Drug-Induced Nutrient Depletions

By

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Where's the Info?

- Many of the side effects from drug therapy may not be directly due to the drug itself, but rather are a result of nutritional deficiencies that are caused by the drug over time. There are a number of ways that drugs can negatively affect the status of nutrients in the body. The mechanism responsible for the depletion of nutrients include inhibition of nutrient absorption, synthesis, transport, storage, metabolism, and excretion.
- There are a large number of studies appearing in the scientific literature reporting the drug-induced depletion of nutrients. Way has this information not been communicated to the patients who are taking these drugs? Most health care professional are not aware of the facts that so many drugs are capable of causing nutritional deficiency-related health problems.
- It has become increasingly apparent that this information needs to become available to patients and health care professionals. At the same time it is important that every individual who takes medications should have this information. It is really a win-win situation, because this information helps reduce potential risks of drug side effects.

Analgesics

- Acetaminophen (Tylenol)
- **Nutrients Depleted**
  - **Glutathione:** Low levels can cause decreased capacity for hepatic detoxification, decreased immunity, and suppression of macrophage activity. A lack of glutathione may lead to increased free radical damage throughout the body, especially in the membranes of red blood cells and mitochondria. Glutathione participates in the hepatic detoxification of many compounds via glutathione S-Tranferase. This enzyme participates in the detoxification of compounds from cigarette smoke, ethanol, and acetaminophen. It is part of the antioxidant enzyme system glutathione peroxidase, which is one of the body's most important antioxidants. It also the most abundant antioxidant in the brain and lungs.
    - ↑ risk of Asthma and COPD
    - ↓ lung function
    - ↑ hepatotoxicty
    - ↓ Phase II liver detoxification (Glutathione conjugation)
    - ↑ Neurodegenerative disease

Acetaminophen and the U.S. Acute Liver Failure Study Group: lowering the risks of hepatic failure.

- ***Hepatology*.** 2004 Jul;40(1):6-9.
- Lee WM.
- Division of Digestive and Liver Diseases, University of Texas, Southwestern Medical Center, Dallas, 75390-9151, USA. William.Lee@utsouthwestern.edu
- **Acetaminophen overdose is the leading cause for calls to Poison Control Centers (>100,000/year) and accounts for more than 56,000 emergency room visits, 2,600 hospitalizations, and an estimated 458 deaths due to acute liver failure each year.** Data from the U.S. Acute Liver Failure Study Group registry of more than 700 patients with acute liver failure across the United States **implicates acetaminophen poisoning in nearly 50% of all acute liver failure in this country**. Available in many single or combination products, acetaminophen produces more than 1 billion US dollars in annual sales for Tylenol products alone. It is heavily marketed for its safety compared to nonsteroidal analgesics. By enabling self-diagnosis and treatment of minor aches and pains, its benefits are said by the Food and Drug Administration to outweigh its risks. It still must be asked: Is this amount of injury and death really acceptable for an over-the-counter pain reliever?
- PMID: 15239078 [PubMed - indexed for MEDLINE]

Antacids
Magnesium & Aluminum

- Tums, Rolaids, Maalox, Mylanta
- **Nutrients Depleted**
  - **Calcium**: Symptoms of deficiency include osteopenia, osteomalacia, osteoporosis, periodontal disease, muscle spasms, and decreases cell wall permeability**.**
  - **Phosphorus:** Low levels can affect mineral balance and result in adverse reactions with kidney function. Decreased bone/tooth formation. Important in the formation of phospholipids.
  - **Copper:** Important in the formation of bone, collagen, elastin , hemoglobin, and copper-zinc-SOD (Cu-Zn-SOD)
  - **Iron:** Low levels can lead to anemia, fatigue, weakness and low energy**.**
  - **Magnesium:** Deficiency symptoms include muscle cramps, weakness, insomnia, loss of appetite, kidney stones, osteoporosis, nervousness, restlessness, irritability, fatigue and high blood pressure. It is a cofactor in over 300 enzymatic reactions in the body. It is necessary for the transmission of nerve impulses, muscular activity, temperature regulation, detoxification reactions, and formation of healthy bones.
  - **Potassium:** Low levels can lead to heart irregularities, elevated blood pressure, muscle spasms, and fluid alterations in the body.
  - **Zinc:** Deficiency leads to slow wound healing, lowered immune function, and impaired sense of taste and smell. It is necessary for prostate health, DNA/RNA synthesis, and promotes conversion of T4 to T3.

Antacids
Sodium Bicarbonate

- Alka-Seltzer, Baking Soda
- **Nutrients Depleted**
  - **Folic Acid:** Can lead to fatigue, weakness, and low energy. It is intimately involved in the synthesis of both DNA and RNA and is essential to cellular division and the transmission of genetic code to newly formed cells. Prevents birth abnormalities such as neural tube defects, cleft palate, and cleft lip. May protect against precancerous cervical dysplasia. Required for the conversion of homocysteine to methionine. High levels of homocysteine are associated with increased risk of cardiovascular disease and dementia. Low level have also been linked to depression.
  - **Magnesium:** Is a nutritional superstar when it come to cardiovascular disease. It influences many activities associated with a variety of cardiac function. Magnesium inhibits platelet aggregation, thins the blood, blocks calcium uptake, and relaxes blood vessels. It also increases oxygenation of the heart muscle by improving cardiac contractibility.
  - **Proteins:** Caused by malabsorption**.**
  - **Potassium**

Antacids and Ulcer Medications
Histamine H2-Receptor Antagonist

- Axid, Pepcid, Tagamet, Zantac
- **Nutrients Depleted**
  - **Vitamin B12:** Deficiencies manifest primarily as anemia and neurological changes. Vitamin B12 deficiency inhibits DNA synthesis, which can affect growth and repair of all cells. Low levels can cause fatigue, peripheral neuropathy, tongue and mouth irregularities, macrocytic anemia (abnormally enlarged red blood cells), depression, confusion and memory loss (especially in the elderly), dermatitis, skin sensitivity, and loss of appetite.
  - **Vitamin D:** Can lead to osteoporosis, osteopenia, osteomalacia, and in children retarded growth, muscle weakness, late development of teeth, and rickets. Promotes absorption of calcium and phosphorus in the intestines for growth of bones and teeth. Cholecalciferol (D3), the active form of Vitamin D may be helpful in the prevention and treatments of some cancers, and is considered by some to have hormone like activity.
  - **Folic Acid**
  - **Zinc**
  - **Zantac and Tagamet** increase alcohol blood levels by inhibiting gastric alcohol dehydrogenase activity.
  - ↓ **Intrinsic Factor caused by low stomach acid**

Antacid and Ulcer Medications
Proton Pump Inhibitors

- Prilosec, Nexium, Prevacid, Acifex, Protonix
- **Nutrients Depleted**
  - **Vitamin B12**
  - **Protein**
  - **Minerals (all)**
- **↑ risk of C. difficile**
- **↑ risk of community acquired pneumonia**
- **↓ ionization of minerals (malabsorption)**
- **↓ stomach acid**
- **↑ risk of hip fracture**
- **↓ gall bladder function**
- **↑ gastrointestinal tract mucosal permeability (leaky gut syndrome)**

Esomeprazole induces upper gastrointestinal tract transmucosal permeability increase.

