Macro and Micronutrients I and II

By Monica Hsu

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Vitamin Overview

LEARNING OBJECTIVES
1. Define vitamins, Classification, Essentiality, Functions
2. Describe concepts of deficiency, acceptable intake range, optimum intake, and toxicity
3. Compare water and fat soluble vitamins with regard to absorption, transport, storage, excretion, toxicity and requirements
4. Define and describe the basis of the RDAs, EARs, AIs, and ULs
5. Identify ways to reduce vitamin losses from foods

Classification of Vitamins
- Water-soluble and fat-soluble
- "B-complex" vitamins and vitamin C

Functions of Vitamins
- Most commonly precursors to, or components of, coenzymes
- Many involved in fundamental metabolic pathways
- Organic nutrients required in small quantities for normal metabolism
- Essential nutrients which cannot be synthesized by the body in adequate amounts to meet normal physiological needs
- Required usually in minute amounts for normal bodily functions (maintenance, growth, development, and/or production)
- Their absence or under-utilization causes a specific deficiency syndrome

Essentiality
1. Deterioration in health/growth with deficient diet
2. Improvement in health/growth when added to deficient diet
3. Reduction in levels in blood/tissues associated with deterioration in health/growth
4. Some other dietary component can't perform function

Vitamin Requirements
- Prevent deficiency
- Maximum body stores
- Optimum amount or range?
- Therapeutic dose
- Toxicity

Classification of Malnutrition
1. **Cause:** Primary (exogenous)
   Secondary (endogenous)
2. **Type:** Excess, toxicity (over-nutrition)
   Deficiency (undernutrition)
3. **Nutrients:** Vitamins, Minerals, Proteins, energy
4. **Degree:** Mild – Moderate – Severe
   Depleted stores – Biochemical lesion – Functional change
5. **Duration:** Acute, Sub-acute, and Chronic
6. **Outcome:** Reversible, irreversible

Typical Avitaminosis
Dietary intake (diet history) + secondary conditioning factors
→ Gradual decrease in tissue levels (blood, urine, tissue analysis)
→ **Biochemical lesions** (reduced enzymes, altered metabolites)
→ **Anatomic lesions** (clinical evaluation)
→ **Pathology – disease** (clinical symptoms)

Potential Causes of Vitamin Deficiencies in Humans

Primary deficiencies: have psychosocial and technological causes
- Poor food habits
- Poverty (low food-purchasing power)
- Ignorance (lack of sound nutrition information)
- Lack of vitamin-rich food (consumption of highly refined foods)
- Lack of total food (crop failure)
- Vitamin destruction (during storage, processing, cooking)
- Anorexia (homebound elderly, dental problem)
- Food taboos and fads (fasting, avoidance of certain foods)
- Apathy (lack of incentive to prepare adequate meals)

High risk group for vitamin deficiencies
- Pregnant women
- Infant and young children
- Elderly people
- Dieters
- Smokers

Secondary Deficiencies: have biological causes
- Poor digestion (achlorhydria: absence of stomach HCl)
- Malabsorption (impaired intestinal absorption of nutrients, as a result of intestinal infection, parasites, and pancreatitis)
- Impaired metabolic utilization (certain drug therapies)
- Increased metabolic need (pregnancy, lactation, rapid growth, infection, nutrient imbalance)
- Increased vitamin excretion (diuresis, lactation, excessive sweating)

Fat-Soluble Vitamins

- Insoluble in water but dissolve in fat and oils
- Relatively stable to normal cooking temperatures
- Slowly inactivated by ultraviolet light and by oxidation
- Absorption requires dietary fat and bile
- Transported via lipoproteins or specific transport proteins
- Storage is mainly in the liver, some in adipose tissue
- Excretion is via the feces in the bile. Some metabolites may be excreted in the urine

Comparison of Water-Soluble and Fat-Soluble Vitamins

	Water-soluble vitamins (B and C)	Fat-soluble vitamins (ADEK)
Absorption	Absorbed mostly in SI, but also in stomach. Absorbed via simple diffusion when intake is high and active transport when intake is low.	Absorbed mostly in SI. Require incorporation into micelles and the action of bile. Once transported into the intestinal cell, vitamins are packaged with other lipids into chylomicrones.
Transport	Travel freely	Many require protein carrier
Storage	Freely circulate in water	Trapped in the cell associated with fat
Excretion	Kidney detect and remove excess in urine	Less readily excreted, remain in fat storage sites
Toxicity	Minimal, unlikely to reach toxic levels when consumed in excess, although some exist	Except for vitamin K, likely to reach toxic levels and sometimes fatal
Requirement	Needed in frequent, small amount	Needed in periodic amount

RDA's and DRI's

- DRI's (Dietary Reference Intake) are a set of recommendations – include RDA's, EAR's, AI's, UL's
- RDA's (Recommended Dietary Allowance) – meet nutrient requirement of nearly all (97-98%) of healthy individuals
- EAR's (Estimated Average Requirement) – amount of nutrient required to meet needs of 50% of healthy individuals (+ measure of variability to give RDA)
- AI (Adequate Intake) – when not enough data to calculate EAR
- UL (Upper Limit) – highest level of daily intake that is likely to pose no risk of adverse effects in a healthy population (but?)

Use of DRI's

- Assessing intake of individuals
- Assessing intake of populations
- Planning diets for individuals
- Planning diets for groups

Client Screening: When screening a client's diet regarding vitamin content, 5 points to keep in mind

1. Amount of the vitamin expected to be in the food
2. Quantity of the food that actually is eaten
3. Frequency with which the food is eaten
4. Stability of the vitamin during processing and cooking
5. Bioavailability of the vitamin, especially when ingested with other foods or dietary supplement and upon body's need

Storage and Preparation to Reduce Vitamin Losses from Foods

1. Eat foods as soon as possible after harvesting or purchasing
2. Refrigerate fresh produce and wrap tightly to retain moisture and decrease exposure to air
3. For longer storage, freezing is best. Blanch first to retain flavor and stop enzymes that destroy vitamins
4. Wait as long as possible before cutting up food for a meal. The smaller the pieces that food is cut into, the greater the nutrient losses due to exposure to light and oxygen
5. The higher the temperature and the longer heat is applied, the greater the losses. Use as low a temperature for as short time as possible, but you must cook hot enough and long enough to ensure the safety of what you are preparing
6. Microwaving uses shorter cooking times, so may in some cases result in greater nutrient retention
7. Water-soluble nutrients are lost in water, so avoid soaking, and cook vegetables in their skins
8. Cook frozen vegetables without thawing
9. Do not add baking soda to vegetable cooking water
10. Use cooking technique that do not bring food into direct contact with water, such as steaming and pressure cooking, or dry heat, such as roasting, grilling, stir-frying, or baking

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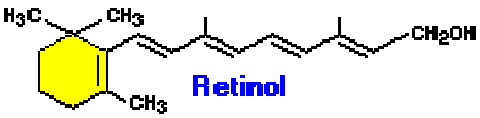
Vitamin A and Carotenoids

LEARNING OBJECTIVES
1. Understand different forms of Vitamin A and carotenoids
2. Outline the functions of Vitamin A and the anti- and pro-oxidant functions of carotenoids
3. Explain the mechanisms for absorption, transport, and metabolism of carotenoids
4. List the major food sources of retinoids and carotenoids
5. Describe deficiencies and toxicities and the therapeutic use

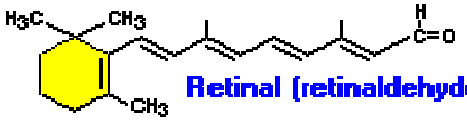
CHEMISTRY, NOMENCLATURE, FORMS

Vitamin A

- Vitamin A consists of 3 biologically active molecules, **retinol, retinal** (retinaldehyde) and **retinoic acid**
- Retinol is the immediate precursor to 2 important active metabolites: retinal, which plays a critical role in vision, and retinoic acid, which serves as an intracellular messenger that affects transcription of a number of genes

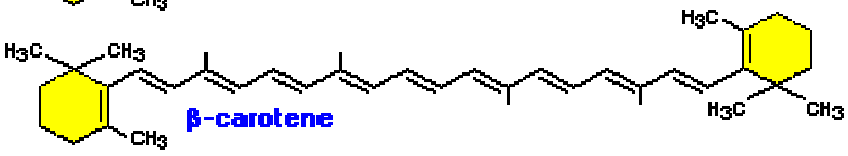


Retinol



Retinal (retinaldehyde)

Retinoic Acid



β-carotene

Carotenoids

- There have been at least 600 carotenoids identified, 50-60 in foods, 30 in blood, 6 found in significant [ ] in human plasma
- *Carotenoids are either 40-carbon hydrocarbons (carotenes) or 40-carbon hydroxylated compounds (xanthophylls)*
- Carotenes include β-carotene (consists of two molecules of retinal linked at their aldehyde ends, is also referred to as the provitamin form of vitamin A), α-carotene, and lycopene
- Xanthophylls include zeaxanthin, lutein, and β-cryptoxanthin; they are often found in plants as esters

FOOD SOURCES

Vitamin A

- Retinyl esters such as Retinyl palmitate, a precursor and storage form of retinol, is generally found in foods from animals. Very rich sources include liver, cod-liver oil, dairy products including whole milk, cheese, and butter, as well as fish (tuna, sardines, and herring)
- Most fat free milk and dried nonfat milk solids sold in the US are fortified with vitamin A to replace the vitamin A lost when the fat is removed. Fortified foods such as fortified breakfast cereals also provide vitamin A

Carotenoids

- Plants contain carotenoids, (e.g. α-carotene and β-carotene): yellow, orange, and green vegetables contain significant quantities
- Only recently have carotenoids been measured accurately in foods: older food tables focused on Vitamin A activity
- There is much variability: generally, the more colored the plant, the higher the carotenoid content; carotenoids seems to be concentrated in a limited number of foods
- *In the American diet, carotenoid intake is about 6-11 mg/day: lycopene >3mg, β-carotene ~3 mg/day, lutein 2-3 mg/day*
- Rich sources *(> 1.0 mg/100g)* of β-carotene are carrots, canteloupe, broccoli, green leafies (including dark lettuce), mango, apricot, peaches, red peppers, pink grapefruit, pumpkin, winter squash, sweet potato, tomato sauce/paste
- Rich sources *(> 1.0 mg/100g)* of α-carotene are carrots and pumpkin
- Rich sources *(> 1.0 mg/100g)* of lycopene are tomato, tomato products, pink grapefruit, guava, watermelon
- Rich sources *(> 1.0 mg/100g)* of lutein/zeaxanthin are green leafies , broccoli, brussel sprouts, celery, leek, green peas, pumpkin, summer squash, yellow corn (zeaxanthin high in corn and persimmons)
- *Rich sources (> 0.2 mg/100g) of β-cryptoxanthin are tangerine, papaya*
- *Other interesting carotenoids are capsaxanthin (paprika), bixin (annatto seeds), astaxanthin (crustaceans), canthaxanthin (artificial tanning!).*
- *Carotenes are very stable to mild heat (lose about 10%) but are destroyed by light (can form up to 25-50% of cis isomers when vegetables are canned).*
- *Xanthophylls are much more easily oxidized: can lose up to 60% in normal cooking (lutein is a little more stable with loss of about 18-25%).*

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The RDA: *The most recent international standard of measure for vit A is retinol activity equivalency (RAE), which represents vit A activity as retinol.*
Adult men ages 19 and older: *900 mcg/day*
Adult women ages 19 and older: *700 mcg/day*
2 mcg of β-carotene in oil provided as a supplement can be converted by the body to 1 mcg of retinol giving it an RAE ratio of 2:1.

RAE ratios for β-carotene and other provitamin A carotenoids		
Quantity Consumed	***Quantity Bioconverted to Retinol***	***RAE ratio***
1 mcg of dietary or supplemental vit A	*1 mcg of retinol*	*1:1*
2 mcg of supplemental β-carotene	*1 mcg of retinol*	*2:1*
12 mcg of dietary β-carotene	*1 mcg of retinol*	*12:1*
24 mcg of dietary α-carotene	*1 mcg of retinol*	*24:1*
24 mcg of dietary β-cryptoxanthin	*1 mcg of retinol*	*24:1*

However, 12 mcg of β-carotene from foods are required to provide the body with 1 mcg of retinol, giving dietary β-carotene an RAE ratio of 12:1. Other provitamin A carotenoids in foods are less easily absorbed than β-carotene, resulting in RAE ratios of 24:1. An older international standard, still commonly used, is the international unit (IU). One IU is equivalent to 0.3 mcg of retinol

DIGESTION, ABSORPTION, TRANSPORT

- Vitamin A in food: 2 different forms – pre-formed retinol (vit A) and pro-vitamins (i.e. carotenoids that can be converted to retinol)
- In food pre-formed retinol is mainly retinyl esters. Most important pro-vitamin is β-carotene (some α-carotene and β-cryptoxanthin)
- Retinol is found typically bound to fatty acid esters (most common retinyl palmitate)
- Retinyl esters and carotenoids are often bound to protein in food from which they must be released
- Hydrolysis from protein occurs by the action of pepsin in the stomach and other proteoytic enzymes in the proximal SI (heating of plant food before consumption is thought to facilitate bioavailability by weakening protein-carotenoid complexes)
- Hydrolysis of retinyl and carotenoid esters by various esterases occurs at the same time TG, PL, and CE are being hydrolyzed by pancreatic enzymes
- Following hydrolysis, retinol is taken up by the enterocytes. The hydrolysis of retinyl esters requires the presence of bile salts that serve to solubilize them in mixed micelles
- Intact carotenoids are absorbed by enterocytes at a lower efficiency than that for the absorption of retinol
- Ingested β-carotene is cleaved in the enterocyte by **β-carotene dioxygenase** to yield retinal. Retinal is reduced to retinol by **retinaldehyde reductase**, an NADPH requiring enzyme within the intestines
- Although the retinal is interconvertible with retinol, some of the retinal may be irreversibly oxidized into retinoic acid. Retinoic acid is picked up by the portal vein and transported in plasma bound to **albumin**
- Retinol formed from the oxidation of carotenoids, follows the same metabolic pathways of reesterification in the intestinal cells as retinol originating from dietary retinyl esters
- Retinol is esterified to palmitic acid and delivered to the blood via **chylomicrons**. The uptake of chylomicron remnants by the liver results in delivery of retinol to this organ for storage as a lipid ester within lipocytes
- Carotenoids reaching the liver may be incorporated into VLDL synthesized in the liver, and then be released as part of VLDL for circulation to various tissues of the body; and some can be stored in the liver
- Transport of retinol from liver to extrahepatic tissues occurs by binding of hydrolyzed retinol to **retinol binding protein (RBP)**
- **Summary: absorption and transport of retinol**
    - Need to hydrolyze retinyl esters (especially retinyl palmitate) first by esterases
    - Absorbed with fat in micelles (so need all lipid digestion systems)
    - ~70-90% of retinol from the diet is absorbed as long as the meal is adequate in fat
    - Often re-esterified in enterocyte
    - All forms apart from retinoic acid enter blood through chylomicrons and lymph
    - Mainly stored in liver, but also adipose and other tissues. When required, retinol is released by the liver and carried in blood bound to a specific protein (RBP). This is the delivery form for use by tissues
- **Summary: absorption and transport of carotenoids**
    - Absorption can vary from about 5-50%. Passively absorbed in duodenum from micelle
    - Excess carotenoids not stored in the liver will be deposited in body lipids
    - Serum carotene levels are reflective of recent intake, and not body stores
    - The most common serum carotenoids are β-carotene, α-carotene, lycopene, lutein, zeaxanthin, and cryptxanthin
    - *β-carotene, α-carotene, and lycopene distributions is similar whereby LDLs carry 58-73%, HDL carry 17-26%, and VLDL carry 10-16%. In contrast, lutein, and zeaxanthin are carried predominantly (53%) by HDL but also by LDL (31%) and VLDL (16%)*

Factors affecting absorption

- Isomerization: cis isomers are generally better absorbed (so cooking usually increases absorption)
- Type of carotenoid: there is not a lot of data but xanthophylls are generally better absorbed than carotenes
- Amount of carotenoid: the more in one dose, the lower the absorption (also better absorbed with meals)
- Food matrix: compared to pure β-carotene dissolved in oil (100%), availability from green leafy vegetables is only 7%, carrots 18-26%, fruit ~30% (believed to be due to binding in cell to protein in chloroplasts in green leafs vs. in oil droplets in fruit, winter squash)
- Physical form (homogenization leads to increased absorption: studies indicated that absorption of carotene was 24% from sliced carrots compared to 56% from homogenized carrots)
- Dietary factors: need fat otherwise poorly absorbed (at least 10% kcal), soluble fiber may reduce (pectin can bind bile acids); olestra (sucrose polyester) markedly reduces absorption
- Other factors: illnesses (intestinal parasites and fat malabsorption lead to reduction)

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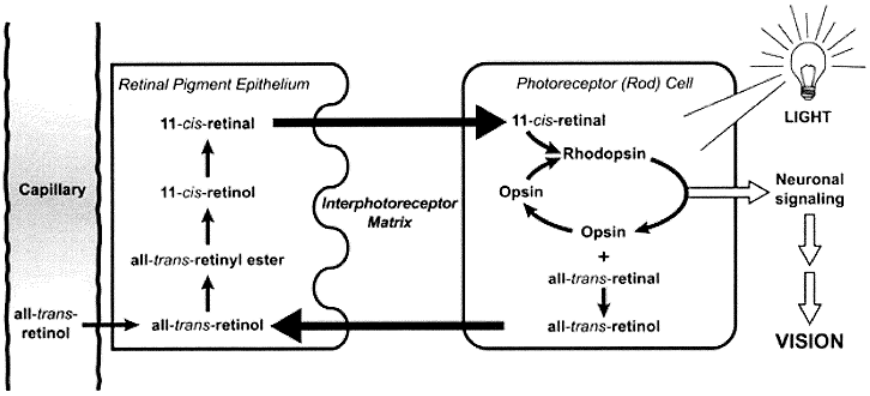
STORAGE, EXCRETION

- Carotenoids can be converted to retinol in the intestine
- Carotenoids are found in all tissues: high [ ] in testes, adrenals, corpus luteum; major storage sites are adipose tissue (65%), liver (12%), less than 10% in plasma
- Lutein and zeaxanthin accumulate in macula of the eye
- Vitamin A metabolites are excreted primarily via the bile into the feces (70%), and urinary excretion accounts for about 30%

FUNCTIONS OF VITAMIN A

1. Vision

- The **retina** is located at the back of the eye. When light passes through the **lens**, it is sensed by the retina and converted to a nerve impulse for interpretation by the brain
- Inadequate retinol available to the retina results in impaired dark adaptation, known as "night blindness"
- **The visual cycle**



Retinol is transported to the retina via the circulation, where it moves into retinal pigment epithelial cells. There, retinol is esterified to form a retinyl ester that can be stored. When needed, retinyl esters are broken apart (hydrolyzed) and isomerized to form 11-*cis* retinol, which can be oxidized to form 11-*cis* retinal. 11-*cis* Retinal can be shuttled to the rod cell, where it binds to a protein called opsin to form the visual pigment, rhodopsin (visual purple). Absorption of a photon of light catalyzes the isomerization of 11-*cis* retinal to all-*trans* retinal and results in its release. This isomerization triggers a cascade of events, leading to the generation of an electrical signal to the optic nerve. The nerve impulse generated by the optic nerve is conveyed to the brain where it can be interpreted as vision. Once released all-*trans* retinal is converted to all-*trans* retinol, which can be transported across the interphotoreceptor matrix to the retinal epithelial cell to complete the visual cycle.

2. Cell differentiation

- Differentiation is growing from immature to mature state of cells
- With vitamin A deficiency, epithelial cells become keratinized and lose their cilia
- Retinoic acid is needed by epithelial cells found in skin, trachea, GI tract, cornea, and testes

3. Immunity

- Vitamin A is commonly known as the anti-infective vitamin, because it is required for normal functioning of the immune system
- Retinol and its **metabolites** are required to maintain the integrity and function of these cells
- Retinoic acid plays a central role in the development and **differentiation** of WBCs, such as **lymphocytes** that play critical roles in the immune response

4. Growth and development

- Both a deficiency and an excess of vitamin A is known to cause birth defects
- Retinol and retinoic acid are essential for embryonic development
- During fetal development, retinoic acid functions in limb development and formation of the heart, eyes, and ears. Additionally retinoic acid has been found to regulate expression of the gene for growth hormone

5. RBC production

- Vitamin A appears to facilitate the mobilization of iron from storage sites to the developing RBC for incorporation into **hemoglobin**, the oxygen carrier in RBC's

6. Bone

- Vitamin A deficiency can lead to excessive deposition of bone by osteoblasts and reduced osteoclasts (mechanism unclear)

7. Reproduction

- Normal levels of vitamin A (Retinol) are required for sperm production, reflecting a requirement for vitamin A by spermatogenic epithelial cells. Similarly, normal reproductive cycles in females require adequate availability of vitamin A

FUNCTIONS OF CAROTENOIDS

1. Antioxidant activity

- They have been shown in vitro to react with lipid peroxides (and be chain-breaking antioxidants) but are not structurally similar to other chain-breaking antioxidants (e.g. tocopherols)
- Under high O_2 tension and/or with high [ ] of carotenoids, they have been shown to form new peroxyl radical so are pro-oxidant; the many double bonds of carotenoids make them susceptible to autooxidation
- Some humans studies have shown no evidence of an effect of β-carotene supplementation on LDL oxidation; others studies have shown that tomato products lower serum measures of lipid peroxidation (high doses of 120mg)

DEFICIENCY OF VITAMIN A

- Failure to grow
- Eye disease
  a) Photophobia
  b) Xerophthalmia and keratomalacia
    - Drying of the eyes, dull appearance of external surface
    - Ulcers
    - Keratinization of the cells stops secretion of tears
    - Bloody lesion and severe infections
    - Blindness
- Loss of cilia of respiratory epithelium: respiratory infections and death
- Lowered resistance to infections
- Failure to reproduce
- Loss of normal taste activity: histological changes in taste bud
- Follicular hyperkeratosis (skin condition)

Severe deficiency of vitamin A is common in the developing countries in preschool children (low-fat diets). Many children in the US may have a low intake, perhaps 5% of 3-5 year olds have hypovitaminosis A. Other populations with higher requirements include those with HIV/AIDS, fat malabsorption disorders, acute infections, parasites, and measles.

TOXICITY OF VITAMIN A

- Acute and chronic
- In adults: headaches, drowsiness, nausea, alopecia (loss of hair), diarrhea
- In children: hydrocephalus, hyperirritability
- Adults may show symptoms with 16,000-40,000 RE per day for 6-15 months; children 8000 RE for 30 days+ (but use 100,000 + in developing countries)
- If have liver or kidney disease, may be toxic at lower [ ]
- The condition caused by vitamin A toxicity is called hypervitaminosis A. It is caused by overconsumption of preformed vitamin A, not carotenoids (except for carotenodermia)
- Severe cases of hypervitaminosis A may result in liver damage, hemorrhage, and coma. Generally, signs of toxicity are associated with long-term consumption of vitamin A in excess of 10 times the RDA (8,000-10,000 mcg/day or 25,000-33,000 IU/day)
- However, there is evidence that some populations may be more susceptible to toxicity at lower doses, including the elderly, chronic alcohol users, and some people with a genetic predisposition to high cholesterol
- In January 2001, the FNB set the UL of vitamin A intake at 3,000 mcg (10,000 IU) of preformed vitamin A/day
- Because excess preformed vitamin A consumed during pregnancy is known to cause birth defects, pregnant women are cautioned not to consume more than 800 mcg RE/day (2600 IU/day) of vitamin A as a supplement
- Additionally, etretinate and isotretinoin (Accutane), synthetic derivatives of retinol, are known to cause birth defects and should not be taken during pregnancy or if there is a possibility of becoming pregnant
- Tretinoin (Retin-A), another retinol derivative, is prescribed as a topical preparation that is applied to the skin. Because of the potential for systemic absorption of topical tretinoin, its use during pregnancy is not recommended

Symptoms of acute toxicity

- Nausea
- Violent headache
- Dizziness
- Slowness
- Desquamation of skin

Toxicity in children

- Loss of appetite
- Weight loss
- Irritability
- Fissuring at corners of the mouth
- Cracking and bleeding of the lips

Symptoms of chronic toxicity

- Dryness
- Maculopapular rash (eruption of skin)
- Fissures
- Desquamation
- Itching of skin
- Hair loss
- Weakness, fatigue
- Bone and joint pain
- Muscle stiffness
- Tenderness of the bones to palpation
- Anorexia
- Headache
- Hepatomegaly
- Liver damage

INTERACTIONS OF VITAMIN A

- Vitamin A status often compromised in protein deficiency (kwashiorkor) – need protein for retinol transport
- Zinc deficiency is thought to interfere with vitamin A metabolism in several ways
  1) Zinc deficiency results in decreased synthesis of retinol binding protein (RBP), which transports retinol through the circulation to tissues (e.g., the **retina**)
  2) Zinc deficiency results in decreased activity of the **enzyme** (retinol dehydrogenase) that releases retinol from its storage form, retinyl palmitate, in the liver
  3) Zinc is required for the enzyme that converts retinol into retinal. At present, the health consequences of zinc deficiency on vitamin A nutritional status in humans are unclear
- Vitamin A deficiency may exacerbate **iron deficiency anemia**. Vitamin A supplementation has been shown to have beneficial effects on iron deficiency anemia and improve iron nutritional status among children and pregnant women. The combination of vitamin A and iron seems to reduce anemia more effectively than either iron or vitamin A alone
- Vitamin E needed to make retinol from β-carotene. Vitamin E can prevent autooxidation of carotenoids (at least in vitro). However, vitamin E supplementation can slightly lower plasma carotenoid [ ]
- Smokers have lower serum β-carotene [ ] that appear to be independent of diet
- Chronic alcohol consumption results in depletion of liver stores of vitamin A, and may contribute to alcohol-induced liver damage. However, the liver toxicity of vitamin A (retinol) is enhanced by chronic alcohol consumption, thus narrowing the therapeutic window for vitamin A supplementation in alcoholics
- Oral contraceptives that contain estrogen and progestin increase retinol binding protein (RBP) synthesis by the liver, increasing the export of RBP-retinol complex in the blood. Whether this increases the dietary requirement of vitamin A is not known

DISEASE PREVENTION AND TREATMENT

Retinol

- *All-trans-retinoic acid (natural) or 13-cis-retinoic acid (synthetic) used in acne and wrinkles but are teratogenic*
- *Childhood viral illnesses: measles, respiratory syncytial virus (RSV), AIDS (but retinoic acid may increase HIV replication)*
- *Dry eyes (topically)*
- *There is very little evidence that pre-formed dietary Vitamin A has any protective effect for cancer*

Carotenoids

- *There is very consistent evidence from epidemiological studies that consumption of fruits and vegetables are protective for cancers of the digestive and respiratory tracts (some evidence for breast and cervix also)*
- *However, a number of large prevention trials of cancer, β-carotene supplementation either showed no benefit or increased the risk of lung cancer in smokers; some suggestions of why include:*
    1) *β-carotene interfering with absorption of lutein*
    2) *pro-oxidant effect of β-carotene in lungs, which have high oxygen tension*
    3) *the specific populations used (i.e. smokers and alcohol users)*
- *For lycopene, there is consistent epidemiological evidence for a protective effect of tomato/tomato product consumption on prostate, lung, and stomach cancer; there is some evidence for protection for cancer of the pancreas, colon, esophagus, breast, cervix, and oral cavity*

Other diseases

- *Similar to cancer there is evidence of a protective effect of high plasma β-carotene levels and high fruit/vegetable diets on risk of coronary heart disease and stroke*
- *Macula of the eye concentrates lutein and zeaxanthin; they may protect against damage from blue light*
- *There is some evidence that a high dietary intake of β-carotene (fruits and vegetables) as well as vitamins C and E may be protective for cataract formation*

Therapeutics: naturopaths use for the following

1. *Enhance Immunity (100,000-150,000 IU for 5-7 days then cut back to 25,000-50,000 IU). Vitamin A can be use in the treatment of AIDS. β-carotene may also be beneficial*
2. *Cancer. Lycopenes, which is found in high amount in tomatoes, have been shown to protect against prostate cancer. Guava, watermelon, and pink grapefruit have significant amount too*
3. *Acne (200,000-300,000 IU/day for 3 months. Vitamin A regulates prostaglandins that control the secretion of sebaceous glands in the skin. Vitamin E may enhance the effectiveness of vitamin A*
4. *Menorrhagia. (50,000-75,000 IU)*
5. *Wound healing (stomach ulcer, colitis, burns, respiratory tract as in emphysema, etc.). Vitamin A is involved in the formation and generation of epithelial cells*
6. *Cervical displasia (60,000-100,000 IU/day of Vitamin A (not β-carotene). Women who consume less than average vitamin A and β-carotene were 3x more likely to have dysplastic changes or carcinoma in situ*
7. *Lupus. Correcting the epithelial skin changes*
8. *Psoriasis*
9. *Seborrheic Keratosis or Senile Keratosis (100,000 IU/day)*
10. *Prevention of sunburn (150,000 IU β-carotene and 100,000 IU vitamin A a few days before exposure to sun)*
11. *Follicular Hyperkeratosis (Keratosis pilaris) (25,000-75,000 IU/day for 4-6 weeks. It is a classic sign of vitamin A deficiency; EFA, folic acid, or zinc deficiency; and hypothyroidism. The typical presentation is a gooseflesh appearance on the posterior arm and anterior thighs, and buttocks*
12. *Photosensitivity disorders including erythropoietic protoporphyria (EPP)*
13. *Night Blindness (5,000-20,000 IU/day)*
14. *Dry Eyes (Sicca Syndrome) (Vitamin A drops 1-2 tid or as needed)*

Hot off the press

- *A combination of carotenoids and Vitamin E resulted in a lesser reaction to ultraviolet light (ie. less sunburn)*
- *In a study in New Guinea, vit A supplementation in young children infected with the malaria parasite led to many fewer symptoms*
- *Based on primate research, this study claims that up to 30,000 I.U. Vitamin A may not be teratogenic*
- *Based on an epidemiologic study, a large intake of pre-formed Vitamin A may be associated with an increased risk for osteoporosis*
- *Vitamin A may be useful in treating Shigella diarrhea in children in developing countries*

By Monica Hsu

VITAMIN D

LEARNING OBJECTIVES
1. Describe the major forms of Vitamins D, including Vitamin D units
2. Outline the functions of Vitamin D
3. Explain the mechanisms for absorption, transport, and metabolism of Vitamin D
4. List the major sources of Vitamin D
5. Describe deficiencies, toxicities and therapeutic use

NOMENCLATURE, FORMS

- This fat-soluble vitamin occurs mainly in two forms
    1. **Ergocalciferol** (activated ergosterol, vitamin D_2), found in irradiated yeast
    2. **Cholecalciferol** (activated 7-dehydrocholesterol, vitamin D_3). Animals (including humans) can convert cholesterol to 7-dehydrocholesterol. Exposure to the ultraviolet light in sunlight (UV radiation) converts 7-dehydrocholesterol in the skin to vitamin D_3

Vitamin D_3	Vitamin D_3	= Cholecalciferol	= Calciol
	25(OH) Vitamin D_3	= 25(OH) Cholecalciferol	= Calcidiol
	$1,25(OH)_2$ Vitamin D_3	= $1,25(OH)_2$ Cholecalciferol	= Calcitriol
Vitamin D_2	Vitamin D_2	= Ergocalciferol	= Ergocalciol
	25(OH) Vitamin D_2	= 25(OH) Ergocalciferol	= Ergocalcidiol
	$1,25(OH)_2$ Vitamin D_2	= $1,25(OH)_2$ Ergocalciferol	= Ergocalcitriol

- Vitamin D is stable to heat, light and storage
- Vitamin D is a prohormone with several active metabolites that act as hormones
- Vitamin D activity is contributed by these two compounds (Vitamin D) plus active metabolites [25-$(OH)D_3$, 1,25(OH)2D3, $24,25(OH)_2D_3$]

SOURCES

Sunlight

- Sunlight exposure provides most people with their entire vitamin D requirement. Children and young adults who spend a short time outside two or three times a week will generally synthesize all the vitamin D they need
- Elderly individuals have diminished capacity to synthesize vitamin D from sunlight exposure, and frequently use sunscreen or protective clothing in order to prevent skin cancer and sun damage
- The application of sunscreen with an SPF factor of 8 reduces production of vitamin D by 95% *(A survey of elderly people who took a multivitamin supplement or drank 3 glasses of milk daily found that about 80% of them were vitamin D deficient by the end of winter. These findings have led some experts to recommend small amounts of regular sun exposure to elderly individuals)*
- About 15 minutes of exposure on the hands, face, and forearms three times a week in the morning or late afternoon during the spring, summer, and fall should provide adequate vitamin D and allow for storage of any excess in fat for use during the winter with minimal risk of skin damage. A sunscreen may be applied after the 15 minutes, if additional sun exposure is planned

Foods

- Vitamin D is found naturally in very few foods. Foods containing vitamin D include some fatty fish (herring, salmon, sardines), fish liver oils, and eggs from hens that have been fed vitamin D
- In the U.S., milk and infant formula are fortified with vitamin D to contain 10 mcg (400 IU)/quart. However, other dairy products such as cheese and yogurt are not usually fortified with vitamin D
- Some cereals and breads are also fortified with vitamin D. Accurate estimates of average dietary intakes of vitamin D are difficult because of the high variability of the vitamin D content of fortified foods

Food	Serving	Vitamin D (IU)	Vitamin D (mcg)
Cod liver oil	1 tablespoon	1360	34
Salmon	3 ounces	425	10.6
Herring	3 ounces	765	19.1
Shrimp, canned	3 ounces	90	2.3
Sardines, canned	3 ounces	255	6.4
Cereal, fortified	1 serving (usually 1 cup)	40 to 50	1 to 1.3
Egg yolk	1	25	0.63
Cow's milk, fortified	8 ounces	100	2.5

Units

1 IU Vit D = 25 ng Vit D
1 IU Vit D = 5 ng 25-$(OH)D_3$
1 IU Vit D = 5 ng $24,25(OH)_2D_3$
1 IU Vit D = 2.5 ng $1,25(OH)_2D_3$

1 μg Vit D = 40 IU Vit D
1 μg 25$(OH)D_3$ = 200 IU Vit D
1 μg $24,25(OH)_2D_3$ = 200 IU Vit D
1 μg $1,25(OH)_2D_3$ = 400 IU Vit D

So the active form of vitamin D is considered to be calcitriol or $1,25(OH)_2D_3$

- *2,5 ug/day protects against rickets; 7.5-10.0 ug/day is for optimum calcium absorption*
- *New RDA = 5 ug/day apart from older people (10 ug/day 51-70 and 15 ug/day 70+). Pregnant and lactating women 5 ug/day.*
- Otherwise it is added to milk (10 ug/quart) and there is some in eggs (if chickens fed Vitamin D) and butter; many foods fortified with Vitamin D
- Large amounts of ergocalciferol (30ug/100g) is found in some wild mushrooms
- Most people do not consume the RDA, getting only about 3 ug from food
- Can get equivalent of about 250 μg/day from sunlight; 10 minutes of summer sun on face and hands equivalent to 10 μg. However above and below latitudes of 40^0 North and South, get no production of D_3 in the skin in winter (Seattle??)

