestinal pH, leading to increased solubility and enhanced absorption of sulfonylureas.[20]

Monitor

Monitor serum magnesium levels to avoid magnesium toxicity.



Adverse Reactions

Dizziness, flushing, pain at injection site, muscle paralysis, troubled breathing, doubled/blurred vision.

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CALCIUM - CLINICAL PEARLS

Other Popular Names
Calcium Citrate, Calcium Carbonate, Calcium Gluconate, Calcium Acetate

Background

Calcium is the most abundant mineral in the human body. Ninety-nine percent of the total body calcium is stored in the bones and teeth where it supports structure and continues remodeling of the bones via resorption and deposition. Calcium has a variety of functions in the body including vascular contraction, vasodilation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion. All of these functions use less than 1% of the total body calcium.[1]

Food sources rich in calcium include milk, cheese, and yogurt. Other natural food sources include kale, broccoli, and fortified sources such as fruit juices, cereals, and tofu. Most people in the United States receive their daily calcium through dietary sources.[2,3]

Over the short term, inadequate intake of dietary calcium will not produce obvious symptoms since circulating blood levels of calcium are tightly regulated. Inadequate dietary calcium intake over the long term can cause osteopenia which can result in osteoporosis. Hypocalcemia is primarily a result of medical problems or treatments, including renal failure, surgical removal of the stomach, and use of medications like diuretics. Hypocalcemia can also lead to rickets.[2]

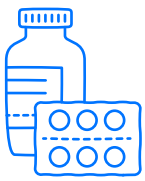
Groups commonly at risk for calcium deficiency are people who follow a vegan diet, are lactose intolerant, consume large amounts of protein or sodium, have osteoporosis, are receiving long-term treatment with corticosteroids, or have bowel disorders that hinder calcium absorption.[4]

Dosing

Common Daily Dose
(Recommended Dietary Allowance): 1000 mg in males and females ages 19-50 years, 1000 mg in males ages 51-70 years, 1200 mg in males ages 71 and older and females ages 51 and older.[4]

Recommended Doses:
Antacid or calcium supplementation: 1000-4000 mg of calcium carbonate (400 -1600 mg of elemental calcium) as symptoms occur, max 8000 mg daily.[12]

Maximum Total Daily Dose:
2500 mg in males and females ages 19-60 years, 2000 mg in males and females ages 51 and older.[4]



Uses

Hyperphosphatemia – FDA Indication[5]
Hypocalcemia – FDA Indication[5]
Antacid – FDA Indication[5]

Drugs Known To Deplete

Anticonvulsants, aluminum salts, corticosteroids, loop diuretics, levothyroxine, mineral oil, stimulant laxatives.[2]

Evidence of Depletion

Anticonvulsants – Anticonvulsants including phenytoin, fosphenytoin, phenobarbital, and carbamazepine can decrease calcium absorption by increasing the metabolism of vitamin D. Hypocalcemia and osteomalacia have occurred in prolonged therapy and with use of more than one of these drugs concurrently.[6]

Aluminum Salts – Large doses can bind dietary phosphate resulting in hypophosphatemia. This will induce movement of calcium into the blood and increase urinary calcium excretion.[7]

Corticosteroids – Prolonged use of corticosteroids can cause decreased absorption and increased excretion of calcium and inhibit bone formation. This may result in increased risk of bone fracture.[8]

Loop Diuretics – Increase urinary excretion and reduce serum calcium levels, especially at high doses.[9]

Levothyroxine – Calcium and levothyroxine form insoluble complexes reducing serum levels of both.[10]

Stimulant Laxatives – Prolonged use of high doses of stimulant laxatives can reduce both dietary vitamin D and calcium absorption and can lead to osteomalacia.[11]

Symptoms of Deficiency

Numbness and tingling of the fingers[1]

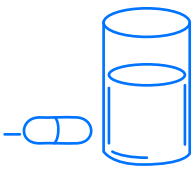
Muscle cramps[1]

Convulsions[1]

Lethargy[1]

Poor appetite[1]

Abnormal heart rhythms[1]



Administration

Take with food.[12]
Take at least 30 minutes before bisphosphonates.[2]