- ***Aliment Pharmacol Ther.*** 2008 Dec 1;28(11-12):1317-25. Epub 2008 Aug 4.
- Mullin JM, Valenzano MC, Whitby M, Lurie D, Schmidt JD, Jain V, Tully O, Kearney K, Lazowick D, Mercogliano G, Thornton JJ.
- The Lankenau Institute for Medical Research, Wynnewood, PA 19096, USA.
- BACKGROUND: Proton pump inhibitors (PPIs) are one of the most widely used drug classes in the US and are now frontline medications for gastro-oesophageal reflux disease (GERD) and dyspepsia. In a previous work, we observed that a transmucosal, upper gastrointestinal (GI) leak exists in Barrett's oesophagus (BO) patients. PPI medications are commonly used by Barrett's patients. AIM: To examine if the PPI, esomeprazole, affects the barrier function of the upper GI tract. METHODS: The sucrose permeability test (SPT) was used to assess the possible effect of the PPI, esomeprazole, on upper GI leak in 37 first-time-presenting GERD patients and 25 healthy controls. RESULTS: Esomeprazole induced a significant transmucosal leak in the upper GI tract of patients taking the drug for the first time. The leak occurred quickly, within days of first taking the drug. The leak was also reversed within days of stopping the medication. **CONCLUSIONS: This is the first patient-based study showing that a PPI compromises upper GI barrier function. There are potential implications for transmucosal leak of other medications that a patient on a PPI may be taking, as well as possible leak of endogenous peptides/proteins. The clinical consequences of this phenomenon are currently unknown, but are potentially important.**
- PMID: 18684245 [PubMed - indexed for MEDLINE]

Proton pump inhibitors reduce gallbladder function.

- ***Surg Endosc***. 2006 Sep;20(9):1364-7. Epub 2006 Jul 20
- Cahan MA, Balduf L, Colton K, Palacioz B, McCartney W, Farrell TM.
- Department of Surgery, University of North Carolina at Chapel Hill, Campus Box 7081, Chapel Hill, North Carolina 27599-7081, USA.
- BACKGROUND: In the authors' previous study of gallbladder function before and after fundoplication, 58% of the patients demonstrated preoperative gallbladder motor dysfunction, and 86% of those retested after operation and cessation of proton pump inhibitors (PPIs) normalized. Because no study has directly assessed the impact of antisecretory agents on gallbladder function, this study measured gallbladder ejection fraction (GBEF) in healthy volunteers before and after initiation of PPIs. METHODS: A total of 19 subjects completed the study, which included baseline determination of GBEF by cholecystokinin-stimulated hepatobiliary acid scan, 30 days of antisecretory therapy with omeprazole (40 mg daily), and repeat GBEF on day 30. Subjects were surveyed regarding compliance and symptoms. RESULTS: For 15 of 19 subjects, PPI therapy was associated with reduced gallbladder motility. Evolution of symptoms consistent with a biliary etiology was reported by 26.7% of these subjects. **CONCLUSIONS: Short-term PPI therapy reduces gallbladder motility in healthy volunteers. Chronic PPI therapy may pose a risk for long-term gallbladder dysfunction and biliary complications.**
- PMID: 16858534 [PubMed - indexed for MEDLINE]

Omeprazole and vitamin B12 deficiency.

- ***Ann Pharmacother***. 1999 May;33(5):641-3
- Bradford GS, Taylor CT. Birmingham Baptist Medical Center--Princeton, AL 35211, USA.
- The mainstay for cobalamin deficiency is correction of the underlying disorder and replacement therapy. Because the defect is often one of absorption, parenteral or intranasal routes are recommended. In most cases, replacement therapy is all that is needed. The vitamin preparation most commonly used is cyanocobalamin (also called vitamin B12), which has no known physiologic role but instead is converted to a biologically active form before it can be used by tissues. The studies reviewed in this article clearly show that omeprazole therapy will decrease the absorption of vitamin B12 by preventing its cleavage from dietary proteins. However, these data are insufficient to infer that clinically significant deficiency will occur over time. In fact, some of the studies suggest that the simple addition of juices or other acidic drinks into the diet may dramatically increase cobalamin absorption. Clearly, well-designed clinical trials are needed to evaluate this theory over an extended follow-up period to determine the clinical significance of omeprazole-associated vitamin B12 deficiency and possibly identify patients at risk for deficiency. In conclusion, the possibility of dietary vitamin B12 malabsorption should be considered in patients receiving chronic omeprazole treatment and presenting with signs and symptoms of deficiency. **All healthcare workers should be made aware of the potential clinical complications of omeprazole-associated vitamin B12 deficiency since it may go unrecognized and is easily corrected. This is particularly relevant for elderly patients with poor dietary intake of vitamin B12, impaired vitamin B12 stores, and certain gastrointestinal disorders.**
- PMID: 10369631 [PubMed - indexed for MEDLINE]

Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs.

- ***JAMA***. 2004 Oct 27;292(16):1955-60
- Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB.
- Department of Gastroenterology, University Medical Center St. Radboud, Nijmegen, The Netherlands. R.Laheij@mdl.umcn.nl
- CONTEXT: Reduction of gastric acid secretion by acid-suppressive therapy allows pathogen colonization from the upper gastrointestinal tract. The bacteria and viruses in the contaminated stomach have been identified as species from the oral cavity. OBJECTIVE: To examine the association between the use of acid-suppressive drugs and occurrence of community-acquired pneumonia. DESIGN, SETTING, AND PARTICIPANTS: Incident acid-suppressive drug users with at least 1 year of valid database history were identified from the Integrated Primary Care Information database between January 1, 1995, and December 31, 2002. Incidence rates for pneumonia were calculated for unexposed and exposed individuals. To reduce confounding by indication, a case-control analysis was conducted nested in a cohort of incident users of acid-suppressive drugs. Cases were all individuals with incident pneumonia during or after stopping use of acid-suppressive drugs. Up to 10 controls were matched to each case for practice, year of birth, sex, and index date. Conditional logistic regression was used to compare the risk of community-acquired pneumonia between use of proton pump inhibitors (PPIs) and H2-receptor antagonists. MAIN OUTCOME MEASURE: Community-acquired pneumonia defined as certain (proven by radiography or sputum culture) or probable (clinical symptoms consistent with pneumonia).

Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. (cont.)

- ***JAMA***. 2004 Oct 27;292(16):1955-60
- Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB.
- Department of Gastroenterology, University Medical Center St. Radboud, Nijmegen, The Netherlands. R.Laheij@mdl.umcn.nl
- RESULTS: The study population comprised 364,683 individuals who developed 5551 first occurrences of pneumonia during follow-up. The incidence rates of pneumonia in non-acid-suppressive drug users and acid-suppressive drug users were 0.6 and 2.45 per 100 person-years, respectively. The adjusted relative risk for pneumonia among persons currently using PPIs compared with those who stopped using PPIs was 1.89 (95% confidence interval, 1.36-2.62). Current users of H2-receptor antagonists had a 1.63-fold increased risk of pneumonia (95% confidence interval, 1.07-2.48) compared with those who stopped use. For current PPI users, a significant positive dose-response relationship was observed. For H2-receptor antagonist users, the variation in dose was restricted. **CONCLUSION: Current use of gastric acid-suppressive therapy was associated with an increased risk of community-acquired pneumonia.**
- PMID: 15507580 [PubMed - indexed for MEDLINE]

Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease.