FORMATION, ABSORPTION, TRANSPORT, METABOLISM

Formation in skin

- We make 7-dehydrocholesterol from cholesterol in sebaceous glands of skin and it is absorbed into the skin
- During exposure to sunlight, some of epidermal cutaneous reservoir of 7-dehydrocholesterol is converted to previtamin D (also called precalciferol)
- The precalciferol naturally isomerizes within 2 or 3 days to form cholecalciferol (vitamin D_3, calciol)
- Cholecalciferol diffuses from the skin into the blood with the help of a specific binding protein (vitamin D-binding protein [DBP], synthesized in the liver). About 60% of plasma cholecalciferol is bound to DBP for transport
- Much of the vitamin is deposited in muscle and adipose tissue prior to hepatic uptake

Dietary vitamin D

- Vitamin D from the diet is absorbed from a micelle, in association with fat and with the aid of bile salts, by passive diffusion into the intestinal cell
- About 50% of dietary vitamin D is absorbed. The rate of absorption is most rapid in the duodenum, the largest amount is absorbed in the distal small intestine
- Within the intestinal cell, vitamin D is incorporated into chylomicrons, which enter the lymphatic system, and general circulation. Chylomicrons transport 40% of the cholecalciferol in the blood
- Gets returned to the liver in chylomicron remnants

Vitamin D in the liver

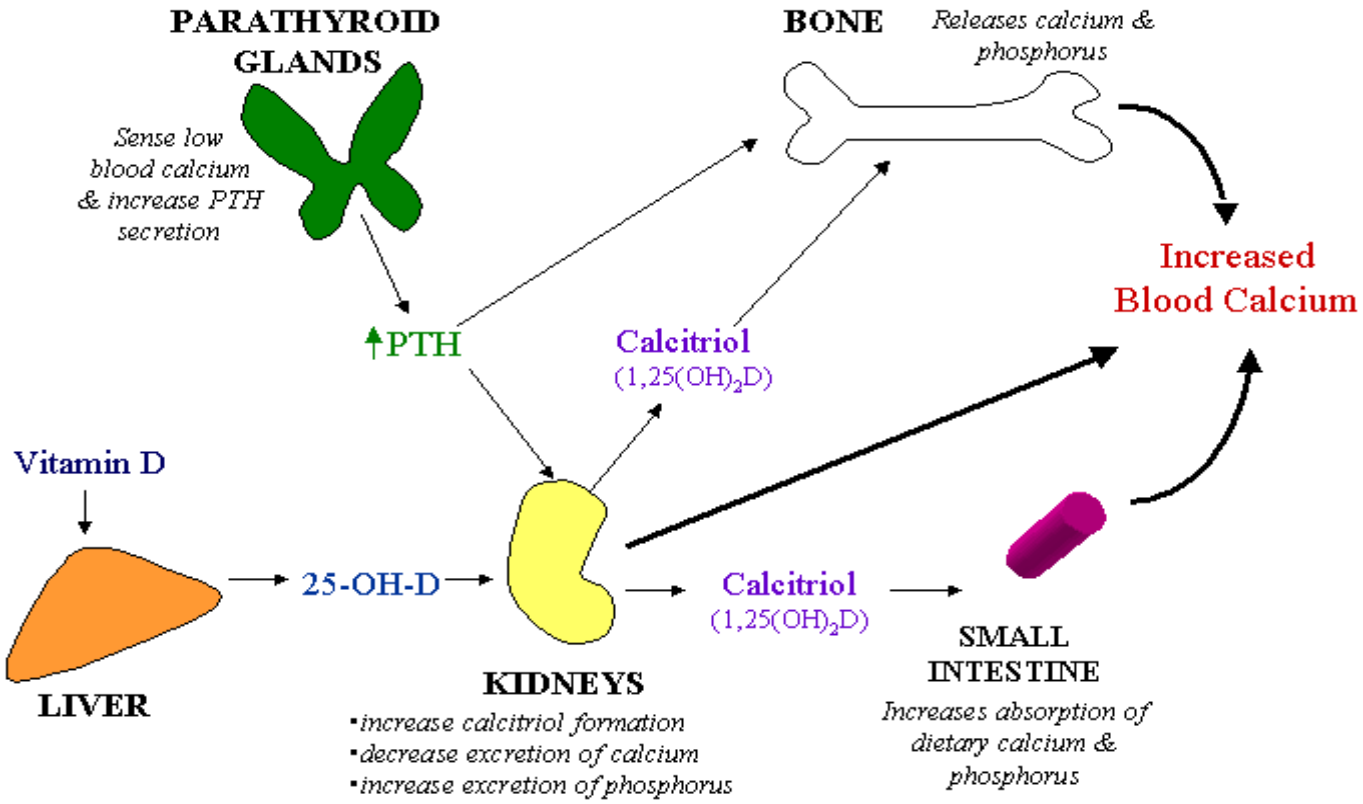
- Vitamin D_3 is **hydroxylated** on carbon 25 to form 25-hydroxyvitamin D_3 (25-OH-D_3), also known as calcidiol
- Though the synthesis of calcidiol is controlled in the liver, increased exposure to sunlight or increased intake of vitamin D_3 results in increased blood levels of calcidiol, making it a useful indicator of vitamin D nutritional status
- **Although calcidiol is the major circulating form of vitamin D, it is not biologically active**
- Because little calcidiol remains in the liver and very little of this metabolite is taken up by the extrahepatic tissue, the blood is the largest storage site with a half-life of about 3 weeks
- When the level of calcidiol is depleted during vitamin D deprivation, maintenance of vitamin D activity is made possible by the release of calcidiol from its skin reservoir and from other sites in muscle and adipose tissue

Vitamin D in the kidney

- 25-OH-D_3 is taken up by the kidney and must be hydroxylated (a second hydroxylation) on carbon #1 to form 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], also called calcitriol. This hydroxylation reaction is **catalyzed by 1-hydroxylase** in the kidneys
- When sufficient amount of calcitriol are present, the activity of 1-hydroxylase decreases and the activity of another enzyme called 24-hydroxylase is increased in the kidney and may be the cartilage and intestine → → 24,25-$(OH)_2D_3$ is formed and this may be involved in bone mineralization
- Activity of 1-hydroxylase is ↑ with parathyroid hormone (PTH), low serum calcium, and low phosphorus intake

Vitamin D synthesis and activation

- Cholesterol → 7-dehydrocholesterol → previtamin D (precalciferol) → calciol (cholecalciferol) → calcidiol → calcitriol



FUNCTIONS OF VITAMIN D

1. Role of calcitriol in small intestine, kidneys, and bone

- Vitamin D is well known as a hormone involved in mineral metabolism and bone growth
- Best known function is in control of blood calcium [ ] along with PTH
- Increased blood levels of calcitriol restore normal blood calcium levels in three different ways
    1) **In SI**: increase intestinal absorption of Ca and P and increase synthesis of CaBP active transport (Calbindin)
    2) **In Kidney**: increase renal reabsorption of Ca and P
    3) **In bone**: increase mobilization of Ca and P from bone into the circulation, and increase extracellular fluid [ ] of Ca. This process is mediated by calcitriol-induced cell differentiation of hemopoietic cells to osteoclasts
- **Role of PTH**
    - The **parathyroid glands** sense the blood calcium level, and secrete parathyroid hormone (PTH) if it becomes too low
    - PTH stimulates the activity of the 1-hydroxylase in the kidney to produce more calcitriol
    - High calcitriol [ ] lead to less PTH production (negative feedback)
    - PTH is also required to increase bone calcium mobilization and calcium reabsorption by the kidneys
- **Control of blood calcium**
    - Calcium in the blood is very tightly regulated: too little and we get tetany (muscle contractions), too much we get calcium deposited in arteries, etc.
    - When serum calcium decreases, we get release of calcitriol and PTH which leads to increased calcium absorption in the small intestine, decreased excretion from the kidney, and release of calcium from bone
    - When serum calcium increases, we get release of calcitonin (produced in the thyroid gland) which leads to increased bone mineralization and removal of calcium from the serum; we also get reduced PTH production (and less calcitriol)

2. Bone remodeling

- Calcitriol is also involved in bone remodeling. Calcitriol is important in synthesis of osteocalcin (protein found in bone and dentine)
- Vitamin D stimulates osteoblasts to synthesize osteocalcin (gamma-carboxylglutamate vitamin K-dependent). Osteocalcin is associated with new bone formation
- Osteocalcin comprises about **15-20% of protein in bone**
- Osteocalcin physiological role is unclear at present. Some osteocalcin is released into the blood and has been used as an index of bone formation

3. Vitamin D receptor (VDR)

- Calcitriol enters the cell and interacts with a vitamin D receptor (VDR) in the **nucleus** to form a complex. The calcitriol/VDR complex combines with another receptor, the retinoic acid X receptor (RXR), to form a **heterodimer** (a dimer or complex of two different molecules, usually proteins), which can then interact with small portions of **DNA** known as vitamin D responsive elements (VDRE)
- The interaction of a VDR/RXR heterodimer with a VDRE results in a change in the rate of **transcription**. In this manner, the activity of vitamin D-dependent calcium transporters in the small intestine, osteoblasts in bone, and the 1-hydroxylase enzyme in the kidneys may be increased

4. Cell differentiation, proliferation, and growth

- Cells that are dividing rapidly are said to be proliferating. Cell **proliferation** can be observed during growth and wound healing (regeneration)
- **Psoriasis** is a disease characterized by the proliferation of skin cells called keratinocytes. The identification of VDR in keratinocytes led to the use of creams containing **analogs of calcitriol** in the treatment of severe cases of psoriasis

5. Immunity

- **Vitamin D receptors** (VDR) have been identified in cells (T lymphocytes) that play a critical role in the immune system. T cells are involved in the recognition of foreign **pathogens** known as **antigens**, and coordinating the immune response
- Immune responses that are mediated by T cells can be inhibited by large doses of calcitriol. However, a deficiency of vitamin D also interferes with T cell mediated immunity
- The presence of VDR in T cells suggests that vitamin D plays a role in the function and/or the development of T cells
- **Pharmacologic doses of calcitriol** have had beneficial effects in animal models of several autoimmune diseases, mediated by T cells

DEFICIENCY OF VITAMIN D

- **Hypocalemia**
    - Low blood calcium levels lead to severe bone disease such as rickets, osteomalcia, vit D resistant rickets
    - Causes: vitamin D deficiency, *Loss of kidney function - can not produce $1,25(OH)_2 D_3$
- **Hypovotaminosis D**
    - Causes: insufficient vitamin production, malabsorption of fats and therefore fat-soluble vitamins which results in ↑ serum alkaline phosphate (indicates low bone mineralization) and ↓ serum calcium and phosphates
- **Rickets (occurs in children)**
    - Soft pliable bones, connect support body altitude and cause bow legs, knock-knees, etc. (so get deformities)
- **Osteomalacia (adult rickets)**
    - Seen in older people who are not exposed to sun and consume little or no vitamin D. Handicap or very ill
- **Vitamin D resistant rickets**
    - Genetic disorder. The synthesis of $1,25(OH)_2 D_3$ is impaired. Administer the most active form (cholecalciferol)
- **Celiac disease**
    - Fat malabsorption causes malabsorption of vitamin D

By Monica Hsu

Risk factors for vitamin D deficiency

1. **Infancy:** infants who have little or no sun exposure, and do not consume vitamin D fortified formula are at increased risk, especially those born just before winter in northern or southern latitudes
2. **Elderly individuals with minimal sun exposure:** the elderly have reduced capacity to synthesize vitamin D in response to sunlight exposure, and are more likely to stay indoors or use sunscreen for the prevention of skin cancer
3. **Dark skin:** individuals with darkly pigmented skin, e.g. those of African or Indian descent living in northern or southern latitudes synthesize less vitamin D on exposure to sunlight than those with light skin
4. **Covering all exposed skin when outside:** osteomalacia has been documented in Arab women who cover all of their skin at all times when going outside for religious or cultural reasons
5. **Fat malabsorption syndromes: cystic fibrosis** and **cholestatic liver disease** impair the absorption of dietary vitamin D
6. **Kidney failure:** severe kidney disease can impair conversion of calcidiol to the biologically active form of vitamin D, calcitriol
7. **Genetic disease:** a rare genetic disease affects the activity of the 1-hydroxylase enzyme in the kidneys that converts calcidiol to its active form, calcitriol
8. **Seizure disorders (epilepsy):** long-term treatment with **anticonvulsant medications**, such as phenytoin, can stimulate liver enzymes that break down and inactivate calcitriol
9. **Cholestyramine**, a **bile acid binding resin** used to treat elevated cholesterol levels, and mineral oil can decrease the intestinal absorption of vitamin D

TOXICITY OF VITAMIN D

- Don't get toxicity from excess sunlight (turn off production in skin)
- Hypercalemia (>12 mg/dl)
- Deposition of Ca in soft tissues (kidney, heart, lung, blood vessels)
- Hypercalciuria
- Kidney stones, irreversible kidney damage
- Mild toxicity can be treated by reducing vit D
- Severe toxicity can be treated by administering glucocorticosteroids or calcitonin
- Vitamin D supplementation over many years at pharmacologic doses of 10,000-50,000 IU/day (250-1250 mcg/day) → hypervitaminosis D
- The induction of hypercalcemia by toxic levels of vitamin D may precipitate cardiac **arrhythmia** in patients on digitalis (digoxin) or verapamil, a calcium channel blocker, used to treat high blood pressure
- UL: in infants > 25µg (1000 IU/day). In adults > 50 µg (2000 IU/day) that is prolonged may be toxic

DISEASE PREVENTION AND TREATMENT

Therapeutics: naturopaths use for the following

1. *Rickets (1000-5000 IU/day vitamin D along with 1 gm of calcium). If there is a liver or kidney problem, or if it is vitamin D-resistance rickets, then use the 1,25 DHCC*
2. *Fractures (elderly) (1000-3000 IU/day) along with calcium*
3. *Osteoporosis (1000-3000IU/day vitamin D, or natural sunshine)*
4. *Cancer prophylaxis (200-400 IU/day), especially for colorectal cancer, and breast cancer*
5. *Psoriasis*

Hot off the press

- *Vegans living in high latitudes may be at risk of low bone density due to inadequate vitamin D in winter. In Denmark it was suggested that veiled Muslim women would need 25µg vitamin D/day for normal serum levels*
- *Obese people may be at risk of increased vitamin D deficiency because of deposition of dietary and synthesized vitamin D in adipose tissue*
- *A preliminary study found that vitamin D was more effective than phototherapy for people with Seasonal Affective Disorder*
- *A recent article proposes that for optimum serum levels of 25-(OH)D_3 need 100 ug/day*
- *Supplementation with Ca (500mg) and vitamin D (17.5µg/day) for 3 years in elderly led to increased bone density and reduced fractures*
- *Elderly women living in nursing homes have a greater chance of being vitamin D deficient than free-living elderly women (8% vs. 1.6%)*
- *In a group of general medical patients, 57% were found to be deficient (42% in under 65 years), 22% severely deficient. Could mainly account for by low dietary intake, winter, and being housebound*

VITAMIN E

LEARNING OBJECTIVES
1. Describe major natural and synthetic forms of Vitamins E and their activity
2. Outline the major functions of Vitamin E
3. Explain the mechanisms for absorption, transport, and metabolism of Vitamin E
4. List the major food sources of Vitamin E
5. Describe deficiencies, toxicities, and therapeutic use

NOMENCLATURE, UNITS

- The term vitamin E describes a family of 8 antioxidants, 4 tocopherols (α, β, γ, δ) and 4 tocotrienols (α, β, γ, δ)
- *To have vitamin activity, compound must have double ring structure, side chain attached at carbon 2, and methyl groups attached at carbons*
- α-tocopherols (most active), followed by β-tocopherols which is greater than γ -tocopherols and δ- tocopherols
- *The tocopherols are characterized by a hydroxylated ring system (chromanol ring) with a long, saturated (phytyl) side chain. Tocotrienol have an unsaturated side chain*
- Synthetic and Natural Vitamin E
    - d-α-Tocopherol is the only naturally occurring stereoisomer and the most potent; the totally synthetic dl-α-tocopherol is completely racemic and has less biologic activity than d-α-tocopherol
    - Synthetic α-tocopherol, which is often found in food additives and nutritional supplements, is usually labeled all-rac-α-tocopherol or dl-α-tocopherol, meaning that all 8 isomers of α-tocopherol are present in the mixture
    - Because some isomers of α-tocopherol present in all-rac-α-tocopherol are not usable by the body, synthetic α-tocopherol is less bioavailable and only about half as potent
    - In supplements and fortified foods, often esterified into acetate or succinate forms for stability. Esterification of the labile hydroxyl (OH) group on the chromanol ring prevents its oxidation and extends its shelf life
    - There is good evidence that natural Vitamin E is more biologically active than synthetic Vitamin E

REQUIREMENTS: RDA

- ***Adult men and women ages 19 and older:*** *15 mg of α-tocopherol/day*
- *The older unit was called the International Unit (IU)*
- "Mixed" tocopherols in supplements are usually 80% α and 20% mixture of β, γ, and δ (these other tocopherols are not thought to have Vitamin E activity)

FOOD SOURCES

- *Many people have low intakes of Vitamin E – in NHANES III data, the median intake for men and women from food was 9.4 mg and 6.4 mg respectively (including supplements it was 9.8 and 6.8 mg/day) well below the recently revised RDA of 15 mg/day*
- Major sources of α-tocopherol in the American diet include vegetable oils, nuts, whole grains, seeds, seafood, wheat germ, and green leafy vegetables. All 8 forms of vitamin E occur naturally in foods, but in varying amounts
- Tocotrienols found mainly in legumes and cereal grain such as wheat, barley, rice and oats. Thus, wheat bran and germ oil represent significant source of tocotrienol
- With ↑ consumption of oils form, esp. soybeans (γ-tocopherol content), the U.S. diet is increasing relative to α-tocopherol
- Individuals limiting fat intake also limit foods that are high in vitamin E
- *Before the body's preference for α-tocopherol was clarified, the vitamin E content of food was often expressed as mg of α-tocopherol equivalents or α-TE. Presently most food composition tables and databases provide vitamin E content information only in terms of α-TE, rather than as mg of α-tocopherol*
- *A rough approximation of the α-tocopherol content in foods can be calculated by multiplying the mg of α-TE by 0.8. mg of α-tocopherol in a meal = mg of α-tocopherol equivalents (TE) in a meal x 0.8.* ***Ex. 2.0 mg α-TE x 0.8 = 1.6 mg α-tocopherol***

Food	Serving	α-tocopherol (mg)	γ-tocopherol (mg)
Olive oil	1 tablespoon	1.6	0.1
Soy oil	1 tablespoon	1.0	10.8
Corn oil	1 tablespoon	1.5	8.2
Canola oil	1 tablespoon	2.9	0.6
Safflower oil	1 tablespoon	4.6	0.1
Sunflower oil	1 tablespoon	6.6	0.7
Almonds	1 ounce	12.8	0.5
Hazelnuts	1 ounce	6.1	0.03
Peanuts	1 ounce	3.2	2.4
Spinach	**1/2 cup, raw chopped**	**1.7**	**0**
Carrots	**1/2 cup, raw chopped**	**0.3**	**0**
Avocado (Haas)	1 medium	3.3	1.2

Supplements

- All α-tocopherol in food is the form of the isomer, RRR-α-tocopherol. Supplements made from entirely natural sources contain only RRR-α-tocopherol (also labeled d-α-tocopherol). RRR-α-tocopherol is the isomer preferred for use by the body, making it the most bioavailable form of α-tocopherol
- *To calculate the number of mg of bioavailable α-tocopherol present in a supplement use the following formulas:*
  RRR-α-tocopherol (natural or d-α-tocopherol): IU x 0.67 = mg RRR-α-tocopherol. Example: 100 IU = 67 mg
  all-rac-α-tocopherol (synthetic or dl-α-tocopherol): IU x 0.45 = mg RRR-α-tocopherol. Example: 100 IU = 45 mg

ABSORPTION, TRANSPORT, METABOLISM, STORAGE

- Tocopherols are found free in foods; tocotrienols often esterified → pancreatic esterase and/or duodenal mucosal esterase are thought to function at the brush border of the intestine to hydrolyze tocotrienol for absorption
- Absorption varies from 20-50% and may be as high as 80%. As vitamin E intake increases, vitamin E absorption decreases
- Free tocopherol is absorbed, as part of micelles, by passive diffusion (bile and pancreatic juices required for micelle formation)
- Simultaneous digestion and absorption of dietary lipids, including medium-chain TG with vit E improves absorption of vit E
- Absorbed tocopherol is incorporated into chylomicrons in the enterocyte and is transported through the lymph into circulation
- Some vitamin E is distributed to all of the circulating lipoproteins (especially LDL and HDL). Chylomicron remnants containing newly absorbed vitamin E are taken up by the liver
- Vitamin E is secreted from the liver in VLDL. Only one form of vitamin E, α-tocopherol, is preferentially secreted by the liver. This lead to preferential enrichment of LDL and HDL with α-tocopherol. This critical role has been demonstrated in patients with familial isolated vitamin E deficiency. Thus, the liver, not the intestine discriminates between tocopherols. **α-TTP** (**α-tocopherol transport protein**) is a likely candidate for this discriminatory function
- During the conversion of VLDL to LDL in the circulation, a portion of tocopherol remains in LDL. As exchange of tocopherol occurs between LDL and HDL, the tocopherol is distributed in all lipoproteins
- **Factors that affect absorption**
  - ↓ pancreatic secretions i.e. lipases (cystic fibrosis or acute pancreatitis)
  - ↓ bile acids (liver or gall bladder diseases)
  - ↓ intestinal surface area due to GI disease (celiac disease, alcoholism) or surgical removal of part of intestinal tract
  - Defect in synthesis of chylomicrons
  - Defect in intestinal lymphatic channels
- **Storage**
  - There is no single storage organ for vit E. The largest amount is in the adipose tissue, and the smaller amount in liver, lung, heart, adrenal gland and brain
  - [ ] of vit E in the adipose tissue ↑ linearly with dosage of vit E, whereas the other tissue remains constant
  - In time of low intake, withdrawal of tocopherol from adipose tissue occurs slowly (not readily available), whereas withdrawal from liver and plasma is rapid

FUNCTIONS OF VITAMIN E

1. The main function of α-tocopherol in humans appears to be that of an antioxidant
   - **Free radicals** are formed primarily in the body during normal metabolism and also upon exposure to environmental factors such as cigarette smoke or pollutants
   - Fats, which are an integral part of all cell membranes, are vulnerable to destruction through oxidation by free radicals
   - The fat-soluble vitamin, α-tocopherol, is uniquely suited to intercepting free radicals and preventing a chain reaction of lipid destruction. Aside from maintaining the integrity of cell membranes throughout the body, α-tocopherol also protects the fats in LDL from oxidation
   - Oxidized LDL has been implicated in the development of cardiovascular diseases. When a molecule of α-tocopherol neutralizes a free radical, it is altered in such a way that its antioxidant capacity is lost. However, other antioxidants, such as vitamin C, are capable of regenerating the antioxidant capacity of α-tocopherol
2. Vitamin E readily donates H from OH to free radicals; so reacts with peroxyl radicals and prevents formation of lipid peroxides. If have lipid peroxidation, may contribute to atherosclerosis, cancer, hemolysis of RBCs, aging, cataracts
3. Cofactor in the electron transport system, probably functions between cytochromes B and C
4. Protects against: heavy metals, hepatotoxins, drugs that cause oxidative damage (chemotherapeutic agents), environmental pollutants (ozone), etc.
5. Needed for normal immune function (T lymphocytes)
6. Important for development of human neuromuscular system and functioning of retina
7. Functions in reproduction
8. **Tocotrienols** can lower serum cholesterol (by inhibiting synthesis), suppression of tumor growth and cell proliferation
9. Vitamin E can inhibit platelet aggregation by increasing prostacylcin production
10. **γ-tocopherol**: function in humans is presently unclear. Because γ-tocopherol is initially absorbed in same manner as α-tocopherol, small amounts are detectable in blood and tissue. Tocopherol metabolites can be detected in urine. More γ-tocopherol metabolites are excreted in urine than α-tocopherol metabolites, suggesting less γ-tocopherol is needed for use by the body. Recently, concern has been raised regarding the fact that taking α-tocopherol supplements lowers γ-tocopherol levels in blood

INTERACTIONS OF VITAMIN E

- Requirement depends on PUFA's (increases or decreases)
- Need vitamin C, NADPH, and GSH to regenerate tocopherol from tocopheryl radical
- Large intakes (>1200 mg TE) may interfere with vit K metabolism. Individuals on anticoagulant therapy (blood thinners) or individuals who are vit K deficient should not take α-tocopherol supplements without close medical supervision because of ↑ risk of hemorrhage
- Requirement for selenium depends on vit E intake (both involved in antioxidant defense)
- Smokers may have higher requirements
- Problems with bone mineralization involving vit D have been reported in animals given high dosage of vit E
- In vitamin A deficiency, vitamin E is able to lower the rate at which vitamin A is depleted from the liver

DEFICIENCY OF VITAMIN E

- In humans, the main manifestations of vitamin E deficiency are
  - Mild hemolytic anemia associated with increased erythrocyte hemolysis
  - Spinocerebellar disease, which occurs mainly in children who have fat malabsorption due to abetalipoproteinemia, chronic cholestatic hepatobiliary disease, celiac disease, or a genetic abnormality in vitamin E metabolism
- Infants are born in a state of relative vitamin E deficiency, with plasma α-tocopherol levels *below 5 µg/mL (11.6 µmol/L)*. The smaller and more premature the infant, the greater the degree of deficiency
- If mother is fed adequate vitamin E diet, the fetus absorbs sufficient vitamin trough placenta, but not enough for storage. Therefore the young animals and infants must be supplied by milk or other means after birth
- Vitamin E deficiency in premature infants persists during the first few weeks of life and can be attributed to limited placental transfer of vitamin E, low tissue levels at birth, relative dietary deficiency in infancy, intestinal malabsorption, and rapid growth. As the digestive system matures, vitamin E absorption improves, and blood vitamin E levels rise
- In a rare genetic form of vitamin E deficiency without fat malabsorption, the liver appears to lack a protein that normally transfers d-α-tocopherol from hepatocytes to VLDL. Thus normal plasma α-tocopherol levels cannot be maintained
- Preventive dose of α-tocopherol is 0.5 mg/kg for full-term infants and 5-10 mg/kg for premature infants. For malabsorption causing overt deficiency, 15-25 mg/kg/day of α-tocopherol should be given po as water-miscible d-α-tocopheryl acetate (1 mg = 1.4 IU)
- Much larger doses (up to 100 mg/kg/day po in divided doses) are required to treat neuropathy early or to overcome defect of absorption and transport in abetalipoproteinemia. Such treatment has alleviated symptoms in young patients and arrested neuropathy in older patients
- In the genetic form of vitamin E deficiency without fat malabsorption, megadoses of α-tocopherol (100-200 IU/day) ameliorate the deficiency and prevent neurologic sequelae

TOXICITY OF VITAMIN E

- Few side effects have been noted in adults taking supplements of less than 2000 mg of α-tocopherol daily (RRR- or all-rac-α-tocopherol). In adults, doses of 200-800 mg/d are well tolerated. The most worrisome possibility is that of impaired blood clotting resulting in an increased likelihood of hemorrhage in some individuals
- The FNB also set an **UL** for α-tocopherol supplements, citing the avoidance of hemorrhage as the basis for the upper limit. The Board felt that an UL of 1000 mg daily of α-tocopherol of any form (equivalent to 1100 IU of all-rac-α-tocopherol) would be the highest dose unlikely to result in hemorrhage in almost all adults
- Although only certain isomers of α-tocopherol are retained in the circulation, all forms are absorbed and the liver must break them down and eliminate them. The rationale that any form of α-tocopherol (natural or synthetic) that can be absorbed is potentially toxic is the basis for an UL that refers to all forms of α-tocopherol
- >1200 mg/day interferes with vitamin K metabolism
- >3200 mg/d should be avoided by childbearing women and persons with liver or renal diseases

DISEASE PREVENTION AND TREATMENT

Therapeutics: naturopaths use for the following

1. *Nocturnal cramping (400-800 IU/day)*
2. *Restless leg syndrome (400-800 IU/day). Consider using along with Ginkgo biloba and Ca/Mg*
3. *Muscular distrophy. Vit. E protect the muscle (antioxidant)*
4. *Dysmenorrhea (75 IU 3x/day)*
5. *Fibrocystic breast disease*
6. *Menopause (up to 3000 IU/day very effective), PMS*
7. *Spontaneous abortion*
8. *Scleroderma and scar tissue (used orally or topically)*
9. *Herpetic lesion and postherpatic neuralgia*
10. *Raynaud's syndrome*
11. *Acne, seborrheic dermatitis, psoriasis*
12. *Allergy and inflammatory thrombophlebitis*
13. *Anemia, sickle cell anemia and other types of hemolytic anemia*
14. *Cystic fibrosis*
15. *SIDS (evidence indicates that vit E is low in these babies)*
16. *Premature infants (for lung)*
17. *Down syndrome (there is an increase oxidative problem)*
18. *AIDS, angina, arthritis, autoimmune disease, cancer, cataracts, diabetes, epilepsy, immunodepression, infections, inflammation, lupus, MS, osteoarthritis, wound healing. In allopathic medicine, effective in treatment of tardive dyskinesia (side effects of psychiatric drugs) and intermittent claudication (poor blood flow in the legs, 400-2000 IU/day)*

Hot off the press

- *In healthy adults, supplementation for 6 weeks with either vit C (500 mg/day) or vit E (73.5mg RRR-α-tocopherol acetate/day) resulted in an ↑ serum level of the other vitamin*
- *In an epidemiological study in Hawaii, use of Vit E and C supplements was associated with a ↓ risk of dementia (but not Alzheimer's) and better cognition in the elderly*
- *In NHANES III, 27% of Americans had low serum [ ] of Vitamin E (42% of African Americans)*
- *Vit E may improve immune function - more cytokines (400 mg/day) and improved cell-mediated immunity (200 mg/day) in healthy elderly*
- *In men and women with atherosclerosis, Vitamin E supplementation (1/2 400 mg/day, 1/2 800/day for of 1.5 years) led to fewer myocardial infarctions*
- *May not prevent coronary heart disease in men with previous infarctions (50mg/day, 5 years), men and women with previous infarctions (300 mg/day, 3.5 years) or male smokers (50 mg/day, 6 years)*
- *High doses (2000 mg over 2 years) may slow progress of Alzheimer's disease*
- *High doses (1050 mg/day for 20 weeks), but not lower doses (70, 140, or 560 mg/day) led to increased peroxidation of RBCs and decreased serum Vitamin C*
- *In summary probably the best evidence of all vitamins for supplementation for disease prevention. Best dosage may be around 400-800 mg/day, natural Vitamin E being more active*

VITAMIN K

LEARNING OBJECTIVES
1. Describe the major forms of Vitamin K and their food sources
2. Outline the functions of Vitamin K
3. Explain the mechanisms for absorption, transport, and metabolism of Vitamin K
4. Identify deficiencies, toxicities, and therapeutic use

NOMENCLATURE, FORMS

- *Chemically they are quinines. The natural forms are substituted in position 3 with an alkyl side chain*
- **Vitamin K_1 (phylloquinone, from plants)** *has a phytyl side chain in position 3 and is the only homologue of vit K found in plants*
- **Vitamin K_2 (menaquinone, from bacteria)** *refers to a family of homologues with 2-methyl-1,4-naphthoquinone substituted in position 3 with isoprenyl side chains containing from 4 to 13 isoprene units.* The menaquinones are synthesized by bacteria in the intestinal tract and can supply part of the vitamin K requirement
- Synthetic Vitamin K is **menadione**
    - Water-soluble, similar in structure, without the side chain
    - Same properties as vitamin K
    - Active
    - More potent than Vitamin K_1 and Vitamin K_2

REQUIREMENTS: RDA

- *In January 2001, the FNB established the AI level for vitamin K in the U.S. based on consumption levels of healthy individuals*
- ***AI for men ages 19 years and older:*** *120 micrograms (mcg) vitamin K/day*
- ***AI for women 19 years and older:*** *90 mcg of vitamin K/day*
- ***NHANES III****: median intake of vitamin K ranged from 79 to 88 mcg/day for women and 89 to 117 mcg/day for men*

FOOD SOURCES

- Phylloquinone (K_1): plant sources – green leafy vegetables, cabbage, and some vegetable oils (soybean, cottonseed, canola, and olive) are major contributors of dietary vitamin K

Food	Serving	Vitamin K (mcg)
Olive oil	1 Tablespoon	6.6
Soybean oil	1 Tablespoon	26.1
Canola oil	1 Tablespoon	19.7
Mayonnaise	1 Tablespoon	11.9
Broccoli, cooked	1 cup (chopped)	420
Kale, raw	1 cup (chopped)	547
Spinach, raw	1 cup (chopped)	120
Leaf lettuce, raw	1 cup (shredded)	118
Swiss chard, raw	1 cup (chopped)	299
Watercress, raw	1 cup (chopped)	85
Parsley, raw	1 cup (chopped)	324

- **Bacteria**: bacteria that normally colonize the large intestine synthesize menaquinones (K_2), which are an active form of vitamin K. Until recently it was thought that up to 50% of the human vitamin K requirement might be met by bacterial synthesis. Recent research indicates that the contribution of bacterial synthesis is much less than previously thought, although the exact contribution remains unclear (The total need of vitamin K cannot be met by bacterial synthesis alone)

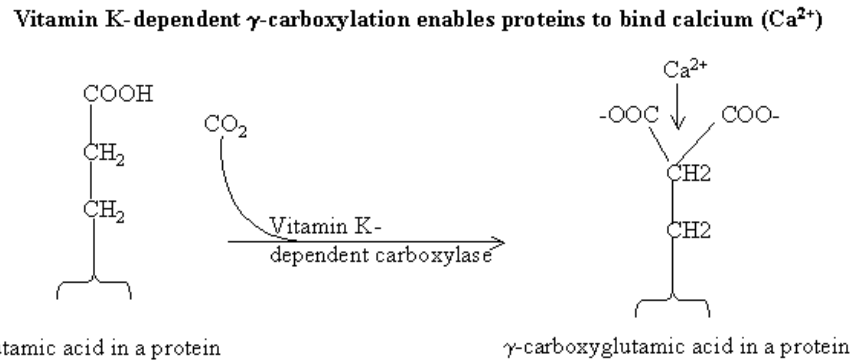
ABSORPTION, TRANSPORT, METABOLISM

- Phylloquinone is absorbed in the SI (jejunum) by a saturable energy-dependent process
- Other forms (menaquinones and menadione) are absorbed by passive diffusion in distal small intestine and colon
- A number of bacterial species can synthesize menaquinones – it is unclear how much can be absorbed
- Bile and pancreatic secretions enhance absorption (just like other fat-soluble vitamins). Absorption varies: 40-80% absorbed (20-30% if fat malabsorption) of dietary vitamin K
- Within the intestinal cell, vitamin K is incorporated into the chylomicron that enters the lymphatic and then the circulatory system for transport to tissues (chylomicron transport the majority of phylloquinone)
- Chylomicron remnants deliver vitamin K to the liver
- In the liver, all forms (medadione is alkylated) are incorporated into VLDL and ultimately carried to extrahepatic tissues in LDLs and via HDLs
- Extrahepatic tissue store vitamin K in large amount (adrenal gland, lung, bone marrow, and kidney)
- Turnover in the liver is rapid and hepatic reserves are rapidly depleted when dietary intake of vitamin K is restricted

FUNCTIONS OF VITAMIN K

1. Carboxylation

- The only known biological role of vitamin K: act as a coenzyme for vitamin K-dependent carboxylase, which catalyzes the **carboxylation of the amino acid, glutamic acid**, resulting in its conversion to γ-carboxyglutamic acid (Gla)
- Although vitamin K-dependent carboxylation occurs only on specific glutamic acid residues in a small number of proteins, it is critical to the calcium-binding function of those proteins



2. Coagulation (clotting)

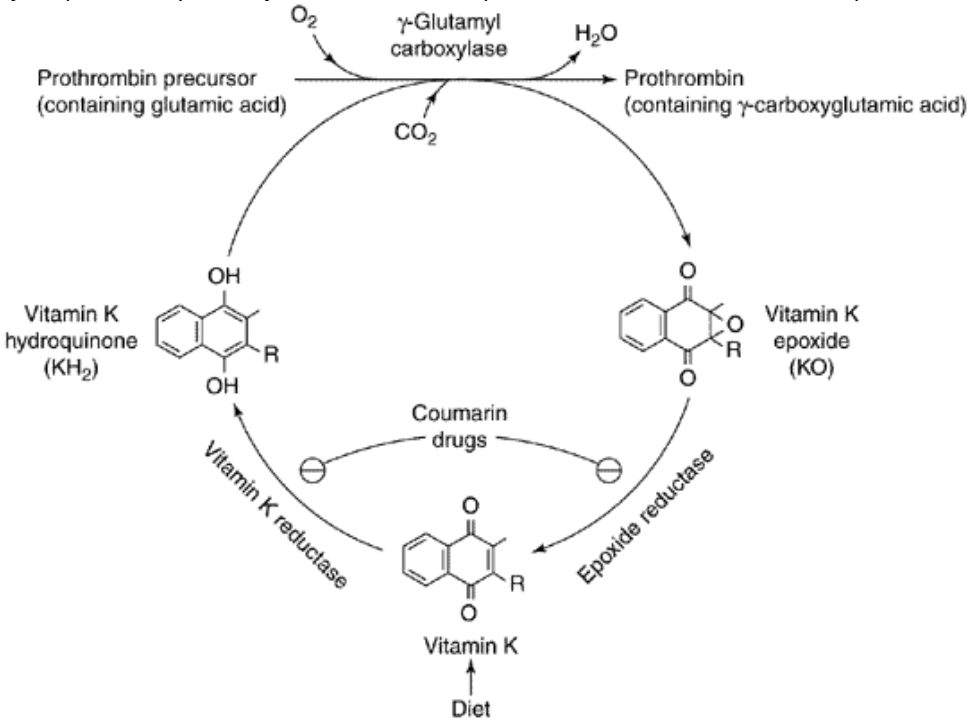
- The **ability to bind calcium ions (Ca^{2+})** is required for the activation of the seven "vitamin K-dependent" clotting factors in the coagulation cascade
- Vitamin K-dependent γ-carboxylation of specific glutamic acid residues in those proteins makes it possible for them to bind calcium. Factors II (prothrombin), VII, IX, and X make up the core of the coagulation cascade

3. Coagulation and specific proteins

- In the liver, vitamin K is involved in the synthesis of different proteins (Z, C, and S)
- Protein Z appears to enhance the action of thrombin by promoting its association with **phospholipids in cell membranes**
- **Protein C and protein S are anticoagulant proteins** that provide control and balance in the coagulation cascade

4. Coagulation factors and vitamin K cycle

- Vitamin K-dependent coagulation factors are synthesized in the liver. Consequently, severe liver disease results in lower blood levels of vitamin K-dependent clotting factors and an increased risk of uncontrolled bleeding (hemorrhage)
- Some people are at risk of forming clots, which could block the flow of blood in arteries of the heart, brain, or lungs, resulting in heart attack, stroke, or pulmonary embolism, respectively
- Although vitamin K is a fat-soluble vitamin, the body stores very little of it, and its stores are rapidly depleted without regular dietary intake. Due to its limited ability to store vitamin K, the body recycles it through a process called "the vitamin K cycle"
- **Vitamin K cycle**
    - Designed to conserve vitamin K and allow a small amount of vitamin K to function in the γ-carboxylation of proteins many times, decreasing the dietary requirement
    - Depending on vitamin K intake, the cycle revolves 200-2000 times per day in humans
    - The product of the vitamin K hydroquinone in γ-carboxylation is vitamin K epoxide, which is reduced in two steps to vitamin K hydroquinone. Some oral **anticoagulants, such as warfarin (also known as coumarin or coumadin)** strongly inhibit these two reductases and prevents the recycling of vitamin K and creating a functional vit K deficiency
    - Large quantities of dietary or supplemental vit K can overcome the anticoagulant effect of vit K antagonists, so patients taking these drugs are cautioned against consuming very large or highly variable quantities of vit K in their diets
    - Experts now advise a reasonably constant dietary intake of vit K that meets current dietary recommendations (60-80 mcg/day) for patients on vit K antagonists, like warfarin



5. Bone mineralization: bone proteins osteocalcin and matrix-Gla protein

- Three vitamin-K dependent proteins have been isolated in bone. Osteocalcin is a protein synthesized by osteoblasts (bone forming cells). The synthesis of osteocalcin by osteoblasts is regulated by the active form of **vitamin D**, $1,25(OH)_2D_3$ or calcitriol. The mineral-binding capacity of osteocalcin requires vitamin K-dependent λ-carboxylation of three glutamic acid residues
- Matrix Gla protein (MGP) has been found in bone, **cartilage**, and soft tissue, including blood vessels. The results of animal studies suggest MGP prevents the calcification of soft tissue and cartilage, while facilitating normal bone growth and development

