Drug Induced Nutrient Depletion

Sahar Swidan, Pharm.D., BCPS,
ABAAHP, FAARFM
Key Tenants of Aging

- Oxidative Stress/Inflammation
- Hormonal Balance
- Stress Hormones
- Glucose/Insulin Regulation
- Immune Balance
Metabolic Activation Pathways

**DIET**
- Sugar
- Carbohydrates
- Trans Fat
- Food Allergies

**DRUGS**
- Over-the-counter
- Prescription
- Drug-induced Nutrient Depletion

**EXERCISE**
- Frequency
- Type

**ENVIRONMENTAL EXPOSURE**
- Pesticides
- Pollens
- Herbicides
- Mold
- Chemicals
- Plastics
- Heavy Metals

**GENETICS**
- MTHFR
- APOB4
- Vitamin D

**STRESS**
- Psychogenic stress
- Physical stress

**DISEASE**
- Past/present conditions
- Active disease
- Syndromes

**CENTRAL ACTIVATION**
- Inflammation
  - IL-6
  - COX
  - TNFα
  - 5-LOX
  - IL-1β
  - NF Kappa β

**Liver / Kidney**
- Detox Abilities

**Hypothalamus Pituitary**
- Corticotropin Releasing Hormone (CRH)
- TH1
- TH2
- Imbalance

**Pancreas**
- Blood Sugar
- Belly Fat
- Insulin
- Inflammation
- Hormones
- Blood Pressure
- Plaque
- Kidney Damage
- Brain

**Thyroid**
- T4 ≠ T3
- Metabolism
- Insulin Receptor effects by 20%
- # of Mitochondria → Energy
- Lactate → More acidic, fatigue, muscle aches
- Global Fatigue

**Brain**
- Serotonin
  - Anxiety, Nervousness, Depression, Food cravings
  - Melatonin
    - Sleep Disturbances
  - Thyroid Binding Globulin
  - Insulin Resistance
  - Grehlin
  - Leptin
  - HGH

**Noropi Epi**
- Palpitation
- Arrhythmia
- Panic / OCD / Depression
- Burnout → Foggy Head
- Blood Pressure
- Cancer Cell

**Immune Gut / Lymph**
- Histamine → more allergies
- Leaky Gut
- Nutrient Absorption
- Serotonin → IBS
- Food Allergies
- Autoimmunity
- Microflora

**Microglia Activation**
- Autoimmunity

**Copyright © IHR 2008**
Metabolic Disruption
3 Primary Components

1. Intestinal
   Food/Dysbiosis

2. Stress/
   Inflammation

3. Environmental
   Toxicity

Neuro-Endocrine-Immune Balance

Copyright © IHR 2008
Nutritional Depletions

- Many agents used in the treatment of pain and psychiatric disorders can lead to nutritional depletions
- Providers should be attentive to symptoms of deficiency and laboratory values and supplement deficiencies when appropriate
Calcium

- **Drugs: Anticonvulsants**
  - Carbamazepine, phenytoin, phenobarbital

- **Mechanism of Deficiency:**
  - Decreased absorption due to increased metabolism of Vitamin D

- **Symptoms of Deficiency:**
  - Tetany, Osteomalacia, Irregular heart beat
Vitamin D

- **Drugs: Anticonvulsants**
  - Carbamazepine, phenytoin, phenobarbital

- **Mechanism of Deficiency:**
  - Increased metabolism

- **Symptoms of Deficiency:**
  - Rickets, Osteomalacia, Irregular heart beat
Selenium

- **Drugs:**
  - Clozapine
  - Valproic Acid

- **Mechanism of Deficiency:**
  - Chelation and increased excretion

- **Symptoms of Deficiency:**
  - Muscle weakness/pain, changes in skin color
Zinc

- **Drugs**
  - Phenytion
  - Disulfiram
  - Valproic Acid

- **Mechanism of Deficiency:**
  - Chelation
  - Decreased intestinal absorption

- **Symptoms of Deficiency:**
  - Dry skin, hair loss, dry nails, delay in wound healing
L-Carnitine

- **Drugs:**
  - Carbamazepine
  - Phenytoin
  - Valproic Acid

- **Mechanism of Deficiency:**
  - Interferes with hepatic biosynthesis

- **Symptoms of Deficiency:**
  - Cardiomyopathy, Skeletal muscle weakness, hypoglycemia
Thiamine

- **Drugs:**
  - Phenytoin

- **Mechanism of Deficiency:**
  - ??