- ***JAMA***. 2005 Dec 21;294(23):2989-95
- Dial S, Delaney JA, Barkun AN, Suissa S.
- Division of Critical Care and Respiratory and Clinical Research, Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec. sandra.dial@mcgill.ca
- CONTEXT: Recent reports suggest an increasing occurrence and severity of Clostridium difficile-associated disease. We assessed whether the use of gastric acid-suppressive agents is associated with an increased risk in the community. OBJECTIVE: To determine whether the use of gastric acid-suppressive agents increases the risk of C difficile-associated disease in a community population. DESIGN, SETTING, AND PATIENTS: We conducted 2 population-based case-control studies using the United Kingdom General Practice Research Database (GPRD). In the first study, we identified all 1672 cases of C difficile recorded between 1994 and 2004 among all patients registered for at least 2 years in each practice. Each case was matched to 10 controls on calendar time and the general practice. In the second study, a subset of these cases defined as community-acquired, that is, not hospitalized in the prior year, were matched on practice and age with controls also not hospitalized in the prior year.

Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. (cont.)

- ***JAMA***. 2005 Dec 21;294(23):2989-95
- Dial S, Delaney JA, Barkun AN, Suissa S.
- Division of Critical Care and Respiratory and Clinical Research, Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec. sandra.dial@mcgill.ca
- MAIN OUTCOME MEASURES: The incidence of C difficile and risk associated with gastric acid-suppressive agent use. RESULTS: The incidence of C difficile in patients diagnosed by their general practitioners in the General Practice Research Database increased from less than 1 case per 100,000 in 1994 to 22 per 100,000 in 2004. The adjusted rate ratio of C difficile-associated disease with current use of proton pump inhibitors was 2.9 (95% confidence interval [CI], 2.4-3.4) and with H2-receptor antagonists the rate ratio was 2.0 (95% CI, 1.6-2.7). An elevated rate was also found with the use of nonsteroidal anti-inflammatory drugs (rate ratio, 1.3; 95% CI, 1.2-1.5). **CONCLUSIONS: The use of acid-suppressive therapy, particularly proton pump inhibitors, is associated with an increased risk of community-acquired C difficile.** The unexpected increase in risk with nonsteroidal anti-inflammatory drug use should be investigated further.
- PMID: 16414946 [PubMed - indexed for MEDLINE

Long-term proton pump inhibitor therapy and risk of hip fracture.

- ***JAMA***. 2006 Dec 27;296(24):2947-53
- Yang YX, Lewis JD, Epstein S, Metz DC.
- Division of Gastroenterology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia 19104, USA. yangy@mail.med.upenn.edu
- CONTEXT: Proton pump inhibitors (PPIs) may interfere with calcium absorption through induction of hypochlorhydria but they also may reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps. OBJECTIVE: To determine the association between PPI therapy and risk of hip fracture. DESIGN, SETTING, AND PATIENTS: A nested case-control study was conducted using the General Practice Research Database (1987-2003), which contains information on patients in the United Kingdom. The study cohort consisted of users of PPI therapy and nonusers of acid suppression drugs who were older than 50 years. Cases included all patients with an incident hip fracture. Controls were selected using incidence density sampling, matched for sex, index date, year of birth, and both calendar period and duration of up-to-standard follow-up before the index date. For comparison purposes, a similar nested case-control analysis for histamine 2 receptor antagonists was performed.

Long-term proton pump inhibitor therapy and risk of hip fracture. (cont.)

- ***JAMA***. 2006 Dec 27;296(24):2947-53
- Yang YX, Lewis JD, Epstein S, Metz DC.
- Division of Gastroenterology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia 19104, USA. yangy@mail.med.upenn.edu
- MAIN OUTCOME MEASURE: The risk of hip fractures associated with PPI use. RESULTS: There were 13,556 hip fracture cases and 135,386 controls. The adjusted odds ratio (AOR) for hip fracture associated with more than 1 year of PPI therapy was 1.44 (95% confidence interval [CI], 1.30-1.59). The risk of hip fracture was significantly increased among patients prescribed long-term high-dose PPIs (AOR, 2.65; 95% CI, 1.80-3.90; P<.001). The strength of the association increased with increasing duration of PPI therapy (AOR for 1 year, 1.22 [95% CI, 1.15-1.30]; 2 years, 1.41 [95% CI, 1.28-1.56]; 3 years, 1.54 [95% CI, 1.37-1.73]; and 4 years, 1.59 [95% CI, 1.39-1.80]; P<.001 for all comparisons). **CONCLUSION: Long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture.**
- PMID: 17190895 [PubMed - indexed for MEDLINE]

Antibiotics
General

- **Nutrients Depleted**
  - **Probiotics** (Lactobacillus and Bifidobacertium)**:** Intestinal microflora are a complex microbial ecosystem that plays a critical role in overall health. Lactobacillus primarily colonize the small intestine, and the anaerobic bifidobacteria are predominately in the large intestine. In a healthy intestinal environment, these bacteria attach themselves to the surface of the intestinal tract where they multiply rapidly and become an important part of our immune system.
  - **Vitamin C:** Plays a major role in the synthesis of collagen and elastin, the major structural components of skin, tendons, bone matrix, tooth dentin, blood vessels and connective tissue. Collectively collagen is the most abundant protein in the body, comprising 25-30% of total body protein. One of the bodies most powerful and most important antioxidants. Being water soluble**,** it provides protection in all body fluids, within every cell in the body, and is highly concentrated in the brain. Called the "stress vitamin" because is required for the synthesis of the body's main stress response hormones in the adrenal glands, including adrenalin and cortisol.
  - **Vitamin K:** Deficiency may lead to impaired blood clotting. Necessary for the synthesis of osteocalcin, a unique protein that attracts calcium to the bones.
  - **B Vitamins (all)**

Antibiotics
Neomycin

- **Nutrients Depleted**
  - **Sodium:** Symptoms of deficiency include muscle weakness, poor concentration, dehydration, and loss of appetite. Has a major role in the regulation of blood pressure, and plays a critical role in the transmission of electrochemical impulses for nerve function and muscle contraction. Regulates the acid/alkaline balance in the blood and lymph fluids, and maintains cellular permeability.
  - **Potassium:** Can lead to heart irregularities, elevated blood pressure, and muscle spasms. The primary cation in intracellular fluids, controls the conduction of nerve impulses, maintains normal cardiac rhythm, muscle contraction, and acid/alkaline balance.
  - **Iron:** Symptoms of deficiency include anemia, weakness, fatigue, spooning of the nails, brittle nails, and greater susceptibility to infection. Plays an important role in the cytochrome P450 liver detoxification enzymes, and is necessary for the synthesis of the amino acid carnitine which plays an essential role in the metabolism of fatty acids.
  - **Vitamin A:** Can lead to susceptibility of cancer, acne, night blindness, or other ocular problems. Plays an important role in maintaining the integrity of all epithelial tissue and is associated with a reduced risk of various epithelial cell cancers. Long term deficiency causes skin to become dry, scaly, and rough.
  - **Calcium**
  - **Magnesium**
  - **Vitamin B12**
  - **Vitamin K**