By Monica Hsu

DEFICIENCY OF VITAMIN K

- Overt vitamin K deficiency results in impaired blood clotting, usually demonstrated by laboratory tests that measure clotting time
- Symptoms include easy bruising and bleeding that may be manifested as nosebleeds, bleeding gums, blood in the urine, blood in the stool, black stools, or extremely heavy menstrual bleeding
- In infants, vitamin K deficiency may result in life-threatening bleeding within the skull (intracranial hemorrhage)
- **Adults:** Vitamin K deficiency is uncommon in healthy adults for a number of reasons:
    1) Vitamin K is widespread in foods
    2) The vitamin K cycle conserves vitamin K
    3) Bacteria that normally inhabit the large intestine synthesize menaquinones (vitamin K_2), though it is unclear whether a significant amount is absorbed and utilized
    4) Adults at risk of vitamin K deficiency include those taking vitamin K antagonist anticoagulant drugs and individuals with significant liver damage or disease
- There are 3 situations that may lead to a deficiency:
    1) Faulty absorption due to a lack of bile and fat
    2) Malabsorption syndrome due to diarrhea, ulcerative colitis, sprue, celiac disease
    3) Use of antibiotics for prolonged period of time which reduced intestinal synthesis. Use of antibiotics for prolonged period of time before surgery → complication → death
- **Infants:** Newborn babies that are exclusively breast-fed are at increased risk of vitamin K deficiency for the following reasons:
    1) Human milk is relatively low in vitamin K compared to formula, containing *only 1-3 µg/L (cow's milk contains 5-10 µg/L)*
    2) Neonatal gut is sterile during the first few days of life (not yet colonized with bacteria that synthesize menaquinones)
    3) The vitamin K cycle may not be fully functional in newborns, especially premature infants
    4) Infants whose mothers are on anticonvulsant medication to prevent seizures are also at risk of vitamin K deficiency
    5) The placenta transmits lipids relatively poorly
    6) The neonatal liver is immature with respect to prothrombin synthesis
- Vitamin K deficiency in newborns may result in a bleeding disorder called **hemorrhagic disease of the newborn (HDN)**. Because HDN is life threatening and easily prevented, the American Academy of Pediatrics and a number of similar international organizations recommend that an injection of phylloquinone (vitamin K1) be administered to all newborns
- **Hemorrhagic disease of the newborn,** caused by vitamin K deficiency, generally occurs 1-7 days postpartum and may be manifested by cutaneous, GI, intrathoracic, or, in the worst cases, intracranial bleeding. **Late hemorrhagic disease,** which has the same clinical manifestations, occurs 1-3 months postpartum
- **Controversy concerning vitamin K administration and the newborn:** in the early 1990's, two **retrospective studies** were published suggesting the possibility of an association between vitamin K injections in newborns and the development of childhood leukemia and other forms of childhood cancer. However, two large retrospective studies in the U.S. and Sweden that reviewed the medical records of 54,000 and 1.3 million children, respectively, found no evidence of a relationship between childhood cancers and vitamin K injections at birth. In a policy statement, the AAP recommended that routine vitamin K prophylaxis for newborns be continued because HDN is life-threatening and the risks of cancer are unproven and unlikely. Full text of the AAP policy statement on vitamin K and the newborn. http://www.aap.org/policy/04357.html
- The most sensitive indicator of vitamin K deficiency is the presence of des-γ-carboxyprothrombin (DCP) in plasma. DCP, also known as PIVKA (*P*rotein *I*nduced in *V*itamin *K A*bsence or *A*ntagonism), can be measured with appropriate antibodies. It is absent from the plasma of healthy persons

TOXICITY OF VITAMIN K

- There is no known toxicity associated with high doses of phyloquinone (vitamin K_1), a natural form of vitamin K. The same is not true for menadione and its derivatives
- IV use of menadione has induced liver toxicity, jaundice, and hemolytic anemia (due to the rupture of RBCs) in infants
- No UL has been established for vitamin K

INTERACTIONS OF VITAMIN K

- Ingestion of diets high in vitamin K, as obtained from ingestion of about a pound of broccoli daily, can lead to warfarin resistance
- Large doses of vitamin A and vitamin E have been found to antagonize vitamin K. Excess vitamin A appears to interfere with vitamin K absorption, while a form of vitamin E (tocopherol quinone) may inhibit vitamin K-dependent carboxylase enzymes
- A relationship between vitamin K and osteoporosis has been suggested. Subclinical vitamin k deficiency may be involved in the pathogenesis of mineral loss from bone. Further studies are warranted. Vitamin K is required for the γ-carboxylation of osteocalcin. Undercarboxylation of osteocalcin adversely affects its capacity to bind to bone mineral, and the degree of osteocalcin γ-carboxylation has been found to be a sensitive indicator of vitamin K nutritional status
- *Lactobacillus acidophilus* may inhibit the growth of *E. Coli*, which in large intestine, synthesized vitamin K

DISEASE PREVENTION AND TREATMENT

Therapeutics: naturopaths use for the following

1. *Blood clotting disorders due to vitamin K deficiency*
2. *Osteoporosis (Vit. K induces an increase in serum osteocalcin, and a decrease in urinary calcium excretion)*
3. *Nausea and vomiting in pregnancy (parentally 5-10mg along with B-complex)*
4. *Fractures (orally 5-10mg/day)*
5. *Rheumatoid arthritis*
6. *Prevention of calcium oxalate kidney stone*

Hot off the press

- *Rats, even ones with no intestinal bacteria, can make menaquinone-4 from phylloquinone*
- *Phylloquinone absorption from broccoli was similar to the pure supplement in oil (cf. β-carotene!)*
- *Low vitamin K intakes may increase the risk of osteoporosis in women*

THIAMIN (VITAMIN B1)

LEARNING OBJECTIVEBS for thiamin and riboflavin
1. Describe the major chemical forms
2. Outline mechanisms for absorption, transport, and metabolism
3. Describe the functions
4. List the major food sources
5. Identify deficiencies, toxicities, and indicate therapeutic use

NOMENCLATURE, CHEMISTRY

- Vitamin B_1 is also known as **thiamine, thiamin and aneurin**
- *Thiamine consists of a pyrimidine ring and a thiazole ring connected by a one carbon link*
- A major biologically active form of thiamin is thiamin pyrophosphate (TPP), sometimes called thiamin diphosphate (TDP)

REQUIREMENTS: RDA

Men (19 years and older): *1.2 mg of thiamin/day*
Women (19 years and older): *1.1 mg of thiamin/day*
Pregnant women: *1.4 mg of thiamin/day*
Lactating women: *1.5 mg of thiamin/day*

FOOD SOURCES

- *In the U.S. the average dietary thiamin intake for young adult men is about 2 mg/day and 1.2 mg/day for young adult women*
- Whole grain cereals (90% enriched in US), legumes (e.g., beans and lentils), nuts, lean pork, and yeast are rich sources of thiamin
- Because most of the thiamin is lost during the production of white flour and polished (milled) rice, white rice and foods made from white flour (e.g., bread and pasta) are fortified with thiamin
- Requirements are affected by: age: children have higher thiamin mg/kg/BW
  activity: more physically active people have a higher requirement
  physiological state: higher need during pregnancy and lactation

Food	Serving	Thiamin (mg)	Food	Serving	Thiamin (mg)
Lentils (cooked)	1/2 cup	0.17	Pork, lean (cooked)	3 ounces	0.74
Peas (cooked)	1/2 cup	0.21	Brazil nuts	1 ounce	0.28
Long grain brown rice (cooked)	1 cup	0.19	Pecans	1 ounce	0.13
Long grain white rice, enriched (cooked)	1 cup	0.26	Spinach (cooked)	1/2 cup	0.09
Long grain white rice, unenriched (cooked)	1 cup	0.03	Orange	1 fruit	0.11
Whole wheat bread	1 slice	0.10	Cantaloupe	1/2 fruit	0.10
White bread , enriched	1 slice	0.12	Milk	1 cup	0.10
Fortified breakfast cereal	1 cup	0.5-2.0	Egg (cooked)	1 large	0.03
Wheat germ breakfast cereal	1 cup	1.89			

DIGESTION, ABSORPTION

- In plant, thiamin exists in its free form. In animal, > 95% occurs in a phosphorylated form (primarily as TDP and TTP)
- Intestinal phosphatases and pyrophosphatases remove the phosphate prior to absorption
- Absorption (free thiamin) can be both active and passive, depending on amount present in the intestine
- If in small amounts, there is a Na-dependent, active, saturable transport mechanism in the upper jejunum, but can occur in duodenum and ileum. If in larger amounts, passive diffusion ethanol ingestion interferes with the active transport

METABOLISM

- Thiamin in the blood is bound to albumin or found as thiamin monophosphate (TMP)
- Following absorption, free thiamin is taken up by the liver and phosphorylated to coenzyme form, TDP (or TPP)
  - Thiamin → ATP and thiamin pyrophosphokinase → TDP → TDP-ATP phosphoryl transferase → TTP
  - > 80% of thiamin in the body exist as TDP, 10% as TTP, and the rest as free thiamin and TMP
- There is not much storage. The human body contains ~30mg of thiamin. About half of the body's thiamin is found in skeletal muscle, and the rest in heart, liver, kidney and brain. Thiamin in excess of tissue needs and storage capacity is excreted in the urine

FUNCTIONS OF THIAMIN

1. Energy production

- TPP is a coenzyme for α-ketoacid dehydrogenases, which catalyzes 2 reactions of Krebs cycle (α-ketoacid decarboxylation)
  1) Oxidative decarboxylation of **pyruvate to acetyl CoA** (this reaction is catalyzed by pyruvate dehydrogenase complex)
  2) Oxidative decarboxylation of **α-ketoglutarate to succinyl CoA**
- Part of large enzyme complex, pyruvate dehydrogenase involving lipoic acid, FAD, NAD, and coenzyme CoA (pantothenic acid)
- All known TPP dependent enzymes also require a divalent cation, commonly Mg^{2+}

2. Thiamine in the pentose phosphate pathway (PPP)

- TPP is a coenzyme for transketolase, which transfers a 2-carbon unit from an α-ketose to an aldose. A 2-carbon unit from the 5-carbon α-ketose xylulose 5-P is transferred to the 4-carbon aldose erythrose 4-P to make the 6 carbon α-ketose fructose 6-P

3. Neurological function of TPP

- It is evident from the neurological disorders caused by thiamine deficiency that this vitamin plays a vital role in nerve function
- It is unclear, however, just what that role is. Thiamine is found in both the nerves and brain

DEFICIENCY OF THIAMIN

Beri-beri

- Characterized by anorexia (loss of appetite) with subsequent weight loss, enlargement of the heart, and neuromuscular symptoms such as paresthesia (spontaneous sensations, such as itching, burning, etc.), muscle weakness, lassitude (weariness, general weakness), and foot and wrist droop
- 5 main types
    1) **Dry** (also neuritic, paraplegic, and pernicious) beri-beri
        - Usually inflicts older adults and affects mainly the **peripheral nerves with little or no cardiac involvement**
        - It is characterized by atrophy and peripheral neuritis of the legs and paraplegia (paralysis of lower extremities)
    2) **Wet** (also edematous or cardiac) beri-beri
        - Substantial cardiac involvement especially tachycardia in addition to peripheral neuropathy
        - Edema progresses from the feet upwards to the heart causing congestive heart failure in severe cases
    3) **Infantile** (also acute cardiac) beri-beri
        - Usually seen in breast-feeding infants whose mothers are thiamin deficient (but not necessarily showing signs of beri-beri). These infants are usually anorectic and often have trouble keeping the milk down
        - Once the disease begins it moves rapidly causing heart failure in a matter of hours
    4) **Shoshin** beri-beri: heart and lungs are affected
    5) **Aphonic** beri-beri: changes in the child's voice

Wernicke-Korsakoff syndrome (Wernicke's encephalopathy)

- Thiamin deficient disease seen most often in the Western hemisphere: mainly affects alcoholics due to the following reasons
    - Diets of alcoholics are usually poor
    - Diets rich in CHO (e.g., alcohol or rice) ↑ the metabolic demands of thiamine
    - Alcohol inhibits intestinal ATPase which is involved in the uptake of thiamine
- Symptoms: confusion, CN6 damage resulting in ophthalmoplegia (paralysis of an eye motor nerve) and nystagmus (rhythmical oscillation of the eyes), psychosis, confabulation, impaired retentive memory and cognitive function, coma in severe cases
- **Clinical applications**
    - Beri beri, alcoholic neuritis, GI disturbances. In hospitals it is routine for alcoholics when they are admitted to get intramuscular injection of thiamin
    - Most WKS sufferers are alcoholics, but also observed in other disorders of gross malnutrition (ex. stomach cancer, **AIDS)**
    - Administration of IV thiamin to WKS patients generally results in prompt improvement of the eye symptoms, but improvements in motor coordination and memory may be less, depending on how long the symptoms have been present

Causes of thiamin deficiency

- **Inadequate thiamin intake**
    - Alcoholism, low income populations whose diets are high in CHO and low in thiamin (e.g., milled or polished rice)
    - Breast fed infants whose mothers are thiamin deficient are vulnerable to developing infantile beriberi
- **An increased requirement for thiamin**
    - Strenuous physical exertion, fever, pregnancy, breastfeeding, and adolescent growth
    - Recently found in malaria patients (Thailand) and **HIV**-infected individuals, whether or not they had developed **AIDS**, were also found to be at increased risk for thiamin deficiency
- **Excessive loss of thiamin from the body**
    - Individuals with kidney failure requiring **hemodialysis** lose thiamin at an ↑ rate, and are at risk for thiamin deficiency
    - By increasing urinary flow, diuretics may prevent reabsorption of thiamin by the kidney and ↑ its excretion in the urine
    - Alcoholics who maintain a high fluid intake and urine flow rate may also experience ↑ loss of thiamin
- **Consumption of anti-thiamin factors (ATF)**
    - Consuming large amounts of tea and coffee (including decaffeinated), as well as chewing tea leaves and betel nut have been associated with thiamin depletion in humans due to the presence of ATF (polyhydroxyphenols such as tannic acid and caffeic acid. Polyhydroxyphenols are thermostable, found in coffee, tea, blueberries, black currant, brussels sprouts and red cabbage)
    - **Thiaminases** are enzymes that break down thiamin in food. Individuals who habitually eat certain raw freshwater fish, raw shellfish, and ferns are at higher risk of thiamin deficiency because these foods contain a thiaminase, which would normally be inactivated by the heat used for cooking
    - Vitamin C and other antioxidants can protect thiamin in some foods by preventing its oxidation to an inactive form

TOXICITY OF THIAMIN

- No UL set for thiamin because there are no known toxic effects from the consumption of excess thiamin in food or through long-term oral supplementation (up to 200 mg/day)
- No evidence of toxicity up to 500 mg/day except if used parenterally (life threatening anaphylactic reactions)
- Symptoms of toxicity: headaches, irritability, weakness, flushing, and itching in humans

DRUG INTERACTIONS

- Individuals with **seizure** disorders (epilepsy) taking the anticonvulsant medication, phenytoin, for long periods of time
- 5-Fluorouracil, a drug used in cancer therapy, inhibits the phosphorylation of thiamin to TPP
- Diuretics, especially furosemide (Lasix), may increase the risk of thiamin deficiency due to increased urinary excretion of thiamin

DISEASE PREVENTION AND TREATMENT

Therapeutics: naturopaths use for the following

- *Impaired mental function in elderly, insomnia, neurosis, sciatica, anemia, depression, sensory neuropathy, glaucoma*

RIBOFLAVIN (VITAMIN B2)

NOMENCLATURE, CHEMISTRY, FORMS

- Riboflavin is a water-soluble B-complex vitamin, also known as vitamin B-2
- In the body, riboflavin is primarily found as an integral component of the **coenzymes**, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). Coenzymes derived from riboflavin are also called flavins

REQUIREMENT: RDA

- ***Adult men of all ages****: 1.3 mg of riboflavin/day*
- ***Adult women of all ages****: 1.1 mg of riboflavin/day*
- Increased requirements for
  - Growth, lactation
  - Burns or surgery, convalescence after severe trauma
  - With increased protein intake

FOOD SOURCES

- Most plant and animal derived foods contain at least small quantities of riboflavin. Wheat flour and bread have been enriched with riboflavin (as well as thiamin, niacin, and iron) since 1943 in the U.S.
- In food found as free or protein-bound riboflavin (milk, eggs, enriched cereals and breads), and in other foods is found as FMN (flavin mononucleotide) and FAD (flavin adenine dinucleotide)
- Found in greatest concentrations milk is (the major source of riboflavin in our diet), meats, organ meats (liver, kidney), fish, eggs, leafy veggies. Fruits and root veggies (moderate quantity)
- Riboflavin is easily destroyed by exposure to light. Up to 50% of the riboflavin in milk contained in a clear glass bottle can be destroyed after two hours of exposure to bright sunlight

Food	Serving	Riboflavin (mg)	Food	Serving	Riboflavin (mg)
Milk (nonfat)	1 cup (8 ounces)	0.34	Beef (cooked)	3 ounces	0.19
Cheddar cheese	1 ounce	0.11	Broccoli (boiled or steamed)	1/2 cup chopped	0.09
Egg (cooked)	1 large	0.27	Asparagus (boiled or steamed)	6 spears	0.13
Almonds	1 ounce	0.24	Spinach (boiled or steamed)	1/2 cup	0.09
Salmon (broiled)	3 ounces*	0.13	Fortified cereal	1 cup	0.59 to 2.27
Halibut (broiled)	3 ounces	0.08	Bread, whole wheat	1 slice	0.07
Chicken, light meat (roasted)	3 ounces	0.10	Bread, white (enriched)	1 slice	0.09
Chicken, dark meat (roasted)	3 ounces	0.18			

DIGESTION, ABSORPTION

- The form of riboflavin in food varies. In some foods riboflavin is found as free or protein-bound riboflavin. In other foods riboflavin is found as FMN or FAD
- Need to remove protein and phosphate (phosphatases) to absorb. Riboflavin attached to protein is freed by the action of HCl and gastric and intestinal enzymes
- Riboflavin in food as FMN and FAD must be freed prior to absorption. Within the intestinal lumen, enzymes such as FAD pyrophosphatase and FMN phosphatase play an important role
  - **FAD → FAD pyrophosphatase → FMN → FMN phosphatase → free riboflavin**
- Animal sources of riboflavin are thought to be better absorbed than plant sources
- Better absorbed with meals (70% absorption) than fasting (15%)
- Divalent metals (Cu, Zn, Fe, Mn) may chelate riboflavin → inhibit absorption
- Free riboflavin absorbed by active transport (Na-dependent), mainly in proximal small intestine. A small amount of riboflavin is absorbed in the large intestine

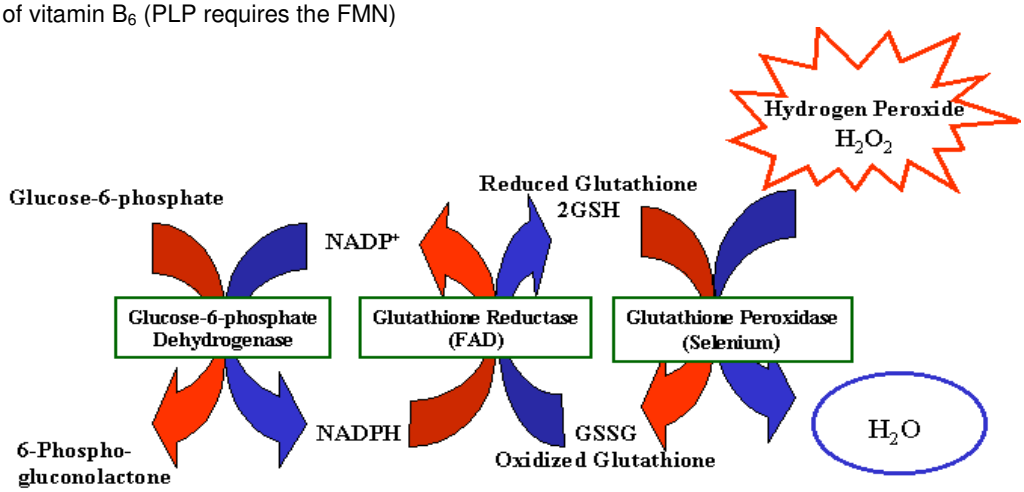
TRANSPORT, METABOLISM

- In the entercoyte, riboflavin is phosphorylated into FMN. Most of the FMN is then dephosphorylated to riboflavin which enters the portal system → carried to the liver, where it is converted to FMN and FAD
  - **Riboflavin** → flavokinase--Zn → **FMN** → FAD synthetase--Mg → **FAD**
- Riboflavin, FMN, and FAD are transported in the plasma by a variety of protein such as albumin, fibrinogen, and globulin (albumin appears to be the primary transport protein)
- Storage: the greatest concentrations are found in the liver, kidney, and heart
- Excretion: urinary excretion of flavins (~ 300mcg/day in normal adult) reflects dietary intake (mainly after 2 hours, florescent yellow)
- For milk from both cows and humans, the flavin in highest [ ] other than free riboflavin is FAD (a third of total flavin). FAD in cow's milk is converted to FMN during pasteurization

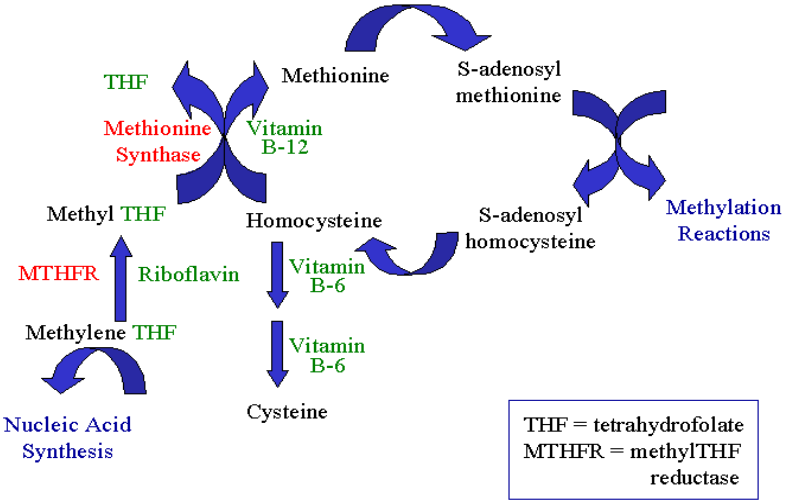
By Monica Hsu

FUNCTIONS OF RIBOFLAVIN

- FMN and FAD are the active coenzymes and are involved in many oxidation-reduction reactions
- Flavins are critical for the metabolism of CHO, fats (FA oxidation), and proteins. FAD is part of the electron transport chain, which is central to energy production
- Oxidative decarboxylation of pyruvate and α-ketoglutarate (see thiamin)
- Interconversion and catabolism of vitamin B_6 (PLP requires the FMN)
- Glutathione reductase is an FAD-dependent enzyme that participates in the redox cycle of glutathione. The glutathione redox cycle plays a major role in protecting organisms from **reactive oxygen species**, such as hydroperoxides. Glutathione peroxidase (contains selenium) requires two molecules of reduced glutathione to break down hydroperoxides. Glutathione reductase requires FAD to regenerate two molecules of reduced glutathione from oxidized glutathione



- The synthesis of the niacin-containing coenzymes, NAD and NADP, from tryptophan requires the FAD-dependent enzyme
- Succinate → fumarate (TCA cycle)
- Riboflavin deficiency alters iron metabolism (athough the mechanism is not clear, research in animals suggests that riboflavin deficiency may impair iron absorption, increase intestinal loss of iron, and/or impair iron utilization for the synthesis of **hemoglobin**). In humans, improving riboflavin nutritional status has been found to increase circulating hemoglobin levels
- Synthesis of the active form of folate (THFA). Methylene tetrahydrofolate reductase (MTHFR) is an FAD-dependent enzyme, which plays an important role in maintaining the specific folate coenzyme required to form methionine from homocysteine



DEFICIENCY OF RIBOFLAVIN

Symptoms of riboflavin deficiency include

- Sore throat, redness and swelling of lining of mouth and throat
- Cracks or sores on the outsides of the lips (cheliosis) and at the corners of the mouth (angular stomatitis)
- Inflammation and redness of the tongue (magenta tongue)
- A moist, scaly skin inflammation (seborrheic dermatitis)
- Vascularization of the cornea

Causes of riboflavin deficiency

- **Inadequate dietary intake**
- **Decreased absorption**: lactase deficiency results in lactose intolerance may prevent people from consuming milk or dairy products, which are good sources of riboflavin, tropical sprue, malignancy, resection of the SI, diarrhea, infectious enteritis
- **Increased destruction**: phototherapy (use of specialized light therapy to treat jaundice in newborns increases the destruction of riboflavin and is a recognized cause of riboflavin deficiency)
- **Drugs**: phenothiazine derivatives, like chlorpromazine (an anti-psychotic medication); tricyclic antidepressants; quinacrine (an anti-malarial medication) and adriamycin (a cancer chemotherapy agent) inhibit incorporation of riboflavin into FAD and FMN
- **Increased requirement**: people who are very active physically (athletes, laborers) may have a slightly ↑ riboflavin requirement

TOXICITY OF RIBOFLAVIN

- No known toxicity: no UL set

DISEASE PREVENTION AND TREATMENT

Therapeutics: naturopaths use for the following

- *Migraines, cataracts, sickle cell anemia, cataracts, depression, acne rosacea*

Hot off the press

- *In a recent Irish study in free-living elderly, 49% had biochemical evidence of sub-optimal riboflavin status despite seemingly adequate dietary intake – when supplemented with riboflavin, both riboflavin and pyridoxine status was improved; in the London hospital study, only 2.7% had biochemical evidence of riboflavin deficiency (vs. 32% for thiamin)*
- *In a recent double-blind, placebo-controlled study, high dose riboflavin (400 mg/day for 3 mo) helped prevent migraine in migraine suffers*

LEARNING OBJECTIVES
1. Describe the major chemical forms of all 3 vitamins (niacin, pantothenic acid, biotin)
2. Describe the functions of all 3 vitamins
3. Outline the mechanisms for absorption, transport, and metabolism of all 3 vitamins
4. List the major food sources of all 3 vitamins
5. Discuss the deficiencies, toxicities, and therapeutic use of all 3 vitamins

NIACIN (VITAMIN B3)

NOMENCLATURE, CHEMISTRY

- The term niacin refers to both nicotinic acid and nicotinamide (also called niacinomide), which are both used by the body to form the **coenzymes**, nicotine adenine dinucleotide (NAD) and nicotine adenine dinucleotide phospate (NADP)
- In addition to its synthesis from dietary niacin, NAD may also be synthesized in the liver from dietary tryptophan (only 3% of Try)

REQUIREMENT: RDA

- ***Adult men of all ages**: 16 mg of niacin equivalents (NE*)/day*
- ***Adult women of all ages**: 14 mg of NE/day*
- *Pellagra can be prevented by about 11 mg NE/day*
- *1 mg NE = 60 mg of tryptophan = 1 mg niacin
    - *However, studies of pellagra in the southern United States during the early twentieth century indicated that the diets of many individuals who suffered from pellagra contained enough NE to prevent pellagra, challenging the idea that 60 mg of dietary tryptophan are equivalent to 1 mg of niacin*

FOOD SOURCES

- Good sources of niacin include yeast, meat, poultry, fish with red meat (e.g. tuna, salmon, beef, chicken, turkey), cereals (especially fortified cereals), legumes, and seeds. Milk, green leafy vegetables, coffee, and tea also provide some niacin
- In plants, especially cereal grains like corn and wheat, niacin may be bound to large molecules in the form of glycosides
- In supplements, niacin is generally found as nicotinamide
- In animals: mainly as micotinamide (NAD and NADP). In plants, mainly as nictotinic acid bound to carbohydrates (called niacytin) or to small peptide (called nicinogens)
- In the U.S., the average intake of niacin is about 30 mg/day for young adult men, and 20 mg/day for young adult women

Food	Serving	Niacin (mg)	Food	Serving	Niacin (mg)
Chicken (light meat)	3 ounces* (cooked without skin)	10.6	Cereal (unfortified)	1 cup	5-7
Turkey (light meat)	3 ounces (cooked without skin)	5.8	Cereal (fortified)	1 cup	20-27
Beef (lean)	3 ounces (cooked)	3.1	Pasta (enriched)	1 cup (cooked)	2.3
Salmon	3 ounces (cooked)	8.5	Peanuts	1 ounce (dry roasted)	3.8
Tuna (light, packed in water)	3 ounces	11.3	Lentils	1 cup (cooked)	2.1
Bread (whole wheat)	1 slice	1.1	Lima beans	1 cup (cooked)	1.8
			Coffee (brewed)	1 cup	0.5

DIGESTION, ABSORPTION

- NAD and NADP may be hydrolyzed within the intestinal tract by glycohydrolase to free nicotinamide
    - NAD and NADP → glycohydrolase → free nicotinamide
- Nicotinaminde and nicotinic acid can be absorbed in stomach, but more readily in small intestine
- Nicotinaminde and nicotinic acid are absorbed from the SI by a Na-dependent, saturable process
- Once in the intestinal cell, nicotinic acid is believed to be converted into nicotinamide
- In blood mainly found as nicotanimide, but nicotinic acid may also be found. From the blood, nicotinamide and nicotinic acid move across cell membranes by simple diffusion
- Nicotinic acid transport into the kidney tubules and RBC requires Na-dependent carrier system
- It is primarily as NAD and NADP that niacin functions in the body
- Storage is non-existent in the body
- Excretion occurs through the urine

FUNCTIONS

- Extremely wide functions, perhaps 200 enzymes require NAD or NADP as cofactors (hydrogen donors or electron acceptors)
- NADH is mainly involved as part of energy production in the electron transfer chain (i.e. generation of ATP) – so involved in glycolysis, oxidative decarboxylation of pyruvate, entry of acetyl CoA into the Krebs cycle (3 reactions), β-oxidation of fatty acids, ethanol metabolism
- NADPH is an important reducing agent in the synthesis of fatty acids, cholesterol and steroid hormones, deoxyribonucleotides (for DNA)

DISEASE TREATMENT

- **High cholesterol and cardiovascular diseases: pharmacologic doses** of nicotinic acid, but not nicotinamide, have been known to reduce blood cholesterol since 1955
    - *One randomized placebo-controlled multicenter trial examined the effect of nicotinic acid therapy alone (3 grams daily) on outcomes of cardiovascular disease. The Coronary Drug Project (CDP) followed over 8,000 men with a previous myocardial infarction (heart attack) for 6 years. In the group that took 3 grams of nicotinic acid daily total blood cholesterol decreased by an average of 10%, triglycerides decreased by 26%, recurrent nonfatal myocardial infarction decreased by 27%, and cerebrovascular events (stroke + transient ischemic attacks) decreased by 26% compared to the placebo group*
- **HIV/AIDS:** It has been hypothesized that HIV increases the risk of niacin deficiency
    - Interferon-gamma (IF-g) is a **cytokine** produced by cells of the immune system in response to infection. IF-g levels are elevated in individuals infected with HIV, and higher IF-g levels have been associated with poorer **prognosis**
    - By stimulating the enzyme, indoleamine 2,3 dioxygenase (IDO), IF-g is known to increase the breakdown of tryptophan, a niacin precursor, supporting the idea that infection with HIV increases the risk of niacin deficiency
    - A study of 281 HIV-positive men found that higher levels of niacin intake were associated with decreased progression rate to AIDS and improved survival

DEFICIENCY OF NIACIN

Pellagra

- Corn contains appreciable amounts of niacin, but it is present in a bound form that is not nutritionally available to humans
- The traditional preparation of corn tortillas in Mexico involves soaking the corn in a lime solution prior to cooking. This process (heating in an alkaline medium) results in the release of bound niacin, increasing its bioavailability
- **4D's of Pellagra**
    - **Dermatitis**: in the skin a thick, scaly, darkly pigmented rash develops symmetrically in areas exposed to sunlight
    - **Diarrhea**: inflammation of the intestinal mucosa
    - **Dementia**: fatigue, insomnia, apathy, confusion, disorientation, hallucination, loss of memory, psychosis
    - **Death**
    - Symptoms related to the digestive system include a bright red tongue, vomiting, and diarrhea. Neurologic symptoms include headache, apathy, fatigue, depression, disorientation, and memory loss. If untreated, pellagra is ultimately fatal

Causes of niacin deficiency

- Inadequate dietary intake of niacin and/or tryptophan
- Patients with **Hartnup's disease** (a hereditary disorder resulting in defective tryptophan absorption), have developed pellagra
- **Carcinoid syndrome**, a condition of increased secretion of **serotonin** and other **catecholamines** by carcinoid tumors, may also result in pellagra due to increased utilization of dietary tryptophan for serotonin rather than niacin synthesis
- Prolonged treatment with the anti-tuberculosis drug Isoniazid has also resulted in niacin deficiency

TOXICITY OF NIACIN

Nicotinic acid

- Flushing, itching (50mg of nicotinic acid can cause severe flushing due to histamine release)
- Skin rashes and dry skin have been noted with nicotinic acid supplementation
- **GI** disturbances such as nausea and vomiting are common
- Hepatotoxicity (liver cell damage), including elevated liver enzymes and **jaundice**, have been observed at intakes > 750 mg of nicotinic acid/day for less than 3 months
- Transient episodes of hypotension and headache have also been reported
- Large doses of nicotinic acid can **impair glucose tolerance**, likely due to decreased insulin sensitivity. Impaired glucose tolerance in susceptible (pre-diabetic) individuals could result in ↑ blood glucose levels and clinical **diabetes mellitus**
- Large doses of nicotinic acid can ↑ blood levels of uric acid, occasionally resulting in attacks of gout in susceptible individuals
- Nicotinic acid at doses of 1.5-5 g/day has resulted in a few case reports of blurred vision and other eye problems, which have generally been reversible upon discontinuation
- People with abnormal liver function or a history of liver disease, diabetes mellitus, active peptic ulcer disease, gout, cardiac arrhythmias, inflammatory bowel disease, migraine headaches, and alcoholism may be more susceptible to the adverse effects of excess nicotinic acid intake than the general population

Nicotinamide

- Nicotinamide is generally better tolerated than nicotinic acid
- It generally does not cause flushing. However, nausea, vomiting, and signs of liver toxicity (elevated liver enzymes, jaundice) have been observed at doses of 3 grams/day
- The FNB set the UL for niacin (nicotinic acid and nicotinamide) at 35 mg/day to avoid the adverse effect of flushing in the general population

DRUG INTERACTIONS

- One of first uses of niacin was large doses *(4-5 g/day)* to treat schizophrenia
- Co-administration of nicotinic acid with lovastatin may have resulted in rhabdomyolysis (muscle cells are broken down, releasing muscle enzymes and electrolytes into the blood, sometimes resulting in kidney failure) in a small number of cases
- Niacin supplementation is recommended during long-term treatment of tuberculosis with isoniazid. Isoniazid is a niacin **antagonist** and long-term treatment has resulted in pellagra-like symptoms
- Estrogen and estrogen-containing oral contraceptives increase the efficiency of niacin synthesis from tryptophan, resulting in a decreased dietary requirement for niacin

PANTOTHENIC ACID

NOMENCLATURE, CHEMISTRY

- *Structure: β-Alanine + Pantoic Acid joined by a peptide bond*
- Name means "everywhere," widely distributed in nature, therefore the deficiency is not likely to occur
- Most (85%) of the **pantothenic acid** in foods occurs in the form of **CoASH**, which is the co-enzyme form of this vitamin. The rest (15%) exists as **phosphopantetheine** and **phosphopantothenate**
- **Pantethine**: not a vitamin (a derivative of pantothenic acid) – two molecules of pantetheine joined by a disulfide bond

REQUIREMENT: AI

- *AI for adult men and women of all ages: 5 mg of pantothenic acid/day*
- *AI for pregnancy and lactation: 6 and 7 mg/day, respectively*

FOOD SOURCES

- Rich sources of pantothenic acid include liver, kidney, yeast, egg yolk, and broccoli. Fish, shellfish, chicken, milk, yogurt, legumes, mushrooms, avocado, and sweet potatoes are also good sources. Royal jelly from bees provide large amount of pantothenate
- Whole grains are good sources of pantothenic acid, but processing and refining grains may result in a 35-75% loss. Freezing and canning of foods have been found to result in similar losses
- **Supplements** commonly contain its more stable alcohol derivative, **pantothenol** (rapidly converted by humans to pantothenic acid). **Calcium and sodium D-pantothenate**, the Ca^{2+} and Na^{+} salts of pantothenic acid, are also available as supplements

Food	Serving	Pantothenic Acid (mg)	Food	Serving	Pantothenic Acid (mg)
Fish, cod (cooked)	3 ounces	0.15	Lentils (cooked)	1/2 cup	0.64
Tuna (canned)	3 ounces	0.18	Split peas (cooked)	1/2 cup	0.59
Chicken, cooked	3 ounces	0.98	Avocado, California	1 whole	1.68
Egg (cooked)	1 large	0.61	Sweet potato (cooked)	1 medium (1/2 cup)	0.74
Milk	1 cup (8 ounces)	0.79	Mushrooms (raw)	1/2 cup (chopped)	0.51
Yogurt	8 ounces	1.35	Lobster (cooked)	3 ounces	0.24
Broccoli (steamed)	1/2 cup (chopped)	0.40	Bread, whole wheat	1 slice	0.16

- **Intestinal bacteria** are capable of making their own pantothenic acid. It is not yet known whether humans can absorb a meaningful amount of the pantothenic acid synthesized by their own intestinal bacteria