- **Symptoms of Deficiency:**
  - Difficulty walking, paresthesias in extremities, confusion, pain, nystagmus, increased heart rate, lower extremity edema, shortness of breath
Niacin

**Drugs:**
- Sinemet
- Phenytoin
- Valproic Acid

**Mechanism of Deficiency:**
- Inhibit enzyme that converts tryptophan to niacin

**Symptoms of Deficiency:**
- Delusions, diarrhea, inflamed mucous membranes, confusion, scaly skin sores
Riboflavin

- **Drugs:**
  - Chlorpromazine

- **Mechanism of Deficiency:**
  - Structural similarities interfere with conversion of riboflavin to active form

- **Symptoms of Deficiency:**
  - Cheliosis/angular stomatitis, glossitis, sore throat, keratitis, scrotal skin changes, neuropathy, seborrheic dermatitis
Biotin

- **Drugs:**
  - Carbamazepine, phenobarbital, phenytoin

- **Mechanism of Deficiency:**
  - Competitive inhibition of transport in the intestine
  - Increased catabolism
  - Decreased renal tubular reabsorption

- **Symptoms of Deficiency:**
  - Thinning hair, loss of hair color, rash around eyes/nose/mouth, depression, lethargy, hallucinations, paresthesias of extremities
Folic Acid

- **Drugs**
  - Carbamazepine, phenytoin, phenobarbital, valproic acid

- **Mechanism of Deficiency**
  - Reduced absorption
  - Increased metabolism by increased hepatic enzymes
  - Increased demand by enzymes

- **Symptoms of Deficiency**
  - Megaloblastic anemia
Vitamin K

- **Drugs**
  - Carbamazepine, phenytoin, phenobarbital

- **Mechanism of Deficiency**
  - Induction of hepatic enzymes increases metabolism of vitamin K

- **Symptoms of Deficiency**
  - Bleeding disorders, fractures
Potassium

- **Drugs**
  - Levodopa

- **Mechanism of Deficiency**
  - Increased urinary losses

- **Symptoms of Deficiency**
  - Muscle weakness/cramps/aches, EKG changes
Drug-Induced Nutrient Depletions

<table>
<thead>
<tr>
<th>Category</th>
<th>Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Hormones:</td>
<td>FA, B6, B1, B2, B3, B12, C, Mg, Se, Zn, tyrosine, CoQ10, E</td>
</tr>
<tr>
<td>Anticonvulsants:</td>
<td>D, K, FA, Ca</td>
</tr>
<tr>
<td>Anti-diabetic Drugs:</td>
<td>CoQ10, B12</td>
</tr>
<tr>
<td>Anti-hypertensives:</td>
<td>B6, CoQ10, Ca, Mg, K, Zn,</td>
</tr>
<tr>
<td>Anti-inflammatory:</td>
<td>Ca, K, Zn, Fe, B6, C, D, FA, K</td>
</tr>
<tr>
<td>Cholesterol-lowering:</td>
<td>CoQ10</td>
</tr>
<tr>
<td>Beta-blockers:</td>
<td>CoQ10, melatonin</td>
</tr>
<tr>
<td>Phenothiazines/Tricyclics:</td>
<td>B2, CoQ10</td>
</tr>
<tr>
<td>Benzodiazepines:</td>
<td>Melatonin</td>
</tr>
<tr>
<td>Anti-ulcer medications:</td>
<td>B12, FA, D, Ca, Fe, Zn, protein</td>
</tr>
<tr>
<td>Antibiotics:</td>
<td>B-vitamins, vitamin K</td>
</tr>
</tbody>
</table>
Drug-Induced Nutrient Depletions

- Drugs can inhibit nutrient absorption, synthesis, transport, storage, metabolism, or excretion

- Health problems are multi-factorial & complex

- Tremendous opportunity for health professionals to improve health outcomes of customers/patients and increase sales of nutritional supplements
Female Hormone Medications

Oral contraceptives: deplete folic acid, B6, B1, B2, B3, B12, C, Mg, Se, Zn, tyrosine

Estrogen replacement therapy (ERT & HRT): deplete B6, Mg

Nutritional Effects of Oral Contraceptive Use: A Review

After 2 decades of use, concern about the nutritional status of women consuming OC prompted this review: OC shown to depress levels of vitamins B2, B6, B12, C, folic acid, Zn