Antibiotics
Tetracyclines

- **Nutrient Depleted**
  - **Vitamin B6:** Can lead to the development of fatigue, carpal tunnel syndrome, water retention, irritability, depression, and PMS symptoms. Necessary for the formation of hemoglobin and growth of red blood cells. Essential for the synthesis of tryptophan and conversion of tryptophan to niacin and serotonin. Deficiency can prevent conversion of homocysteine to cysteine and increase risk of cardiovascular disease or dementia.
  - **Zinc:** Necessary for the functioning of well over 300 different enzymes and as such, it plays a vital role in an enormous number of biological processes.
  - **Probiotics:** Lactobacillus produce lactic acid that maintains an acidic intestinal pH balance, and hydrogen peroxide which inhibits the growth of yeast such as Candida. They also produce the enzyme lactase.
  - **Calcium**
  - **Magnesium**
  - **Vitamin B12**

Antibacterials
Trimethoprim and Sulfa

- **Nutrients Depleted**
  - **Folic Acid:** Trimethoprim may adversely affect homocysteine concentration due to an inhibition of dihydrofolate-reductase (DHFR) enzyme which converts folic acid to biologically active L-5-tetrahydrofolate. L-5-Tetrahydrofolate is needed for the remethylation of homocysteine to methionine.

Antibacterial
Anti-Tuberculosis

- Isoniazid and Rifampicin
- **Nutrients Depleted**
  - **Niacin:** Can lead to impaired metabolism of starches, fats, and proteins. Niacin containing coenzymes NAD and NADP are involved in more than 200 different reactions in the metabolism of carbohydrates, fatty acids, and amino acids making it critical in supplying energy to every cell of the body. Niacin is especially important in the oxidation-reduction reactions in the Krebs cycle involving the production of energy from carbohydrates.
  - **Vitamin B6**
  - **Vitamin D**

Anticonvulsants

- Barbuturates
- **Nutrients depleted**
  - **Vitamin D:** Log-term use interferes with calcium metabolism and may reduce calcium absorption.
  - **Calcium**
  - **Folic Acid:** Levels are lowered in both plasma and erythrocytes.
  - **B12, B6**
  - **Carnitine**
- Dilantin (Phenytoin)
- **Nutrients Depleted**
  - **Vitamin D**
  - **Calcium**
  - **Folic Acid:** Absorption is decreased.
  - **B6, B12, B1**
  - **Glutathione**
  - **Carnitine**

Anticonvulsants

- Tegretol (Carbamazepine)
- **Nutrients Depleted**
  - **Folic Acid:** Inhibits folate absorption.
  - **Glutathione**
  - **Vitamin D**
  - **B6, B12**
  - **Biotin**
  - **Carnitine**
- **↑ Homocysteine**

Anticonvulsants

- Mysoline (Primidone)
- **Nutrients Depleted**
  - **Biotin:** Deficiency symptoms are characterized progressive hair loss, loss of hair color, scaly dermatitis, and seborrhea. Biotin-dependent enzymes are involved in the metabolism of sugar, fat, and amino acids. Specifically, biotin is involved in the utilization of glucose, and the breakdown and utilization of fatty acids.
  - **Folic Acid**
- Valproic Acid and Derivatives (Depakene, Depakote, Depacon)
- **Nutrients Depleted**
  - **Carnitine:** Symptoms of deficiencies include elevated blood lipids, abnormal liver function, muscle weakness, reduced energy, and impaired glucose control. It regulates fat metabolism (especially in the heart) by facilitating the transport of fat across cell membranes into the mitochondria for energy production.
  - **Folic Acid**

Anticonvulsants

- Zonisamide (Zonegran)
- **Nutrients Depleted**
  - **Biotin**
  - **Inositol:** Is an essential component of phospholipids in cellular membranes.
  - **Vitamin B1:** Deficiencies manifest primarily as disorders of the neuromuscular, gastrointestinal (decrease in stomach acid), and cardiovascular systems. Symptoms include depression, irritability, memory loss, mental confusion, indigestion, muscular weakness, heart palpitations, and defective muscle coordination. Required by every cell in the body to make ATP. Necessary for the maintenance of nerve tissues, function, and transmission. Required for the synthesis of acetylcholine, the neurotransmitter involved in thought and memory processes.
  - **Folic acid**
  - **Calcium**

Antidepressants

- Tricyclics (Amitriptyline, Doxepin, Impramine, Desipramine, Nortryptyline, Protriptyline)
- Phenothiazines (Chlorpromazine, Haloperidol, Perphenazine, Prochlorperazine, Thioridazine)
- **Nutrients Depleted**
  - **Coenzyme Q10 (Ubiquinone):** Deficiencies can cause congestive heart failure, increased blood pressure, cardiomyophy, muscle cramps, and periodontal disease. CoQ10 plays a critical role in the production of energy within the mitochondria. It is a coenzyme for numerous enzymes that are involved in the production of adenosine triphosphate (ATP), which is a high energy fuel in every living cell. It is also and important antioxidant. Because it is fat-soluble, it is able to reside in the mitochondrial cell membrane where it provides protection against free radical damage to DNA.
  - **Vitamin B2:** These drugs inhibit the absorption of B2. Deficiencies primarily affect the skin and mucus membranes. Symptoms include Cheilosis (cracks in the corners of the mouth), and inflamed mucous membranes. Redding, tearing, burning, and itching of the eyes, eyes that tire easily, and eyes the are very sensitive to light. Seborrheic dermatitis can occur.

Antidepressants

- SSRI's (Selective serotonin Re-Uptake Inhibitors) (Prozac, Paxil, Zoloft, Celexa, Lexapro)
- **Nutrients Depleted**
  - **Melatonin:** A deficiency could cause insomnia. Melatonin is involved in the synchronization of hormone secretions. The natural biorhythm of hormone secretion is referred to as the "circadian rhythm". The human body is governed by an internal clock that signals the secretion of various hormones at different times to regulate body functions. Melatonin plays a key role as the biological time keeper of hormone secretions. It also control periods of sleepiness and wakefulness.

Antidiabetics

- Sulfonylureas: Chlorpropamide, Tolazamide, Tolbutamide, Glipizide, Glyburide, Glimepiride (Amaryl)
- **Nutrients Depleted**
  - **Coenzyme Q10**

- Biguanides: Metformin
- **Nutrients Depleted**
  - **Vitamin B12**
  - **Folic acid**

Anti-Inflammatory

- Corticosteroids
- **Nutrients Depleted**
  - **Selenium:** Deficiency can cause cardiac abnormalities and weak muscles. Chronically low selenium intake is associated with and increased risk for cancer, heart disease, and low immune function. Selenium is an indispensable cofactor for glutathione peroxidase, which is one of the most important antioxidant enzymes in our immune system. As an antioxidant, selenium helps prevent lipid peroxidation and neutralizes destructive hydrogen peroxide. It increases T lymphocytes and enhances natural killer cell activity. It is capable of detoxifying heavy metal toxins such as mercury and cadmium. The conversion of T4 to T3 is a selenium-dependent reaction.
  - **Calcium**
  - **Vitamin D**
  - **Potassium**
  - **Zinc**
- Sulfasalazine
- **Nutrients Depleted**
  - **Folic Acid:** Intestinal absorption of folic acid is inhibited.