DIGESTION, ABSORPTION, METABOLISM

- CoA is hydrolyzed in small intestine to pantotheine and then to pantothenic acid; free pantothenic acid absorbed by saturable Na^{+}-dependent active process
- About 40-60% of ingested pantothenic acid is absorbed, less (10%) if taken in larger amounts (10× recommended amount)
- Panthenol (alcohol form of the vitamin) may be absorbed and converted to pantothenate
- Within cells, pantothenic acid is metabolized to CoA. CoA is used for the synthesis of ACP (acyl carrier protein) of the fatty acid synthase enzyme, which catalyzes fatty acid synthesis
- Storage: CoA is found in greatest [ ] in the liver, adrenals, kidneys, brain, heart and testes
- There are no known catabolites of pantothenic acid; only pantothenic acid is excreted in urine

FUNCTIONS OF PANTOTHENIC ACID

- Pantothenic acid functions mainly as part of CoA, but also as part of Acyl Carrier Protein
- Pantothenic acid is a component of coenzyme A (CoA), an essential **coenzyme** in a variety of reactions that sustain life
- CoA is required for chemical reactions that generate energy from food (fat, carbohydrates, and proteins)
- CoA is crucial (with coenzymes from thiamin, riboflavin, niacin, and lipoic acid) in oxidative decarboxation of pyruvate and α-ketoglutarate as carrier of acyl groups for energy production
- CoA also needed in synthesis of cholesterol (Acetoacetyl CoA and Acetyl CoA react to form HMG CoA), ketone bodies, CoQ_{10}, acetylcholine, phospholipid, and sphingomyelin

DEFICIENCY OF PANTOTHENIC ACID

- Does not occur under normal conditions, could occur with severe malnutrition
- Groups at risk include those with alcoholism, diabetes mellitus, and inflammatory bowel disease
- Abnormal skin sensations of feet and lower legs, exacerbated by warmth and diminished with cold
- Experimental deficiency: use of **pantothenic acid antagonist (thiopanic acid)** causes fatigue, cardiovascular deficiencies, GI disturbances, numbness and tingling of extremities ("burning feet syndrome"), mental depression, upper respiratory infections

TOXICITY OF PANTOTHENIC ACID

- *No real toxicity known: large amounts (10-20g) lead to diarrhea; no UL set*

DISEASE TREATMENT

High cholesterol

- Several studies found that doses of 900 mg of pantethine daily (300 mg, 3× daily) to be significantly more effective than placebo in lowering total cholesterol and TG levels in the blood of both diabetic and non-diabetic individuals. **PA does not lower lipids**

Wound healing

- *Administration of pantothenic acid orally and application of pantothenol ointment to the skin have been shown to accelerate the closure of skin wounds and increase the strength of scar tissue in animals*
- *A randomized, double blind study examining the effect of supplementing patients undergoing surgery for tattoo removal with 1000 mg of vitamin C and 200 mg of pantothenic acid could not document any significant improvement in the wound healing process in those that received the supplements*

Therapeutics: naturopaths use for the following

- *Adrenal support, stress, atherosclerosis, osteo and rheumatoid arthritis, high serum lipids (panthethine), eczema (especially related to allergic atopic eczema), anemia, SLE (2 studies, 1 yes and 1 no)*

BIOTIN

NOMENCLATURE, CHEMISTRY

- Sulfur containing compound
- Biotin is found bound to protein or as biocytin (also called biotinyllysine [has lysine and is biologically active derivative])

REQUIREMENT: AI

- ***AI for adult men and women of all ages:*** *30 micrograms (mcg) of biotin/day*

FOOD SSOURCES

- Rich sources of biotin are egg yolk, liver, soybeans, and yeast. Biotin is also from some plant species. The natural isomer has the D (+) configuration. *Studies estimate average daily intakes of biotin to be from 40-60 mcg/day in adults*
- The bioavailability of biotin contained in food is highly variable, ranging from 100% in corn to 0% in wheat

Food	Serving	Biotin (µg)	Food	Serving	Biotin (µg)	Food	Serving	Biotin (µg)
Yeast, bakers active	1 packet (7g)	14	Cheese, cheddar	1 ounce	2	Avocado	1 whole	6
Wheat bran, crude	1 ounce	14	Liver, cooked	3 ounces	27	Raspberries	1 cup	2
Bread, whole wheat	1 slice	6	Chicken, cooked	3 ounces	3	Artichoke, cooked	1 medium	2
Egg, cooked	1 large	25	Pork, cooked	3 ounces	2	Cauliflower, raw	1 cup	4
Cheese, camembert	1 ounce	6	Salmon, cooked	3 ounces	4			

- **Bacterial synthesis:** bacteria that normally colonize the colon are capable of making their own biotin. It is not yet known whether humans can absorb a meaningful amount of the biotin synthesized by their own intestinal bacteria

FUNCTIONS OF BIOTIN

- In its physiologically active form biotin is attached at the active site of 4 important carboxylases
- **Acetyl-CoA carboxylase** catalyzes binding of bicarbonate to acetyl-CoA to form malonyl-CoA, which is required for FA synthesis
- **Pyruvate carboxylase** is a critical enzyme in gluconeogenesis (conversion of pyruvate to oxaloacetate)
- **Methylcrotonyl-CoA carboxylase** catalyzes an essential step in the metabolism of leucine, an essential amino acid
- **Propionyl-CoA carboxylase** catalyzes essential steps in the metabolism of amino acids, cholesterol, and odd chain FA. Catabolism of isoleucine, threonine, and methionione (convert proprionate to succinate)

DEFICIENCY OF BIOTIN

- Although biotin deficiency is very rare, it has been observed in **2 different situations**
    1. Prolonged intravenous feeding without biotin supplementation
    2. Consumption of raw egg white for a prolonged period (many weeks to years, 12/day!). Avidin (denatured by heat) is a glycoprotein found in egg white, which binds biotin and prevents its absorption
    - Also seen in inherited enzyme disorders, malabsorption (e.g. achlorhydria, alcohol prevents biotin absorption) and some drugs (anticonvulsant medications used to prevent seizures in individuals with epilepsy ↑ risk of biotin depletion)
    - Recent research suggests that a substantial number of women develop marginal or **subclinical** biotin deficiency during normal pregnancy
- **Symptoms:** hair loss and a scaly red rash around the eyes, nose, mouth, and genital area. Neurologic symptoms in adults have included depression, lethargy, hallucination, and numbness and tingling of the extremities. The characteristic facial rash, together with an unusual facial fat distribution, has been termed the **"biotin deficient face"**

TOXICITY OF BIOTIN

- *No toxicity known up to 200mg/day, and no Ul was set*

VITAMIN C

LEARNING OBJECTIVES
1. Describe the major forms and functions of vit C
2. Explain mechanisms for absorption, transport, and metabolism
3. List the major food sources of vit C
4. Identify deficiencies, toxicities, and therapeutic use
5. Describe the conflicting evidence for optimal intake and toxicity

CHEMISTRY, NOMENCLATURE

- Very simple structure, similar to glucose
- Two compounds have Vitamin C activity: L-ascorbic acid and L-dehyroascorbic acid
- D-ascorbic acid has little Vitamin C activity, but is used as a preservative in meat
- Man, guinea pigs, birds and primates are the only ones that require Ascorbic Acid from the diet. The rest possess the enzyme (**Gulonolactone Oxidase)** to synthesize the vitamin from glucose: Glucose → L-Gulonolactone → L-Ascorbate

REQUIREMENT: RDA

- ***Non smoking adult men ages 19 and older****: 90 mg of vitamin C/day*
- ***Non smoking adult women ages 19 and older****: 75 mg/day*
- ***Adult men who smoke****: 125 mg/day*
- ***Adult women who smoke****: 110 mg/day*

FOOD SOURCES

- Almost all plant foods, especially citrus, peppers, melons, berries, tomatoes, green peppers, parsley, green fresh vegetables, cantaloupes, strawberries, cabbage, turnips, milk
- Ascorbic acid is good reductant so is easily oxidized (destroyed by age, light, oxygen, heat, leaching, alkali)
- Maximize by freshest food, stored well, cooked minimally, larger pieces. Quick heating methods and stir fry are safer, boiling and over cooking can destroy much of the vitamin. Also, quickly destroyed in the presence of metals (esp. Fe, Cu)
- *Mean intake in US is about 90-120 mg/day. Different fruits and vegetables vary in their vitamin C content, but 5 servings should average out to at least 200 mg of vitamin C*

Food	Serving	Vitamin C (mg)	Food	Serving	Vitamin C (mg)
Orange juice	3/4 cup (6 ounces)	75	Tomato	1 medium	23
Grapefruit juice	3/4 cup (6 ounces)	60	Sweet red pepper	1/2 cup, raw chopped	141
Orange	1 medium	70	Broccoli	1/2 cup, cooked	58
Grapefruit	1/2 medium	44	Potato	1 medium, baked	26
Strawberries	1 cup, whole	82			

- **Supplements:** sodium ascorbate, calcium ascorbate, potassium ascorbate, magnesium ascorbate, zinc ascorbate, molybdenum ascorbate, chromium ascorbate, manganese ascorbate, Ester-C®, Vitamin C with bioflavonoids, ascorbyl palmitate

ABSORPTION, TRANSPORT, METABOLISM

- **Absorption**
  - AA absorbed in SI (ileum) by active transport (Na^+-dependent, energy requiring, carrier mediated transport system)
  - Losses up to 20% occur during absorption (destroyed in GI tract)
- **Cellular uptake**
  - Prior to absorption, ascorbate may be oxidized to dehydroascorbate (DHAA, absorbed by passive diffusion)
  - Ascorbate → semidehydroascorbate (a free radical) → dehydroascorbate (crosses the cell membrane)
- **Within the cell**
  - DHAA is rapidly reduced back to ascorbate by dehydroascorbate reductase (require reduced glutathione [GSH])
  - During the reduction of DHAA, glutathione is oxidized (GSSH). Glutathione has been shown to spare vitamin C and improve the antioxidant protection capacity of blood
- **Factors affecting absorption**
  - Ascorbic acid found in foods is readily available for absorption. Absorption depends on dose, with high intakes, saturation is reached quickly and absorption rate (%) is decreased:
    - 15 mg (89% absorbed), 100 mg (80%), 200 mg (72%), 500 mg (63%), 1250 mg (26%), 12 g (16%)
  - Similar absorption with supplements and food
  - Pectin (14.2 g/day, mechanism unknown) and zinc (9.3 mg/day) may impair the absorption of vitamin C
  - In the GI tract, a high iron [ ] present with vitamin C results in the oxidative destruction of vitamin C yielding → 2,3-diketogulonic acid (no vitamin C activity)
    - 2,3-diketogulonic acid → oxalic acid (25%) + threonic acid (four-carbon sugar) OR
    - 2,3-diketogulonic acid → xylose or xylonic acid (five-carbon sugar)
    - The four- and five-carbon sugar can be oxidized and excreted as H_20 and CO_2
- **Transportation**
  - Ascorbic acid is transported as a free anion (with albumin)
  - Some tissues have higher [ ] than others
    - **Highest [ ]**: Adrenal cortex, pituitary gland and retina
    - **Intermediary [ ]**: liver, lungs, pancreas, kidneys, spleen, heart, WBCs
    - **Low [ ]**: RBC's, muscle
- **Excretion**
  - Metabolites in excess are excreted in kidneys (oxalic acid, ascorbate 2-sulfate, 2-ketoascorbitol, 2-O-methyl ascorbate)
  - The kidneys reabsorb Vitamin C in an effort to maintain a 1500 mg body pool. If body pool is > 1500 mg, then metabolites appear in the urine. If < 1500 mg, little or no ascorbic acid appears in urine

FUNCTIONS OF VITAMIN C

1. Collagen synthesis

- Best known is role in collagen synthesis: proline and lysine in procollagen need to be hydroxylated by proline and lysine hydroxylase (also called dioxygenase to form collagen)
- Need vitamin C to keep Fe in reduced form for reactions catalyzed by proline hydroxylase and lysine hydroxylase
- During the hydroxylation reaction, the iron cofactor in the enzymes is oxidized; that is, it is converted from a ferrous (+2) to a ferric (+3) state. Ascorbate is needed to function as a reductant, thereby reducing iron back to its ferrous state (+2) in the prolyl and lysyl hydroxylases
- Collagen is major constituent of connective tissue: bone, teeth, cartilage, skin, capillary basement membranes, scar tissues

2. Carnitine synthesis

- Carnitine is used for fatty acid transport across mitochondrial membrane
- AA needed for two steps in carnitine synthesis (hydroxylations involving Fe)
    - Iron-containing enzyme trimethyllysine dioxygenase catalyses the conversion of
        - trimethyllysine → trimethyllysine dioxygenase → 3-hydroxy trimethyllysine
    - Iron containing enzyme 4-butyrobetaine hydroxylase catalyses the conversion of
        - 4-butyrobetaine → 4-butyrobetaine hydroxylase → carnitine

3. Tyrosine synthesis and catabolism

- Needed for tyrosine synthesis from phenylalanine via phenylalanine hydroxylase (iron-dependent), the reaction occur in the liver, and possibly kidney
- Also catabolism of tyrosine (hydroxylation requiring Fe)

4. Neurotransmitter synthesis

- Co-factor in norepinephrine and epinephrine synthesis from dopamine (originally from tyramine) through a Cu-dependant monooxygenase
- Involved in hydroxylation of tryptophan to 5-hydroxytryptophan (which is decarboxylated to serotonin)

5. Antioxidant

- In small amounts vitamin C can protect indispensable molecules in the body, such as proteins, lipids, carbohydrates, and nucleic acids (DNA and RNA) from damage by free radicals and reactive oxygen species that can be generated during normal metabolism as well as through exposure to toxins and pollutants (e.g. smoking)
- Can directly react with free radicals and scavenge other ROS (reactive oxygen species) (e.g. hydroxyl radical [OH-], hydroperoxyl radical [$HO2^-$], peroxyl radical [$RO2^-$] and may be the best water soluble antioxidant. Some examples include
    - Ascorbate + OH^- → semidehyroascorbate radical (AH^-) + H_2O
    - Ascorbate + O_2^- → dehyroascorbate + H_2O_2
    - Ascorbate + H_2O_2 → dehyroascorbate + $2H_2O$
- May be pro-oxidant by reducing ferric (Fe^{+3}) to ferrous (Fe^{+2}) and cupric (Cu^{+2}) to cuprous (Cu^{+1}) while itself becomes oxidized to semidehyroascorbate
    - Ascorbate (AH_2) + Fe^{3+} or Cu^{2+} → semidehyroascorbate radical (AH^-) + Fe^{2+} or Cu^{1+}

6. Other functions

- Activate certain vitamins into their active form (folacine → THFA)
- Antihistamine effects (6-8 grm/day)

DEFICIENCY OF VITAMIN C

- **Causes**: inadequate dietary intake, High alcohol consumption, Smoking, Stress, Elderly, Achlorhydria, Rheumatic fever, Rheumatoid arthritis, Institutionalized, and Surgical and cancer patients
- Severe vitamin C deficiency has been known for many centuries as the potentially fatal disease, **scurvy**. Symptoms include
    - Bleeding and bruising easily → Anemia (microcytic, hypochromic)
    - Gums disease: swelling, tenderness, gingivitis, redness, ulceration
    - Hair and tooth loss
    - Joint pain and swelling
    - Defects in bone calcification
    - Slow wound healing
    - Such symptoms are related to the weakening of blood vessels, connective tissue, and bone, which contain collagen
    - Early symptoms of scurvy such as fatigue may result from ↓ levels of carnitine, needed to derive energy from fat, or ↓ synthesis of the neurotransmitter norepinephrine

TOXICITY OF VITAMIN C

- A number of possible problems with very large doses of vitamin C have been suggested, mainly based on in vitro experiments or isolated case reports, including: genetic **mutations**, birth defects, cancer, atherosclerosis, kidney stones, increased oxidative stress, excess iron absorption (hemachromatosis?), vitamin B12 deficiency, and erosion of dental enamel
- However, none of these adverse health effects have been confirmed, and there is no reliable scientific evidence that large amounts of vitamin C (up to 10 grams/day in adults) are toxic or detrimental to health
- UL set at 2000mg/day based on diarrhea and gas
- Can interfere with a number of tests (False positive or negative laboratory test) for:
    - Fecal occult blood: false negative
    - Occult blood in urine: false negative
    - Urinary glucose in diabetes: false positive (e.g. fecal blood)
- May increase urinary uric acid and oxalic acid (metabolite) in some people but little evidence of link with kidney stones

INTERACTIONS

- Estrogen-containing contraceptives are known to lower vitamin C levels in plasma and white blood cells
- Aspirin can lower vitamin C levels if taken frequently. For example, two aspirin tablets taken every six hours for a week has been reported to lower white blood cell vitamin C by 50%, primarily by increasing urinary excretion of vitamin C
- There is some evidence, though controversial, that vitamin C interacts with anticoagulant medications (blood thinners) such as warfarin (coumarin). Large doses of vitamin C may block the action of warfarin, requiring an increase in dose to maintain its effectiveness. (Individuals on anticoagulants should limit their vitamin C intake to 1 gram/day and have their prothrombin time monitored by the clinician following their anticoagulant therapy)
- Facilitates conversion of inactive folic acid to active dihydro- and tetrahydro- folic acid

DISEASE PREVENTION AND TREATMENT

- ***Cardiovascular diseases***
  - *Treatment with vitamin C has consistently resulted in improved dilation of blood vessels in individuals with atherosclerosis as well as those with angina pectoris, congestive heart failure, high cholesterol, and high blood pressure. One recent study found that a daily supplement of 500 mg of vitamin C improved blood vessel dilation → resulted in an average drop in systolic blood pressure of 9% after 4 weeks*
  - *A study reported suggested that, contrary to the results of previous research, vitamin C may actually increase* ***atherosclerosis***
- ***Vitamin C and stroke***
  - *A study found that higher blood levels of vitamin C were associated with a significantly lower risk of* stroke*. More than 2000 residents of a rural Japanese community participated in a* prospective study*, which assessed their fruit and vegetable intake, as well as the level of vitamin C in their blood. After 20 of follow up, the risk of stroke in individuals whose blood levels of vitamin C were in the highest quartile (1/4) of the group was only 59% of the risk in those whose blood levels were in the lowest quartile*
  - *Additionally, the risk of stroke in those who consumed vegetables 6-7 days of the week was only 42% of the risk in those who consumed vegetables 0-2 days of the week*
- ***Cancer***
  - *Very large doses of vitamin C (10 grams/day IV for 10 days followed by at least 10 grams/day orally indefinitely) were helpful in increasing the survival time and improving the quality of life of terminal cancer patients*
  - *However, IV administration can result in much higher blood levels of vitamin C than oral administration, and levels that are toxic to certain types of cancer cells in culture can be achieved with IV but not oral administration of vitamin C. Thus, it may be valuable to reevaluate the use of high-dose vitamin C as cancer therapy*
  - *Vitamin C should not be used in place of therapy (*chemotherapy *or* radiation therapy*) that has been demonstrated effective in the treatment of a particular type of cancer. While research is underway to determine whether combinations of antioxidant vitamins might be beneficial as an* adjunct *to conventional cancer therapy, definitive conclusions are not yet possible*
  - *A study shows that lipid hydroperoxides (rancid fat molecules) can react with vitamin C to form products that could potentially harm DNA, although the reaction of these products with DNA was not demonstrated in the study. Hence, it was suggested that vitamin C can form genotoxins (DNA-damaging agents) from lipid hydroperoxides, the implication being that vitamin C may enhance mutagenesis and the risk of cancer*
  - *However, such a conclusion would be unwarranted. The study is a test tube experiment, showing some intriguing chemistry of vitamin C. The study does not, however, describe biochemistry or biology, and its relevance to reactions occurring in cells and tissues of the human body is unknown. Many reactions of vitamin C occur in vitro (in the test tube) that will not and cannot occur in vivo (in the living organism). Why? Because the physiological environment of the cell and the body contains thousands of substances that also react with vitamin C and lipid hydroperoxides, "derailing" the chemistry observed in a test tube system*
- ***Diabetes mellitus***
  - *Numerous observational studies have found that people with diabetes have lower plasma levels of vitamin C (approximately 30% lower) than do people without diabetes. However, it is not clear whether diabetes is the cause of lower plasma levels of vitamin C. Recently a large population-based study found no difference between blood levels of vitamin C in over 200 individuals with newly diagnosed diabetes when compared to 1800 individuals without diabetes once dietary intake of vitamin C and cigarette smoking were taken into consideration*
  - *While the role of vitamin C in the management of diabetes is by no means clear, maintaining an adequate intake of vitamin C may help prevent some of the complications of diabetes*
- ***Common cold***
  - *Large doses (greater than 1 gram/day) of vitamin C have shown to prevent infection with the viruses responsible for the common cold. Reviews of the research conducted on this issue over the past 20 years conclude that, in general, large doses of vitamin C do not have a significant effect on the incidence of the common cold*
  - *However, a few studies have indicated that certain susceptible groups (e.g., individuals with low dietary intake and marathoners) may be less susceptible to the common cold when taking supplemental vitamin C*
- ***Vitamin C and gallbladder disease***
  - *A large cross-sectional study of more than 7,000 women and 6,000 men found an association between lower blood levels of vitamin C and a history of* ***gallbladder*** *disease, as well as the presence of* ***gallstones*** *without symptoms in women but not men*
  - *The reason for the relationship between vitamin C intake and gall stones could not be determined by this study, but the authors hypothesized that it might be related to the ability of vitamin C to increase the activity of an enzyme that breaks down cholesterol to* ***bile acids*** *(gallstones are composed of cholesterol), or the* ***antioxidant*** *activity of vitamin C*
- ***Cataracts***
  - *Decreased vitamin C levels in the lens of the eye have been associated with increased severity of cataracts in humans. Those studies that have found a relationship suggest that vitamin C intake may have to be higher than 300 mg/day and may be required for a number of years before a protective effect can be detected*
- ***Hot off the press***
  - *500mg of supplemental Vitamin C led to a much lower incidence of reflex sympathetic dystrophy (7% in Vit.C group, 22% in placebo) in people who had fractured wrists*
  - *a high intake of Vitamin C (1000 mg/day) may lower serum lead levels*
  - *Vit C supplements didn't seem to protect against coronary heart disease in post-menopausal women or in elderly (but Vit E did)*
  - *Vit C deficiency was associated with a fourfold risk of myocardial infarction*
  - *Vit C did not reduce progression of coronary atherosclerosis or the oxidizability of LDL (but Vit E did)*

VITAMIN B6

LEARNING OBJECTIVES
1. Describe the major forms of Vitamins B_6, both in food and the body
2. Explain the mechanisms for digestion, absorption and transport of Vitamin B_6
3. Outline the functions of Vitamin B_6 (including reactions)
4. List the major food sources of Vitamin B_6
5. Describe the deficiencies, toxicities, and therapeutic use.

CHEMISTRY, NONEMCLATURE

- **Pyridoxal (PL), pyridoxamine (PM)** and **pyridoxine (PN)** are collectively known as **vitamin B_6**
- All three compounds are metabolized and phosphorylated in the body to the biologically active form of vitamin B_6, **pyridoxal phosphate (PLP)** which functions as a coenzyme in many reactions

REQUIREMENT: RDA

- ***Men and women between 19 and 50 years of age:*** *1.3 mg of vitamin B-6/day*
- ***Men 51 years of age and older:*** *1.7 mg/day*
- ***Women 51 years of age and older:*** *1.5 mg/day*

FOOD SOURCES

- Rich sources are whole grains, bananas, legumes, nuts, potato, chicken, liver, beef, legumes, fruits, vegetables, egg yolk, fish, milk, cabbage. Large losses of vitamin B_6 can occur during heating and by leaching of the vitamin during food preparation
- **PN** is usually the major form of in plant foods, and a large proportion of the PN in plants can be present as PN glucoside
- **PLP** and **PMP** are found in animal sources (sirilon steak, salmon, and chicken)

Food	Serving	Vitamin B-6 (mg)	Food	Serving	Vitamin B-6 (mg)
Banana	1 medium	0.68	Potato, baked, with skin	1 medium	0.70
Fortified cereal	1 cup	0.5-2.5	Spinach, cooked	1 cup	0.44
Salmon	3 ounces*	0.48	Hazelnuts, dry roasted	1 ounce	0.18
Turkey, without skin	3 ounces	0.39	Vegetable juice cocktail	6 ounces	0.25
Chicken, light meat without skin	3 ounces	0.46			

ABSORPTION, TRANSPORT, METABOLISM

- **General rule: the vitamin is absorbed and transported in the unphosphorelated form, and is phosphorelated upon entering the cell**
- For absorption, the phosphorulated forms need to be dephosphorylated
- AP (alkaline phosphatase) found at the brush borer of the intestine hydrolyze the phosphate → yield either PN, PL, and PM. absorb about 70-80% depending on glycosides (more poorly absorbed) by passive diffusion in jejunum
- PN glucoside is deconjugated by a mucosal glucosidase. Some PN glucoside is absorbed intact and the complex will be excreted unchanged in the urine. In an average U.S. diet, absorption range from 71-85%
- In enterocytes they are (all forms) rephosphorylated (by kinases) and most is converted to PLP
    - PN → kinase → PNP
    - PL → kinase → PLP
    - PM → kinase → PMP
    - PNP → oxidase-FMN → PLP
    - PMP→ oxidase-FMN → PLP
    - PMP→ transamination → PLP
- PLP is the major form in blood and cells (~ 60%). Thus, normal vitamin B-6 metabolism is closely interrelated with B-2
- In the plasma, PLP and PL are bound to albumin; tissues can only take up PL so must hydrolyze PLP for entry in cell
- The liver is the main organ that takes up by passive diffusion the newly absorbed vitamin B-6. The liver store 5-10% of the vitamin
- Unphosphorylated forms of the vitamin are typically phosphorylated within the cytoplasm of the hepatocyte. PNP and PMP are then converted to PLP
- From the liver, PLP and PL are released for transport to extrahepatic tissues. The extrahepatic tissue such as the **muscle posses the majority of PLP** (75-80%)
- Only PL is taken up by the extrahepatic tissue → PLP in blood must be hydrolyzed before cellular uptake
- Within the cell, PL is phosphorylated to PLP by kinases (found almost in all tissues, and phosphorylation traps the vitamin in the cells)
- Pyridoxic acid (PIC) is the major excretory product resulting from the oxidation of PL. The amount of PIC is more indicative of recent vitamin intake than of vitamin store
    - PL → **NAD-**dependent aldehyde dehydrogenase → PIC
    - PL → **FAD**-dependent aldehyde oxidase → PIC

By Monica Hsu

FUNCTIONS OF VITAMIN B6

- PLP has an extremely important role in ***Amino Acid Metabolism*** as a co-enzyme with 100's of enzymes
- In **transamination** (PMP can also be coenzyme) transfer amino group to amino acid carbon skeleton or α-keto acid to make new amino acid (and catabolized carbon skeleton of old amino acid)
- In **deamination**, remove amino acids – crucial for catabolism of amino acids (urea and urea cycle)
- In **trans- and de- sulfhydration** involved in cysteine synthesis from methionine and catabolism of cysteine
- A **cleavage** reaction is, for example, when serine is formed from glycine (and the hydroxy-methyl group is transferred to THF)
- **Racemization** is where D- and L- amino acid interconvert (mainly bacteria)
- **Nervous system function:** The synthesis of the **neurotransmitter**, serotonin, from the amino acid, tryptophan **(decarboxylation**, remove carboxyl groups) in the brain is catalyzed by a PLP-dependent enzyme. Other neurotransmitters such as dopamine, norepinephrine and gamma-aminobutyric acid (GABA) are also synthesized using PLP-dependent enzymes
- **RBC formation and function:** PLP functions as a coenzyme in the synthesis of heme, a component of hemoglobin. Both PL and PLP are able to bind to the hemoglobin molecule and affect its ability to pick up and release oxygen. However, the impact of this on normal oxygen delivery to tissues is not known
- **Niacin formation:** The human requirement for niacin can be met in part by the conversion of dietary tryptophan to niacin, as well as through dietary niacin intake. PLP is a coenzyme for a critical reaction in the synthesis of niacin from tryptophan
- **Hormone function:** PLP binds to steroid receptors in such a manner as to inhibit the binding of steroid hormones, thus decreasing their effects. The binding of PLP to steroid receptors for estrogen, progesterone, testosterone, and other steroid hormones suggest that the vitamin B-6 status of an individual may have implications for diseases affected by steroid hormones, such as breast cancer and prostate cancer
- **Nucleic acid synthesis:** PLP serves as a coenzyme for a key enzyme involved in the mobilization of single-carbon functional groups (one-carbon metabolism). Such reactions are involved in the synthesis of **nucleic acids (DNA and RNA)**. The effect of B-6 deficiency on immune system function may be partly related to the role of PLP in one-carbon metabolism

DEFICIENCY OF VITAMIN B6

- Alcoholics are thought to be most at risk of vitamin B-6 deficiency, due to a low intake and impaired metabolism of the vitamin
- In the early 1950's **seizures** were observed in infants as a result of severe vitamin B-6 deficiency due to an error in the manufacture of infant formula. Abnormal EEG patterns have been noted in some studies of vitamin B-6 deficiency
- Other **neurologic** symptoms include irritability, depression, and confusion, inflammation of the tongue, sores or ulcers of the mouth (glossitis), and ulcers of the skin at the corners of the mouth, and peripheral neuritis
- Other signs: dermatitis, depression, confusion, and convulsions. Vitamin B6 deficiency also can cause anemia
- Increased dietary protein results in an increased requirement for vitamin B-6, probably because PLP is a coenzyme for many enzymes involved in **amino acid** metabolism
- Populations at risk include some breast fed infants, elderly (poor intake, possible changed metabolism), and alcoholics (changes in B6 metabolism)
- Low intake possible cause of homocysteinemia
- Many drugs can adversely affect B_6 status, particularly oral contraceptives, anticonvulsants

TOXICITY OF VITAMIN B6

- Very high doses of pyridoxine over long periods of time may result in painful neurological symptoms known as sensory **neuropathy. Symptoms** include pain and numbness of the extremities, and in severe cases difficulty walking
- Naturopaths often prescribe in 100-300 mg amounts; UL set at 100 mg/day - in England want to restrict to 50mg/day max
- In order to prevent sensory neuropathy in virtually all individuals, the FNB set the UL for pyridoxine at 100 mg/day for adults

DISEASE PREVENTION AND TREATMENT

- ***Side effects of oral contraceptives***
  - *Because vitamin B-6 is required for the metabolism of tryptophan, the tryptophan load test was used as a functional assessment of vitamin B-6 status. Abnormal tryptophan load tests in women taking high-dose oral contraceptives in the 1960's and 70's suggested that these women were vitamin B-6 deficient*
  - *The abnormal results in the tryptophan load test led a number of clinicians to prescribe high doses (100 -150 mg/day) of vit B6 to women in order to relieve depression and other side effects sometimes experienced with oral contraceptives*
  - *However, most other indices of vitamin B-6 status were normal in women on high-dose oral contraceptives. A recent study of women on the low-dose oral contraceptives prescribed currently showed no benefit of up to 150 mg/day of vitamin B-6 (pyridoxine) over a placebo in the prevention of side effects, such as nausea, vomiting, dizziness, depression, and irritability*
- ***Premenstrual syndrome (PMS)***
  - *The use of vitamin B-6 to relieve the side effects of high-dose oral contraceptives led to the use of vitamin B-6 in the treatment of PMS. A review of 12 placebo-controlled double-blind trials of vitamin B-6 in PMS concluded that evidence for a beneficial effect was weak. A more recent review of 25 studies of vitamin B-6 and PMS suggested that doses of vitamin B-6 up to 100 mg/day may be of value, but conclusions were limited by the poor quality of most of the studies evaluated*
- ***Depression***
  - *Because the synthesis of serotonin and norepinephrine is PLP-dependent, it has been suggested that vitamin B-6 deficiency may lead to depression. However, clinical trials have not provided evidence that vitamin B-6 supplementation is effective in the treatment of depression*

- ***Morning sickness (nausea and vomiting in pregnancy)***
    - *Vitamin B-6 has been used since the 1940's to treat nausea during pregnancy. Vitamin B-6 itself is considered safe during pregnancy, and has been used in pregnant women without any evidence of fetal harm. The results of two double-blind placebo-controlled trials (25 mg of pyridoxine every 8 hrs for 3 days and 10 mg of pyridoxine every 8 hrs for 5 days) suggest vitamin B-6 may be beneficial in alleviating morning sickness. However, it should be noted that morning sickness also resolves without any treatment, making it difficult to perform well-controlled trials*
- ***Carpal tunnel syndrome***
    - *Carpal tunnel syndrome causes numbness, pain, and weakness of the hand and fingers due to compression of the median nerve at the wrist. Several studies suggested that vitamin B-6 status was low in individuals with carpal tunnel syndrome and that supplementation with 100-200 mg/day over several months was beneficial*
    - *While a few trials have noted some symptomatic relief with vitamin B-6 supplementation, double-blind placebo-controlled trials have not generally found vitamin B-6 to be effective in treating carpal tunnel syndrome*
- ***Hot off the press***
    - ***Alcohol and Homocysteine:*** *Serum homocysteine can increase with moderate consumption of red wine and spirits; however not with beer, probably due to B_6 content. PLP levels were negatively correlated with homocysteine levels in the blood, leading the investigators to suggest that increased blood levels of vitamin B-6 might contribute to a lower risk of cardiovascular diseases*
    - ***Vitamin B-6 and kidney stones:*** *In a group of more than 85,000 women without a prior history of kidney stones, followed over 14 years, those who consumed 40 mg or more of vitamin B-6 daily had only two thirds the risk of developing kidney stones compared with those who consumed 3 mg or less. However, in a group of more than 45,000 men followed over 6 years no association was found between vitamin B-6 intake and the occurrence of kidney stones. It is less clear that supplementation actually resulted in decreased formation of calcium oxalate kidney stones. Presently, the relationship between vitamin B-6 intake and the risk of developing kidney stones is under investigation*
    - *Two recent feeding studies on women suggest that the new RDA is not sufficient for normal enzyme activity or B6 status in women*
    - *In a British study in those over 65 years, 48% of elderly living in the community and 75% living in institutions had biochemical evidence of B6 deficiency*

By Monica Hsu

VITAMIN B12 (COBALAMIN)

CHEMISTRY AND NOMENCLATURE

- Vitamin B12 is the largest and most complex of all the vitamins. It is unique among vitamins in that it contains a metal ion, cobalt. For this reason cobalamin is the term used to refer to compounds having B12 activity
- The following groups may be attached to the cobalt molecule:
  - -CN → Cyanocobalamin
  - -OH → Hydroxy-cobalamin
  - $-H_2O$ → Aqua-cobalamin
  - $-NO_2$ → Nitrito-cobalamin
  - *-5'-deoxy adenosyl → 5'-deoxyadenosyl-cobalamin
  - $*-CH_3$ → Methyl cobalamin
  - * Only these two forms are coenzymatically active. The human body can convert all other forms to these metabolically active forms
- Cyanocobalamin & Hydroxy-cobalamin are the two forms of cobalamin used in most supplements
- Cyanocobalamin is readily converted to 5-deoxyadenosyl and methylcobalamin

REQUIREMENT: RDA

- ***Adults ages 50 and younger****: 2.4 mcg of vitamin B-12/day*
- ***Adults ages 51 and older****: 2.4 mcg of vitamin B-12/day from supplements or fortified foods, probably because of gastric atrophy resulting in hypchlorhydria or achlorhydria*
- ***Pregnant women****: 2.6 mcg of vitamin B-12/day*

FOOD SOURCES

- Bacteria can synthesize vitamin B12. Vitamin B12 is present in animal products (meat, poultry, eggs [especially the yolk], fish [including shellfish]) and in milk. Fresh pasteurized milk contains 0.9 mcg per cup and is an important source of vitamin B12 for some vegetarians. There are cobalamins without B12 activity in some herbs and fermented products (e.g. tempeh, shoyu)
- Those vegetarians who eat no animal products need supplemental vitamin B12 to meet their requirements. AND individuals over the age of 50 should obtain their vitamin B12 in supplements or fortified foods, like fortified cereal, because of the increased likelihood of food-bound vitamin B12 malabsorption
- *In a sample of adults over the age of 60, men were found to have an average dietary intake of 3.4 μg/day and women 2.6 μg/day*

Food	Serving	Vitamin B-12 (mcg)	Food	Serving	Vitamin B-12 (mcg)
Clams (steamed)	3 ounces	84.0	Chicken (roasted)	3 ounces	0.3
Mussels (steamed)	3 ounces	20.4	Turkey (roasted)	3 ounces	0.3
Crab (steamed)	3 ounces	8.8	Egg (poached)	1 large	0.4
Salmon (baked)	3 ounces*	2.4	Milk	8 ounces	0.9
Rockfish (baked)	3 ounces	1.0	Brie (cheese)	1 ounce	0.5
Beef (cooked)	3 ounces	2.1			

ABSORPTION, TRANSPORT, METABOLISM

- Absorption of vitamin B-12 from food requires normal function of the stomach, **pancreas**, and **small intestine** (distal ileum). Vitamin B-12 in food is bound to protein and is released in the stomach by the acid environment and proteolitic enzyme pepsin
- Stomach acid and enzymes free vitamin B-12 from food, allowing it to bind to other proteins, known as R proteins
- R proteins are degraded by pancreatic enzymes, freeing vitamin B-12 to bind to intrinsic factor (IF), a protein secreted by the parietal cells in stomach
- The IF-B-12 complex binds to the IF receptor (on the surface of the SI) in the presence of calcium, and the complex is internalized by a receptor-mediated endocytotic process. The IF is degraded and the B-12 is released into the cytosol
- Vitamin B-12 is released from the gut epithelial cells as a complex bound to a glycoprotein called transcobalamin II (TC-II is synthesized in the liver)
- The TC-II-B12 complex carries newly absorbed vitamin B-12 around the body and provides tissues with vitamin B-12
- Plasma contains 2 additional vitamin B-12 binding protein called transcobalamin I (TC-I), and transcobalamin III (TC-III). Although newly absorbed vitamin B-12 is associated with TC-II, about 80% of the plasma B-12 is associated with TC-I
- The role of **TC-I** and **TC-III** is not clear, but may be involved in the delivery of cobalamin from periphery tissue to the liver
- Vitamin B-12 can be absorbed by passive diffusion, but this process is very inefficient, allowing only about 1% absorption of a vitamin B-12 dose
- Most of the body store of vitamin B-12 (estimated about 2 to 3 mg) is in the **liver** mainly as **deoxyadenosylcobalamin**. Whereas **methylcobalamin** is the major form in **plasma**. Small amount exist in muscle, bone, kidney, heart, spleen, brain
- Most of cobalamin excretion occurs via the bile and very little via the urine