Interactions

Aluminum salts – Calcium citrate can increase absorption of aluminum when taken with aluminum hydroxide. The increase in aluminum levels may be toxic due to the citrate ion.[13]

Bisphosphonates – Calcium supplements decrease absorption of bisphosphonates and should be taken 30 minutes prior to bisphosphonates.[14]

Ceftriaxone – Case reports in neonates show that administering intravenous ceftriaxone and calcium can result in precipitation of a ceftriaxone-calcium salt in the lungs and kidneys. There are no reports yet in adults.[15]

Dolutegravir – Taking calcium carbonate 1200 mg concomitantly with dolutegravir 50 mg reduces blood levels of dolutegravir by almost 40%. Patients should take dolutegravir at least two hours prior or six hours after calcium supplements.[16]

Elvitegravir – Pharmacokinetic research suggests that taking calcium along with elvitegravir can reduce blood levels of elvitegravir through chelation.[17]

Levothyroxine – Calcium carbonate supplements reduce effectiveness of levothyroxine in patients with hypothyroid by forming insoluble complexes.[18]

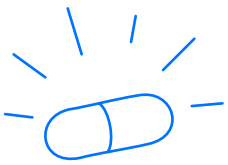
Quinolones and tetracyclines – Taking calcium at the same time as these antibiotics can reduce the antibiotic absorption.[19]

Sotalol – Calcium can reduce the absorption of sotalol by forming insoluble complexes.[20]

Thiazides – Reduce calcium excretion by the kidneys and in combination with calcium carbonate can result in milk-alkali syndrome.[9]

Monitor

Monitor serum calcium and phosphorus levels.[5]



Adverse Reactions

Belching, flatulence, constipation, diarrhea, upset stomach, hypercalcemia, milk-alkali syndrome, nephrocalcinosis, and renal insufficiency.[2]

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PROBIOTIC - CLINICAL PEARLS

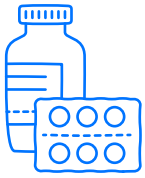
Background

Probiotics were first introduced therapeutically as lactic acid-producing organisms to acidify the intestines. The intention was to prevent the growth of putrefactive organisms in the gut.

With understanding of the gut's role in many bodily processes expanding, new focus is being placed on the maintenance of a healthy gut microbiome. Many bacterial and yeast strains are used and considered "probiotics" but the most common include Lactobacillus Spp., Bifidobacterium Spp., Enterococcus, Streptococcus, and the yeast Saccharomyces boulardii.[1]

Dosing[1]

It is likely that efficacy is related to the dose administered, strain used, and indication being treated. Given this variability, it is not possible to issue a blanket dosing recommendation.



Uses

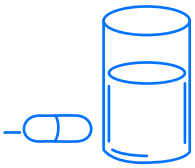
Gastrointestinal disorders

Evidence suggests that probiotics may be effective in acute infectious diarrhea.[2] Additionally they have been shown to benefit patients in the prevention of antibiotic associated diarrhea. It is worth noting that while there may be promise in the use of probiotics to prevent recurrent C. difficile infections, the risk of potential bacteremia in this population may outweigh the benefits.[3]

The maintenance of healthy gut flora may also be beneficial to patient populations struggling with inflammatory bowel disease and ulcerative colitis though data is less clear with its use in Crohn's disease.[1]

Urogenital infections

Some small studies have been conducted evaluating the efficacy of probiotic use in vulvovaginal candidiasis and bacterial vaginosis. While some indication of benefit was seen, there is need for larger controlled studies and therefore cannot be recommended in any guideline.[4,5]



Administration

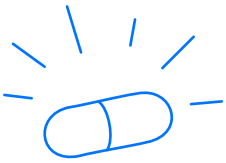
Probiotics are administered orally and should be separated from antibiotic regimens by two hours.[6]

Interactions

No known drug interactions.

Monitor

No monitoring parameters aside from recurrent intestinal symptoms or urogenital infections. Probiotics should be monitored for efficacy.



Adverse Reactions

Be aware of potential allergic reactions.

Properties of probiotics are specific to species and strain. As such, reports on safety and recommendations cannot be generalized from one product to another.

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