Anti-Inflammatory

- Indomethacin
- **Nutrients Depleted**
  - **Amino Acids:** Increases rate of gastric emptying which decreases absorption of proteins.
  - **Vitamin C**
  - **Folic Acid**
  - **Iron**

- Colchicine
- **Nutrients depleted**
  - **Beta-Carotene:** It is important antioxidant and the most important natural agent capable of quenching single oxygen free radicals in humans.
  - **Vitamin B12**
  - **Sodium**
  - **Potassium**

Anti-Inflammatory

- Nonsteroidal
- **Nutrients Depleted**
  - **Folic Acid:** Competitively inhibit the enzymatic synthesis of folic acid.
- **Aspirin, Choline Salicylate, Choline Magnesium Trisalicylate**
- **Nutrients Depleted**
  - **Vitamin C**
  - **Folic Acid**
  - **Iron**
  - **Potassium**
- Salsalate
- **Nutrients Depleted**
  - **Folic Acid**

Antiretoviral

- Retrovir, Ribavirin, Zidovudine
- **Nutrients Depleted**
  - **Copper:** Deficiency causes fatigue (due to anemia), loss of color in skin and hair (due to decreased synthesis of melanin), nervous system disorders, and reduced resistance to infection. Copper is a component of many important enzymes like copper-zinc Superoxide dismutase which is one of the body's most important antioxidant enzymes, and dopamine beta-hydroxlase which synthesizes norepinephrine.
  - **Zinc:** Deficiency slows wound healing and can lead to lowered immune function.

Cardiovascular

- Digoxin
- **Nutrients Depleted**
  - **B1 (thiamine)**
  - **Magnesium**

- Potassium Supplements
- **Nutrients Depleted**
  - **Vitamin B12**

Lipid Reducing Drugs

- Cholestryamine (Questran)
- **Nutrients Depleted**
  - **Beta-Carotene**
  - **Calcium**
  - **Folic Acid**
  - **Iron**
  - **Magnesium**
  - **Phosphorus**
  - **Vitamins A, B12, D, E, K**
  - **Zinc**
- Colestopol (Colestid)
- **Nutrients Depleted**
  - **Beta-Carotene**
  - **Folic Acid**
  - **Iron**
  - **Vitamin A**
  - **Vitamin B12**
  - **Vitamin D**
  - **Vitamin E**

Lipid Reducing Drugs

- Statins
- **Nutrients Depleted**
  - **Coenzyme Q10:** Statins inhibit the enzyme HMG CoA reductase that is required to make cholesterol and Coenzyme Q10.
  - **Selenium**
  - **Zinc**
  - **Copper**
  - **Lower serum fatty acid concentrations and alter the relative % of PUFA's**
- Gemfibrozil (Lopid)
- **Nutrients Depleted**
  - **Coenzyme Q10**
    Vitamin E (Alpha & Gamma tocopherol)
- Fenofibrate (Tricor)
- **Nutrients Depleted**
  - **Coenzyme Q10**
  - **Vitamin E**
  - **increases homocysteine**

Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke.

- ***Arch Neurol.*** 2004 Jun;61(6):889-92
- Rundek T, Naini A, Sacco R, Coates K, DiMauro S.
- Department of Neurology, Columbia University College of Physicians & Surgeons, New York, NY 10032, USA.
- BACKGROUND: Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely used for the treatment of hypercholesterolemia and coronary heart disease and for the prevention of stroke. There have been various adverse effects, most commonly affecting muscle and ranging from myalgia to rhabdomyolysis. These adverse effects may be due to a coenzyme Q(10) (CoQ(10)) deficiency because inhibition of cholesterol biosynthesis also inhibits the synthesis of CoQ(10). OBJECTIVE: To measure CoQ(10) levels in blood from hypercholesterolemic subjects before and after exposure to atorvastatin calcium, 80 mg/d, for 14 and 30 days. DESIGN: Prospective blinded study of the effects of short-term exposure to atorvastatin on blood levels of CoQ(10). SETTING: Stroke center at an academic tertiary care hospital.Patients We examined a cohort of 34 subjects eligible for statin treatment according to National Cholesterol Education Program: Adult Treatment Panel III criteria. RESULTS: The mean +/- SD blood concentration of CoQ(10) was 1.26 +/- 0.47 micro g/mL at baseline, and decreased to 0.62 +/- 0.39 micro g/mL after 30 days of atorvastatin therapy (P<.001). A significant decrease was already detectable after 14 days of treatment (P<.001). **CONCLUSIONS: Even brief exposure to atorvastatin causes a marked decrease in blood CoQ(10) concentration. Widespread inhibition of CoQ(10) synthesis could explain the most commonly reported adverse effects of statins, especially exercise intolerance, myalgia, and myoglobinuria.**
- PMID: 15210526 [PubMed - indexed for MEDLINE]

Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study.

- ***J Clin Pharmacol.*** 1993 Mar;33(3):226-9
- Ghirlanda G, Oradei A, Manto A, Lippa S, Uccioli L, Caputo S, Greco AV, Littarru GP.
- Institute of Internal Medicine, Catholic University Medical School, Rome, Italy.
- Inhibitors of HMG-CoA reductase are new safe and effective cholesterol-lowering agents. Elevation of alanine-amino transferase (ALT) and aspartate-amino transferase (AST) has been described in a few cases and a myopathy with elevation of creatinine kinase (CK) has been reported rarely. The inhibition of HMG-CoA reductase affects also the biosynthesis of ubiquinone (CoQ10). We studied two groups of five healthy volunteers treated with 20 mg/day of pravastatin (Squibb, Italy) or simvastatin (MSD) for a month. Then we treated 30 hypercholesterolemic patients in a double-blind controlled study with pravastatin, simvastatin (20 mg/day), or placebo for 3 months. At the beginning, and 3 months thereafter we measured plasma total cholesterol, CoQ10, ALT, AST, CK, and other parameters (urea, creatinine, uric acid, total bilirubin, gamma GT, total protein). Significant changes in the healthy volunteer group were detected for total cholesterol and CoQ10 levels, which underwent about a **40% reduction after the treatment.** The same extent of reduction, compared with placebo was measured in hypercholesterolemic patients treated with pravastatin or simvastatin. **Our data show that the treatment with HMG-CoA reductase inhibitors lowers both total cholesterol and CoQ10 plasma levels in normal volunteers and in hypercholesterolemic patients. CoQ10 is essential for the production of energy and also has antioxidative properties.** A diminution of CoQ10 availability may be the cause of membrane alteration with consequent cellular damage.
- PMID: 8463436 [PubMed - indexed for MEDLINE]

Lipid-lowering drugs and essential omega-6 and omega-3 fatty acids in patients with coronary heart disease.