By Monica Hsu

FUNCTIONS OF VITAMIN B12

- **Cofactor for methionine synthase**
  - Methylcobalamin is required for the function of the folate-dependent enzyme, methionine synthase
  - This enzyme is required for the synthesis of **methionine, from homocysteine**
- **Cofactor for L-methylmalonyl-CoA mutase**
  - 5-Deoxyadenosylcobalamin is required by the enzyme that catalyzes the conversion of L-methylmalonyl-CoA to succinyl-CoA. This biochemical reaction plays an important role in the production of energy from fats and proteins
- **Regeneration of Methionine and the "Folate Trap"**
  - Cobalamin picks up the methyl group from N^5-methyl THF and transfers it to homocysteine; in the process, N^5-methyl THF is converted to THF
  - Need $N^{5,10}$-THF to make DNA and can only make $N^{5,10}$-THF from THF, therefore if there is a B_{12} deficiency, folate will get "trapped" in N^5-THF; that is why it is believed that a deficiency of B_{12} and folate have identical effects on the blood

DEFICIENCY OF VITAMIN B12

- Takes a very long time to occur by diet (20-30 years?) unless child of vegan mother
- Very common in elderly, partly due to gastric atrophy with age (this leads to hypo- or achlorhydria and bacterial overgrowth); perhaps 10-15% of elderly have low B_{12} status and 10-30% can't effectively absorb B_{12} from food
- **Causes of vitamin B-12 deficiency**

State	Cause
Lack of B-12 in food	Vegan
Failure to digest food protein	Decreased gastric acid
Absence of IF	Pernicious anemia, gastrectomy
Failure to digest R protein	Pancreatic diseases
Inadequate absorption	Ileal resection, Crohn's disease
Altered intestinal utilization	Bacterial growth
Malabsorption syndromes	HIV infection, MS, celiac disease
Congenital disease	Transcobalamin deficiency
Mucosal or receptor defect	Certain drugs

- **Food-bound vitamin B-12 malabsorption**
  - In the elderly, food-bound vitamin B-12 malabsorption is thought to result mainly from atrophic gastritis (affect 10-30% of people over 60 years of age, and is frequently associated with infection by *Heliobacter pylori*, which ultimately results in the loss of glands in the stomach (atrophy) and decreased stomach acid production → B-12 absorption is diminished
- **Symptoms**
  - **Megaloblastic anemia:** Diminished activity of methionine synthase in vitamin B-12 deficiency inhibits the regeneration of THF and traps folate in a form that is not usable by the body → folate deficiency symptoms
  - **Neurologic symptoms:** numbness and tingling of the arms and more commonly the legs, difficulty walking, memory loss, disorientation, and **dementia**, with or without mood changes (Neurologic complications are not always reversible with treatment of vitamin B-12 deficiency). The biochemical processes leading to neurological damage in B-12 deficiency are not well understood
  - **GI symptoms:** sore tongue, appetite loss, and constipation. Their origins are unclear (may be related to the stomach inflammation, the increased vulnerability of the rapidly dividing cells along the GI tract to **impaired DNA synthesis**)
  - **Hyperhomocystenemia:** due to impaired activity of methionine synthase. While impaired activity of L-methylmalonyl-CoA mutase results in increased levels of a metabolite of methylmalonyl-CoA, called methylmalonic acid (MMA). People with B_{12} deficiency excrete large quantities of methylmalonic acid in urine

TOXICITY OF VITAMIN B12

- Doses as high as 1 mg (1000 mcg) daily by mouth or 1 mg monthly by IM injection have been used to treat **pernicious anemia**, without significant side effects
- When high doses of vitamin B-12 are given orally only a small percentage can be absorbed, which may explain its low toxicity, however sublingual B_{12} may be well absorbed. No known toxicity → no UL was set

INTERACTIONS

- Gastric acid inhibitors known as H_2-receptor antagonists (e.g., Tagamet, Pepsid, Zantac), used to treat **peptic ulcer disease**, has also been found to decrease the absorption of vitamin B-12 from food
- Large doses of folic acid given to an individual with an undiagnosed vitamin B-12 deficiency could correct megaloblastic anemia without correcting the underlying vitamin B-12 deficiency → irreversible neurologic damage

DISEASE PREVENTION AND TREATMENT

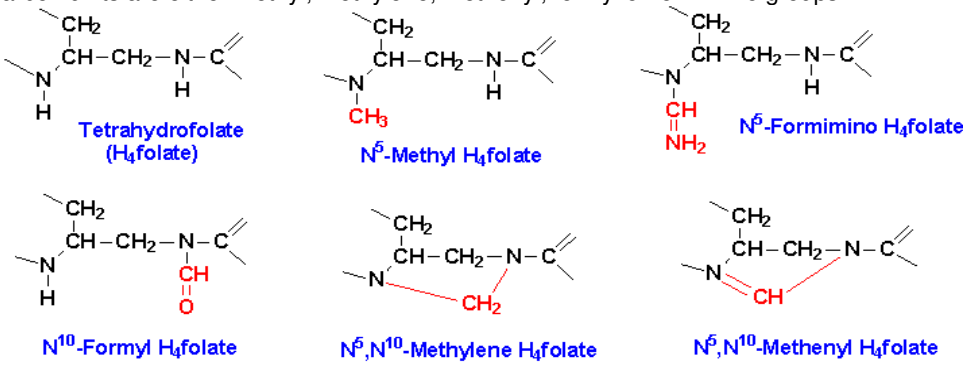
Hot off the press

- *21% of adolescents who were brought up (to age 6) as strict vegan/macrobiotic had evidence of B12 deficiency as adolescents despite now following lactoovo veg or omnivorous diets*
- *Low serum B12 concentrations are associated with progression of HIV/AIDS*
- *Smoking may be associated with reduced B_{12} status*

FOLATE

NOMENCLATURE, FORMS

- Also called folacin
- *Folic acid = pteroylglutamic acid (or pteroylmonoglutatamate)*
- *Pteroylglutamic acid = pteroic acid (pterin + para-amino-benzoic acid [PABA]) + glutamic acid*
- There are di- and tetra hydro forms (DHF and THF)
- The function of THF derivatives is to carry and transfer various forms of one-carbon units during biosynthetic reactions. The one-carbon units are either methyl, methylene, methenyl, formyl or formimino groups



Active center of tetrahydrofolate (THF). Note that the N^5 position is the site of attachment of methyl groups, the N^{10} the site for attachment of formyl and formimino groups and that both N^5 and N^{10} bridge the methylene and methenyl groups

REQUIREMENT: RDA

- ***Determination of the RDA:*** *When the FNB set the new dietary recommendation for folate, they introduced a new unit, the Dietary Folate Equivalent (DFE). Use of the DFE reflects the higher* **bioavailability** *of synthetic folic acid found in supplements and fortified foods compared to that of naturally occurring food folates*
  - ***1 mcg of food folate provides 1 mcg of DFE***
  - ***1 mcg of folic acid taken with meals or as fortified food provides 1.7 mcg of DFE***
  - ***1 mcg of folic acid (supplement) taken on an empty stomach provides 2 mcg of DFE***
  - *For example, a serving of food containing 60 mcg of folate would provide 60 mcg of DFE, while a serving of pasta fortified with 60 mcg of folic acid would provide 1.7 x 60 = 102 mcg DFE due to the higher bioavailability of folic acid. A folic acid supplement of 400 mcg taken on an empty stomach would provide 800 mcg of DFE*
- **Men and non pregnant women:** 400 mcg of DFE/day
- **Pregnant women:** 600 mcg of DFE/day
- **Women who are breast feeding:** 500 mcg of DFE/day
- **Women capable of becoming pregnant:** 400 mcg/day of folic acid from supplements or fortified foods, **in addition to dietary sources**

FOOD SOURCES

- Green leafy vegetables (foliage) are rich sources of folate. Citrus fruit juices, legumes, and fortified cereals are also excellent sources of folate
- Very good sources are wheat germ, yeast, liver, kidney, asparagus, broccoli, brussels sprouts, green turnip, legumes (lima beans)
- Raw foods are higher in folate than cooked foods (very susceptible to destruction by heat, UV, oxidation, or leaching into water [can lose 50-90%])
- Although natural folates rapidly lose activity in foods over periods of days or weeks, folic acid (Synthetic form in fortified foods) is almost completely stable for months
- Availability of folate from food is also affected by inhibitory compounds known as **conjugase inhibitors** (found in cabbage, orange, pinto beans, lentils), which prevent the digestion of polyglutamate forms to the monoglutamate form
- In order to help prevent neural tube defects, folic acid has been added to grains and cereals at 140 µg/100g white wheat flour (an extra 100 µg or so per day)

Food	Serving	Folate (mcg)	Food	Serving	Folate (mcg)
Orange juice (from concentrate)	6 ounces	82	Lima beans (cooked)	1/2 cup	78
Spinach (cooked)	1/2 cup	131	Bread	1 slice	20 (Folic acid)
Asparagus (cooked)	1/2 cup (~ 6 spears)	131	Pasta (cooked)	1 cup	60 (Folic acid)
Lentils (cooked)	1/2 cup	179	Rice (cooked)	1 cup	60 (Folic acid)
Garbanzo beans (cooked)	1/2 cup	141	Breakfast cereals (ready to eat)	1 cup	100 (Folic acid)

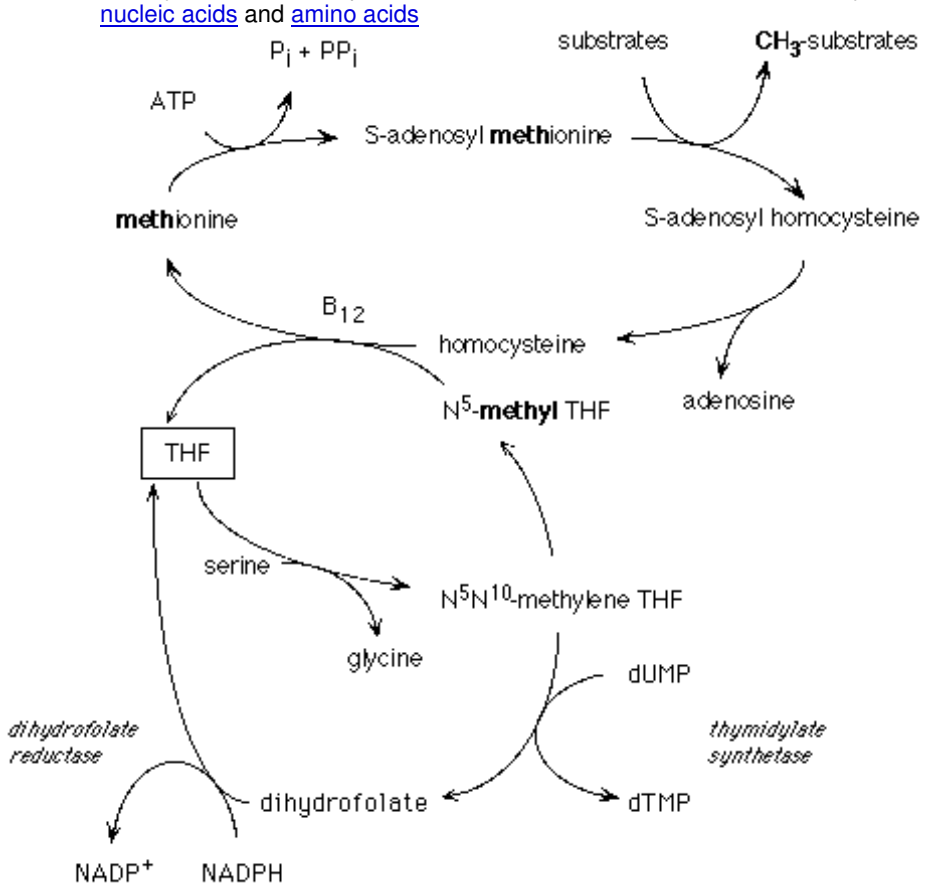
By Monica Hsu

DIGESTION, ABSORPTION

- Natural folate is delivered by food in bound form which is combined with a string of amino acids known as polyglutamates (up to 9 glutamate), which are hydrolyzed at the brush border membrane to monoglutamate, by the γ-glutamylcarboxypeptidases (also called conjugases-Zn dependent). The conjugases are also found in the pancreatic juice and bile
  - **Polyglutamates ---- conjugases-Zn dependent -----→ Monoglutamate ---→ Uptake**
- In enterocyte, folate in reduced to THF and mainly **methylated** as N^5- methyl-THF through the action of **dihydrofolate reductase (DHFR)**, an NADPH-requiring enzyme
- The intestine absorbs this folate form with only one monoglutamate attached. Absorption is via a saturable active transport, carrier-mediated, Na-dependent, mainly in the **jejunum**. Optimal transport occurs between a pH of 5 & 6
- Special transport systems then go on to deliver the monoglutamate form to the liver and other cells of the body (Folate binding proteins (FBP) in brush border, also called folate receptors, are believed to form a part of the transport system). Folate will be stored mainly as polyglutamate (4-7 glutamates added) in the liver
- If the folate needs to be released the cells hydrolyze it back to the monoglutamate form. If the body wants to dispose of excess folate the liver secretes it to bile and transports it to the gallbladder, from there it returns to the intestine
- For folate coenzyme to function, the CH3 group needs to be removed from CH3-THF. **Folate needs vitamin B12 to function**. Vitamin B12 acts to remove a methyl group (CH3) from the THF. If this does not occur folate will become trapped in cells in its methyl form leaving it unavailable to support DNA synthesis and cell growth
- Transported in portal vein mainly as N^5- methyl-THF. In the blood folate is found as monoglutamate, and 2/3 of the folate in blood is bound to protein (mainly albumin)

FUNCTIONS OF FOLATE

- **One-carbon metabolism**
  - The only function of folate coenzymes in the body appears to be mediating the transfer of one-carbon units. Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the metabolism of nucleic acids and amino acids



- **Serine, Glycine, and Histidine**
  - $N^{5,10}$-methylene THF is involved in the reversible conversion of glycine ←→ Serine (serine is an important methyl donor) – cofactor is PLP
  - Glycine ←—— serine hydroxymethyltransferase (PLP-dependent) ——→ Serine
  - Histidine → FIGLU (N-formiminoglutamate) → glutamate
- **Methylation reactions**: the most important carrier of methyl groups is S-adenosyl-methionine (SAM)
  - SAM is a methyl group donor used in many methylation reactions
  - Product after the methyl group is transferred is S-adenosyl-homocysteine (SAH). Hydrolysis gives homocysteine (and adenosine)
  - Methionine Regeneration from Homocysteine: in order to regenerate the methionine, homocysteine must be methylated. The methylating agent is the N^5-methyl THF (B_{12} also involved). If have deficiency of folate (especially) or B_{12} → get accumulation of homocysteine

DEFICIENCY OF FOLATE

- **Causes of deficiency**
  - **Inadequate dietary intake**: poor diet
  - **Inadequate absorption**: malabsorption syndrome (gluten-induced entheropathy, Tropical sprue)
  - **Inadequate utilization**: enzyme deficiency, alcohol consumption, folic acid antagonist, ascorbic acid deficiency
  - **Increased requirement**: infancy, increase metabolic activity, pregnancy
  - **Increased excretion**: liver and kidney disease
- **Symptoms**
  - In folate deficiency (takes about 4 months) → abnormal cell division (rapidly dividing cells), immature red cells are released → this is called **megaloblastic or macrocytic anemia**
  - Progression of such an anemia leads to a decreased oxygen carrying capacity of the blood and may ultimately result in symptoms of fatigue, weakness, and shortness of breath
  - Megaloblastic anemia resulting from folate deficiency is identical to the megaloblastic anemia resulting from vitamin B12 deficiency, and further clinical testing is required to diagnose the true cause of megaloblastic anemia. Folate will mask B12 symptoms (folate will not cure nervous degeneration caused by B12 deficiency)
  - Other symptoms: depression, dementia and peripheral neuropathy (new research), high blood levels of homocysteine
  - **Summary of symptoms**
    - **Blood/circulatory system**: Megaloblastic anemia
    - **GI**: Heart burn, diarrhea
    - **Mouth**: smooth, red, sore tongue (Glossitis)
    - **Nervous system**: depression, mental confusion, insomnia, irritability
    - **Immune system**: frequent infection

TOXICITY OF FOLATE

- *UL set at 1000 μg/day* based the possibility of masking B_{12} deficiency (probably need at least 5 mg/day to do this)
- Excessive folate may results in: Insomnia, Alterations in sleep patterns, Malaise, Irritability, GI problems

INTERACTIONS

- Zinc needed for conjugase (so Zn deficiency may reduce folate absorption)
- Some drugs interfere with folate metabolism: oral contraceptives, nosteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants (Dilantin), in particular (all have been shown to inhibit the intestinal absorption of folate)
- Medications have been shown to have antifolate activity, including trimethoprim (an antibiotic), pyrimethanine (an antimalarial), triamterene (a blood pressure medication), sulfasalazine (a treatment for ulcerative colitis), and Methotrexate (treat rheumatoid arthritis and psoriasis).

DISEASE PREVENTION AND TREATMENT

- ***Pregnancy complications***
  - *Neural tube defects (NTD) can be prevented with sufficient folate (400 to 4000 μg/day) but needed in early pregnancy*
  - *NTD result in either anencephaly or spina bifida. The defects occur between the 21st and 27th days after conception, when many women do not realize they are pregnant*
  - *The risk of NTD in the U.S. prior to fortification of foods with folic acid was estimated to be one per 1000 pregnancies. Results of randomized trials have demonstrated 60-100% reductions in NTD cases when women consumed folic acid supplements in addition to a varied diet during the periconceptional period*
  - *Adequate folate status may also prevent the occurrence of other types of birth defects, including certain heart defects and limb malformations; decreased the risk of premature delivery and infant low birth weight*
  - *More recently, elevated blood homocysteine levels have been associated with increased incidence of miscarriage, as well as pregnancy complications like preeclampsia and placental abruption*
- ***Cardiovascular diseases***
  - *Folate and homocysteine: ↑ folate intake through folate-rich foods or supplements has been found to lower homocysteine levels. A supplement regimen of 400 mcg of folic acid, 2 mg of vitamin B-6, and 6 mcg of vitamin B12 has been advocated by the AHA if an initial trial of a folate-rich diet is not successful in adequately lowering homocysteine levels*
- ***Cancer***
  - *Because of the important roles played by folate in DNA synthesis and methylation it is possible for folate intake to affect both DNA repair and gene expression*
  - *The consumption of at least five servings of fruits and vegetables daily has been consistently associated with a decreased incidence of cancer. Observational studies have found diminished folate status to be associated with cancers of the cervix, colon and rectum, lung, esophagus, brain, pancreas, and breast*
- ***Hot off the press***
  - *nuns who had low serum folate levels were more likely to show signs of Alzheimers's disease on autopsy*
  - *the elderly may have a higher need for folate*
  - *since folate has been added to enriched grain products, there is evidence that serum folate levels have increased and high serum homocysteine have decreased (19 to 10%) in Americans*
  - *To decrease plasma homocysteine effectively in coronary patients, may require more than the present food supplementation level (3.7% decrease with 127 μg/day and 11% with 499 μg/day)*
  - *perhaps 5-15% of the population are homozygous for a thermolabile variant of N5,10-methyleneTHF reductase so may have greater requirements – this is one of the first common gene/nutrient interactions*
  - *low serum folate is associated with an ↑ risk of coronary heart disease and high folate intake may protect against CHD*

Glucosamine

INTRODUCTION

- A simple molecule manufactured in the body from glucose and an amine
- A major component of Chitine
- Primary physiological role: in the joints where it stimulates the manufacture of glucosaminoglycans, key structural components of cartilage
- Promotes the incorporation of sulfur into cartilage: glucosamine sulfate (GS) is thought to be the best source of glucosamine

FOOD SOURCES

- No food sources of glucosamine
- Commercially available sources are derived from chitin, the exoskeleton of shrimp, lobsters, and crabs

DEFICIENCY OF GLUCOSAMINE: SIGNS AND SYMPTOMS

- A major factor in developing osteoarthritis
- Joints most often affected: knee, hips, and hands
- Cartilage destruction, hardening and the formation of large bone spurs in the joint margins
- Pain, deformity, and limited joint motion
- Morning joint stiffness is the first symptoms

CLINICAL APPLICATIONS OF GLUCOSAMINE

- Safe and effective natural alternative to aspirin and non-steroid anti-inflammatory drugs (NSAIDs)
- While NSAIDs are fairly effective in suppressing the symptoms, they possibly worsen the condition by inhibiting cartilage formation and repair (inhibit glucosaminoglycan synthesis) and accelerating cartilage destruction
- GS addresses the cause of osteoarthritis, by promoting cartilage synthesis, thus treating the root of the problem
- GS not only relieves the problem, but also helps the body to repair damaged joints
- *Numerous studies*
    - *GS and placebo*
        - *252 patients with osteoarthritis were given either a placebo or 500mg of GS 3 times/day/4 weeks*
        - *Result → GS significantly more effective than placebo in improving pain and movement after 4 weeks*
    - *GS and NSAIDs*
        - *GS (1,500mg/day) was compared with Ibuprofen (1,200mg/day), pain scores decreased faster in the first 2 weeks in the ibuprofen groups*
        - *However, after 4 weeks the group receiving GS experienced significantly better improvement than the ibuprofen group*
        - *Side-effects of GS were mild, while ibuprofen produced more significant side-effects more frequently*
- Dosage:
    - Standard dosage is 500mg/3times/day
    - Obese individuals need higher dosage based on body weight (20mg/kg/BW/daily)
    - Individuals taking diuretics may need higher dosages

TOXICITY OF GLUCOSAMINE

- Has excellent safety record
- GI, stomach upset, heartburn, diarrhea, nausea, and indigestion

CLINICAL SIGNIFICANCE OF GLUCURONATE

- In the adult human, a significant number of erythrocytes die each day. This turnover releases significant amounts of the iron-free portion of heme, **porphyrin**, which is subsequently degraded
- The breakdown of porphyrin yields **bilirubin**, a product that is non-polar (insoluble in water)
- In the liver bilirubin is solubilized by conjugation to glucuronate. The soluble conjugated **bilirubin diglucuronide** is then secreted into the bile
- An inability to conjugate bilirubin, for instance in *hepatic disease* or when the level of bilirubin production exceeds the capacity of the liver, is a contributory cause of **jaundice**

By Monica Hsu

Fiber

3 DEFINITIONS FO FIBERS

- **Dietary fiber: nondigestible carbohydrates and lignin that are intrinsic and intact in plants**
  - Examples of sources are cereal bran, flaked corn cereal, sweet potatoes, and legumes
  - **Lignin, Cellulose, Beta-Glucans, Hemicelluloses, Pectins, Gums, Inulin, Oligofructose, Resistant starch**
- **Functional fiber: isolated, nondigestible carbohydrates that have beneficial physiological effects in humans, but are extracted from natural sources or are synthetic**
  - **Psyllium, Chitin and chitosan, Fructooligosaccharides, Polydextrose and polyols, Resistant dextrins**
- **Total fiber: dietary fiber plus added fiber**
- **Adequate intake (AI) for total fiber**
  - Adults under 50 years: **38 g** for male & **25 g** for female
  - Adults over 50 years: **30 g** for male & **21 g** for female

SIGNIFICANT CHARACTERISTICS OF FIBERS

1. Solubility in water
2. Water-holding capacity and viscosity
3. Adsorption or binding capacity
4. Degradability and fermentability

1. SOLUBILITY IN WATER

- **Water-soluble**
  - Pectin, gum, mucilages, some hemicellulose
  - Dissolve in hot water
  - Delay gastric empting
  - Increase transit time (slower movement) through the intestine
  - Decrease nutrient (e.g. glucose) absorption
- **Water-insoluble**
  - Cellulose, lignin, some hemicellulose
  - Do not dissolve in hot water
  - Decrease transit time (speed up movement) through the intestine
  - Increase fecal bulk

2. WATER-HOLDING CAPACITY AND VISCOSITY

- Viscosity or gel formation (soluble fiber): fiber as a dry sponge moving through the digestive tract hydrating or soaking up water and digestive juices
- **Delayed (slowed) empting from the stomach**
  - The release of chyme from the stomach to duodenum (proximal SI) is delayed
  - Nutrients remain in stomach longer
  - This creates a feeling of postprandial (after eating) and satiety (fullness) → slow down the digestion process
- **Reduced mixing of GI contents with enzymes**
  - The gel formation provides a physical barrier that can impair the ability of the nutrients in the food to interact with the digestive enzyme
- **Decrease nutrient diffusion rate → decreases nutrient absorption**
  - Gums appears to slow glucose absorption by ↓ convective movement of glucose within the intestinal lumen
  - Convective currents induced by peristaltic movements are responsible for bringing the nutrients from the lumen to epithelial surface for absorption
  - Gum, pectin, psyllium have been shown to
    - Slow transit movement
    - Delay glucose absorption
    - Lower glucose concentrations
- All are beneficial to individuals with diabetes and reduce postprandial blood glucose and insulin need/response

By Monica Hsu

3. ADSORPTION OR BINDING CAPACITY

- Gum, pectin, and some hemicellulose can bind (adsorb) substances such as enzymes and nutrients in the GI tract
- Binding depends on: GI's pH level, particle size, food processing, and fermentability
- The physiological effects of the ingestion of fibers with adsorption properties within the GI tract are as follow
- **Diminished absorption of lipids**
    - Pectin, gums, and oat bran may affect lipid absorption by binding to FA, cholesterol, or bile acid within GI tract
    - FAs and cholesterol that are bound to fiber cannot form micelles and cannot be absorbed in the bound form (only FFAs, monoacylglycerols, and cholesterol can be incorporated into micelles)
    - Thus, fiber-bound lipids are not absorbed in the SI and pass into the LI to be excreted in the feces or degraded by intestinal bacteria
- **Lowered blood cholesterol [ ]**
    - Mechanism 1: increase fecal bile acid excretion
        - Binding of bile acid to fiber prevent the use of bile for micelle formation
        - Fiber-bound bile acid are sent into the LI to be excreted in the feces or degraded by intestinal bacteria
        - With excretion of bile acid in the feces, less bile undergo enterohepatic circulation
        - A decrease in bile acid returned to the liver necessitates the use of cholesterol for synthesis of new bile acids → lower serum cholesterol
    - Mechanism 2: shift of bile acid pools away from cholic acid and toward chenodeoxycholic acid
        - Chenodeoxycholic acid inhibit HMG-CoA reductase, a regulatory enzyme needed for cholesterol biosynthesis → decrease hepatic cholesterol synthesis → lower blood cholesterol
    - **Psyllium, gums, oat gum, and pectin → greatest effect in lowering serum cholesterol**
    - **Oat bran, soybean fiber → intermediate effect**
    - **Corn, wheat, and rice bran → ineffective**
    - Ingestion of fruits + vegetables containing both soluble and insoluble fiber have been shown to decrease serum cholesterol
- **Altered mineral balance**
    - Hemicellulose, pectins, and gums contain uronic acid can form cationic bridges with minerals within the GI tract
    - The overall effect (+ or -) depends on its degree of fermentability or its accessibility to bacterial enzymes in colon
    - Microbial proliferation from slowly fermentable fibers may result in increased binding of minerals → loss of minerals from the body (assuming colonic mineral absorption)
    - In contrast, pectin (rapidly fermentable fiber) have a favorable effect on mineral balance
    - Zn, Ca, and Fe bound to these fibers are released as fermentation occurs and may possibly be absorbed in colon

4. DEGRADABILITY AND FERMENTABILITY

- **Fermentable fibers**
    - The principle metabolites of fermentable fibers are lactate and short chain FAs (SCFAs)
    - Pectins, beta-glucans, guar gum, inulin and oligofructose are readily fermented → degraded to SCFAs
    - Foods that are rich in fermentable fibers include oats and barley and fruits and vegetables
    - SCFAs include primarily acetic, butyric, and propionic acid. Other products include hydrogen, carbon dioxide, and methane gases that are excreted as flatus or are expired by the lungs
    - Ingestion of pectin resulted in higher proprionate [ ] in colon vs. wheat bran, which resulted in higher butyrate [ ]
    - General effects of SCFAs generated from fiber fermentation include
        - increased colonic sodium and water absorption
        - Increased mucosal cell proliferation
        - increased provision of energy
        - increased acidification of luminal environment
    - **Provision of energy**
        - Butyric acid is an energy source for colonic epithelial cells
        - Those FAs not used by the colonic cells (proprionic and acetic acids) are carried by the portal vein to the liver, where they are taken up and metabolized
        - Most of the acetate passes to the peripheral tissue, where it is metabolized by skeletal and cardiac muscle
- **Nonfermentable fibers**
    - **Cellulose and lignin are nonfermentable.** Others more slowly fermentable include some hemicellulose (these are particularly valuable in promoting the proliferation of microbes in the colon)
    - Microbial proliferation may be important in detoxification and in increasing fecal volume (bulk)
    - Cereal fibers that are rich in cellulose, such as wheat bran, are relatively resistant to bacterial fermentation. Wheat bran and rice bran are very effective in eliciting an increased fecal bulk → helpful in treating constipation
    - Wheat bran is one of the most effective fiber laxatives because it can absorb 3 times its weight of water → producing a bulky stool

HEALTH EFFECT OF FIBERS

- Fiber helps to prevent several GI disorders including: hemorrhoids, appendicitis, diverticulosis, colon cancer, constipation, and gallstones

EXAMPLES OF FIBER

- **Cellulose**
  - A polysaccharide consisting of a linear molecule composed of glucose subunits held together by β-1,4-glucosidic linkages. Is the main structural component of plant cell walls. Humans lack digestive enzymes to cleave β-1,4 linkages and thus cannot absorb glucose from cellulose
  - Powdered cellulose is purified mechanically disintegrated cellulose obtained as a pulp from wood or cotton and is added to food as thickening and texturizing agent
  - Dietary cellulose can be classified as dietary fiber or functional fiber depending on whether it is naturally occurring food (dietary fiber) or added to foods (functional fiber)
- **Hemicellulose**
  - Groups of polysaccharides found in plant cell walls that surround cellulose
  - Hemicellulose can be linear or branched and consist of xylose, mannose, arabinose, and other monosaccharides
  - Dietary Hemicellulose is classified as a dietary fiber
- **Pectins**
  - A complex group of polysaccharides found in cell wall and intracellular tissues of many fruits and berries (fruits and vegetables contain 5-10% naturally occurring pectin)
  - Apples or packaged pectin are often added to jams and jellies to ensure that jelling occurs
  - Composed of a backbone of molecules derived from galactose (galacturonic acid) with occasional side chains containing arabinose, galactose and other monosaccharides. These substances are usually water-soluble and gel forming
- **Beta-Glucans**
  - Viscous, easily fermented, soluble fibers found naturally in oats, barley, mushrooms, yeast, bacteria and algae
  - Beta-glucans extracted from oats, mushrooms and yeast are available in a variety of nutritional supplements without a prescription
- **Lignin**
  - A noncarbohydrate component of fiber, is a highly complex molecule composed of a mixture of phenolic compounds. These molecules are of research interest because they have both carcinogenic and anticarcinogenic effects due to the phenolic compounds
  - Lignin is a major component in bark but is found in limited quantities in some plant foods such as the edible seeds of strawberries and root vegetables such as carrots
  - Lignin is classified as a dietary fiber if it is relatively intact in the plant
  - Lignin isolated and added to foods could be classified as functional fiber
- **Gums**
  - Consist of a diverse group of polysaccharides usually isolated from seeds and have viscous feature
  - The major polysaccharide in guar gum is galactomannan (is highly viscous and known as food thickening, gelling, and stabilizing properties)
  - Gum arabic is a plant that is used as a food additive
  - Gums in the diet can therefore be classified as dietary or functional fiber
- **Guar gum**
  - A viscous, fermentable fiber derived from the Indian cluster bean
  - It is used as a thickener or emulsifier in many food products
- **Psyllium**
  - A viscous, soluble fiber isolated from psyllium seed husks, is available without a prescription in laxatives, ready-to-eat cereals and dietary supplements
  - The FDA has approved health claims like the following on the labels of foods containing at least 1.7 g/serving of soluble fiber from psyllium: “Diets low in saturated fat and cholesterol that include 7 g/day of soluble fiber from psyllium may reduce the risk of heart disease”
- **Inulin, Oligofructose, and Fructologosaccharides**
  - Naturally occurring in a variety of plants
  - Inulin is a β-1,4 linked frucatn with a glucose molecule at the end of each fructose chain. The naturally occurring fructans that are found in plants such as chicory, onions, and Jerusalem artichoke, would be classified as dietary fiber, whereas the synthesized or extracted fructans could be classified as functional fiber
  - Inulins and oligofructose are highly fermentable fibers that are also classified as prebiotics because of their ability to stimulate the growth of potentially beneficial *Bifidobacteria* species in the human colon. Encouraging the growth of *Bifidobacteria* could promote intestinal health by suppressing the growth of pathogenic bacteria known to cause diarrhea or enhancing the immune response
- **Chitin and Chitosan**
  - Chitin is an amino-polysaccharide containing β-1,4 linkages
  - Chitosan is the deacetylated product of chitin
  - Both are found in the exoskeletons of arthropods (crabs and lobsters) and the cell walls of most fungi
  - Neither one is digested by mammalian digestive enzyme
  - They are primarily consumed as supplement and can be classified as functional fiber
- **Mucilages**
  - Like guar, are produced by plants to protect the seed's endosperm from desiccation
  - The algal polysaccharides, carrageenan and agar, are derived from algae and seaweed
  - These non-metabolizable natural products are used to enhance processed foods (used as food additives)

FOOD SOURCES OF FIBER

Food	Serving	Fiber (g)
Legumes		
Navy beans, cooked from dried	1 cup	19.1
Kidney beans, canned	1 cup	16.4
Split peas, cooked from dried	1 cup	16.3
Lentils, cooked from dried	1 cup	15.6
Refried beans, canned	1 cup	13.4
Cereals and grains		
100% (wheat) Bran Cereal	1 cup	17.6
Quinoa, cooked	1 cup	9.3
Bulgur, cooked	1 cup	8.2
Pearled barley, cooked	1 cup	6.0
Oat bran, cooked	1 cup	5.7
Instant oatmeal, cooked	1 cup	3.7
Rice, long-grained brown, cooked	1 cup	3.5

Food	Serving	Fiber (g)
Vegetables		
Artichoke hearts, cooked	1 cup	9.1
Spinach, frozen, cooked	1 cup	7.0
Brussel sprouts, cooked	1 cup	6.4
Winter squash, cooked	1 cup	5.7
Mushrooms, cooked from fresh	1 cup	3.4
Fruits		
Prunes, uncooked	1 cup, pitted	12.1
Asian pear	1 pear	9.9
Guava, fresh	1 cup	8.9
Raspberries, fresh	1 cup	8.0
Blackberries, fresh	1 cup	7.6
Nuts and Seeds		
Almonds	1 ounce (23 kernels)	3.3
Pistachio nuts	1 ounce (47 kernels)	2.9
Pecans	1 ounce (20 halves)	2.7
Peanuts	1 ounce (33 kernels)	2.4

Food Sources of Insoluble Fiber			Food Sources of Soluble Fiber	
Cellulose	***Hemicellulose***	***Lignin***	***Gum***	***Pectin***
Whole Wheat Flour Unprocessed Bran Cabbage Peas Green Beans Wax Beans Broccoli Brussel Sprouts Cucumber with Skin Green Peppers Apples Carrots	Bran Cereals Whole Grains Brussels Sprouts Mustard Greens Beet Root	Bran Cereals Unprocessed Bran Strawberries Eggplant Pears Green Beans Radishes	Oatmeal Rolled Oat Products Dried Beans Cauliflower Green Beans Cabbage Dried Peas Carrots Potatoes Strawberries	Squash Apples Citrus Fruits

By Monica Hsu

Protein: PEM, PKU, Homocysteine

PROTEIN FACTS

- The average American consumes 80-125 g of protein per day: twice as much that is set by the RDA
- The amount of protein consumption has not changed that much, but the composition of protein that we eat has changed
- In the old time, most of the protein was coming from plant sources and now almost all of the protein we consume is from animal sources
- 12% of our energy on a daily basis comes from proteins

PROTEIN-ENERGY MALNUTRITION (PEM)

- **Kwashiorkor**
  - A diet with excessive nonprotein calories from starch or sugar, but deficient in total protein and essential a.a.
  - Kwashiorkor: the evil spirit that infects the first child when the second child is born
  - When the second child is born, the first child can no longer be breast-fed because it is time for the second child to be breast-fed. The source of quality protein is cut off for the first child
- **Marasmus (to waste away)**
  - Severe deprivation or impaired absorption of energy and protein
- **Marasmic-kwashiorkor**
  - Intermediate forms
- **Epidemiology**
  - Marasmus is the predominant form of PEM throughout most developing countries. It is associated with the early abandonment or failure of breast-feeding and with consequent infections, most notably those causing infantile gastroenteritis
  - Kwashiorkor is less common and is usually manifest as the intermediate marismic-kwashiorkor state. It tends to be confined to those parts of the world (rural Africa, the Caribbean and Pacific islands) where staple and weaning foods such as yam, cassava, sweet potato, or green banana are protein deficient and excessively starchy
- **Pathophysiology**
  - **In marasmus**, energy intake is insufficient to match requirements and the body draws on its own stores. The cause is a diet very low in calories from all sources (including protein), often from early weaning to bottled formula diluted because of poverty
  - **In kwashiorkor**, increased carbohydrate intake with decreased protein intake leads to decreased visceral protein synthesis. The resulting hypoalbuminemia (<2.2g/100ml) causes dependent edema
  - Kwashiorkor can result when a hospitalized patient is fed glucose (IV) for many days, such as when a slow recovery from surgery prevents normal food consumption. IV glucose meet energy needs but provide no protein
- **Signs and Symptoms** (see attached paper)
- **Diagnosis**
  - Differential diagnosis includes secondary growth failure due to malabsorption, congenital defects, or deprivation. Skin changes in kwashiorkor differ from those of pellagra where they occur on parts exposed to light and are symmetrical. Edema in nephritis, nephrosis and cardiac failure is accompanied by features of these diseases
- **Treatment**
  - Treatment is essentially the same whether it is marasmus or kwashiorkor. Three phases:
  1. Resuscitation: correction of dehydration, nutrient deficiency, low body temperature and treatment of infections
  2. The cure begins with mixed foods, usually including milk, providing increasing calories and protein per kilogram of body weight. Appetite may be poor and the child must be fed by hand. A multivitamin preparation and supplements of potassium, magnesium, and zinc are needed
  3. Rehabilitation takes place after about three weeks when the child usually has improved and has a good appetite, but is still underweight. It will take many weeks of good nutrition before catch-up growth is complete. If the home background is unfavorable because of poverty or social disorganization, the mother will need support as well as advice
- **Prognosis**
  - Mortality varies between 15 and 40%. Death in the first days of treatment is usually due to electrolyte imbalance, infection, hypothermia, or heart failure
  - Behavioral development may be markedly retarded in the severely malnourished child
  - The degree of mental impairment is related to the duration of malnutrition and age of onset