Effect of Oral Contraceptive Agents on Vitamin Nutrition Status

- Women using low-dose OCs for 6 to 12 months
- ↑ excretion of kynurenic and xanthurenic acid
- ↑ EGOT activity with B6 challenge
- ↓ in erythrocyte folate levels
- ↓ in erythrocyte transketolase activity (B1)
- ↓ in erythrocyte riboflavin conc. and fall in erythrocyte glutathione reductase activity

Folic Acid Depletion with Oral Contraceptive Use

- Anemia: weakness, low energy
- Birth defects
- Cervical dysplasia
- Elevated homocysteine
- Depression
- ↑ breast and colorectal cancer

Vitamin B6 Depletion with Oral Contraceptive Use

- Reduced synthesis of serotonin and melatonin; elevated homocysteine
- Symptoms: depression, anxiety, decreased libido, impaired glucose tolerance
- Therapy: 40 mg B6/day restores biochemical values and relieves clinical symptoms

B6 Depletion and Oral Contraception

- Glutamic oxaloacetic transaminase from erythrocytes of 75 women taking oral contraceptives were determined. Data from this study indicated 1-5 mg B6 not sufficient for most women on OCs. Dose of 50-100 mg may be required.

Oral Contraceptives & Depression

- 30 women using OCs for 2 to 5 years, ten were suffering from depression. “Alterations in tryptophan metabolism are usually well compensated in the non-depression group but may accentuate/precipitate the development of depression in susceptible women.”

- In 9 of 12 clinical trials: depression occurs in 16-56% of women using oral contraceptives.
Oral Contraceptives and Riboflavin Nutrition

- 42 women on OCs vs 31 controls
- Erythrocyte reductase activity, which is an accurate index of riboflavin nutrition, was found to be significantly lower in the women taking OCs compared to controls

Oral Contraceptives: Effect of Folate and Vitamin B12 Metabolism

- Women using OC have significantly lower serum and erythrocyte folic acid
- Serum B12 is also significantly lower
- “Clinicians are advised to ensure that women who stop taking ‘the pill’ have adequate folate before becoming pregnant”

Shojania AM, Can Med Assoc J. 1982 Feb 1; 126(3): 244-47.
Effect of OCs on Nutrients. III
Vitamins B6, B12, and Folic Acid

- Reduction in plasma pyridoxal phosphate
- Lower red cell and serum folic acid
- No significant effect on serum B12

OCs: Folic Acid and Cervical Tissue

- Changes were observed in cervical epithelium in 101 women who had used OCs for over 6 months.
- Significant difference in cervical megaloblastic changes vs. controls.
- 29 out of the study were treated with Folate; cervical changes disappeared in 26 treated women.

OCs and Vitamin C

A: 18W taking low-dose OCs; 9W taking high-dose OCs; + 17 controls

B: 8W on low-dose OCs; data collected before and during the first 3 to 4 months of use

- ↓ serum ascorbic acid (30% to 42%)
- ↑ serum triglycerides (30% to 33%)
- ↑ LDL lipoproteins (27% to 29%)
- ↓ serum antithrombin III (22% to 29%)

Oral Contraceptives and Ascorbic Acid

- “Plasma, leukocyte, and platelet ascorbic acid levels are decreased in women ingesting oral contraceptive steroids.”

- “It is the estrogenic component of OCs that is associated with the decreased ascorbic acid concentrations.”

Effect of OC on tryptophan & tyrosine availability: evidence for a possible contribution to mental depression

- Progestogen users = no difference
- Estrogen/progestogen = elevated plasma tryptophan and decreased tyrosine
- Tyrosine $\rightarrow$ dopamine $\rightarrow$ norepinephrine
- Suggested that decreased brain tyrosine contributes to depressive symptoms

Tyrosine Depletion and Oral Contraceptives

- OCs significantly increased tyrosine transaminase activity and decreased plasma tyrosine at the mid cycle and luteal phase.

- Author suggests substrate limited reduction in norepi and contributed to food craving and mood alterations.

OCs and Depletion of CoQ10 & Vitamin E

- 2006 study measured nonfasting blood samples in 65 premenopausal women
  - Collected randomly in 40 women not on OC
  - Collected randomly in 15 women on OC for at least 6 months
  - Collected during follicular phase & luteal phase in 10 women

- OC use significantly decreased coenzyme Q10 & alpha-tocopherol (P<0.001)

Estrogen Replacement Therapy
ERT or HRT

- Vitamin B6

- Magnesium


Increased Need for Mg with the Use of Combined Oestrogen and Ca for Osteoporosis Treatment

“Prophylactic treatment of postmenopausal osteoporosis with oestrogen and Ca, often in combination, disregards the likelihood that an excess of each agent may increase Mg requirements and decrease Mg levels.”