- ***Nutr Metab Cardiovasc Dis.*** 2005 Feb;15(1):36-41
- de Lorgeril M, Salen P, Guiraud A, Zeghichi S, Boucher F, de Leiris J.
- Laboratoire Nutrition, Vieillissement et Maladies Cardiovasculaires (NVMCV), UFR de Médecine, Université Joseph Fourier, Grenoble, France. michel.delorgeril@ujf-grenoble.fr
- BACKGROUND AND AIM: There are only little data about the effects of lipid-lowering drugs (LLDs) on the metabolism of essential n-6 and n-3 fatty acids in patients with established coronary heart disease (CHD). METHODS AND RESULTS: Male patients with CHD and high cholesterol levels (>6.2 mmol/L) were randomized (double-blind protocol) to receive either simvastatin 20mg (S) or fenofibrate 200mg daily (F) for 3 months. Dietary habits and plasma fatty acids were not different in the two groups at baseline. After treatment, there were significant changes in both the groups for the main n-6 fatty acids, with an increase in arachidonate (from 6.5+/-1.7% of total fatty acids to 7.5+/-2.1, $p<0.001$ in S and from 6.2+/-1.4 to 6.8+/-1.4, $p<0.005$ in F) and a decrease in linoleate (from 26.9+/-3.9 to 24.2+/-3.6, $p<0.001$, and from 27.8+/-3.4 to 26.1+/-4.2, $p<0.05$, in S and F, respectively). In addition, there was a decrease in two major n-3 fatty acids (alpha-linolenate and docosahexanoate, both $p<0.05$), but only in F. **CONCLUSIONS: For the first time in a double-blind randomized study in CHD patients, we report that LLDs significantly alter the metabolism of essential fatty acids that are critically important for the pathogenesis and prevention of CHD.** Further studies are urgently needed to examine the effects of higher dosages of statins (as currently proposed to reduce more cholesterol) on these essential fatty acids in the clinical setting and the crucial questions of whether specific dietary intervention (combining low intake of n-6 fatty acids and high intake of n-3 fatty acids) may improve the effectiveness of these drugs.
- PMID: 15871849 [PubMed - indexed for MEDLINE]

Statin treatment alters serum n-3 and n-6 fatty acids in hypercholesterolemic patients.

- ***Prostaglandins Leukot Essent Fatty Acids.*** 2004 Oct;71(4):263-9
- Harris JI, Hibbeln JR, Mackey RH, Muldoon MF.
- Department of Medicine, Center for Clinical Pharmacology, School of Medicine, University of Pittsburgh, 4015 O'Hara Street, Old Engineering Hall, Room 506, Pittsburgh, PA 15260, USA.
- Statins are highly effective cholesterol-lowering drugs but may have broader effects on metabolism. This investigation examined effects of simvastatin on serum levels of n-6 and n-3 polyunsaturated fatty acids (PUFAs). Subjects were 106 healthy adults with hypercholesterolemia randomly assigned to receive placebo or 40 mg simvastatin daily for 24 weeks. Serum fatty acids were analyzed by gas chromatography. Total fatty acid concentration fell 22% in subjects receiving simvastatin (P<.001), with similar declines across most fatty acids. However, concentrations of arachidonic acid (AA, 20:4n-6), eicosapentanoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) were unchanged. Relative percentages of linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (LNA, 18:3n-3), decreased while AA and DHA increased (P's < or = .007). In addition, simvastatin increased the AA:EPA ratio from 15.5 to 18.8 (P<.01), and tended to increase the AA:DHA ratio (P=.053). **Thus, simvastatin lowered serum fatty acid concentrations while also altering the relative percentages of important PUFAs.**
- PMID: 15310527 [PubMed - indexed for MEDLINE

Antihypertensives/Diuretics

- Hydralazine
- **Nutrients Depleted**
  - **Vitamin B6**
  - **Coenzyme Q10**
  - **Magnesium**

- Betablockers (Atenolol, Propranolol, Metoprolol, Statolol, Carvedilol)
- **Nutrients Depleted**
  - **Coenzyme Q10**

- Clonidine
- **Nutrients Depleted**
  - **Coenzyme Q10**

Antihypertensives/Diuretics

- Loop Diuretics (Bumetanide, Furosemide)
- **Nutrients depleted**
  - **Vitamins B6**
  - **Magnesium**
  - **Potassium**
  - **Zinc**
  - **Vitamin C**

- Thiazide Diuretics (Chlorothiazide, Hydrochlorthiazide)
- **Nutrients Depleted**
  - **Magnesium**
  - **Potassium**
  - **Zinc**
  - **Increases homocysteine**

Antihypertensives/Diuretics

- Potassium-sparing Diuretics (Triamterene, Spironolactone)
- **Nutrients Depleted**
  - **Folic Acid**
  - **Coenzyme Q10**
  - **Calcium**

- Misc Diuretics (Indapamide, Metolazone, Chlorthialdone)
- **Nutrient Depleted**
  - **Magnesium**
  - **Potassium**
  - **Zinc**

Female Hormones

- Estrogen Replacement
- **Nutrients Depleted**
  - **Vitamin B6:** Deficiency could cause depression.
  - **Magnesium:** Low levels have been associated with headaches.
  - **CoQ10 and gamma tocoperol:** Decrease in antioxidant status.

- Oral contraceptives
- **Nutrients Depleted**
  - **Vitamin B2**
  - **Vitamin B6**
  - **Vitamin B12**
  - **Vitamin C**
  - **Folic Acid**
  - **Magnesium**
  - **Zinc**

Nutritional effects of oral contraceptive use: a review.

- ***J Reprod Med***. 1980 Oct;25(4):150-6
- Webb JL.
- Oral contraceptives agents (OCA) have been in use for more than two decades, and at the present time, **150 to 200 million women** are using the preparations. Apart from their gynecologic influence, the hormones have been shown to affect a number of metabolic and nutritional processes, some advantageously and others disadvantageously. **Concern over the nutritional status of females consuming OCA prompted this review. Eight vitamins and three minerals were investigated. Contraceptive steroid ingestion was shown to depress the physiologic levels of six nutrients (riboflavin, pyridoxine, folacin, vitamin B12, ascorbic acid and zinc)**, elevate the levels of three others (vitamin K, iron and copper) and provide little or no change in one (alpha tocopherol) and questionable increases in another (vitamin A). It was concluded that females consuming OCA should pay particular attention to vitamin and mineral intake and, if warranted, consume physiologic supplements of needed nutrients.

Nutritional effects of oral contraceptive use: a review. (cont.)