METABOLIC DISORDER: PHENYLKETONURIA (PKU)

- Initially was named oligophrenia phenylpyruvical, the first metabolic disease known to be associated with mental illness
- A decrease in dietary phenylalanine can lower the blood phenylalanine [ ]
- A microbial inhibition assay was developed to measure blood phenylalanine: screening test for early diagnosis and treatment of PKU – one of the most widely applied genetic tests in humans
- Classic PKU: deficiency of phenylalanine hydroxylase, causing phenylalanine to accumulate in liver and blood
  - The metabolic block was due to the inability to convert phenylalanine to tyrosine in the liver
  - Congenital impairment: gene for phenylalanine hydroxylase is located on chromosome 21

- Abnormally high [ ] of phenylalanine in the kidney are converted to phenylpyruvic acid, a ketone body, by aminotransferese
- Excess phenylalanine, its metabolites (phenylpyruvic acid) and metabolites of phenylpyruvic acid (phenylacetic acid) cause brain damage (pathogenesis of brain damage is not fully understood)
- Classic PKU: a hidden disease – newborn infants are clinically normal, and tests for urinary phenylpyruvic acid may be negative during the first few days after birth. Diagnosis of classic PKU depend upon blood phenylalanine levels
- Dietary management must begin in the earliest weeks: a diet with only enough phenylalanine necessary for growth
- All naturally occurring food proteins contain substantial amounts (averaging 5%) of phenylalanine
- Diet therapy goal for PKU children: maintain serum phenylalanine levels within acceptable limits (5-10 mg/100 mL) while supplying nutrients and energy in amounts to support growth and normal intellectual development
- Medical evaluation should include a history, physical examination, laboratory blood tests, and development assessment. Serum phenylalanine levels should be obtained from all sibling, both parents, and available relatives to discover possible previously undetected cases

METABOLIC DISORDER: HOMOCYSTINEMIA

- Homocysteine (tHcy) is a sulfur-containing AA formed during the metabolism of methionine
- **Metabolism of homocysteine: by two pathways**
    1. **Remethylation cycle**: tHcy is salvaged by the acquisition of a methyl group in a reaction catalyzed by methionine synthase (require vit B12). N5-methyltetrahydrofolate is the methyl donor in this reaction, and N-5, N-10-methylenetetrahydrofolate reductase functions as a catalyst in the remethylation process
    2. **Transsulfuration**: tHcy condense with serine to form cystathionine in a reaction catalyzed by cystathionine B-synthase (require vit B6). Cystathionine is subsequently hydrolyzed to form cysteine, which may in turn be incorporated into glutathione or further metabolized to sulfate and excreted in urine
- Nutritional deficiency in the vitamin cofactor (B6, B12, and folic acid) may promote hyperhomocystinemia
- Population with abundant dietary methionine from animal protein, coupled with nutritional deficiency of vitamins B6, B12, and folic acid are at increased risk of atherosclerosis
- Normal tHcy values are: 6-10 micromol/L for women & 8-12 micromol/L for men. Vascular disease is directly correlated with tHcy level, even in the normal range, and levels over 14 micromol/L are associated with increased risk of CHD
- Clinical symptoms include those of the nervous, cardiovascular, muscular-skeletal, and hematopoetic systems. Although mental retardation is associated with homocystinemia, some older adults have been found to be normal in intelligence
- Other causes of hyperhomocystinemia: chronic renal failure, hypothyroidism, pernicious anemia, carcinoma (breast, ovarian, pancreas, and acute lymphoblastic leukemia), drugs (Methotrexate, Phenytoin, Theophylline), cigarette smoking
- **tHcy, lipoproteins and cholesterol**
    - tHcy, like other sulfhydryl compounds, increases the formation of oxycholesterols and other oxidized lipids and proteins during the modification of LDL in the presence of ferric or cupric ions
    - Interaction between tHcy, lipoproteins, and cholesterol involve altered oxidative processes within cells of developing atherosclerotic plaques
    - The highly reactive thiolactone form of tHcy causes elevation of serum TG, LDL, and cholesterol in animals
    - Thiolactone reacts with LDL to produce an aggregated, dense form of lipoprotein that is taken up by macrophages to form foam cells
    - LDL containing tHcy, bound by peptide bonds to amino groups of apoB protein in patient with hypercholesterolemia
    - These findings suggest that LDL aggregates carry tHcy in the blood stream to foam cells of early plaque, where the AA modifies the oxidative and synthetic processes of artery wall cells, promoting atherosclerosis
- **tHcy and vascular damage**
    - Because of dietary, genetic, toxic, or hormonal factors, decreased remethylation or transsulfuration of tHcy leads to overproduction of tHcy thiolactone from methionine
    - Excess tHcy thiolactone converts LDL to aggregates that are transported in blood and taken up by vascular macrophages of arterial intima
    - Oxidized LDL promotes formation of foam cells, which release lipids and cholesterol into fibrolipid plaques
    - tHcy thiolactone is also released from foam cells and facilitates conversion of thioretinaco ozonide of mitochondria to thioco, resulting in smooth muscle cell hyperplasia and fibrosis
    - Consequent overproduction of oxygen radicals causes intimal damage, oxidizes thioretinamide to sulfate of glucosaminoglycans, activates elastase, incites thrombogenesis, and increase calcium deposition, forming the pathological feature of atherosclerosis plaques
- **Other mechanisms**
    - tHcy is rapidly auto-oxidized when added to plasma, forming tHcy, mixed disulfide, and tHcy thiolactone
    - Potent **ROS**, including superoxide and hydrogen peroxide are produced during the auto-oxidation of tHcy, and hydrogen peroxide in particular, has been implicated in the vascular toxicity of hyperhomocysteinemia
    - tHcy-induced **endothelial-cell injury** in vitro is largely due to the generation of hydrogen peroxide
    - tHcy auto-oxidation has been shown to support **oxidation of LDL** through the generation of superoxide radical
    - tHcy auto-oxidation produces superoxide and hydroxyl radical. Superoxide-dependent formation of the hydroxyl radical has been shown to initiate **lipid peroxidation**, an effect that occurs at the level of endothelial plasma membrane and within lipoprotein particle
    - tHcy is also thrombogenic, increasing thromboxane formation, enhancing the binding of lipoprotein(a) to fibrin, enhancing platelet aggregation at the site of intimal damage, inhibiting protein C and thrombomodulin and activating factor XII and factor V → facilitate the formation of thrombin and create prothrombotic environment

Lipids (EFAs, Eicosanoids)

ESSENTIAL FATTY ACIDS (EFAs)

- The majority of body fatty acids are acquired in the diet. However, the lipid biosynthetic capacity of the body (fatty acid synthase and other fatty acid modifying enzymes) can supply the body with all the various fatty acid structures needed
- EFAs are polyunsaturated FAs (PUFA) that cannot be completely synthesized in the body. Two types of PUFA: omega-6 (ω-6) and omega-3 (ω-3)
- **Omega-6 (ω-6)**
  - **Linoleate (18:2)**: is the main PUFA
  - **Arachidonate (20:4)**: is the main substrate for the synthesis of eicosanoid mediators including PG and LT. Much of the arachidonate in the body is synthesized from linoleate
  - **Adrenate (22:4)**: it functions as an intracellular storage form of arachidonate. Accumulate in tissues that have a higher arachidonate
  - **γ-Linolenic acid (18:3)**, and **Dihomo-γ-linolenic acid (20:3)**
- **Omega-3 (ω-3)**
  - **Linolenate (18:3)**: FA contained in commercially prepared infant formula
  - **Eicosapentaenoate (EPA) (20:5)**: major component of tissue
  - **Docosahexaenoate (DHA) (22:6)**: major component of membrane phospholipids in retinal photoreceptor, cerebral gray matter, and sperm
- *The new AI for Linoleic acid (vegetable oils such as safflower or corn oil) is 17 grams/day for men and 12 grams/day for women. For alpha linolenic acid (soybean and flaxseed oils) is 1.6 grams/day for men and 1.1 grams/day for women. Requirements of EFAs are 1-2% of dietary calories for adults and 3% for infants, with a suggested ratio of 10:1 for ω-6:ω-3 FAs*
- *A typical Western diet contains much less ω-3 FAs. Available evidence suggests that between 0.2 and 0.4 g of ω-3 FA should be consumed daily. Some experts recommend a higher intake of ω-3 FA is desirable (2-4 g/day)*
- The essentiality of linoleic and linolenic acids is due to the fact that vertebrates lack enzymes called Δ12 and Δ15 desaturases, which incorporate double bonds at these positions. These enzymes are found only in plants. Vertebrates therefore incapable of forming double bonds beyond the Δ9 carbon in the chain
- Plants are capable of synthesizing linoleic and linolenic acid. They are able to introduce double bonds at Δ6, Δ9, Δ12, and Δ15 therefore, they can synthesize EFAs
- Humans can acquire these fats by consuming a variety of plants or else by eating the meat of animals that have consumed these plant fats

SOURCES: *Omega-6 Fatty Acids*

- **Linoleic Acid (LA):** vegetable oils, such as soybean, safflower and corn oil, nuts, seeds and some vegetables
  - *US dietary surveys indicate that the average adult intake of LA ranges from 12-17 g/day for men and 9-11 g/day for women*

Some Food Sources of Linoleic Acid (18:2n-6)					
Food	**Serving**	**Linoleic Acid (g)**	**Food**	**Serving**	**Linoleic Acid (g)**
Safflower oil	1 tablespoon	10.1	Soybean oil	1 tablespoon	6.9
Sunflower seeds, oil roasted	1 oz	9.7	Pecans, oil roasted	1 oz	6.4
Pine nuts	1 oz	9.4	Brazil nuts	1 oz	5.8
Sunflower oil	1 tablespoon	8.9	Sesame oil	1 tablespoon	5.6
Corn oil	1 tablespoon	7.2			

- **Arachidonic Acid:** animals, but not plants, can convert LA to AA. Therefore, AA is present in the diet in small amounts in meat, poultry and eggs

SOURCES: *Omega-3 Fatty Acids*

- ***Alpha-linolenic acid (ALA):*** flaxseeds, walnuts, and their oils, and Canola oil
  - *US dietary surveys indicate that average adult intakes for ALA range from 1.2-1.6 g/day for men and from 0.9-1.1 g/day for women*

Food	**Serving**	**Alpha-Linolenic acid (g)**	**Food**	**Serving**	**Alpha-Linolenic acid (g)**
Flaxseed oil	1 tablespoon	8.5	Mustard oil	1 tablespoon	0.8
Walnuts, English	1 ounce	2.6	Soybean oil	1 tablespoon	0.9
Flaxseeds	1 tablespoon	2.2	Walnuts, Black	1 ounce	0.6
Walnut oil	1 tablespoon	1.4	Olive oil	1 tablespoon	0.1
Canola oil	1 tablespoon	1.2	Broccoli, raw	1 cup, chopped	0.1

By Monica Hsu

- ***Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)***: fish oils and fatty fish
    - *US dietary surveys in the U.S. indicate that average adult intakes of EPA range from 0.04-0.07 g/day and average adult intakes of DHA range from 0.05-0.09 g/day*
    - *Omega-3 fatty acid-enriched eggs are now available in the U.S. One such egg produced by adding flaxseed to hens' feed is reported to contain 0.25 g of EPA and 0.15 g of DHA*

Food	Serving	EPA (g)	DHA (g)	Amount providing 1 g of EPA + DHA	Food	Serving	EPA (g)	DHA (g)	Amount providing 1 g of EPA + DHA
Herring, Pacific, cooked	3 ounces	1.06	0.75	1.5 ounces	Tuna, white, packed in water	3 ounces	0.20	0.54	4 ounces
Salmon, chinook, cooked	3 ounces	0.86	0.62	2 ounces	Crab, Dungeness, cooked	3 ounces	0.24	0.10	9 ounces
Salmon, Atlantic, cooked	3 ounces	0.28	0.95	2.5 ounces	Shrimp, cooked	3 ounces	0.15	0.12	11 ounces
Oysters, Pacific, cooked	3 ounces	0.75	0.43	2.5 ounces	Cod, Pacific, cooked	3 ounces	0.09	0.15	12.5 ounces
Salmon, sockeye, cooked	3 ounces	0.45	0.60	3 ounces	Fish oil, menhaden	1 gram	0.13	0.09	5 grams
Trout, rainbow, cooked	3 ounces	0.40	0.44	3.5 ounces	Fish oil, salmon	1 gram	0.13	0.18	3 grams

SUPPLEMENTS

- ***Omega-6 Fatty Acids:*** Borage seed oil, evening primrose oil and black currant seed oil are rich in gamma-linolenic acid (GLA) (often marketed as GLA or EFA supplements)
- ***Omega-3 Fatty Acids:*** Flaxseed oil (also known as flax oil or linseed oil) is available as an ALA supplement. Since EPA and DHA content will vary in fish oil and ethyl ester preparations, it is necessary to read the label to determine the EPA and DHA content of a particular supplement. DHA supplements derived from algae are also available
    - All omega-3 fatty acid supplements are absorbed more efficiently with meals. Dividing one's daily dose into two or three smaller doses throughout the day will decrease the risk of GI side effects
    - Although cod liver oil is a rich source of EPA and DHA, it should be avoided as an omega-3 fatty acid supplement since it also contains high levels of vitamin A (in the form of preformed retinal) and vitamin D
    - DHA supplements derived from algal and fungal sources are also available

INFANT FORMULA

- In 2001, the U.S. Food and Drug Administration began permitting the addition of DHA and arachidonic acid to infant formula. Presently, manufacturers are not required to list the amounts of DHA and arachidonic acid added to infant formula on the label. However, most infant formula manufacturers will provide this information when contacted by telephone or email
- *The amounts added to formulas in the U.S. range from 8-17 mg DHA/100 calories (5 fluid ounces) and from 16-34 mg arachidonic acid/100 calories. For example, an infant drinking 20 fluid ounces of formula daily would receive 32-68 mg/day of DHA and 64-136 mg/day of arachidonic acid*

METABOLISM OF EICOSANOIDS

- Eicosanoids are chemical messengers derived from 20-carbon polyunsaturated fatty acids that play critical roles in immune and **inflammatory** responses. Both 20-carbon omega-6 fatty acids (arachidonic acid) and 20-carbon omega-3 fatty acids (EPA) can be found in cell membranes
- During an inflammatory response, arachidonic acid and EPA are metabolized by enzymes known as cyclooxygenases and lipoxygenases to form eicosanoids
- In those who consume typical western diets, the amount of arachidonic acid in cell membranes is much greater than the amount of EPA, resulting in the formation of more eicosanoids derived from arachidonic acid than EPA. However, increasing omega-3 fatty acid intake increases the EPA content of cell membranes and decreases the arachidonic acid content, resulting in higher proportions of eicosanoids derived from EPA
- Eicosanoids consist of the prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs). The PGs and TXs are collectively identified as prostanoids
- Prostaglandins were originally shown to be synthesized in the prostate gland, thromboxanes from platelets (thrombocytes) and leukotrienes from leukocytes, hence the derivation of their names
- The principal eicosanoids of biological significance to humans are a group of molecules derived from the C20 fatty acid, arachidonic acid. Minor eicosanoids are derived from eicosopentaenoic acid (EPA)
- The major source of arachidonic acid is through its release from cellular stores. Within the cell, it resides predominantly at the C-2 position of membrane phospholipids and is released from there upon the activation of phospholipase A2
- The immediate dietary precursor of arachidonate is linoleate. Therefore, the absence of linoleic acid from the diet would seriously threaten the body's ability to synthesize eicosanoids
- All eicosanoids function locally at the site of synthesis, through receptor-mediated G-protein linked signaling pathways leading to an increase in cAMP levels

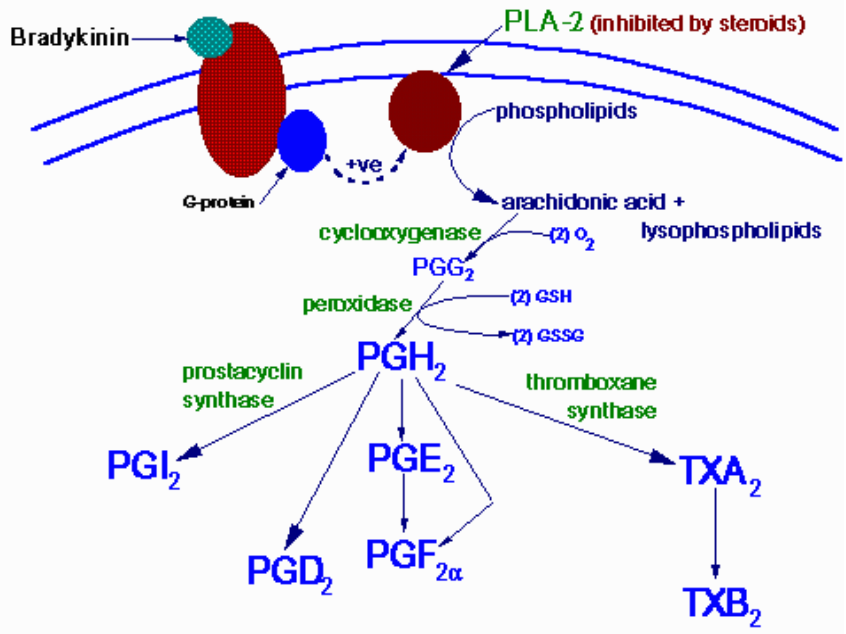
By Monica Hsu

The Pathways

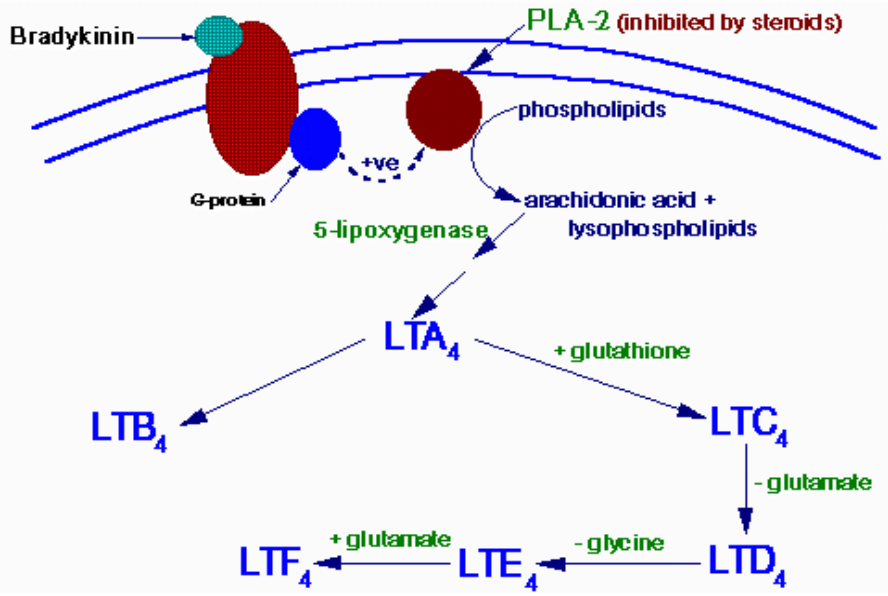
- Two main pathways are involved in the biosynthesis of eicosanoids. The prostaglandins and thromboxanes are synthesized by the **cyclic** pathway, the leukotrienes by the **linear** pathway
- The **cyclic pathway** is initiated through the action of prostaglandin endoperoxide synthetase. This enzyme possesses two activities, cyclooxygenase and peroxidase. It catalyzes the oxygenation of arachidonic acid together with the cyclization of an internal segment of arachidonate chain, the hallmark structure of PG and TX
- The **linear pathway** is initiated through the action of lipoxygenases. It is the enzyme, 5-lipoxygenase that gives rise to the leukotrienes
- A widely used class of drugs, the non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, indomethacin, naproxen, phenylbutazone and aspirin, all act upon the **cyclooxygenase activity**
- Another class, the **corticosteroidal drugs, act to inhibit phospholipase A2,** thereby inhibiting the release of arachidonate from membrane phospholipids and the subsequent synthesis of eicosinoids

The mechanism of action of EPA

- The cyclooxygenase pathway can convert EPA to PGI3 and TXA3 (contain 3 double bonds)
- EPA competes with arachidonate for incorporation into tissue lipids, including phospholipid pools that supply substrate for eicosanoid synthesis
- When the phospholipase subsequently is activated, there is less arachidonate available in the phospholipids for release, further contributing to a reduction in the formation of eicosanoid product derived from arachidonate → → this makes EPA an effective inhibitor of arachidonate metabolism
- This suggests 2 possible reasons why omega-3-FAs are essential for health
    1. The eicosanoids produced from EPA play some vital role even though the amounts formed are usually small
    2. EPA prevents the excessive production of eicosanoids from arachidonate, thereby fine-tuning processes such as intercellular singling and reducing eicosanoids-mediated responses such as inflammation so that they do not become uncontrolled
- **Synthesis of the clinically relevant prostaglandins and thromboxanes from arachidonic acid. Numerous stimuli (e.g. epinephrine, thrombin and bradykinin) activate phospholipase A2 which hydrolyzes arachidonic acid from membrane phospholipids. The prostaglandins are identified as PG and the thromboxanes as TX. Prostaglandin PGI2 is also known as prostacyclin. The subscript 2 in each molecule refers to the number of -C=C-present**



- **Synthesis of the clinically relevant leukotrienes from arachidonic acid. Numerous stimuli (e.g. epinephrine, thrombin and bradykinin) activate phospholipase A2 which hydrolyzes arachidonic acid from membrane phospholipids. The leukotrienes are identified as LT. The leukotrienes, LTC4, LTD4, LTE4 and LTF4 are known as the peptidoleukotrienes because of the presence of amino acids. The peptidoleukotrienes, LTC4, LTD4 and LTE4 are components of slow-reacting substance of anaphylaxis The subscript 4 in each molecule refers to the number of -C=C-present**



FUNCTIONS

- **Alpha-linolenic acid (ALA)**
  - Presently, the only known function of ALA in humans is to serve as a precursor for the synthesis of the long-chain omega-3 fatty acids, EPA and DHA
- **Docosahexaenoic acid (DHA)**
  - ***Vision***
    - DHA is found in very high [ ] in the cell membranes of the **retina**, which conserves and recycles DHA even when omega-3 fatty acid intake is low. Studies in animals indicate that DHA is required for the normal development and function of the retina
    - Moreover, these studies suggest that there is a critical period during retinal development when inadequate DHA will result in permanent abnormalities in retinal function. Recent research indicates that DHA plays an important role in the regeneration of the visual pigment rhodopsin, which plays a critical role in the visual transduction system that converts light to vision
  - ***Nervous system function***
    - Several possible roles for DHA in the nervous system have been proposed. DHA can protect neurons cultured outside the body from **apoptosis** (programmed cell death), leading to the hypothesis that **high levels of DHA in the brain may serve to enhance the survival of neurons**. Increased incorporation of DHA into cell membranes is known to affect membrane physical properties, such as fluidity
    - Although DHA is thought to be important to neurologic function, the mechanisms of DHA action in the nervous system require further clarification

DEFICIENCY OF EFA

- Early in EFA deficiency, **plasma levels of linoleic and arachidonic acids are low,** and the **ω-9 eicosatrienoic** acid (5,8,11-20:3), an abnormal **by-product of oleic acid** desaturation, is present. An elevated triene/tetraene ratio in plasma usually is a sign of EFA deficiency
- Triene and tetraene refer to the number of double bonds in PUFAs. **A triene has 3 double bonds and a tetraene has 4 double bonds.** Arachidonate is the main tetraenoic FA in plasma, and it normally composes of 8-10% of the plasma FA
- Because little trienoic FA ordinarily is present in plasma, the normal triene/tetraene ratio is very low, about 0.1 to 0.2. This ratio becomes abnormally high in EFA deficiency
- Due to a lack of ω-6 FA, the arachidonate content of the plasma decreases and is replaced by ω-9 eicosatrienoic acid (5,8,11-20:3). → → this produces an increase in triene/tetraene ratio in plasma (this is one of the **clinical tests** that is used to establish a diagnosis of EFA deficiency). Evidence of EFA deficiency based on this ratio has been observed in patients with fat malabsorption, serious trauma, and burns
- Full-term babies fed a skim-milk formula low in linoleic acid may have growth failure, thrombocytopenia, alopecia, and a generalized scaly dermatitis, with increased water loss from the skin. This syndrome is reversed by linoleic acid supplementation
- Deficiency is unlikely to occur with balanced diets, although cow's milk has only about 25% of the amount of linoleic acid in human milk. Although total fat intake in many developing countries is very low, much of the fat is of vegetable origin and is rich in linoleic acid with some linolenic acid
- EFA deficiency used to be a hazard of long-term fat-free TPN, but fat emulsions, now in general use, prevent it
- **Patients with Cystic Fibrosis (CF):** Alterations in fatty acid metabolism have been extensively reported in plasma from CF patients. Some of these alterations are summarized here:
  - An increase in 20:3n-9 also known as eicosatrienoic acid or ETA; the 20 refers to the number of carbons, the 3 to the number of double bonds, and the n-9 to the corresponding pathway
  - A decrease in 18:2n-6 also known as linoleic acid; and
  - A decrease in 22:6n-3 also known as docosahexaenoic acid or DHA
  - These changes indicate that patients with CF have a defect in essential fatty acid metabolism

ADVERSE EFFECTS OF OVER-CONSUMPTION

- ***Gamma-Linolenic Acid (18:3n-6)***
  - Supplemental gamma-linolenic acid is generally well-tolerated, and serious adverse side effects have not been observed at doses up to 2.8 g/day for 12 months
  - High doses of borage seed oil, evening primrose oil or black currant seed oil may cause GI upset, loose stools or diarrhea
  - Because of case reports that supplementation with evening primrose oil induced seizure activity in people with undiagnosed temporal lobe epilepsy, people with a history of seizures or seizure disorder are generally advised to avoid evening primrose oil and other gamma-linolenic acid-rich oils
- **Alpha-Linolenic Acid (18:3n-3)**
  - Although flaxseed oil is generally well tolerated, high doses may cause loose stools or diarrhea. Allergic and **anaphylactic** reactions have been reported with flaxseed and flaxseed oil ingestion

By Monica Hsu

- **Eicosapentaenoic Acid (20:5n-3) and Docosahexaenoic Acid (22:6n-3)**
    - **Immune Function**
        - Although the suppression of inflammatory responses resulting from increased omega-3 FA intakes may benefit individuals with inflammatory or autoimmune diseases, anti-inflammatory doses of omega-3 FAs could decrease the potential of the immune system to destroy pathogens
        - Numerous studies have shown suppression of various aspects of human immune function in vitro or ex vivo in peripheral blood mononuclear cells, or in isolated neutrophils or monocytes, in subjects provided n-3 PUFA as a supplement or as an experimental diet compared with baseline value before the intervention
        - *The minimum dose observed for such an effect was 0.9 g/day of EPA and 0.6 g/day for DHA given as fish oil for 6 to 8 weeks to healthy adults*
        - *The level of EPA that caused immunosuppression ranged from 0.9 to 9.4 g/day, when fed for 3-24 weeks. The level of DHA that caused immunosuppression ranged from 0.6 to 6.0 g/day*
    - **Bleeding and increasing Risk of Hemorrhagic Stroke**
        - The US FDA has ruled that intakes up to 3 g/day of long-chain omega-3 fatty acids (EPA and DHA) are Generally Recognized As Safe (GRAS) for inclusion in the diet, and available evidence suggests that **intakes less than 3 g/day are unlikely to result in clinically significant bleeding**
        - Although the IOM did not establish a UL of intake for omega-3 FAs, caution was advised with the use of supplemental EPA and DHA, especially in those who are at increased risk of excessive bleeding
        - One of a number of factors that has been suggested with n-3 PUFA intake is reduced platelet aggregation, and therefore, prolonged bleeding time
        - Although prolonged bleeding times have been shown to be beneficial in preventing heart disease, bleeding time can become prolonged enough to result in excessive bleeding and bruising
        - Data on bleeding time are mixed and a dose-response effect was not observed. Although excessively prolonged bleeding time and increased incidence of bleeding have been observed in Greenland Eskimos, whose diet is rich in EPA and DHA, information is lacking to conclude that EPA and DHA were the sole basis for these observation
        - A number of short-term studies (4 to 11 weeks) have shown significant increased bleeding time with taking EPA/DHA supplements ranging from 2 to 15 g/day
        - Other studies using similar intake levels resulted in no difference
    - **Oxidative damage**
        - DHA and EPA are vulnerable to lipid peroxidation, resulting in oxidative damage of various tissues
        - Numerous feeding studies using laboratory animals have demonstrated increased lipid peroxidation and oxidative damage of erythrocytes, liver, and kidney membranes and bone marrow DNA with consumption of DHA
        - The oxidative damage was shown to be reduced or prevented with the co-consumption of vitamin E
    - CONCLUSION: EPA and DHA are available as dietary supplements and until more information is available on the adverse effects of EPA and DHA, use of these supplements should be taken with caution

DRUG INTERACTIONS

- Gamma-linolenic acid supplements, such as evening primrose oil or borage seed oil, **may increase the risk of seizures in people on phenothiazines, such as chlorpromazine**
- High doses of black currant seed oil, borage seed oil, evening primrose oil, flaxseed oil and fish oil may **inhibit platelet aggregation**, and should be used with caution in people on anticoagulant medications. In particular, people taking fish oil or long-chain omega-3 fatty acid (EPA and DHA) supplements in combination with anticoagulant drugs, including aspirin, copidogrel (Plavix), dalteparin (Fragmin), dipyridamole (Persantine), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid) and warfarin (Coumadin), should have their coagulation status monitored using a standardized prothrombin time assay (INR)
- One small study found that 3 g/day or 6 g/day of fish oil did not affect INR values in 10 patients on warfarin over a 4-week period
- However, a recent case report described an individual who required a reduction of her warfarin dose when she doubled her fish oil dose from 1-2 g/day

Overview of Essential Elements (Minerals)

- Can divide into macro *(>0.005% body weight)* and micro *(<0.005% body weight*), also called "trace"
- Functions include being part of essential compounds in body (Ca/P in bone, I in thyroxin, S in thiamin), cofactors in enzymes (metalloenzymes), facilitation of absorption, digestion, and transport, acid-base balance (acid- and alkali-forming foods), water balance, transmission of nerves, regulation of muscle contraction

	Major Minerals	**Minor Minerals**
Food Sources	Seafood, meat, and dairy products tend to be the best sources. Vegetables and legumes are sometimes good sources. Whole-grain products are better sources than milled products.	Amount often dependent on mineral content of soil. Found in all food groups. Whole-grain products tend to contain more than milled cereal products.
Digestion & Absorption	Very little is needed. Absorbed mostly in SI, but sometimes in LI. Bioavailability often influenced by nutritional status, and interactions with other dietary components.	Very little is needed. Absorbed mostly in SI, but also in stomach. Bioavailability often influenced by form, nutritional status, and interactions with other dietary components.
Circulation	Via blood	
Toxicity	Rare and usually associated with excess supplemental or medicinal intake.	
Functions	Many are cofactors for enzymes, some of which are involved in energy metabolism. Some have major structural roles such as maintaining bone and tooth health. Involved in muscle and nerve function. Electrolytes involved in fluid balance.	Many are cofactors for enzymes, some of which are involved in redox reactions. Some have structural roles (such as mineralization).