- Mg necessary for normal bone structure
- ↑ Thromboembolic cardio/cerebrovascular

Estrogen Replacement Therapy and Magnesium Depletion

Estrogen induced magnesium shifts can be deleterious when estrogen levels are high and serum magnesium is low; can shift Ca/Mg ratios resulting in a shift toward coagulation.

### Blood Pressure Regulators

<table>
<thead>
<tr>
<th>Category</th>
<th>Required Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>B6, CoQ10</td>
</tr>
<tr>
<td>Loop</td>
<td>Ca, Mg, K, Zn, B1, B6, C</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Mg, K, Zn, CoQ10</td>
</tr>
<tr>
<td>Potassium-sparing</td>
<td>Ca, Zn, FA</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>CoQ10, melatonin</td>
</tr>
<tr>
<td>Clonidine/Methyldopa</td>
<td>CoQ10</td>
</tr>
<tr>
<td>ACE</td>
<td>Zn</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>Zn</td>
</tr>
</tbody>
</table>


Magnesium and Loop Diuretics

- Loop diuretics increase Mg excretion and inhibit passive Mg absorption.

Magnesium

- Muscle relaxant-Ca channel blocker
- ↓ platelet aggregation (like aspirin)
- Thins the blood (like Coumadin)
- Blocks Ca uptake (like Procardia)
- Relaxes blood vessels (ACE inhibitors)
- Improves cardiac contractility which ↑ oxygenation of the heart

Magnesium Deficiency: Pathophysiologic and Clinical Review

- Cofactor for ATP, critical in energy production, protein synthesis and anaerobic phosphorylation
- If Mg is depleted, bone stores contribute to Extracellular Fluid
- “The serum Mg can be normal in the presence of intracellular Mg depletion, and the occurrence of a low serum level usually indicates significant Mg deficiency.”

Lanoxin

- Calcium, magnesium, phosphorus via increased urinary excretion

- Magnesium deficiencies increase likelihood of cardiac dysrhythmias and atrial fibrillation


Bioenergetics in Clinical Medicine. III. Inhibition of Coenzyme Q10-enzymes by Clinically used Anti-hypertensive Drugs

- Propranolol: ↓ CoQ10-succinoxidase and CoQ10-NADH-oxidase
- Metoprolol, HCTZ, hydralazine and clonidine inhibit CoQ10-NADH-oxidase
- Methyldopa: weak succinoxidase inhibitor

## Cholesterol Lowering Drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA Reductase Inhibitors “statins”:</td>
<td>deplete Coenzyme Q10</td>
</tr>
<tr>
<td>The “fibrates”:</td>
<td>depletes B12, E, Cu, Zn</td>
</tr>
<tr>
<td>Gemfibrozil:</td>
<td>depletes CoQ10, E</td>
</tr>
<tr>
<td>Bile Acid Sequest:</td>
<td>depletes A, D, E, K, B12, Ca, Mg, P, Zn, Fe, Folic Acid, beta-carotene, fat</td>
</tr>
</tbody>
</table>


Mortensen: Dose-related CoQ10 Decline

- CoQ10, an essential mitochondrial redox-component; endogenous antioxidant packaged into LDL and VLDL fractions of cholesterol; and it is an important protector against atherosclerosis

- 45 hypercholesterolemic patients DB, 18 weeks; lovastatin (20-80 mg/d); pravastatin (10-40 mg/d)

- Significant dose-related decline in serum CoQ10

- **Pravastatin:** 1.27 to 1.02 mmol/l = - 19.7%

- **Lovastatin:** 1.18 to 0.84 mmol/l = - 28.8%
Effect of CoQ10 Therapy in Patients with Congestive Heart Failure: A Long-term Multicenter Randomized Study

CHF = frequent hospitalization/life-threatening arrhythmias, pulmonary edema, cardiac asthma.

- 1 year DB trial Q=319 (2mg/kg/d), P=322
- Hosp: Q=73 (22.9%) P=118 (36.6%) = ↓ 37.4%
- PulEdema: Q=20 (6.3%) P=51 (15.8%) = ↓ 60%
- C-Asth: Q=97 (30.4%) P=198 (61.5%) = ↓ 50.6%

Addition of CoQ10 to conventional therapy significantly reduces hospitalization for worsening of heart failure.