- ***J Reprod Med***. 1980 Oct;25(4):150-6
- Webb JL.
- PIP: The state of knowledge concerning the effects of OCs (oral contraceptives) and mineral metabolism is assessed. A review of the literature indicates that OCs depress the levels of Vitamin B2, or riboflavin, Vitamin B6, or pyridoxine, folacin, Vitamin B12, Vitamin C, or ascorbic acid, zinc and elevate levels of Vitamin K, copper, and iron. The ingestion of OCs produces little effect on Vitamin E, or alpha tocopherol. Findings on the effects of OC ingestion on Vitamin A are ambiguous. OC users have 50%-80% higher serum levels of Vitamin A than nonusers; however, OC users may have a greater need for Vitamin A than nonusers. The need for riboflavin may also be higher for OC users. OC users need more pyridoxine and riboflavin is needed to oxidize pyridoxine phosphate to pyridoxal phosphate. **Most studies support the contention that OC usage leads to a deficiency of Vitamin B6. Approximately 80% of all women using OCs for 6 or more months experience abnormal typtophan metabolism.** In order to correct this problem, 25 mg daily, or 12 times the normal daily requirement, is needed. Some investigators recommend givng this dosage to women, who experience abnormal tryptophan metabolism, while others warn that the long-term effects of such high dosages are unknown. Most investigators recommend that OC users, with Vitamin B12 or Vitamin C deficiencies, should be given supplementary vitamins.
- PMID: 7001015 [PubMed - indexed for MEDLINE]

Laxatives

- Mineral oil
- **Nutrients Depleted**
  - **Vitamin A**
  - **Beta-Carotene**
  - **Vitamin D**
  - **Vitamin E**
  - **Vitamin K**

- Bisacodyl
- **Nutrients Depleted**
  - **Potassium**

Drugs that Deplete Vitamin B12

Cephalosporins
Cholestyramine
Cimetadine
Doxycycline
Esomeprazole
Famotidine
Fluoroquinolones
Kanamycin
Lanoprazole
Lansoprazole
Macrolides
Metformin
Minocycline
Neomycin
Nizatidine
Omperazole
Oral Contraceptives
Oxytetracycline
Pantoprazole
Penicillins
Phenytoin
Rabeprazole
Ranitidine
Sulfonamides
Tetracycline
Trimethoprim

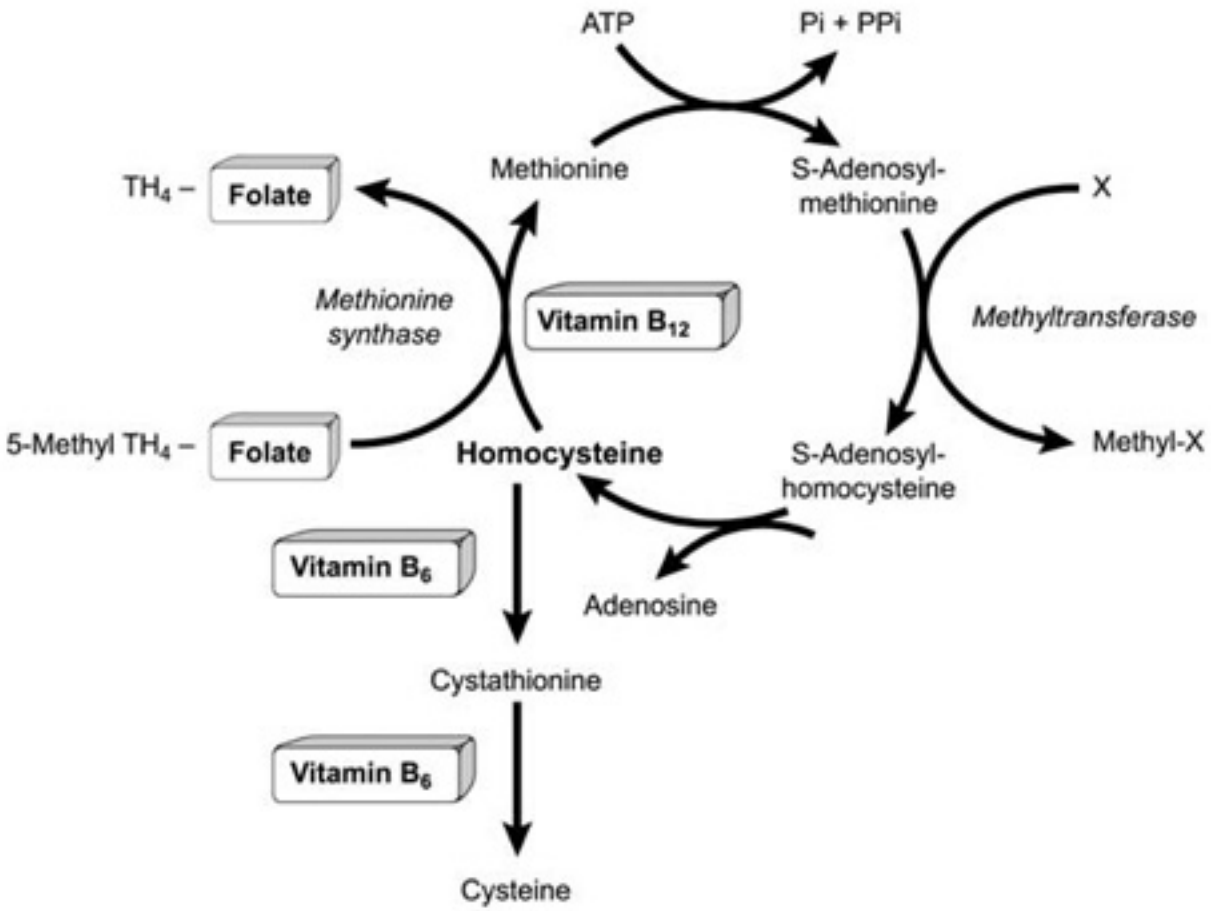
Drugs that Deplete Vitamin B6

Bumetanide
Cephalosporins
Demeclocycline
Doxycycline
Estrogens
Fluoroquinolones
Furosemide
Hydralizine
Hydrochlorothiazide
Isoniazide
Kanamycin
Macrolides
Minocycline
Oral Contraceptives
Oxytetracycline
Neomycin
Penicillins
Raloxifene
Sulfonamides
Tetracycline
Theophylline
Torsemide
Trimethoprin

Drugs that Deplete Folic Acid

Aspirin
Barbiturates
Carbamazepine
Celecoxib
Cholestyramine
Cimetidine
Colestipol
Corticosteroids
Famotidine
Hydrochlorothiazide
Indomethacin
Methotrexate
NSAIDs
Oral Contraceptives
Phenytoin
Primidone
Ranitidine
Salsalate
Triamterene
Trimethoprim
Valproic Acid