Water

- The vast majority of healthy people adequately meet their daily hydration needs by letting thirst be their guide. The **AI for total water intake** for young men and women (19-30 years) from a combination of drinking water, beverages, and food) is set based on the median total water intake from the U.S. data survey
- *For women at approximately 2.7 liters (91 ounces) of total water -- from all beverages and foods -- each day, and men an average of approximately 3.7 liters (125 ounces daily) of total water*. The panel did not set an upper level for water
- About 80% of people's total water intake comes from drinking water and beverages -- including caffeinated beverages -- and the other 20% is derived from food
- While concerns have been raised that caffeine has a diuretic effect, available evidence indicates that **this effect may be transient**, and there is **no convincing evidence that caffeine leads to cumulative total body water deficits**. Therefore, the panel concluded that when it comes to meeting daily hydration needs, caffeinated beverages can contribute as much as noncaffeinated options
- Prolonged physical activity and heat exposure will increase water losses and therefore may raise daily fluid needs. Some athletes who engage in strenuous activity and some individuals with certain psychiatric disorders occasionally drink water in excessive amounts that can be life-threatening. However, such occurrences are highly unusual

SODIUM

- Sodium found either as free in solution or as salt
- Salt (sodium chloride) is essential for life. The health implications of excess salt intake represent an area of controversy among scientists, clinicians, and public health experts

REQUIREMENT: AI

- **AI for sodium and sodium chloride (salt)** is based on the amount needed to replace losses through sweat in moderately active people and to achieve a diet that provides sufficient amounts of other essential nutrients

Life Stage	***Age***	***Males and Females: Sodium (g/day)***	***Males and Females: Salt (g/day)***
Infants	*0-6 months*	*0.12*	*0.30*
Infants	*7-12 months*	*0.37*	*0.93*
Children	*1-3 years*	*1.0*	*2.5*
Children	*4-8 years*	*1.2*	*3.0*
Children	*9-13 years*	*1.5*	*3.8*
Adolescents	*14-18 years*	*1.5*	*3.8*
Adults	*19-50 years*	*1.5*	*3.8*
Adults	*51-70 years*	*1.3*	*3.3*
Adults	*71 years and older*	*1.2*	*3.0*
Pregnancy	*14-50 years*	*1.5*	*3.8*
Breastfeeding	*14-50 years*	*1.5*	*3.8*

FOOD SOURCES

- Naturally found more in animal protein foods: milk, cheese, eggs, meat; also sea vegetables, celery (about 10% of intake in U.S.)
- Used in very large amounts in processing: smoked, cured, pickled foods, snack foods, salad dressings, sauces, commercial soups, some breakfast cereal (so about 75% of sodium in U.S. diets from processed foods or manufacturing)
- Other sources: cooking and added at the table (15% of intake), drinking water, baked goods (baking soda and powder), and MSG and foods containing it
- The lowest salt intakes are associated with diets that emphasize unprocessed foods, especially fruits, vegetables, and legumes. *Recent surveys have found that the average dietary salt intake in the U.S. is 7.8-11.8 grams/day for adult men and 5.8-7.8 grams/day for adult women*. These figures may be underestimations since they did not include salt added to food at the table
- *Healthy 19-50-year-old adults should consume 1.5 grams (65 mmol) of sodium and 2.3 grams (65 mmol) of chloride each day -- or 3.8 grams of salt -- to replace the amount lost daily on average through sweat and to achieve a diet that provides sufficient amounts of other essential nutrients*
- *The NHBPEP and the NHLBI recommend consuming no more than 6 grams/day of salt (~2.4 grams/day of sodium) to reduce the risk of hypertension and its complications*
- *Since the majority of sodium and chloride intake comes from salt, dietary salt content can be estimated from sodium content by multiplying sodium content by 2.5 (ex. 2,000 mg of sodium x 2.5 = 5,000 mg (5 g) of salt)*

High-Salt Foods				Low-Salt Foods			
Food	**Serving**	**Sodium (g)**	**Salt (g)**	**Food**	**Serving**	**Sodium (g)**	**Salt (g)**
Hot dog (beef)	1	0.46	1.2	Olive oil	1 tablespoon	0.000	0.000
Dill pickle	1 medium	0.83	2.1	Pear, raw	1 medium	0.000	0.000
Tomato juice, canned (salt added)	1 cup (8 fl. ounces)	0.88	2.2	Popcorn, air-popped (unsalted)	1 cup	0.000	0.000
Fish sandwich w/ tartar sauce & cheese	1 sandwich	0.94	2.4	Almonds (unsalted)	1 cup	0.001	0.003
Corn dog	1	0.97	2.4	Brown rice	1 cup, cooked	0.002	0.005
Corned beef hash	1 cup	1.0	2.5	Orange juice (frozen)	1 cup (8 fl ounces)	0.003	0.008
Ham	3 ounces	1.0	2.5	Mango	1 fruit	0.004	0.010
Pretzels, salted	2 ounces (10 pretzels)	1.0	2.5	Tomato	1 medium	0.011	0.028
Canned, chicken noodle soup	1 cup	1.1	2.8	Fruit cocktail, canned	1 cup	0.015	0.038
Macaroni and cheese, canned	1 cup	1.3	3.3	Potato chips, unsalted	8 ounces (1 bag)	0.018	0.045
Potato chips, salted	8 ounces (1 bag)	1.3	3.3	Carrot	1 medium	0.021	0.053
				Tomato juice, canned (no salt added)	1 cup (8 fl ounces)	0.024	0.060

This report present intake data primarily as g (mmol)/day of sodium and of Chloride, rather than g (mmol)/day of sodium chloride. To convert mmol to mg of sodium, chloride, or of sodium chloride, multiply mmol by 23, 35.5, or 58.5 (the molecular weight of sodium, chloride, and sodium chloride)

ABSORPTION, DISTRIBUTION, EXCRETION

- About 95% of ingested sodium is absorbed with the remaining 5% excreted in the feces
- 3 pathways for absorption
    1. **Na^+/glucose cotransport system**: absorbed rapidly in SI mainly by active transport. A carrier on the luminal membrane of the mucosal cell transports sodium together with a solute such as glucose into the cell. Once in the cell, Na^+ is pumped across the basolateral membrane by Na^+/K^+-ATPase, while glucose exits through the membrane by facilitated diffusion
    2. ***Electroneutral Na^+ and Cl^- cotransport system*** *is active in both the SI and the proximal portion of the colon. The cotransport of Na^+/H^+ exchange and a Cl^-/HCO^{3-} exchange. Sodium is then pumped basolaterally, with Cl^- diffusing passively*
    3. ***Electrogenic sodium absorption*** *mechanism is active in the colon. Sodium enters the luminal membrane via a Na^+ channel*
- *It is important to recognize that the main driving force for all these is the basolateral Na^+ pump – i.e. pumping sodium out of the enterocyte*

By Monica Hsu

FUNCTIONS OF SODIUM

- Sodium (Na^+) and chloride (Cl^-) are the principal **ions** in the fluid outside of cells, which includes blood **plasma**. Potassium is the principal positively charged ion (**cation**) inside of cells
- **Maintenance of membrane potential**
  - The [ ] differences between potassium and sodium across cell membranes create an electrochemical gradient known as the **membrane potential**
  - The cell's membrane potential is maintained by **ion** pumps in the cell membrane, especially the sodium, potassium-ATPase pumps. These pumps use **ATP** to pump sodium out of the cell in exchange for potassium.
  - Tight control of cell membrane potential is critical for nerve impulse transmission, muscle contraction, and cardiac function
- **Nutrient absorption and transport**
  - Absorption of sodium in the small intestine plays an important role in the absorption of chloride, **amino acids**, **glucose**, and water
  - Chloride, in the form of hydrochloric acid is also an important component of gastric juice
- **Maintenance of blood volume and blood pressure**
  - A number of physiological mechanisms that regulate blood volume and blood pressure work by adjusting the body's sodium content
  - In general, sodium retention results in water retention and sodium loss results in water loss
  - **Renin angiotensin-aldosterone-system**: In response to a significant decrease in blood volume or pressure (e.g, serious blood loss or dehydration), the kidneys release renin into the circulation
  - Renin is an **enzyme** that splits a small **peptide** (Angiotensin I) from a larger **protein** (angiotensinogen) produced by the liver
  - Angiotensin I is split into a smaller peptide (angiotensin II) by angiotensin converting enzyme (ACE), an enzyme present on the inner surface of blood vessels, and in the lungs, liver, and kidneys
  - Angiotensin II stimulates the constriction of small arteries, resulting in increased blood pressure. Angiotensin II is also a potent stimulator of aldosterone synthesis by the **adrenal glands**
  - Aldosterone is a **steroid hormone** that acts on the kidneys to increase the reabsorption of sodium and the excretion of potassium
  - Retention of sodium by the kidneys → increase water retention → increased blood volume and blood pressure
  - **Anti-diuretic hormone (ADH)**: Secretion of ADH by the posterior **pituitary gland** is stimulated by a significant decrease in blood volume or pressure. ADH acts on the kidney to increase the reabsorption of water

DEFICIENCY OF SODIUM (Hyponatremia)

- Hyponatremia is defined as a **serum** sodium [ ] of less than 136 mmol/liter, and may result from increased fluid retention or increased sodium loss
- **Conditions that increase the loss of sodium and chloride** include severe or prolonged vomiting or diarrhea, excessive and persistent sweating, the use of some diuretics, and some forms of kidney disease
- **Symptoms of hyponatremia** include headache, nausea, vomiting, muscle cramps, fatigue, disorientation, and fainting.
- **Complications of severe hyponatremia** may include cerebral edema (swelling of the brain), seizures, coma, and brain damage. Acute or severe hyponatremia may be fatal without prompt and appropriate medical treatment
- **Prolonged endurance exercise and hyponatremia**
  - Hyponatremia has recently been recognized as a potential problem in individuals competing in very long endurance exercise events, such as marathons, ultramarathons, and Ironman triathlons
  - *In 1997, 25 out of 650 participants in an Ironman triathlon (almost 4%) received medical attention for hyponatremia*
  - *Participants who developed hyponatremia during an Ironman triathlon had evidence of fluid overload despite relatively modest fluid intakes, suggesting that fluid excretion was inadequate*

TOXICITY OF SODIUM

- Ingestion of large amounts of salt may lead to nausea, vomiting, diarrhea, and abdominal cramps
- *The UL for salt is set at 5.8 grams per day. More than 95% of American men and 90% of Canadian men ages 31 to 50, and 75% of American women and 50% of Canadian women in this age range regularly consume salt in excess of the UL*
- Severe hypernatremia may result in edema (swelling), hypertension, rapid heart rate, difficulty breathing, convulsions, coma, and death
- *In end-stage renal disease, impaired urinary sodium excretion may lead to fluid retention, resulting in edema, high blood pressure, or congestive heart failure if salt and water intake are not restricted*
- *Health effects of excess dietary salt*
  - *Hypertension: salt sensitivity, salt and target organ damage, nutrient interactions and hypertension*
  - *Gastric (stomach) cancer*
  - *Osteoporosis*
  - *Kidney stones*

By Monica Hsu

POTASSIUM

- *American men consume just 2.8-3.3 g of potassium daily on average, and women get an average of only 2.2-2.4 g daily*

REQUIREMENT: AI

- *Adults should consume at least 4.7 grams (120 mmol) of potassium per day to lower blood pressure, blunt the effects of salt, and reduce the risk of kidney stones and bone loss. However, most American women 31 to 50 years old consume no more than half of the recommended amount of potassium, and men's intake is only moderately higher*
- *There was no evidence of chronic excess intakes of potassium in apparently healthy individuals and thus no UL was established*

Life Stage	***Age***	***Males (g/day)***	***Females (g/day)***
Infants	*0-6 months*	*0.4*	*0.4*
Infants	*7-12 months*	*0.7*	*0.7*
Children	*1-3 years*	*3.0*	*3.0*
Children	*4-8 years*	*3.8*	*3.8*
Children	*9-13 years*	*4.5*	*4.5*
Adolescents	*14-18 years*	*4.7*	*4.7*
Adults	*19 years and older*	*4.7*	*4.7*
Pregnancy	*14-50 years*	*-*	*4.7*
Breastfeeding	*14-50 years*	*-*	*5.1*

SOURCES

- **Food sources:** the richest sources of potassium are fruits and vegetables. Among foods with the highest amounts of potassium per calorie are spinach, cantaloupes, almonds, brussels sprouts, mushrooms, bananas, oranges, grapefruits, and potatoes
  - People who eat large amounts of fruits and vegetables have a high potassium intake (8-11 grams/day)
  - *In the U.S. the average dietary potassium intake in women is about 2,300 mg/day for adult women and 3,100 mg/day for adult men*

Food	Serving	Potassium (mg)	Food	Serving	Potassium (mg)
Banana	1 medium	467	Raisin bran cereal	1 ounce	437
Potato, baked with skin	1 medium	721	Artichoke, cooked	1 medium	425
Prune juice	6 fluid ounces	530	Lima beans, cooked	1/2 cup	478
Prunes, dried	1/2 cup	633	Acorn squash, cooked	1/2 cup (cubes)	448
Tomato juice	6 fluid ounces	400	Spinach, cooked	1/2 cup	419
Tomato	1 medium	273	Sunflower seeds	1 ounce	241
Raisins	1/2 cup	598	Almonds	1 ounce	211

- **Supplements:** *Multivitamin/mineral supplements do not contain more than 99 mg of potassium per serving*
  - Potassium supplements are available as a number of different salts, including potassium chloride, citrate, gluconate, bicarbonate, and aspartate

ABSORPTION, EXCRETION

- Readily absorbed (> 90%) in small intestine and colon
- It is believed that K^+ may be absorbed through the apical membrane of the colonic mucosal cell by a K^+/H^+-ATPase pump
- Freely filtered into glomerulus, reabsorbed easily, and about 10% enters distal tubule where it is regulated
- Small amount is excreted in the feces

FUNCTIONS OF POTASSIUM

- **Maintenance of membrane potential**
- **Cofactor for enzymes**: The presence of potassium is also required for the activity of pyruvate kinase, an important enzyme in **carbohydrate metabolism**

By Monica Hsu

DEFICIENCY OF POTASSIUM

- Hypokalemia is most commonly a result of excessive loss of potassium, e.g., from prolonged vomiting, the use of some **diuretics**, some forms of kidney disease, or disturbances of metabolism
- The **symptoms of hypokalemia** include fatigue, muscle weakness and cramps, and intestinal paralysis, which may lead to bloating, constipation, and abdominal pain
- **Severe hypokalemia** may result in muscular paralysis or cardiac **arrhythmias** (fatal)
- **Conditions that increase the risk of hypokalemia**
    - CHF, use of potassium-wasting diuretics (e.g., thiazide diuretics or furosemide)
    - Alcoholism, anorexia nervosa or bulimia
    - Severe vomiting or diarrhea, overuse or abuse of laxatives
    - In rare cases, habitual consumption of large amounts of black licorice has resulted in hypokalemia. Licorice contains a compound (glycyrrhizic acid) with similar physiologic effects to those of aldosterone, a **hormone** that increases urinary excretion of potassium

TOXICITY OF POTASSIUM

- Hyperkalemia occurs when potassium intake exceeds the capacity of the kidneys to eliminate it
- Symptoms of hyperkalemia may include tingling of the hands and feet, muscular weakness, and temporary paralysis. The most serious complication of hyperkalemia is the development of cardiac **arrhythmia**, which can lead to cardiac arrest

DISEASE PREVENTION AND TREATMENT

- *High blood pressure, stroke, osteoporosis, kidney stones*

MAGNESIUM

- *The adult human body contains about 25 g of magnesium. Over 60% of all the magnesium in the body is found in the skeleton, about 27% is found in muscle, while 6-7% is found in other cells, and less than 1% is found outside of cells*

REQUIREMENT: RDA

- ***Men 19 through 30 years of age:*** *400 milligrams (mg)/day*
- ***Women 19 through 30 years of age:*** *310 mg/day*
- ***Men 31 years of age and older:*** *420 mg/day*
- ***Women 31 years of age and older:*** *320 mg/day*
- *A large national survey indicated that the average magnesium intake for men (about 320 mg/day) and the average intake for women (about 230 mg/day) were significantly below the RDA*

FOOD SOURCES

- Because magnesium is part of chlorophyll, the green pigment in plants, green leafy vegetables are rich in magnesium
- Unrefined grains and nuts also have high magnesium content, while refined foods generally have the lowest magnesium content. Meats and milk have intermediate magnesium content
- Water is a variable source of intake; harder water usually has a higher [ ] of magnesium salts

Food	Serving	Magnesium (mg)	Food	Serving	Magnesium (mg)
100% Bran Cereal (e.g., All Bran)	1/2 cup	128.7	Lima beans	1/2 cup cooked	62.9
Oat bran	1/2 cup dry	96.4	Spinach, chopped	1/2 cup cooked	78.3
Brown rice	1 cup cooked	83.8	Swiss chard, chopped	1/2 cup cooked	75.2
Almonds	1 ounce (22 almonds)	81.1	Molasses, blackstrap	1 tablespoon	43.0
Hazelnuts	1 ounce	49.0	Banana	1 medium	34.2
Peanuts	1 ounce	49.8	Milk 1% fat	8 fluid ounces	33.7

ABSORPTION

- Generally 30-65% of Mg is thought to be absorbed in adult with normal intake
- Absorption mainly in jejunum and ileum
- Mg absorption is more efficient when Mg status is poor or marginal and/or when Mg intake is low *(65% of Mg is absorbed with an intake of 36 mg versus only 11% absorption with an intake of 973 mg)*
- Two systems: carrier mediated and saturable at low [ ] and simple diffusion at higher [ ]

TRANSPORT, STORAGE, EXCRETION

- In plasma 55% free, 32% bound to protein
- 70-80% is filtered by the kidney, but 95%-97% reabsorbed → 3-5% of the filtered Mg is excreted in the urine
- 25-50 mg/day of Mg may be excreted daily in feces, and may be lost in the sweat (15 mg/day)

NUTRIENT INTERACTIONS

- **Zinc**: high doses of zinc in supplement (142 mg/day) in healthy adult males significantly decreased magnesium absorption
- **Fiber**: large increase in dietary fiber intake have been found to decrease magnesium utilization in experimental studies
- **Protein**: dietary protein may affect magnesium absorption. One study found that magnesium absorption was lower when protein intake was less than 30 grams/day, and higher protein intakes (93 grams/day vs. 42 grams/day) were associated with improved magnesium absorption in adolescents
- **Vitamin D and calcium**: active form of vitamin D (calcitriol) may increase the intestinal absorption of magnesium to a small extent. Inadequate blood magnesium levels are known to result in low blood calcium levels, and resistance to PTH
- **Unabsorbed FA** present in high quantities, as occur with steatorrhea, may bind to Mg, as to calcium, to form soaps. These Mg-FA soaps are excreted in the feces

FUNCTIONS OF MAGNESIUM

- **Energy production**
  - Mg is required by the ATP synthesizing protein in mitochondria. ATP exists primarily as a complex with magnesium (MgATP)
  - Mg is involved in more than 300 essential metabolic reactions
    - Glycolysis (hexokinase and phosphofructokinase)
    - Kreb's cycle (oxidative decarboxylation)
    - Hexose monophosphate shunt (transketolase)
    - Creatine phosphate formation (creatine kinase)
    - Beta-oxidation of fatty acids (acyl CoA synthase)
- **Synthesis of essential molecules**
  - Mg is required at a number of steps during the synthesis of **nucleic acids (DNA and RNA)** and proteins
  - Glutathione, an important **antioxidant**, requires magnesium for its synthesis
- **Structural roles**
  - Mg plays a structural role in bone, **cell membranes**, and **chromosomes**
- **Ion transport across cell membranes**
  - Mg is required for the active transport of **ions** like potassium and calcium across cell membranes
  - Through its role in ion transport systems, magnesium affects the conduction of nerve impulses, muscle contraction, and the normal rhythm of the heart
- **Cell signaling**
  - **Cell signaling** requires MgATP for the **phosphorylation** of proteins and the formation of the cell signaling molecule, cyclic adenosine monophosphate (cAMP)
  - cAMP is involved in many processes, including the secretion of PTH from the **parathyroid glands**

DEFICIENCY OF MAGNESIUM

- Magnesium deficiency in healthy individuals who are consuming a balanced diet is quite rare because magnesium is abundant in both plant and animal foods and because the kidneys are able to limit urinary excretion of magnesium when intake is low
- **GI disorders**: prolonged diarrhea, Crohn's disease, malabsorption syndrome, surgical removal of a portion of the intestine, and intestinal inflammation due to radiation may all lead to magnesium depletion
- **Renal disorders (magnesium wasting)**: **Diabetes mellitus** and long-term use of certain diuretics may result in increased urinary loss of magnesium
- **Chronic alcoholism**: poor dietary intake, GI problems, and increased urinary loss of magnesium may all contribute to magnesium depletion, which is frequently encountered in alcoholics
- **Age**: several studies have found that elderly people have relatively low dietary intakes of magnesium. Because intestinal magnesium absorption tends to decrease and urinary magnesium excretion tends to increase in older individuals, suboptimal dietary magnesium intake may increase the risk of magnesium depletion in the elderly
- **Hypocalcemia**: over time blood calcium levels also began to decrease despite adequate dietary calcium. Hypocalcemia persisted despite increased PTH secretion
  - Usually, increased PTH secretion quickly results in the mobilization of calcium from bone and normalization of blood calcium levels
  - As the magnesium depletion progressed, PTH secretion diminished to low levels. Along with hypomagnesemia, signs of severe magnesium deficiency included hypocalcemia, hypokalemia, retention of sodium, low circulating levels of PTH, neurological and muscular symptoms (tremor, muscle spasms, tetany), loss of appetite, nausea, vomiting, and personality changes

TOXICITY OF MAGNESIUM

- Adverse effects have **not** been identified from magnesium occurring naturally in food, and have been observed with intakes of various supplemental magnesium salts.
- Symptoms include diarrhea, a well known side effect of magnesium, which is used therapeutically as a laxative (Individuals with impaired kidney function are at higher risk for adverse effects from magnesium supplementation)
- Some of the **later effects** of magnesium toxicity, such as lethargy, confusion, disturbances in normal cardiac rhythm, and deterioration of kidney function, are related to severe hypotension
- As hypermagnesemia progresses muscle weakness and difficulty breathing may occur. Severe hypermagnesemia may result in cardiac arrest

CALCIUM

INTRODUCTION

- Calcium is the most common mineral in the human body
- About 99% of the calcium in the body is found in bones and teeth, while the other 1% is found in the blood and soft tissue
- Calcium levels in the blood and extracellular fluid must be maintained within a very narrow [ ] range for normal physiological functioning

REQUIREMENT: AI

- *FNB set the AI rather than the RDA which reflects the difficulty of estimating the intake of dietary calcium when other factors such as genetics, hormones, and physical activity, also interact to affect bone health*

Age and life stage group	***Adequate intake level (mg/day)***
9-18 years	*1,300*
19-50 years	*1,000*
51 years and older	*1,200*
Pregnancy: 18 years and younger	*1,300*
Pregnancy: 19 years and older	*1,000*
Breastfeeding: 18 years and younger	*1,300*

FOOD SOURCES

- Average dietary intakes of calcium in the U.S. are well below the levels recommended by the FNB for every age and gender group, especially in females
- *Only about 25% of boys and 10% of girls aged 9 to 17 are estimated to meet the FNB recommendations. Dairy foods provide 75% of the calcium in the American diet*

Food	Serving	Elemental Calcium (mg)	% Calcium Absorbed	Estimated Absorbable Ca (mg)	Servings needed to equal 8 oz of milk
Milk	8 ounces	300	32	96	1.0
Yogurt	8 ounces	300	32	96	1.0
Cheddar cheese	1.5 ounces	303	32	97	1.0
Cheese food	1.5 ounces	241	32	77	1.2
Pinto beans	1/2 cup, cooked	45	27	12	8.1
Red beans	1/2 cup, cooked	41	24	10	9.7
White beans	1/2 cup, cooked	113	22	25	3.9
Tofu, calcium set	1/2 cup	258	31	80	1.2
Bok choy	1/2 cup, cooked	79	54	43	2.3
Kale	1/2 cup, cooked	61	49	30	3.2
Chinese cabbage	1/2 cup, cooked	239	40	95	1.0
Broccoli	1/2 cup, cooked	35	61	22	4.5
Spinach	1/2 cup, cooked	115	5	6	16.3
Rhubarb	1/2 cup, cooked	174	9	10	9.5
Fruit punch with calcium citrate	8 ounces	300	52	156	0.62

SUPPLEMENTS

- Most experts recommend obtaining as much calcium as possible from foods, because calcium in foods is accompanied by other important nutrients that assist the body in utilizing calcium
- Calcium supplements may be necessary for those who have difficulty consuming enough calcium from foods. No multivitamin/multimineral tablet contains 100% of the recommended daily value for calcium because it is **too bulky**, and the resulting pill would be too large to swallow
- Calcium supplements come in several forms: **Calcium carbonate** (40% elemental calcium), **Calcium citrate** (21% elemental calcium), **Calcium lactate** (13% elemental calcium), and **Calcium gluconate** (9% elemental calcium)

By Monica Hsu

FACTORS THAT ENHANCE CALCIUM ABSORPTION

- **Vitamin D** enhances calcium absorption. 1,25-Dihydroxyvitamin D, the major metabolite, stimulates active transport of calcium in the small intestine and colon
    - Deficiency of 1,25-dihydroxyvitamin D, caused by inadequate dietary vitamin D, inadequate exposure to sunlight, impaired activation of vitamin D, or acquired resistance to vitamin D, results in reduced calcium absorption
- **Lactose** appears to improve calcium absorption possiblly by improving solubility (more pronounced in infants than adults)

FACTORS THAT DECREASE CALCIUM AVAILABILITY

- **Oxalic acid**, also known as oxalate, is the most potent inhibitor of calcium absorption (may chelates Ca and increase fecal excretion of the complex), and is found in **high** [ ] in spinach, rhubarb, Swiss chard, and beetroot; **moderate** [ ] in peanuts, okra, eggplant, and squash; and **somewhat lower** [ ] in sweet potato and dried beans
- **Phytic acid** is a less potent inhibitor of calcium absorption than oxalic acid. Yeast possess an enzyme (phytase) which breaks down phytic acid in grains during fermentation, lowering the phytic acid content of breads and other fermented foods
    - Only concentrated sources of phytate such as wheat bran or dried beans substantially reduce calcium absorption
    - Fiber may decrease calcium absorption. Nonfermentable fiber (cellulose or those found in wheat bran) can increase bulk and decrease transit time → decreasing the time available for calcium absorption
- **Caffeine**: Caffeine in large amounts increases urinary calcium for a short time. On average, one 8-ounce cup of coffee decreases calcium retention by only 2-3 mg. One observational study found accelerated bone loss in postmenopausal women who consumed less than 744 mg of calcium per day and reported that they drank 2-3 cups of coffee per day
- **Magnesium** and Ca compete with each other for absorption whenever an excess of either is present in the GI tract
- **Sodium**: Increased sodium intake results in increased loss of calcium in the urine, possibly due to competition between sodium and calcium for reabsorption in the kidney. Each 2.3 gram increment of sodium (6 grams of salt; NaCl) excreted by the kidney has been found to draw about 24-40 mg of calcium into the urine. In adult women, each extra gram of sodium consumed per day is projected to produce an additional rate of bone loss of 1% per year if all of the calcium loss comes from the skeleton
- **Phosphorus**: A dietary calcium:phosphorus ratio of 1:1 is recommended. Diets high in phosphorus and low in calcium (4:1 ratio) have been found to increase PTH secretion (secondary hyperpapathyroidism). The substitution of large quantities of soft drinks for milk or other sources of dietary calcium is cause for concern with respect to bone health in adolescents and adults
- **Fat malabsorption** (steatorrhea > 7g of fecal fat/day) can interfere with Ca absorption through the formation of insoluble soaps (Ca-FA complex) in the lumen of the SI. These Ca soaps cannot be absorbed and are excreted in the feces
- **Protein**: As dietary protein intake increases, the urinary excretion of calcium also increases. Because only 30% of dietary calcium is generally absorbed, each one-gram increase in protein intake/day would require an additional 5.8 mg of calcium/day to offset the calcium loss

DIGESTION, ABSORPTION

- Absorption can vary from 10% to 75% (75% children); 25-35% usual diet
- Calcium can only absorb in its ionized form (Ca^{2+}), so it must first be released from the salts. Calcium is solubilized from most calcium salts in about 1 hour, preferably under acidic conditions
- **Absorption in the Small and Large Intestines: Two main absorption processes**
- **First**
    - In duodenum and proximal jejunum, there is a saturable, energy-requiring, process with special calcium binding protein (CBP or calbindin), regulated by calcitriol (1,25[OH]2D3)
    - For calcium to be absorbed by this active process, three sequential steps must occur:
        - Entry at the brush border
        - Intracellular movement, and
        - Extrusion at the basolateral membrane
    - The CBP carries the Ca to the basal membrane of the enterocyte where it is extruded into the extracellular fluid. The extrusion of Ca from the enterocyte into the extracellular fluid requires ATP and vitamin D-regulated Ca^{2+}-Mg^{2+} ATPase, an enzyme that hydrolyze ATP and release energy for pumping Ca^{2+} outside the cell, as Mg^{2+} moves in. Sodium is also exchanged for Ca^{2+}
- **Second**
    - There is also some passive, paracellular uptake mainly in jejunum and ileum
    - Increased absorption via this mechanism becomes possible when there is an increased intake of Ca
    - Small amounts of calcium (4%) may be absorbed from colon (around 8 mg/day) but maybe more in people who are absorbing less Ca in the SI. Bacteria in the colon may release Ca bound to some fermentable fibers such as pectin
- **Transport**
    - Ca is transported in the blood in 3 forms
        - About 40% bound to proteins, mainly albumin and prealbumin
        - Up to 10% with sulfate, phosphate, or citrate
        - About 50% free (ionized)
- **Excretion**
    - Lose about 100-150 mg/day in feces, about 60 mg/day in perspiration
    - In kidneys it is filtered and 99% reabsorbed, 1% (about 100-240mg/day) excreted

FUNCTIONS OF CALCIUM

- **Bone mineralization**
  - Calcium is a major structural element in bones and teeth. The mineral component of bone consists mainly of **hydroxyapatite** crystals, which contain large amounts of calcium and phosphorus (about 40% calcium and 60% phosphorus)
  - 60-66% of the weight of the bones is due to minerals, with the remaining 34-40% of bone weight due to water and protein
  - Protein in bone includes collagen, osteonectin (phosphoprotein that binds both calcium and collagen), osteopontin, osteocalcin, and MGP (matrix Gla protein)
  - Bone cells called **osteoclast** begin the process of remodeling by dissolving or resorbing bone. Bone-forming cells called **osteoblasts** then synthesize new bone to replace that which was resorbed
  - As the osteoblasts secrete the proteins and mineralization occurs, the osteoblasts become embedded in the proteins and matrix. Osteoclasts respond to PTH, calcitriol, and calcitonin
- **Intracellular messenger**
  - Calcium plays a role in mediating the constriction and relaxation of blood vessels, nerve impulse transmission, and muscle contraction
  - **3 calcium-binding proteins**
    - **Troponin-c** (found in skeletal muscle): skeletal muscle stimulated by nerve impulses (acetylcholine) triggers increased [ ] of calcium. The calcium can then bind to troponin-c allowing muscle contraction
    - **Calmodulin**: The binding of calcium to calmodulin activates enzymes that breakdown muscle glycogen to provide energy for muscle contraction
    - **Calbindin** is synthesized in response to calcitriol and is associated with increased absorption of calcium in the intestine
- **Cofactor for enzymes and proteins**
  - The binding of calcium **ions** is required for the activation of the "vitamin K-dependent" clotting factors in the **coagulation** cascade
- **Hormonal control and regulation of calcium levels**
  - When blood calcium decreases, calcium-sensing proteins in the parathyroid glands send signals resulting in the secretion of PTH
  - PTH stimulates the conversion of vitamin D to its active form, calcitriol, in the kidneys. Calcitriol increases the absorption of calcium from the small intestine. Together with PTH, calcitriol stimulates the release of calcium from bone by activating **osteoclasts** (bone resorbing cells), and decreases the urinary excretion of calcium by increasing its reabsorption in the kidneys. When blood calcium rises to normal levels, the parathyroid glands stop secreting PTH and the kidneys begin to excrete any excess calcium in the urine

DEFICIENCY OF CALCIUM

- Tetany, muscle pain, and paresthesias (numbness or tingling in the hands and feet)

TOXICITY OF CALCIUM

- **Toxicity:** Abnormally elevated blood calcium (hypercalcemia) resulting from the over consumption of calcium has **never been documented** to occur from foods, only from calcium supplements
- **Mild hypercalcemia**: may result in loss of appetite, nausea, vomiting, constipation, abdominal pain, dry mouth, thirst, and frequent urination
- **Severe hypercalcemia**: may result in confusion, delirium, coma, and if not treated, death
- *The FNB set the UL of intake for calcium at 2,500 mg of calcium/day*

NUTRIENT INTERACTIONS

- The presence of calcium decreases iron absorption from non-heme sources (i.e., most supplements and food sources other than meat)
- Individuals taking iron supplements should take them two hours apart from calcium rich foods or supplements to maximize iron absorption

By Monica Hsu

PHOSPHOROUS

- Phosphorus is an essential mineral that is required by every cell in the body for normal function. The majority of the phosphorus in the body is found as phosphate (PO_4). Approximately 85% of the body's phosphorus is found in bone

REQUIREMENT: RDA

- ***Adult men and women ages 19 through 50 years:*** *700 mg phosphorus/day*
- ***Adult men and women ages 51 years and over:*** *580 mg phosphorus/day*

FOOD SOURCES

- Dairy products, meat, and fish are particularly rich sources of phosphorus. Phosphorus is also a component of many polyphosphate food additives, and is present in most soft drinks as phosphoric acid
- *The average phosphorus intake in US men is 1495 mg daily and in women is 1024 mg/day*
- The phosphorus in all plant seeds (beans, peas, cereals, and nuts) is present in a storage form of phosphate called phytic acid or phytate. Only about 50% of the phosphorus from phytate is available to humans because we lack enzymes (phytases) that liberate it from phytate
- Yeasts possess phytases, so whole grains incorporated into leavened breads have more bioavailable phosphorus than whole grains incorporated into breakfast cereals or flat breads

Food	Serving	Phosphorus (mg)	Food	Serving	Phosphorus (mg)
Milk, skim	8 ounces	247	Fish, halibut	3 ounces, cooked	242
Yogurt, plain nonfat	8 ounces	383	Fish, salmon	3 ounces, cooked	252
Cheese, mozarella; part skim	1 ounce	131	Bread, whole wheat	1 slice	64
Egg	1 large, cooked	104	Carbonated cola drink	12 ounces	44
Beef	3 ounces, cooked	173	Almonds	1 ounce	139
Chicken	3 ounces, cooked	155	Peanuts	1 ounce	101
Turkey	3 ounces, cooked	173	Lentils	1/2 cup, cooked	356

DIGESTION, ABSORPTION, TRANSPORT, EXCRETION

- Phosphorous in food exists as inorganic and organic forms (e.g. phosphoproteins, phospholipids)
- Most phosphorous is absorbed in its inorganic form – there are phosphatases in the lumen of the SI, such as
    - **Phospholipase C** hydrolyzes phosphate from phospholipids
    - **Alkalin phosphatase**, a Zn-dependent enzyme whose activity is stimulated by calcitriol, functions at the brush border of the SI to free phosphorous from its bound form
- About 50-70% of phosphorous is absorbed with normal intake, and up to 90% when intake is low
- We don't know if active transport or diffusion
- Vitamin D (calcitriol) increases absorption, and dietary Ca, Mg, and Al reduces absorption
- 70% of phosphorous in blood is found as part of phospholipid. The remaining 30%, may be bound to protein, bound to Ca, Mg, or as inorganic phosphates
- 65-90% of phosphorous is excreted in inorganic form in the urine. The remaining 10-30% is excreted in the feces

FUNCTIONS OF PHOSPHORUS

- Phosphorus is a major structural component of bone in the form of a calcium phosphate salt called **hydroxyapatite**
- **Phospholipids** (e.g., phosphatidylcholine) are major structural components of **cell membranes**
- All energy production and storage are dependent on **phosphorylated** compounds, such as **ATP** and **creatine phosphate**
- **Nucleic acids** (**DNA** **and** **RNA**) are long chains of phosphate-containing molecules

DEFICIENCY OF PHOSPHORUS

- Inadequate phosphorus intake results in abnormally low blood phosphate levels (hypophosphatemia)
- The effects of hypophosphatemia may include loss of appetite, **anemia**, muscle weakness, bone pain, **rickets** (in children), **osteomalacia** (in adults), increased susceptibility to infection, numbness and tingling of the extremities, and difficulty walking. Severe hypophosphatemia may result in death

By Monica Hsu

TOXICITY OF PHOSPHORUS

- **Is high phosphorus intake detrimental to bone health?**
  - High amounts of phosphates in the diet can be attributed to phosphoric acid in soft drinks and phosphate additives in a number of commercially prepared foods
  - Because phosphorus is not as tightly regulated by the body as calcium, blood phosphate levels can rise slightly with a high phosphorous diet, especially after meals. High blood phosphate levels → reduce the formation of the active form of vitamin D (calcitriol) in the kidneys → reduce blood calcium, and lead to → increased PTH release. Elevated PTH levels could have an adverse effect on bone mineral content. High dietary phosphorus leads to high serum phosphorus, which leads to increased urinary phosphorus excretion
  - The amount of dietary phosphorus and absorbed phosphorus has approximately a linear relationship with urinary phosphorus if the amount of phosphorus filtered is greater than the tubular maximum for phosphorus. (the tubular maximum for phosphorus [TmP] is the amount (mmol) of phosphorus reabsorbed per unit time
  - PTH [ ] are inversely related to TmP. Therefore, high levels of PTH decrease TmP and thus increase the amount of phosphorus excreted in the urine
- Because the kidneys are very efficient at eliminating excess phosphate from the circulation, hyperphosphatemia from dietary causes is a problem mainly in people with severe kidney failure (end-stage renal disease)
- When kidney function is only 20% of normal, even typical levels of dietary phosphorus may lead to hyperphosphatemia. Pronounced hyperphosphatemia has also occurred due to increased intestinal absorption of phosphate salts taken by mouth, as well as due to colonic absorption of the phosphate salts in enemas
- ***Men and women 19 through 70 years:*** *4.0 grams (4000 milligrams) of phosphorus/day*
- ***Men and women over 70 years:*** *3.0 grams (3000 milligrams) of phosphorus/day*

IRON

INTRODUCTION

- Iron is an essential component of hundreds of proteins and **enzymes**. About 2-4g in body
- Can divide into functional and non-functional iron (storage)
  - ***Functional** includes hemoglobin, myoglobin, and metallo-enzymes
  - ***Nonfunctional** iron includes storage in liver, spleen, and bone marrow (ferritin and hemosiderin)
- About 65% in hemoglobin, 10% myoglobin, 1-5% as part of enzymes, rest in blood/storage; in body and food only found in **Fe^{3+} (ferric) and Fe^{2+} (ferrous)** forms

REQUIREMENT: RDA

Age and Life Stage Group	*RDA for Males (mg/day)*	*RDA for Females (mg/day)*
0-6 months	*0.27 (AI)*	*0.27 (AI)*
7-12 months	*11*	*11*
1-3 years	*7*	*7*
4-8 years	*10*	*10*
9-13 years	*8*	*8*
14-18 years	*11*	*15*
19-50 years	*8*	*18*
51 years and older	*8*	*8*
Pregnancy all ages	*-*	*27*

SOURCES

- **Food Sources:** The amount of iron in food (or **supplements**) that is absorbed and used by the body is influenced by the iron nutritional status of the individual and whether or not the iron is in the form of **heme**
- **Heme iron:** Heme iron comes mainly from **hemoglobin** and **myoglobin** in meat, poultry, and fish. Heme iron may provide up to **one-third** of total absorbed dietary iron
- **Nonheme iron:** Plant foods (nuts, fruits, vegetables, grains, and tofu), dairy products (milk, cheese, and eggs), and iron salts added to foods are all sources of nonheme iron. The absorption of nonheme iron is strongly influenced by enhancers and inhibitors present in the same meal
- *U.S surveys indicate that the average dietary iron intake is 16-18 mg/day in men, 12 mg/day in pre- and postmenopausal women, and about 15 mg/day in pregnant women*
- Thus, the majority of premenopausal and pregnant women in the U.S. consume less than the RDA for iron and many men consume more than the RDA

By Monica Hsu

Food	Serving	Iron content (mg)	Food	Serving	Iron content (mg)
Beef	3 ounces, cooked	2.31	Raisin bran cereal	1 cup, dry	5.00
Chicken, dark meat	3 ounces, cooked	1.13	Raisins, seedless	1 small box (1.5 ounces)	0.89
Oysters	6 medium	5.04	Potato, with skin	1 medium potato, baked	2.75
Shrimp	8 large, cooked	1.36	Kidney beans	1/2 cup, cooked	2.60
Tuna, light	3 ounces, canned	1.30	Lentils	1/2 cup, cooked	3.30
Black-strap molasses	1 tablespoon	3.50	Tofu, firm	1/4 block (~1/2 cup)	6.22
			Cashew nuts	1 ounce	1.70

- **Supplements:** Individuals who are not at risk of iron deficiency **should not** take iron supplements without an appropriate medical evaluation for iron deficiency

Iron Supplement	***% Elemental Iron***
Ferrous sulfate	*33%*
Ferrous gluconate	*12%*
Ferrous fumarate	*33%*

DIGESTION, ABSORPTION

- **Heme iron**
  - Heme iron is hydrolyzed from the globin part of hemoglobin and myoglobin by proteases from stomach and SI → heme iron is released
  - Heme iron is absorbed intact as a metalloporphyrin into the mucosal cell of the SI
  - Proportion of heme iron absorbed depends mainly on iron status, usually 15-35% in persons who are iron-deficient
  - Iron absorption occur throughout the SI but more efficient in duodenum
  - Within the mucosal cell the absorbed heme porphyrin ring is hydrolyzed by heme oxygenase into inorganic ferrous iron and protoporphyrin
  - The released iron is used by the intestinal mucosal cell or following transport through the intestinal cell and subsequent transport through the blood is used by other tissues
- **Nonheme Iron**
  - Non-heme iron is also usually bound to protein or other food components and must be enzymatically liberated by gastric secretions such as protease and HCl (HCl and pepsin aid in the release of nonheme iron from food component)
  - Once released from food, most nonheme iron is present as ferric (Fe^{+3}) iron in the stomach
  - In the acidic environment of the stomach, much of the ferric iron may be reduced to the ferrous state. As ferrous move to the alkaline environment in the SI, some ferrous iron may be oxidized to become ferric iron
  - Ferric iron may further complex to produce Fe(OH)3 (ferric hydroxide is relatively insoluble and tend to precipitate → less iron available for absorption)
  - Ferrous ion is absorbed much better than ferric – there are specific receptors on the enterocyte for ferrous (a membrane protein known as **integrin** is thought to facilitate iron absorption at the brush border of the enterocyte)
  - Mechanisms of absorption of ferric iron are not well understood, but chelation by ligands is thought to be involved
  - It is free iron, not chelated iron that is absorbed into the enterocyte