Treatment of Essential Hypertension with Coenzyme Q10

- 109 patients: in 80% of patients, average time of diagnosis = 9.2 yr.
- Average dose = 225 mg/day added to their existing antihypertensive medications
- 51% of patients were able to completely discontinue from 1 to 3 medications within the first 6 months (average time 4.4 months)
- Only 3% required addition of 1 more drug

Usefulness of CoQ10 in Clinical Cardiology: A Long-Term Study

- 424 patients: primary diastolic dysfunction, ischemic & dilated cardiomyopathy, mitral valve prolapse, hypertension, valvular heart disease.
- T=17.8 mo ave; D = 75-600 mg/d (ave. 242 mg)
- Large improvements on NYHA functional scale
- 43% completely discontinued from 1 to 3 meds
- “CoQ10 safe/effective treatment for broad range of CV diseases; gratifying clinical response; eases the medical/financial burden of multi-drug therapy.”

## Anticonvulsants

<table>
<thead>
<tr>
<th>Anticonvulsant</th>
<th>Nutrients Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>Vits D, K, FA, Biotin, Ca</td>
</tr>
<tr>
<td>Dilantin</td>
<td>Vits D, K, FA, B12, B1, Biotin, Ca</td>
</tr>
<tr>
<td>Tegretol</td>
<td>Vit D, FA, Biotin</td>
</tr>
<tr>
<td>Mysoline</td>
<td>Vits D, K, FA, Biotin, Ca</td>
</tr>
<tr>
<td>Depakene</td>
<td>FA, Carnitine, Cu, Se, Zn</td>
</tr>
</tbody>
</table>


Anticonvulsants, Folate Levels, and Pregnancy Outcome: A Prospective Study

- Serum and red cell folate levels: 50 non-pregnant and 46 pregnant epileptic women (49 pregnancies)
- 23 NP ↓ serum folate and 4 ↓ red cell folate levels
- All women: serum and red cell folate inversely related to plasma levels of Phenobarb and Dilantin
- 10 abnormal (20.4%): 4 spontaneous abortions (8.2%) and 6 congenital malformations (12.2%)
- Folate significantly lower in abnormal outcomes

Carnitine and Valproate

- Valproate is associated with decreased carnitine levels and at times true carnitine deficiency. Carnitine is essential for fatty acid utilization and regulates free coenzyme A to acylcoenzyme A in the mitochondrion.

Anti-diabetic Drugs

Sulfonylureas: deplete CoQ10

Biguanides: deplete CoQ10, B12, FA


Bioenergetics in Clinical Medicine. XI. Studies on CoQ10 and Diabetes Mellitus

- Activity of succinate dehydrogenase-CoQ10 reductase was much lower and % deficiency much higher than controls
- Dymelor, Glyburide, Phenformin and Tolazamide inhibit CoQ10 NADH-oxidase
- “A deficiency of CoQ10 in the pancreas could impair bioenergetics, the generation of ATP, and the biosynthesis of insulin.”

Malabsorption of Vitamin B12 and Intrinsic Factor Secretion during Biguanide Therapy

- 46 diabetic patients: 30% had malabsorption of vitamin B12
- Withdrawal normalized absorption in only half of those with malabsorption
- Biguanides can induce malabsorption by 2 different mechanisms: 1 is temporary and unrelated to intrinsic factor; other causes permanent ↓ in intrinsic factor secretion

Metformin Increases Total Serum Homocysteine Levels

- Non diabetic males with CVD
- 60 males open randomized trial 40 wk
- Results in significant increase in homocysteine with metformin administration
- B12 and folate levels were decreased

Thiazolidinediones (TZDs)

- Activation of peroxisome proliferator-activated receptor-gamma (PPARgamma) results in lower bone mass in mice
- PPARgamma regulates glucose metabolism & bone mass
  - Activation of PPARgamma led to changes in marrow structure & function such as decreasement of osteoblast #, increase in marrow fat cells, increase in osteoclast #, and loss of multipotential character of marrow mesenchymal stem cells
  - Study concludes that “rosiglitazone induces changes in bone reminiscent of aged bone & appears to induce bone loss by altering phenotype of marrow mesenchymal stem cells”


Thiazolidinediones (TZDs)