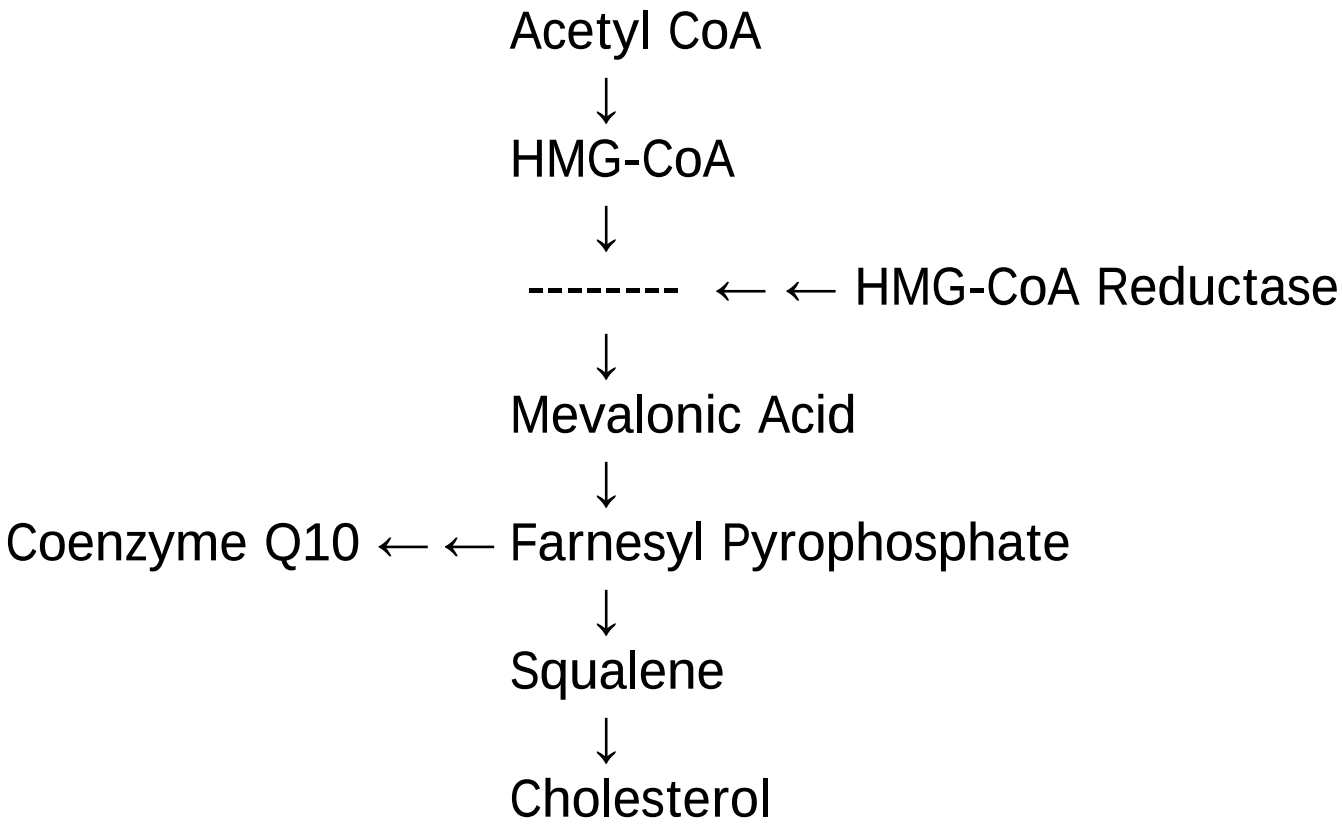
Homocysteine Metabolism



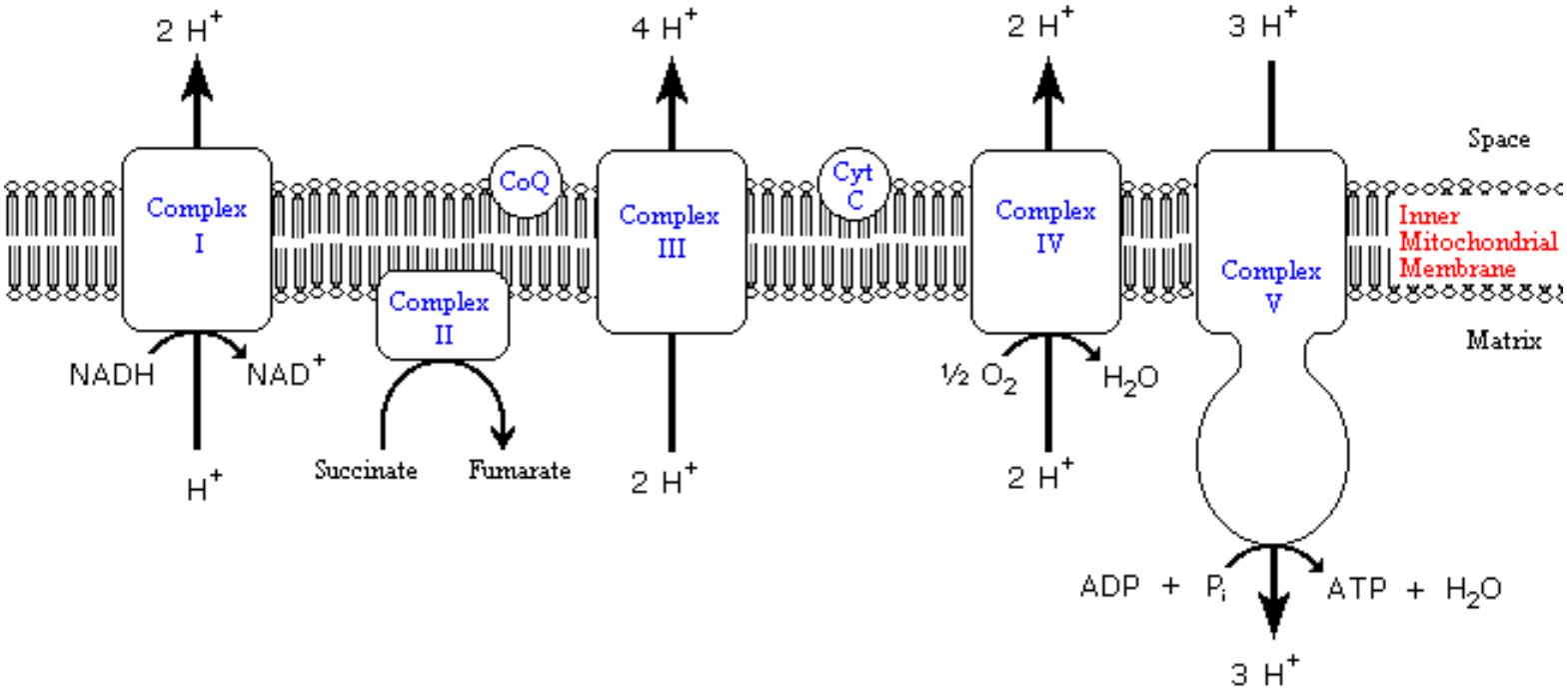
Drugs that Deplete Coenzyme Q10

Amiloride
Amoxapine
Beta Blockers
Candesartan\HCTZ
Chlorpromazine
Chlorpropamide
Clonidine
Desipramine
Doxepin
Enalapril\HCTZ
Fenofibrate
Gemifobrozil
Glimepiride
Glipizide
Glyburide
Haloperidol
Hydralazine
Imipramine
Indapamide
Irbesartan\HCTZ
Losartan\HCTZ
Methyldopa
Moexipril\HCTZ
Nortriptyline
Prochlorperazine
Protriptyline
Repaglinide
Statins
Thiazides
Thioridazine
Tolazamide
Tolbutamide
Valsartan\HCTZ

Biosynthetic Pathway of Cholesterol



Oxidative Phosphorylation



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