TRANSPORT AND STORAGE

- **Iron in the Enterocyte**
  - The heme protoporphyrin ring is hydrolyzed in enterocyte by heme oxidase into inorganic ferrous (the non-heme is mainly as ferrous ion) and protophorphyrin
  - The iron can be (a) transported to the blood; (b) stored in the enterocyte; or (c) used by the enterocyte
    - If transported to blood, Fe leaves the basolateral side of the enterocyte in ferrous form (i.e. it is oxidized in the cell)
    - Can store Fe in enterocyte by being incorporated into apoferritin to make ferritin (in ferric form) and can be then be excreted when enterocyte is shed (2-3 days)
    - May use iron in enterocyte, especially as cofactor for enzymes
- **Iron in the Blood**
  - After secretion from the basolateral membrane of the enterocyte, Fe is attached in blood to transferrin; need a copper–dependent enzyme (ceruloplasmin) to convert ferrous to ferric form (need ferric form for proper binding)
- **Storage**
  - Stored in liver hepatocytes (about 60%) and (about 40%) in reticuloendothelial cells (in liver, spleen, bone marrow)
  - The main storage form of iron in cells is as ferritin, which is synthesized in liver, spleen and bone marrow and consists of apoferritin (iron molecule which have been deposited)
  - Iron can also be stored as hemosiderin (probably a degradation product of ferritin)
  - To release Fe from ferritin, need to reduce it (so FMN, NAD, or ascorbate) from ferric to ferrous and reoxidize it to ferric to bind with transferring for transport to tissue

- **Enhancers of nonheme iron absorption**
  - **Vitamin C (ascorbic acid):** Vitamin C strongly enhances the absorption of nonheme iron by reducing dietary ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) and forming an absorbable iron-ascorbic acid complex
  - **Other organic acids:** Citric, malic, and lactic acids have some enhancing effects on nonheme iron absorption
  - **Meat, fish, and poultry (MFP):** Aside from providing highly absorbable heme iron, meat, fish, and poultry also enhance nonheme iron absorption. The mechanism for this enhancement of nonheme iron absortion is not clear
- **Inhibitors of nonheme iron absorption**
  - **Phytic acid (phytate):** Phytic acid is present in **legumes**, grains, and rice
    - Small amounts of phytic acid (5-10 mg) can reduce nonheme iron absorption by 50%. Absorption of iron from legumes, such as soybeans, black beans, lentils, and split peas, has been shown to be as low as 2%
  - **Polyphenols**, found in some fruits, vegetables, coffee, tea, wines, and spices, can markedly inhibit the absorption of nonheme iron
  - **Soy protein,** such as that found in tofu**,** has an inhibitory effect on iron absorption that is independent of its phytic acid content

FUNCTIONS OF IRON

- **Oxygen transport and storage**
  - Hemoglobin and myoglobin are heme-containing proteins that are involved in the transport and storage of oxygen
- **Electron transport and energy metabolism**
  - Cytochromes are **heme**-containing compounds that are critical to cellular energy production. They serve as electron carriers during the synthesis of **ATP**
- **Antioxidant and beneficial prooxidant functions**
  - Catalase and peroxidase are heme-containing **enzymes** that protect against the accumulation of hydogen peroxide, a potentially damaging ROS, by converting it to water and oxygen
- **DNA synthesis**
  - Ribonucleotide reductase is an iron-dependent enzyme that is required for **DNA** synthesis
- **Iron in Enzyme**
  - phenylalanine mono-oxygenase (synthesis of tyrosine from phe for neurotransmitter synthesis)
  - tryptophan dioxygenase (amino acid metabolism)
  - trimethyl lysine dioxygenase (carnitine synthesis)
  - lysine dioxygenase (collagen synthesis)
  - beta-carotene dioxygenase (Vitamin A synthesis from beta-carotene)
  - *catalase (conversion of hydrogen peroxide to water)*
  - *xanthine oxidase (purine catabolism)*
  - *ribonucleotide reductase (for DNA synthesis)*
  - *glycerol phosphate dehyrogenase (glycolysis)*
  - *NADH dehyrogenase (electron transport chain)*
  - *aconitase (conversion of citrate to isocitrate in Krebs cycle)*
  - *thyroperoxidase (for synthesis of thyroid hormones)*

NUTRIENT INTERACTIONS

- **Iron and vitamin A:** vitamin A deficiency may exacerbate iron deficiency anemia. Vitamin A supplementation has been shown to have beneficial effects on iron deficiency anemia and improve iron **status** among children and pregnant women
  - Combination of vitamin A and iron seems to reduce anemia more effectively than either iron or vitamin A alone
- **Iron and copper:** adequate copper nutritional **status** is necessary for normal iron metabolism and RBC formation
  - **Anemia** is a clinical sign of copper deficiency. Iron has been found to accumulate in the livers of copper deficient animals, indicating that copper is required for iron transport to the bone marrow for RBC formation
- **Iron and zinc:** High doses of iron supplements taken together with zinc **supplements** on an empty stomach can inhibit the absorption of zinc. When taken with food, supplemental iron does not appear to inhibit zinc absorption
- **Iron and calcium:** When consumed together in a single meal, **calcium** has been found to reduce the absorption of iron. However, little effect has been observed on serum ferritin levels (iron stores) with calcium supplement levels ranging from 1,000 to 1,500 mg/day

DEFICIENCY OF IRON

- Iron deficiency is the most common nutrient deficiency in the U.S. and the world
- **Three levels of iron deficiency are generally identified**
  1. **Storage iron depletion:** Iron stores are depleted, but the functional iron supply is not limited
  2. **Early functional iron deficiency:** The supply of functional iron is low enough to impair RBC formation, but not low enough to cause measurable anemia
  3. **Iron deficiency anemia:** There is inadequate iron to support normal RBC formation, resulting in anemia
- The anemia of iron deficiency is characterized as microcytic and hypochromic, meaning RBC are measurably smaller than normal and their hemoglobin content is reduced
- It is important to remember that iron deficiency is not the only cause of anemia, and that the diagnosis or treatment of iron deficiency solely on the basis of anemia may lead to misdiagnosis or inappropriate treatment of the underlying cause
- **Symptoms of iron deficiency**
  - Fatigue, rapid heart rate, palpitations, and rapid breathing on exertion
  - Ability to maintain a normal body temperature on exposure to cold is impaired in iron-deficient individuals

- **Individuals at increased risk of iron deficiency**
  - **Infants** and children between the ages of 6 months and 4 years: A full-term infant's iron stores are usually sufficient to last for 6 months
  - **Adolescents**: in female, blood loss from menstruation adds to the increased iron requirement of adolescence
  - **Pregnancy**: Increased iron utilization by the developing fetus and placenta, as well as blood volume expansion significantly, increase the iron requirement during pregnancy
  - **Blood loss**: Chronic bleeding or acute blood loss may result in iron deficiency. Individuals who donate blood frequently, especially menstruating women, may need to increase their iron intake to prevent deficiency because each 500 mL of blood donated contains between 200 and 250 mg of iron
  - **Vegetarians**: Because iron from plant sources is less efficiently absorbed than that from animal sources, the FNB has estimated that the bioavailability of iron from a vegetarian diet is only 10%, while it is 18% from a mixed diet. Therefore, the RDA for iron from a completely vegetarian diet should be adjusted as follows: **14 mg/day for adult men and postmenopausal women, 33 mg/day for premenopausal women, and 26 mg/day for adolescent girls**
  - **Individuals** who **engage in regular, intense exercise:** Daily iron losses have been found to be greater in athletes involved in intense endurance training. This may be due to increased fragility and hemolysis of red blood cells. The FNB estimates that the average requirement for iron may be 30% higher for those who engage in regular intense exercise
- **Health effects of iron deficiency**
  - **Impaired physical and work performance**: impairs athletic performance and physical work capacity in several ways
  - **Impaired intellectual development in children**: Most observational studies have found relationships between iron deficiency anemia in children and poor cognitive development, poor school achievement, and behavior problems
  - **Lead toxicity**: Iron deficiency may increase the risk of lead poisoning in children
  - **Pregnancy complications**: there is an association between severe anemia in pregnant women and adverse pregnancy outcomes, such as low birth weight, premature birth, and maternal mortality
  - **Impaired immune function**: sufficient iron is critical to several immune functions, including differentiation and proliferation of T cells and the generation of ROS by iron-dependent enzymes, which are used to kill pathogens
  - **Restless legs syndrome (RLS)**: RLS occurs in some people with iron deficiency and some RLS patients benefit from iron supplementation. The mechanism by which low brain iron [ ] contributes to RLS is not known, but may be related to the fact that the activity of an iron-dependent enzyme (tyrosine hydroxylase) is a limiting factor in the synthesis of the neurotransmitter, dopamine

IRON OVERLOAD

- Several genetic disorders may lead to pathological accumulation of iron in the body. Hereditary hemochromatosis results in iron overload despite normal iron intake
- **Hereditary hemochromatosis**
  - Up to 1 in 200 individuals of northern European descent are affected by this disorder
  - It is characterized by iron deposition in the liver and other tissues as a result of a small increase in intestinal iron absorption over many years
  - If untreated, tissue iron accumulation may lead to cirrhosis of the liver, diabetes, cardiomyopathy, or arthritis
  - Iron overload in HH is treated by phlebotomy, the removal of 500 mL of blood at a time

TOXICITY OF IRON: OVERDOSE

- Symptoms of acute toxicity may occur with iron doses of 20-60 mg/kg of body weight
- Acute iron poisoning produces symptoms in four stages
  1. Within **1-6 hours** of ingestion, symptoms may include nausea, vomiting, abdominal pain, tarry stools, lethargy, weak and rapid pulse, low blood pressure, fever, difficulty breathing, and coma
  2. If not immediately fatal, symptoms may subside for **about 24 hours**
  3. Symptoms may return **12 to 48** hours after iron ingestion and may include serious signs of failure in the following organ systems: cardiovascular, kidney, liver, and CNS
  4. Long-term damage to the CNS, cirrhosis, and stomach may develop **2-6 weeks** after ingestion
- *The UL for infants and children < 14 years is 40 mg/day and the UL for adolescents and adults > 14 years, including pregnant and breastfeeding women is 45 mg/day*
- **Health effects of iron excess**
  - *Cardiovascular diseases: Epidemiologic studies of iron nutritional status and cardiovascular diseases in humans have yielded conflicting results*
  - *Cancer: A dramatically increased risk of liver cancer (hepatocellular carcinoma) in individuals with cirrhosis due to iron overload in hereditary hemochromatosis has been well documented. However, the relationship between dietary iron and cancer risk in individuals without hemochromatosis is less clear*
  - *Neurodegenerative diseases (Alzheimer's disease): Iron is required for normal brain and nerve function through its involvement in cellular metabolism, as well as the synthesis of neurotransmitters and myelin. Accumulation of excess iron can result in increased oxidative stress*

By Monica Hsu

ZINC

- Zinc is an essential trace element for all forms of life. Zinc insufficiency has been recognized by a number of experts as an important public health issue, especially in developing countries

REQUIREMENT: RDA

The RDA for Zinc			
Life Stage	***Age***	***Males (mg/day)***	***Females (mg/day)***
Infants	*0-6 months*	*2 (AI)*	*2 (AI)*
Infants	*7-12 months*	*3*	*3*
Children	*1-3 years*	*3*	*3*
Children	*4-8 years*	*5*	*5*
Children	*9-13 years*	*8*	*8*
Adolescents	*14-18 years*	*11*	*9*
Adults	*19 years and older*	*11*	*8*
Pregnancy	*18 years and younger*	*-*	*13*
Pregnancy	*19 years and older*	*-*	*11*
Breastfeeding	*18 years and younger*	*-*	*14*
Breastfeeding	*19 years and older*	*-*	*12*

FOOD SOURCES

- Zinc is typically associated with the protein fraction and/or nucleic acid fraction of foods
- Shellfish and red meats (beef) are rich sources of zinc. Nuts and legumes are relatively good plant sources
- Zinc **bioavailability** (the fraction of zinc retained and used by the body) is relatively high in meat, eggs, and seafood because of the relative absence of compounds that inhibit zinc absorption and the presence of certain AA (cysteine and methionine) that improve zinc absorption
- The zinc in whole grain products and plant proteins is less bioavailable due to their relatively high content of phytic acid
- The enzymatic action of yeast reduces the level of phytic acid in foods. Therefore, **leavened whole grain breads have more bioavailable zinc** than unleavened whole grain breads
- Heat treatment can cause food zinc to form complexes that are resistant to hydrolysis → make zinc unavailable for absorption
- Recently, national dietary surveys in the U.S. estimated that the average dietary zinc intake was 9 mg/day for adult women and 13 mg/day for adult men

Food	Serving	Zinc (mg)	Food	Serving	Zinc (mg)
Oysters	6 medium (cooked)	43.4	Yogurt, fruit	1 cup (8 ounces)	1.8
Crab, Dungeness	3 ounces (cooked)	4.6	Almonds	1 ounce	1.0
Beef	3 ounces* (cooked)	5.8	Peanuts	1 ounce	0.9
Pork	3 ounces (cooked)	2.2	Beans, baked	1/2 cup	1.8
Chicken (dark meat)	3 ounces (cooked)	2.4	Chickpeas (garbanzo beans)	1/2 cup	1.3
Turkey (dark meat)	3 ounces (cooked)	3.5			

- **Supplements**

Zinc Supplement	% Elemental Zinc
Zinc Acetate	30%
Zinc Gluconate	14%
Zinc Picolinate (more absorbable)	35%
Zinc Sulfate	23%

DIGESTION, ABSORPTION

- Zinc needs gastric acid and proteases (also nucleases) to hydrolyze Zn from attachment to protein and nucleic acid
- The main site of absorption is the proximal SI (jejunum). Absorption varies from 12-59% (research indicated that 33% absorption from a nonvegetarian diet providing 11 mg of zinc and 26% absorption from a lactovovegetarian diet providing 9 mg of zinc)
- Absorption into the enterocyte is by a carrier-mediated process (the need of energy is unclear) with lower intake and some simple diffusion with higher intake
- Passive diffusion and paracellular zinc absorption are thought to occur with high zinc intake
- In enterocyte Zn can be used/stored in cell or be transported across the basolateral membrane
- An intestinal cell protein that is rich in cysteine (**CRIP** [cysteine Rich Intestinal Protein]) is thought to transport zinc within the enterocyte
- If good Zn status, Zn bound with **metallothionein** (a copper-binding protein) and is excreted in feces. **(Thionein has a stronger affinity for Cu than Zn – so high Zn intakes "trap" Cu in metallothionein)**

TRANSPORT, STORAGE, EXCRETION

- Zinc travels in blood mainly attached to albumin (60%) and Ig and transferrin (40%) transport zinc in the blood
- Two AAs (histidine and cysteine) also bind 2-8% of the zinc for transport (form a histidine-zinc-cysteine complex in blood)
- Zinc is found in all body organs (liver, kidney, muscle, skin). When intake low, Zn comes from plasma Zn-containing enzymes and some from metallothionein
- Release of zinc from metallothionein involves lysosomal proteases → releasing the apoprotein thionein and zinc, which is available for use by cells or other tissues
- Lose 1-2 mg of Zn in feces, 0.3-0.7 mg in urine, 0.7-1mg/day in skin (more in burns, trauma)

FUNCTIONS OF ZINC

- Zinc plays important roles in growth and development, immune response, neurological function, and reproduction
- **On the cellular level**, the function of zinc can be divided into three categories
    - **Catalytic:** Nearly 100 different **enzymes** depend on zinc for their ability to catalyze vital chemical reactions
    - **Structural**: Zinc plays an important role in the structure of proteins and cell membranes. A finger-like structure, known as a zinc finger, stabilizes the structure of a number of proteins. Loss of zinc from biological membranes increases their susceptibility to oxidative damage and impairs their function
    - **Regulatory**: Zinc finger proteins have been found to regulate **gene** expression by acting as **transcription** factors

NUTRIENT INTERACTIONS

- **Copper**: Taking large quantities of zinc (50 mg/day or more) over a period of weeks can interfere with copper **bioavailability**. High intake of zinc induces the intestinal synthesis of a copper-binding protein called metallothionein. Metallothionein traps copper within intestinal cells and prevents its systemic absorption
- **Iron**: Supplemental (38-65 mg/day of elemental iron) but not dietary levels of iron may decrease zinc absorption
- **Calcium**: High levels of dietary Ca impair zinc absorption in animals, but it is uncertain whether this occurs in humans
- **Folic acid**: The **bioavailability** of dietary folate is increased by the action of a zinc-dependent **enzyme**, suggesting a possible interaction between zinc and folic acid

DEFICIENCY OF ZINC

- **Severe zinc deficiency**
    - Much of what is known about severe zinc deficiency was derived from the study of individuals born with acrodermatitis enteropathica, a genetic disorder resulting from the impaired uptake and transport of zinc
    - Before the cause of acrodermatitis enteropathica was known, patients typically died in infancy. Oral zinc therapy results in the complete remission of symptoms
    - Symptoms
        - Slowing or cessation of growth and development, delayed sexual maturation
        - Characteristic skin rashes
        - Chronic and severe diarrhea
        - Immune system deficiencies
        - Impaired wound healing
        - Diminished appetite, impaired taste sensation
        - Night blindness, swelling and clouding of **corneas**
        - Behavioral disturbances
- **Mild zinc deficiency**
    - Mild zinc deficiency contributes to impaired physical and neuropsychological development, and increased susceptibility to life-threatening infections in young children
- **Individuals at risk of zinc deficiency**
    - Infants and children
    - Pregnant and lactating women
    - Patients receiving TPN
    - Malnourished individuals, including those with PEM and anorexia nervosa
    - Individuals with severe or persistent diarrhea
    - Older adults (65 years and older)
    - Individuals with alcoholic liver disease have increased urinary zinc excretion and low liver zinc levels
    - Individuals with **malabsorption** syndromes, including **sprue** and **short bowel syndrome**
    - Individuals with inflammatory bowel disease, including **Crohn's disease** and **ulcerative colitis**
    - Strict vegetarians: requirement for dietary zinc may be as much as 50% greater for strict vegetarians whose major food staples are grains and legumes because high levels of phytic acid in these foods reduce the absorption of zinc

TOXICITY OF ZINC

- **Acute toxicity**
    - Isolated outbreaks of acute zinc toxicity have occurred as a result of the consumption of food or beverages contaminated with zinc released from galvanized containers → abdominal pain, diarrhea, nausea, and vomiting
    - Milder *GI distress has been reported at doses of 50-150 mg/day of supplemental zinc*
- **Chronic toxicity**
    - The major consequence of long-term consumption of excessive zinc is copper deficiency
    - The FNB set *the UL at 40 mg/day, including dietary and supplemental zinc*

DISEASE PREVENTION AND THERAPEUTICS

- *Prevention of diseases related to zinc deficiency*
  - *Impaired growth and development: growth retardation, delayed neurological & behavioral development in young children*
  - *Impaired immune system function: increased susceptibility to infectious disease in children, diarrhea, pneumonia, malaria*
  - *Pregnancy complications*
- *Disease treatment using zinc*
  - *Common cold*
  - *Age-related macular degeneration (AMD)*
  - *Diabetes*
  - *HIV/AIDS*

COPPER

- In the body, copper shifts between the cuprous (Cu^{1+}) and the cupric (Cu^{2+}) forms, though the majority of the body's copper is in the Cu^{2+} form

REQUIREMENT: RDA

- ***Adult men and women ages 19 years and older:*** *900 micrograms (mcg)/day*

FOOD SOURCES

- Copper is found in a wide variety of foods and is most plentiful in organ meats, shellfish, nuts, and seeds
- Wheat bran cereals and whole grain products are also good sources of copper
- *The average dietary intake of copper in the U.S. is approximately 1,000 to 1,100 mcg/day for adult women and 1,200 to 1,600 mg/day for adult men*

Food	Serving	Copper (mcg)	Food	Serving	Copper (mcg)
Liver (beef), cooked	1 ounce	1,265	Almonds	1 ounce	332
Oysters, cooked	1 medium oyster	670	Peanut butter (chunky)	2 tablespoons	165
Clams, cooked	3 ounces	585	Lentils, cooked	1 cup	497
Crab meat, cooked	3 ounces	624	Mushrooms, raw	1 cup (sliced)	344
Cashews	1 ounce	629	Shredded wheat cereal	2 biscuits	143
Sunflower seeds	1 ounce	519	Chocolate (semisweet)	1 ounce	198
Hazelnuts	1 ounce	496	Hot cocoa mix	1 ounce (1 packet)	169

DIGESTION, ABSORPTION

- About 30-50% usually absorbed
- Usually bound to amino acids in proteins of foods so need HCl and pepsin to release copper in the stomach. Other proteolytic enzymes may hydrolyze protein and release copper in SI
- Mainly absorbed in the duodenum and rest of small intestine, but some in the stomach. There is a saturable, energy-dependant system and (low amounts) and a nonsaturable passive diffusion system
- Cu absorption enhanced by some amino acids (especially histidine and sulfur amino acids), organic acids such a citric acid and low body stores
- Once in the enterocyte, copper may be used, stored, or transported across the basolateral membrane
- Like Zn, Cu can be bound to metallothioneins and enter the GI tract when the enterocyte is sloughed off
- Zinc intake stimulates thionein synthesis, but thionein has a stronger affinity for Cu than Zn – so high Zn intakes “trap” Cu in metallothionein

TRANSPORT, STORAGE, EXCRETION, HOMEOSTASIS

- Carried to liver mainly on albumin. Believed to have a specific, saturable process for uptake of Cu by hepatocytes
- In liver copper can bind to apoceruloplasmin to form ceruloplasmin – this is the major form of Cu delivery from the liver to the tissue and the major carrier for copper in blood
- The liver is the major storage site. Other copper-containing tissues include brain, heart, bone, muscle, intestine, spleen, hair, nail, and skin
- Only small amounts lost in urine and sweat; 97% lost in feces from sloughed cells

By Monica Hsu

FUNCTIONS OF COPPER

- **Energy production**: copper-dependent enzyme, cytochrome c oxidase, plays a critical role in cellular energy production
- **Connective tissue formation**: Another cuproenzyme, lysyl oxidase, is required for the cross-linking of collagen and elastin, which are essential for the formation of strong and flexible connective tissue
- **Iron metabolism**: Two copper-containing enzymes, ceruloplasmin (ferroxidase I) and ferroxidase II have the capacity to oxidize ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), the form of iron that can be loaded onto the protein, transferrin, for transport to the site of RBC formation
- **CNS**: A number of reactions essential to normal function of the brain and nervous system are catalyzed by cuproenzymes
    - **Neurotransmitter synthesis: Dopamine-beta-monooxygenase** catalyzes the conversion of dopamine to norepinephrine
- **Melanin formation:** The cuproenzyme, tyrosinase, is required for the formation of the pigment melanin
- **Antioxidant functions**
    - **Superoxide dismutase (SOD)** functions as an antioxidant by catalyzing the conversion of superoxide radicals (free radicals or ROS) to hydrogen peroxide
    - Two forms of SOD contain copper:
        - Copper/zinc SOD is found within most cells of the body, including RBC
        - Extracellular SOD is found in high levels in the lungs and low levels in blood plasma
- **Regulation of gene expression:** Copper-dependent transcription factors regulate transcription of specific genes

NUTRIENT INTERACTIONS

- **Iron:** Adequate copper nutritional status appears to be necessary for normal iron metabolism and RBC formation. **Anemia** is a clinical sign of copper deficiency, and iron has been found to accumulate in the livers of copper deficient animals, indicating that copper (probably in the form of ceruloplasmin) is required for iron transport to the bone marrow for RBC formation
- **Zinc**: High **supplemental** zinc intakes of 50 mg/day or more for extended periods of time may result in copper deficiency. High dietary zinc increases the synthesis an intestinal cell protein called metallothionein (high levels of metallothionein induced by excess zinc cause a decrease in intestinal copper absorption)

DEFICIENCY OF COPPER

- Serum copper levels and ceruloplasmin levels may fall to 30% of normal in cases of severe copper deficiency
- One of the most common clinical signs of copper deficiency is an **anemia** that is unresponsive to iron therapy but corrected by copper supplementation
- The anemia is thought to result from defective iron mobilization due to decreased ceruloplasmin activity
- Copper deficiency may also result in abnormally low numbers of **neutrophils** (neutropenia) → increased susceptibility to infection
- **Individuals at risk of deficiency**: cow's milk is relatively low in copper, and cases of copper deficiency have been reported in high-risk infants and children fed only cow's milk formula

TOXICITY OF COPPER

- Symptoms of acute copper toxicity include abdominal pain, nausea, vomiting, and diarrhea, which help prevent additional ingestion and absorption of copper. More serious signs of acute copper toxicity include severe liver damage, kidney failure, coma, and death
- *The FNB set the UL at 10 mg/day from food and supplements*

DISEASE PREVENTION

- **Cardiovascular disease**
- **Immune system function**
- **Osteoporosis**

By Monica Hsu

SELENIUM

- Selenium is a trace element that is essential in small amounts but can be toxic in larger amounts. Humans and animals require selenium for the function of a number of selenium-dependent enzymes, also known as selenoproteins

REQUIREMENT: RDA

- *The most* recent *RDA is based on the amount of dietary selenium required to maximize the activity of the glutathione peroxidase in blood plasma.*
- ***Adult men and women ages 19 years and over:*** *55 micrograms selenium/day*

SOURCES

- **Food sources**
  - The richest food sources of selenium are organ meats and seafood
  - Selenium occurs naturally in foods almost exclusively in the form of organic compounds, mainly as selenomethionine, selenocystine, selenocysteine, and Se-methyl selenomethionine. Inorganic compound may be found in some vegetables
  - Brazil nuts grown in areas of Brazil with selenium-rich soil may provide more than 100 mcg of selenium in one nut, while those grown in selenium-poor soil may provide 10 times less
  - In the U.S., grains are a good source of selenium, but fruits and vegetables tend to be relatively poor sources of selenium. Drinking water is not a significant source of selenium in North America
  - The average *dietary intake of adults in the U.S. has been found to range from about 80-110 mcg/day*

Food	Serving	Selenium (mcg)	Food	Serving	Selenium (mcg)
Brazil nuts (from selenium-rich soil)	1 ounce (6-8 kernels)	839*	Chicken (light meat)	3 ounces	20
Shrimp	3 ounces (10-12)	34	Pork	3 ounces	33
Crab meat	3 ounces	40	Beef	3 ounces	17
Salmon	3 ounces	40	Whole wheat bread	2 slices	15
Halibut	3 ounces	40	Milk	8 ounces (1 cup)	5
Noodles, enriched	1 cup, cooked	35	Walnuts, black	1 ounce, shelled	5
Rice, brown	1 cup, cooked	19			

*Above the recommended upper level of intake (UL) of 400 mcg/day

- **Supplements**
  - Sodium selenite and sodium selenate are inorganic forms of selenium
  - Selenate (H_2SeO_4) is almost completely absorbed, but a significant amount is excreted in the urine before it can be incorporated into proteins
  - Selenite (H_2SeO_3) is only about 50% absorbed, but is better retained than selenate, once absorbed
- **Selenium-enriched vegetables**
  - Selenium-enriched garlic and ramps (wild leeks) have been shown to reduce chemically induced tumors in rats

ABSORPTION, TRANSPORT

- Both inorganic and organic forms of selenium are all efficiently absorbed primarily in the duodenum (duodenum > jejunum and ileum > stomach)
- Following absorption from the intestine, selenium is bound to transport proteins for travel through the blood and other tissues
- In blood, selenium bind to sulfhydryl groups in α and β globulins [VLDL (an α globulin) and LDL (a β globulin)] have been shown to contain and transport selenium
- The mechanism by which selenium is freed from plasma transport proteins is not known
- Tissues that contain higher [ ]: kidney, liver, heart, muscle, and pancreas
- The Lungs, brain, and RBCs also contain less selenium
- Dietary selenium in the inorganic form such as selenite leads to greater incorporation of the mineral into glutathione peroxidase than when selenomethionine, the organic form, is the dietary form
- Vitamins C, A, and E enhance selenium absorption
- Mercury and phytates are thought to inhibit selenium absorption through chelation and precipitation

FUNCTIONS OF SELENIUM

- **Selenoproteins:** At least 11 selenoproteins have been characterized, and there is evidence that additional selenoproteins exist
- **Glutathione peroxidases:** Four selenium-containing glutathione peroxidases (GPx) have been identified:
  - **(1) Cellular or classical GPx, (2) plasma or extracellular GPx, (3) phospholipid hydroperoxide GPx, and (4) gastrointestinal GPx**
  - Although each GPx is a distinct selenoprotein, they are all antioxidant enzymes that reduce potentially damaging **reactive oxygen species** (ROS), such as hydrogen peroxide and lipid hydroperoxides, to harmless products

NUTRIENT INTERACTIONS

- **Iodine**
  - Selenium deficiency may exacerbate the effects of iodine deficiency. Iodine is essential for the synthesis of thyroid hormone, but the selenoenzymes, iodothyronine deiodinases, are also required for the conversion of thyroxine (T4) to the biologically active thyroid hormone triiodothyronine (T3)
  - Selenium supplementation in elderly individuals decreased plasma T4, indicating increased deiodinase activity with increased conversion to T3
- **Lead**
  - Lead and selenium appear to react such that sub-clinical amounts of lead intake are found to lower tissue [ ] of selenium (mechanism unclear)
- **Iron**
  - Iron deficiency in rats has been shown to decrease the synthesis of hepatic glutathione peroxidase → lead to decrease hepatic selenium [ ] (mechanism unclear)
- **Copper**
  - Copper deficiency decreases the activity of the selenium-dependent enzyme glutathione peroxidase
- **Arsenic**
  - Arsenic inhibit the uptake of selenium (the significance of this interaction in human nutrition is not known)

DEFICIENCY OF SELENIUM

- Insufficient selenium intake results in decreased activity of the glutathione peroxidases
- **Individuals at increased risk of selenium deficiency**
  - Clinical selenium deficiency has been observed in chronically ill patients who were receiving TPN without added selenium for prolonged periods of time. Muscular weakness, muscle wasting, and cardiomyopathy have been observed in these patients
  - People who have had a large portion of the small intestine surgically removed or those with Crohn's disease, are also at risk for selenium deficiency due to impaired absorption
  - Specialized medical diets used to treat PKU, are often low in selenium
  - **Keshan disease**: Keshan disease is a cardiomyopathy that affects young women and children in a selenium deficient region of China

TOXICITY OF SELENIUM

- High doses can be toxic. Acute and fatal toxicities have occurred with accidental or suicidal ingestion of gram quantities of selenium. *Clinically significant selenium toxicity was reported in 13 individuals after taking supplements that contained 27.3 milligrams (27,300 mcg) per tablet due to a manufacturing error*
- **Chronic selenium toxicity (selenosis)** may occur with smaller doses of selenium over long periods of time
- The most frequently reported symptoms of selenosis are hair and nail brittleness and loss. GI disturbances, skin rashes, a garlic breath odor, fatigue, irritability, and nervous system abnormalities, were also reported
- *The FNB set the UL 400 mcg/day in adults based on the prevention of hair and nail brittleness and loss, early signs of chronic selenium toxicity*

DISEASE PREVENTION

- ***Immune function:*** *Selenium deficiency has been associated with impaired function of the immune system. Moreover, selenium supplementation in individuals who are not overtly selenium deficient appears to stimulate the immune response*
- *Viral infection: Selenium deficiency appears to enhance the virulence or progression of some viral infections*
- **Cancer:** Several mechanisms have been proposed for the cancer prevention effects of selenium
  - Maximizing the activity of antioxidant selenoenzymes and improving antioxidant status
  - Improving immune system function
  - Affecting the metabolism of carcinogens
  - Increasing the levels of selenium metabolites that inhibit tumor cell growth.

DISEASE TREATMENT

- ***HIV/AIDS***
  - *There appears to be a unique interaction between selenium and HIV that cause AIDS. Declining selenium levels in HIV-infected individuals are sensitive markers of disease progression and severity, even before malnutrition becomes a factor*
  - *Low levels of plasma selenium have also been associated with a significantly increased risk of death from HIV*
  - *Adequate selenium nutritional status may increase resistance to HIV infection by enhancing the function of important immune system cells known as T helper cells*
  - *As an integral component of glutathione peroxidase and thioredoxin reductase, selenium plays an important role in decreasing oxidative stress in HIV-infected cells and possibly suppressing the rate of HIV replication*

IODINE

- Iodine, a non-metallic trace element, is required by humans for the synthesis of thyroid hormones

REQUIREMENT: RDA

Age group	*RDA for Iodine in Males (mcg/day)*	*RDA for Iodine in Females (mcg/day)*
Infants 0-6 months	*110 (AI)*	*110 (AI)*
Infants 7-12 months	*130 (AI)*	*130 (AI)*
Children 1-3 years	*90*	*90*
Children 4-8 years	*90*	*90*
Children 9-13 years	*120*	*120*
Adolescents 14-18 years	*150*	*150*
Adults 19 years and older	*150*	*150*
Pregnancy	*-*	*220*
Breastfeeding	*-*	*290*

SOURCES

- The average iodine intake in the U.S. is 240-300 mcg/day for adult men and 190-210 mcg/day for adult women
- Iodine intake in the U.S. has decreased significantly over the past 20 years. Between 1988 and 1994, 11% of the U.S. population was found to have low urinary iodine [ ]
- **Food sources**
  - Dietary iodine (I) is either bound to AAs or is found free, primarily in the form of iodate (IO3-) or iodide (I-).
  - Iodide is found in water and seafoods [sea fish contain higher [ ] (300-3000 mcg I/Kg); fresh water (20-40 mcg I/Kg)]
  - Certain types of seaweed (e.g. wakame) are also very rich in iodine. Processed foods may contain slightly higher levels of iodine due to the addition of iodized salt or food additives, such as calcium iodate and potassium iodate
  - Vegetarian and non-vegetarian diets that exclude iodized salt, fish, and seaweed have been found to contain very little iodine
  - Dairy products are relatively good sources of iodine because iodine is commonly added to animal feed in the U.S.

Food	Serving	Iodine (mcg)	Food	Serving	Iodine (mcg)
Salt (iodized)	1 gram	77	Egg, boiled	1 large	29
Cod	3 ounces*	99	Navy beans, cooked	1/2 cup	35
Shrimp	3 ounces	35	Potato with peel, baked	1 medium	63
Fish sticks	2 fish sticks	35	Turkey breast, baked	3 ounces	34
Tuna, canned in oil	3 ounces (1/2 can)	17	Seaweed	1 ounce	Variable; may be greater than 18,000 mcg (18 mg)
Milk (cow's)	1 cup (8 fluid ounces)	56			

- **Supplements:** *A multivitamin/multimineral supplement that contains 100% of the daily value (DV) for iodine provides 150 mcg of iodine*
- Some foods contain substances that **interfere with iodine utilization or thyroid hormone production, known as Goitrogens**
  - Casava contains a compound that is metabolized to thiocyanate and blocks thyroidal uptake of iodine
  - Some species of millet and cruciferous vegetables (for example, cabbage, broccoli, cauliflower, and Brussel sprouts) also contain goitrogens
  - The soybean isoflavones, genistein and daidzein, have also been found to inhibit thyroid hormone synthesis

DIGESTION, ABSORPTION, TRANSPORT

- Dietary iodine (I) is either bound to AAs or is found free, primarily in the form of iodate (IO_3^-) or iodide (I^-). During digestion, iodate (from breads) is reduced to iodide by glutathione
- Iodide is absorbed rapidly and completely throughout the GI tract, including the stomach
- Following absorption, free iodide appears in the blood. Iodide is distributed throughout the extracellular fluid from which it is capable of permeating all tissues
- Higher [ ] in thyroid *(contains 70-80% of the total body iodide, and takes up about 120 mcg of iodide/day),* salivary, and gastric glands. Lesser amounts of iodide are found in mammary glands, ovaries, placenta, and skin

By Monica Hsu

FUNCTIONS OF IODINE

- Iodine is an essential component of the **thyroid hormones**, triiodothyronine (T3) and thyroxine (T4) and is therefore, essential for normal thyroid function
- T4, the most abundant circulating thyroid hormone, can be converted to T3 by **enzymes known as deiodinases** in target tissues
- The regulation of thyroid function is a complex process that involves the brain (**hypothalamus**) and pituitary gland. Iodine deficiency results in inadequate production of T4. In response to decreased blood levels of T4, the pituitary gland increases its output of thyroid-stimulating hormone (TSH). Persistently elevated TSH levels may lead to hypertrophy of the thyroid gland, also known as **goiter**

DEFICIENCY OF IODINE

- Thyroid enlargement, or goiter, is one of the earliest and most visible signs of iodine deficiency. Severe cases of iodine deficiency result in hypothyroidism
- **The effects of iodine deficiency by developmental stage**
    - **Prenatal development:** Fetal iodine deficiency is caused by iodine deficiency in the mother → Congenital hypothyroidism (**cretinism**) → irreversible mental retardation
    - Congenital hypothyroidism occurs in two forms, the **neurologic** form is characterized by mental and physical retardation and deafness. The **myxedematous** or hypothyroid form is characterized by short stature and mental retardation
    - **Newborns and infants:** Infant mortality is increased in areas of iodine deficiency. Iodine deficiency during infancy may result in abnormal brain development and, consequently, impaired intellectual development
    - **Children and adolescents:** Iodine deficiency in children and adolescents is often associated with goiter. School children with iodine deficient show poorer school performance, lower IQs, and a high incidence of learning disabilities
    - **Adults:** Inadequate iodine intake may also result in goiter and hypothyroidism in adults
    - **Pregnancy and lactation:** Iodine deficiency during pregnancy has been associated with increased incidence of miscarriage, stillbirth, and birth defects. Moreover, severe iodine deficiency during pregnancy may result in cretinism in the offspring
    - Iodine deficient women who are breastfeeding may not be able to provide sufficient iodine to their infants. A daily prenatal supplement providing 150 mcg of iodine will help to ensure that pregnant and breastfeeding women consume sufficient iodine during these critical periods

TOXICITY OF IODINE

- **Acute toxicity:** Symptoms of acute iodine poisoning include burning of the mouth, throat, and stomach, fever, nausea, vomiting, diarrhea, a weak pulse, and coma
- *The FNB set the UL at 1,100 mcg/day for adults. Prolonged intakes of more than 18,000 mcg/day (18 mg/day) have been found to increase the incidence of goiter*

By Monica Hsu