- Osteoblasts & marrow adipocytes derived from common mesenchymal progenitor so incr adipogenesis may occur at expense of osteoblasts, leading to bone loss
- Study provides evidence that PPARgamma is negative regulator of bone mass

## Psychotherapeutic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenothiazines</td>
<td>depletes B2 &amp; CoQ10, melatonin</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>deplete B2 &amp; CoQ10</td>
</tr>
<tr>
<td>Phelozine (MAOI)</td>
<td>depletes vitamin B6</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>depletes CoQ10, vit. E &amp; melatonin</td>
</tr>
<tr>
<td>Lithium</td>
<td>depletes inositol</td>
</tr>
</tbody>
</table>


Phenothiazines and Tricyclics: B2

“Chlorpromazine, imipramine and amitriptyline, drugs structurally related to riboflavin, each inhibited in vivo formation of FAD from riboflavin in the rat heart.”

“All 3 drugs inhibited FAD formation in the heart within 5 hrs after a single dose (25mg/kg).”


Phenothiazines and Tricyclics: CoQ10

- “All the phenothiazines and tricyclic anti-depressants inhibited succinoxidase and NADH-oxidase activities”
- “Also inhibited succinate dehydrogenase-CoQ reductase activity”
- Butyrophenones (Haldol) inhibited NADH-oxidase activity

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Studies show:
  - Use of SSRIs, not TCAs, assoc w/ incr risk of bone loss at hip in cohort of older women
  - Bone mineral density lower among SSRI users & not in users of other antidepressants
  - Daily SSRI use causes 2-fold incr risk of clinical fragility fracture after adjusting for potential covariates

SSRIs and Bone Loss

- Mechanism not completely understood
- Serotonin transporters have recently been described in bone
  - Medications that block serotonin reuptake could affect bone metabolism
  - Osteoblasts & osteoclasts express functional serotonin transporters
    - SSRIs block serotonin transporter

Anti-ulcer Drugs

H-2 Receptor Antagonists: B12, folic acid, D, Ca, Fe, Zn, protein

Proton Pump Inhibitors: Beta Carotene, Ca, B12 (protein)


Proton Pump Inhibitors and Beta Carotene

- Higher pH decreased serum trans and cis beta-carotene levels poss. due to slower movement of negatively charged micelles.

Helicobacter Pylori and Vitamin C

- 60 patients with dyspeptic symptoms & proven chronic gastritis & H. pylori
- 28 patients/antacids x 4 weeks
- 32 patients/5 grams vitamin C/day x 4 wks
- Results: 30% (8 of 27) vitamin C patients had total eradication of H. pylori

PPIs and Bone Loss

- Through induction of hypochlorhydria, PPIs may interfere with Ca absorption
- Through inhibition of osteoclastic vacuolar proton pumps, PPIs may also reduce bone resorption
- Study concluded that long-term therapy w/ PPIs (particularly at high doses) is assoc w/ incr hip fracture risk

# Anti-inflammatory Drugs

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Required Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Vit A, C, D, B6, B12, FA, Ca Cr, Mg, K, Se, Zn</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Vit B12, Ca, Na, K, P, B-carotene</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Folic acid</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Folic acid, iron</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>Folic acid, melatonin</td>
</tr>
<tr>
<td>Aspirin/salicylates</td>
<td>Vit C, FA, B5, Ca, Fe, Na, K</td>
</tr>
</tbody>
</table>

Corticosteroids and Calcium Depletion

- Low dose prednisone on calcium and bone metabolism. Prednisone was noted to have a negative effect on bone metabolism.

Anti-Anxiety Agents

Diazepam (Valium) and Alprazolam (Xanax)

Both drugs deplete melatonin:

- Insomnia, greater cancer risk, increased free radical aging damage


Antibiotics

- Beneficial bacteria manufacture B vitamins and vitamin K in the GI tract
- Beneficial bacteria produce proteases, lipases, and lactase that aid in digestion of nutrients
- Bifidobacteria produce SCFAs that provide from 5-10% of our daily energy supply
- Dysbiosis further disrupts digestion and absorption of nutrients

## Antiviral Agents

### Zidovudine and related HIV/AIDS drugs

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carnitine</td>
<td>abnormal lipids, liver function, glucose</td>
</tr>
<tr>
<td>Copper</td>
<td>anemia, cardio &amp; connective tissue problems</td>
</tr>
<tr>
<td>Zinc</td>
<td>↓ immunity, wound healing, taste &amp; smell</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>anemia, ↑ CVD risk, depression</td>
</tr>
</tbody>
</table>


Zidovudine and Carnitine Depletion

- Impairment of mitochondrial function in muscle caused by AZT resulted in pathological changes including: The accumulation of fat, reduction in muscle carnitine and the depletion of muscle fiber energy stores.
- Authors recommended the use of oral carnitine.

Chemotherapy Drugs

- Most nutrients are depleted

- Cytotoxic drugs can cause:
  - damage to gastric & GI mucosa/malabsorption
  - inflamed GI tract/painful, decreased appetite
  - nausea and vomiting
  - dysbiosis
Lupron/leuprolide

In human males:
- 21% decrease in bone calcium deposition
- Significant increase in urinary Ca excretion
- Decrease in osteocalcin concentrations

In animals:
- Lower bone volume; higher bone turnover
- Large ↓ in BMD of vertebra & femoral bone
Depletes Beta-carotene


Depletes Vitamins A and E

Timed Release KCl Drugs

- Vitamin B12 depletion
- Slow release of KCl salts alters intestinal pH, which decreases B12 absorption
- Anemia, elevated homocysteine, depression, neurological problems

Bronchodilators

- **Theophylline**: depletes vitamin B6- inhibits synthesis of the enzyme pyridoxal kinase which is necessary to convert B6 to pyridoxal-5-phosphate


- **Beta₂ adrenergic agonists**: deplete potassium

Coumadin

- Vitamin K depletion
- Interferes with the enzyme responsible for the synthesis of vitamin K

Aspirin

- **Vitamin C:** drug most likely to deplete in normal individuals
- **Iron:** due to blood loss in GI tract
- **Folic acid:** displaces bound serum folate
- **Potassium:** increased urinary loss


Acetaminophen

1) Depletes glutathione and cysteine in kidneys
   ↓ 34%/young, 58%/mature, 64% old
   24-hr recovery 95%/young, 98% mature, 56% old


2) Depletes glutathione & catalase in liver; GSH 83% ↓ in 60 min;
   ↑ in H₂O₂ & hydroperoxides, which causes cell/tissue injury

   Toxicological Sciences 76, 229-236 (2003)

3) Depletes glutathione in testes and lung; substantial increase in toxic exposure to lung tissue

Laxatives

- **Mineral oil**: ↓ absorption of vitamins A, D, E, K, and beta-carotene, calcium & phosphorus

- **Bisacodyl**: depletes potassium. Intense peristalsis and rapid bowel emptying can cause hypokalemia.

- **Sodium phosphate enema**: depletes Ca & Mg
Antacids

- **Mg/Al antacids**: deplete calcium, phosphorus and folic acid (protein)


- **Sodium bicarbonate**: depletes potassium and folic acid (protein)

National Cholesterol Education Program
Diagnostic Criteria -
Combination of 3 or more of the following:

Elevated waist circumference:
  Men — Equal to or greater than 40 inches (102 cm)
  Women — Equal to or greater than 35 inches (88 cm)

Elevated triglycerides:
  Equal to or greater than 150 mg/dL

Reduced HDL (“good”) cholesterol:
  Men — Less than 40 mg/dL
  Women — Less than 50 mg/dL

Elevated blood pressure:
  Equal to or greater than 130/85 mm Hg

Elevated fasting glucose:
  Equal to or greater than 100 mg/dL
Metabolic Syndrome

The fact that the individual has already developed insulin resistance indicates possible nutrient deficiencies as several nutrients effect the efficiency of insulin (chromium, magnesium, and zinc) and glucose transport (alpha lipoic acid)
Drug Therapies

- **Blood pressure** -
  - Thiazide diuretics (Diuril, HCTZ, Lozol, Zaoxolyn) - reduce water and sodium in the body and dilate blood vessels
  - Loop diuretics - Lasix (furosemide) - reduce water in the body
  - K sparing diuretics - Dyaxide, Maxzide and Dyrenium (Triamterene) - reduce water in the body

All cause reduced blood volume, which decreases blood pressure and workload on the heart
Drug Therapies

ACE Inhibitors - Vasotec, Accupril, Altace, inhibit angiotensin converting enzyme which narrows blood vessels.

Beta Blockers - Lopressor (metaprolol,) Atenolol (Tenormin) - inhibit action of adrenalin leading to slower weaker heartbeat. Beta blockers are no longer recommended as first line for high blood pressure (Aug.6 2007, Journal of the American College of Cardiology) because they are not as effective as the other drugs and have worse side effects.
Drug Therapies/Depletions

- Thiazide diuretics - Co Q10, Mg, K, Na, Zn
- K sparing diuretics - Ca, Folate, Zn
- Statin drugs - Co Q10
- Metformin - B12, Folate, Co Q10, B6
- Sulfonylureas - CoQ10
- ACE inhibitors - NA, Zn
- Beta Blockers - Co Q10, Melatonin
### Signs/Symptoms of Magnesium Deficiency

1. Muscle cramps and spasms, including vasospasm
2. Constipation
3. Arrhythmia and heart palpitations
4. Anxiety, nervousness, and insomnia
5. Increased BP
6. Blood sugar dysregulation
7. Depression
8. Migraines
9. Kidney Stones
10. Osteoporosis
11. Low energy/fatigue
Listed side effects of Thiazide Diuretics

- Irregular heartbeat
- Low back pain
- Mood changes
- Constipation
- Glucose intolerance

- Muscle pain, weakness or cramps
- Headache
- Unusual tiredness or weakness
Repletion of Magnesium

300 to 800 mg/day
Better absorbed forms:
Magnesium citrate
Magnesium glycinate
Magnesium taurate
Magnesium malate

Magnesium carbonate and oxide not effective at repleting magnesium status
Coenzyme Q10

- Depleted by Thiazide diuretics, Statins, Metformin, Sulfonylureas and Beta Blockers
- Functions- co-factor in the electron transport chain and generation of ATP, antioxidant, principle gene regulator in muscle tissue
Depletion of Co Q10

- Cardiomyopathy
- Fatigue
- Leg weakness, restless legs
- Hypertension
- Angina
- Stroke
- Cardiac dysrhythmia
- Lowered immunity
- Decreased cognitive function
- Insulin dysfunction
Co Q10 and Muscle Fibers

- Co Q10 increased fast twitch muscle fibers in elderly populations compared to placebo
- Co Q10 influenced genetic expression for increased fast twitch muscle fiber
- Co Q10 protects against aging of muscle tissue

Co Q 10 and Hypertension

- CoQ10 decreased diastolic and systolic BP, decreased total Chol, and increased HDL (Mol Aspects Med 1994;15 Suppl:S257-S263)
- CoQ10 reduced Hypertension Medications (Mol Aspects Med 1994;15 Suppl:S265-S272)
Co Q10 and Myopathies


This study suggested that myopathies (a common side effect of drug therapies) can occur even if cellular level histochemical changes are not present with mild CoQ10 depletion.
CoQ10 Repletion

- 30 to 1800 mg/day
- Various forms available:
  - Monoglyceride
  - Lipid soluble
  - Powder
  - Propylene glycol
CoQ10 and Alzheimer’s

- Decreases in mitochondrial ATP are associated with increased free radical activity in cells secondary to lack of glutathione production.
- These cellular changes can lead to the amyloid plaque production seen in Alzheimer’s.
- Brain mitochondria of diabetic rats treated with CoQ10 had decreased hydrogen peroxide production changing the conditions that lead to amyloid plaque formation.

CoQ10 and Parkinson’s

- Decrease concentrations of CoQ10 within the mitochondria create disturbances in Complex I-II in electron transport.
- Increased free radical damage to cell.
- Increased rate of neuronal cell death.

Zinc

Depleted by Thiazide diuretics, Potassium sparing diuretics, and ACE inhibitors

Functions: needed for growth and repair of all proteins in the body, therefore very important in immunity and wound healing, helps synthesize DNA and RNA, needed as part of the superoxide dismutase enzyme
Zinc Deficiency

- Loss of taste and smell
- Poor wound healing
- Alterations immunity
- Increased inflammatory cytokines
- Frequent infections
- Disorders of hair, skin and nails
- Alterations in hormones
Comprehensive Approach

- Lifestyle Approach should be tried first
- Drug Therapy minimized
- Dietary Revision Low Glycemic
- Multivit/mineral
- Repletion of glutathione and other antioxidants and cofactors
- Energy Nutrients Acetyl L Carnitine, CoQ10, NADH, and phospholipids
- Chelation of Heavy Metals
- Improve Liver Detoxification
Questions???

Sahar Swidan

(734) 821-8000

sswidan@umich.edu
LIFE IS THE ONLY GAME

IN WHICH

THE OBJECT

OF THE GAME

IS TO

LEARN

THE

RULES.

© Ashleigh Brilliant 1973